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CAN FETUS, INFANTS, AND CHILDREN SURVIVE SOY-ESTROGENS?
By, Gail Elbek

[Redacted] are autistic, so is [Redacted] [Redacted] [Redacted] is infertile, as is [Redacted] [Redacted] As a teenager, [Redacted] has extreme allergies and asthma. [Redacted] has an immune deficiency disease. Is it, or is it not merely coincidence that in all of these cases there is an important common link: early exposure to soy phyto-estrogens.

In fact, Freedom of Information Act (FOIA) "Adverse Event Reporting System-Related to Soy Infant Formula," reveals a long list of adverse soy effects that are reported as experienced by multiple infants and children.

13 FACTS CONFIRM SOY AS DEVELOPMENTALLY PHYTO-TOXIC:

1. **Soy plant-estrogens cause hormone disruptions-** The National Institute of Health web sites: Toxnet and Pubmed reveal literally hundreds upon hundreds of published studies that conclude soy isoflavones: genistein, daidzein, glycitein, and daidzein metabolite equol, are biologically active phyto-chemicals that exert estrogenic effects recognized as, "endocrine (hormone) disruptors." Exposures to hormone disruptors are overwhelmingly proven as increasingly dangerous during most sensitive developmental timeframes.

Dr. Michael Shelby of the National Institute of Health (NIH), Center for Food Safety and Applied Nutrition (CFSAN) also confirms, "Soy is an endocrine disruptor."

With the only exception being soy as an established endocrine disruptor, other examples of endocrine disruptors including: pesticides, herbicides, pollutions, plastics, and alcohol, are all well-known as anatomically damaging to all hormone systems, and especially damaging to fetus, infants, and children.

Beginning several decades ago, endocrine disruptors became of scientific interest while repeatedly proving to cause disorders in; sexual behavior, reproductive organs, and fertility, as well as causing limb defects in a variety of animal species. Endocrine disruptors cause chromosome damage contributing to DNA breakage resulting in multiple primary and/or cascading ill-effects of which are repeatedly proven as responsible for physiological and neurological developmental disorders and diseases.

2006, *Journal of Health Science*, S Ikegami et al report, *".....isoflavones are well known as endocrine-disrupting chemicals. The possibility that soy food might adversely affect the reproductive system of others and infants should be considered. Genistein and daidzein were detected in the blood of the dams and the stomach contents of the suckling*

pups. We also found the transfer of isoflavones to the fetus. Our experiments suggest that soy isoflavones have the possibility of inducing adverse effects on the endocrine functions and others in animal studies…."

Numerous published studies conclude that maternal consumption of soy transfers active estrogenic endocrine disruptors through her bloodstream to developing fetus.

From the Department of Environmental Medical Science, Chiba University reports, *"We detected that the concentrations of Genistein and Daidzein were significantly higher in (fetal) cord serum than in maternal serum. These data suggest that the phytoestrogen affected the hormonal condition of human fetuses, and the response to the phytoestrogen of fetuses was different from the adults."*

Soy's estrogenic endocrine disruptors can pass a second time to her infant while breast feeding.

It remains controversial whether the adult male soy-consumer will supply endocrine disrupting chromosome-damaged sperm during fertilization. If so, miscarriage will likely occur.

2. Soy-based infant formulas are not FDA approved- It is true that soy-based infant formulas are not FDA or NIH approved. There is no evidence that soy is a remedy for colic and crying, or the safe solution for lactose intolerance.

Alarmingly, and without reason, throughout more recent years soy is increasingly added to milk-based infant formulas. Therefore, babies diagnosed as lactose-intolerant may instead be showing signs of intolerance to soy endocrine disruptor phyto-toxicity. The FDA confirms that there are no known safe levels of exogenous estrogens to be injected or fed to fetus, infants, and children.

According to the USDA, depending upon the manufacturer, total soy-based infant formula estrogenic (endocrine disruptor) isoflavone content can largely range from 2.63mg to 28.01mg per 100 grams. Soy-based estrogenic endocrine disruptor formulas, as 100% of infant's complete dietary intake, are stated throughout published studies as capable of causing an assortment of potentially irreversible developmental damage to health. There is no question that consumption of soy phyto-estrogens increase estrogen levels of which can cause entire body hormone disruptions that are well-known as biologically health-threatening particularly during developmental timeframes.

June, 2002, *The National Institute of Environmental Health Sciences (NIEHS) News*, Volume 110, No. 6 states, "*Increasingly, new research is questioning the purported health benefits of soy in adults, as well as raising concerns about adverse effects in children. Soy formula is available off the shelf in the United States, but available only by prescription in Europe. Researchers agree that a biological response to phytoestrogens in infants and young children is likely … ……..NIEHS researcher Retha Newbold says, 'I hope I'm wrong, but in case I'm not, experimental animals are telling this is something to worry about.'"*.

The overwhelming marketing of soy foods, soy fillers, and soy beverages may have GRAS (Generally Regarded As Safe) status of which is simply determined by industry profiteers, or the furthest from FDA approval as safe or healthy. To advertise

soy products and supplements as safe and nutritional may be misbranding because increasing numbers of published studies conclude extensive soy phyto-toxic events that are confirmed as most threatening to the smallest thus weakest link; fetus, infants and children.

United States Department of Agriculture (USDA) Database on the Isoflavone Content of Selected Foods reports high estrogenic levels: soy cheeses range from 6.02 to 25.72mg total isoflavones. Soy lecithin is increasingly added to multiple packaged foods is reported at 15.70mg total isoflavones. Soy yogurt equals 33.17mg, and tofu (firm, cooked) at 22.05mg total isoflavones per 100g. Soy milk is reported to range from 0.70mg to 196.05mg per 100g. It is increasingly difficult to find food products that do *not* contain soy endocrine disruptors and therefore qualifying as phyto-toxic.

The FDA "Poisonous Plant Database" includes, *"soy bean*" on their list while stating, *"This database contains references to the scientific literature describing studies of the toxic properties and effects of plants and plant parts."* In addition to, *"soy bean,"* the named soy phyto-estrogens: *"genistein, daidzein, and equol"* are also individually listed within the FDA "Poisonous Plants Database."

3. Soy is a trypsin inhibitor, and soy is loaded with anti-nutrients- Besides estrogen-secreting isoflavones, soybeans contain a large assortment of health-threatening anti-nutrients such as; nitrates, phytic acid, lectins, hemagglutinins, cyanogens, furan, lysinoalanine, corn syrup, sugar, and more.

1999, the FDA *Federal Register* reports, "*GRAS status of soy protein food ingredients, did not include a thorough evaluation of the safety of potentially harmful components, e.g. lysinoalanine, nitrites, and nitrosamines, trypsin inhibitors, phytate, and isoflavones."*

Produced in the pancreas, trypsin is an essential enzyme necessary for protein digestion with multiple anatomical functions. Soy is a trypsin inhibitor, debilitating the body's ability to digest proteins and further encourage intestinal obstructions. Soy inhibition of trypsin causes chronic deficiencies in amino acid uptake required to facilitate the production of protein for the development and repair of cells and tissues.

Cystic fibrosis, a common type of chronic lung disease in children and young adults, is reportedly caused by a deficiency in transport of trypsin and other digestive enzymes from the pancreas. Soy inhibition of trypsin jeopardizes normal pancreatic functions, resulting in a number of damaging cascading effects that are health-threatening to all people, with greatest threat during the most vulnerable stages of fetal, infant, and child development.

A report in the 1999 FDA *Federal Register* concludes trypsin inhibitors, (such as soy) cause damaging effects to pancreatic functions, and that *"Trypsin inhibitors are responsible for pancreatic hyperplasia and formation of nodules as seen in animal studies."*

Studies confirm that soybean inhibition of trypsin also causes an increase in cholecystokinin (CCK) levels resulting in hyper-stimulation of the pancreas. CCK is a

protein and when in excess leads to the causation of damaging hormonal activities, particularly involving the gastrointestinal system.

Trypsin enzymes are also involved in neurotransmitter functions, and the soy inhibition of trypsin increases CCK to further encourage cascading neurological-damaging effects.

2001, journal of *Neuropsychopharmacology*, J.L. Abelson et al report, *"CCK neurotransmitter modulates hypothalamic-pituitary-adrenal axis (HPA) activity and may be involved in fear or anxiety states."*

4. Fluctuating plant-estrogens and anti-nutrients levels in soy products-

Unlike all other marketed foods and beverages, a paramount problem with the soybean is that soy estrogenic and anti-nutrient levels can largely fluctuate depending upon several factors such as; plant location, soil and weather conditions, fertilizers, pesticides, time of harvesting, conditions of processing, and packaging.

Although genistein is known to be the contributor to the highest levels of plant-estrogens, and daidzein second, alarmingly, in regards to consumers of soy products, 33 to 50 per cent of people are reported as having qualifying intestinal bacteria that metabolizes soy phyto-estrogen daidzein to the higher estrogenic potency of equol.

2002 book review: *"Phytoestrogens and Health"* by G.S. Gilani and J.J.B. Anderson report, *"Assuming that consumption of phytoestrogens is always beneficial would be naïve because excessive or inappropriate consumption may be harmful. In addition the estrogenic effect of phytoestrogens may be unpredictable. Excessive intake of phytoestrogens could exert detrimental, if not toxic, estrogenic effects. This issue is a cause for serious concern."*

5. Soy inhibition of tyrosine kinase, damages MET, related to autism- Soy inhibition of trypsin enzymes is not to be confused with inhibition of protein tyrosine kinase or PTK. There are 58 known receptor tyrosine kinases that play pivotal roles in diverse cellular activities such as: differentiation, metabolism, adhesion, motility, and death. PTK are key enzymes in signal-transduction pathways responsible for a wide range of anatomical cellular processes, including those that regulate normal cell processes necessary for central nervous system (CNS) neuronal functions. PTK are highly expressed in the CNS and are most important in a variety of neuronal functions, and soy causation of PTK inhibition is stated to encourage the cause of neurological disorders such as autism.

1998, journal of *Teratology*, T. E. Grafton and D. K. Hansen of the FDA National Center for Toxicological Research report, "*This compound (genistein) is known to inhibit tyrosine protein kinases that are necessary for the function of epidermal growth factor. This suggests an antiproliferative effect and concern for potential developmental toxicity."*

2007, *Journal of Nutritional Biochemistry*, study title: "Soy isoflavone and cognitive function" reports, "*Genistein can have negative influence on cognitive function when it is present at a high level due to its action as a tyrosine kinase inhibitor, which*

enables it to block long-term potentiation (LTP, neuron communication) and cognitive function"

As a cascading event, soy inhibition of tyrosine kinase disrupts and inhibits the MET gene. MET signaling controls cell growth and migration during embryogenesis, of which regulates multiple functions including endocrine secretions and alterations in cerebellar and cortical formations and functions. Soy causes MET deficiencies, and several published studies report that decreased MET signaling may lead to autism susceptibility.

2006, journal of *National Academy of Sciences,* D.B. Campbell et al report, "*MET signaling participates in neocortical and cerebellar growth and maturation, immune function and gastrointestinal repair, consistent with reported medical complications in some children with autism. These data implicate reduced MET gene expression in autism susceptibility, providing evidence of a previously undescribed pathophysiological basis for this behaviorally and medically complex disorder."*

6. Soy damage to essential minerals encourages body and brain damage- Soy is reported throughout published studies to cause dangerous deficiencies in essential minerals such as: iron, copper, thiamin, iodine, and magnesium. On the other hand, soy is also reported to cause dangerously high amounts of: calcium, calbindin D28k, fluoride, manganese, selenium, and phosphorus. When essential minerals are soy-manipulated into levels of deficiencies or overexposures, both extremes are overwhelmingly documented to cause body and brain damaging effects especially while occurring during development.

Critical for neurological development, soy is reported to cause zinc deficiency. FDA *Federal Register* 64, October 1999, reports, "*Increased intake of soy protein could lead to zinc deficiency."*

Zinc deficiency has been associated with lowered learning ability, apathy, lethargy, and mental retardation.

Fluoride contributes to zinc deficiency. Average fluoride content of dairy milk is 0.030ppm, while soy milk is reported to contain as much as 0.491ppm. Excessive fluoride may cause; gastrointestinal, cardiovascular, and neurological abnormalities.

Calcium selective ion channels are important for synaptic transmission through the release of neurotransmitters and specialized junctions of which neurons signal to other neurons, muscles, and glands. Soy causes excessive calcium levels called hypercalcemia known to be responsible for an assortment of damaging health effects such as: nausea, headache, rapid heart rate, heart dysfunction, kidney damage, stiff and swollen joints, bone disease, severe mental confusion, personality changes, lethargy, coma, and death.

2007, *Journal of Biomedical Science,* U. Ying et al report, "*Both genistein and daidzein…… increased the intracellular calcium level (Ca2+) significantly."*

1993, the *Neuroreport,* C. Batini et al report, "*Excessive intracellular calcium in neurons is thought to underlie the pathophysiology of several neurodegenerative diseases."*

Calbindin D28k is an important calcium-buffering protein that is neuro-protective by preventing cellular toxic calcium levels that leads to neurodegeneration. Studies report that soy increases Calbindin D28k that promotes neuronal injury and seizures.

2004, journal of *Toxicological Sciences*, A Scallet et al from the FDA Division of Neurotoxicology report, "*Endocrine disruptors (EDs) may also alter brain development by mimicry or modulation of endogenous hormone systems. Two EDs that have recently been studied…… Both genistein and nonylphenol were found to increase the volume of calbindin D-28k…….. in male rats."*

Manganese is an essential trace mineral that is toxic in higher levels, and an increasing threat to infants.

2005, Kaayla Daniel PhD reports in her book, "*The Whole Soy Story- Manganese is an essential trace mineral, but high levels are neurotoxic to newborns. Infants fed soy formula ingest as much as 80 times more manganese per day than those who are breast fed…..neonates exposed to high levels of manganese present in soy formula are at increased risk for neurodevelopmental abnormalities. These findings suggest that soy infant formula is a likely contributor to the epidemic of ADD/ADHD and other cognitive and behavioral disorders."*

7. Soy-causation of heavy metal contamination- Soy is reported throughout published studies to encourage heavy metal: aluminum, cadmium, and thallium toxicity. Heavy metal contamination is well-known to cause physiological and neurological damage with greatest risk during developmental exposures.

Regarding aluminum contamination most prevalent in soy, 2008, "Pediatrics," (official journal of the American Academy of Pediatrics) J Bhatia et al report, *"….aluminum content of human milk is 4 to 65ng/mL, that of soy protein-based formula is 600 to 1300ng/mL. The toxicity of aluminum is traced to increased deposition in bone and in the central nervous system."*

Cadmium is a heavy metal proven to be toxic even in low concentrations. The *Journal of Association of Official Analytical Chemists*, reports, "*Soy-based formula contained 8-15 times more cadmium than did milk-based formulas."*

Thallium is a highly toxic metal, with highest levels accumulating in plants. 2002, journal of *Food Chemistry*, A. Ikem et al report, "*The results suggest that soy-based powder infant formulas generally had higher element levels than milk-based powder formulations..…and in the US EPA standard for thallium were violated in some infant formula brands."*

8. Soy-causation of glucose overdose- Soy-based infant formulas and many soy products contain dangerously high levels of sugar and corn syrup. Diabetes is a condition where the glucose or sugar levels are too high in the blood.

2006, from the NIH, National Toxicological Program, Fort et al report, *"Almost twice as many diabetic children had been fed soy formulas compared to controls."*

Soy is also reported to dangerously increase adiponectin protein that regulates the metabolism of lipids and glucose. Excessive levels of corn syrup and sugars, in addition to the evidence of soy increase of adiponectin can encourage the cause of childhood diabetes, and other diseases.

2008, journal of *Menopause,* C. Charles et al report, "*……a small but significant increase in serum adiponectin levels in the isoflavone group compared with placebo group."*

2005, journal of *Current Diabetes Reports,* S Maxaki-Tovi et al report, *"….adiponectin, a modulator of insulin resistance, is subject to investigation during gestation. Furthermore, conditions associated with increased insulin resistance, such as gestational diabetes and preeclamsia may be influenced by this hormone. Adiponective a key modulator of insulin action and glucose metabolism, both known to regulate fetal growth is a plausible candidate for regulation of intrauterine fetal development."*

9. Soy-hormone damage to reproductive organs- A 2000 study published in the journal of *Neurotoxicology*," FDA Senior Advisor Dr. Schweiz reports, "*Developmental Neurotoxicity (brain poisoning) of Endocrine Disruptors: Focus on Estrogens- Adverse effects of (estrogenic endocrine disruptors) on reproductive tissues have been primary focus of attention while effects on other organ systems and processes such as carcinogenesis have also been reported. Chemicals with estrogenic activity can affect the development and function of neural tissues through several different mechanisms. Studies on (soy genistein) will compare toxicity in neural, immune and reproductive systems, and evaluate potential carcinogenicity."*

Soy's estrogenic endocrine disruptors are overwhelmingly reported to cause extensive reproductive damage to animals and humans such as: infertility, miscarriage, early onset of puberty, breast changes or disease, extensive reproductive organ-damage respective of males and females, as well as gender alterations of both sexes.

The journal, *Hormones and Behavior,* T. Kouki et al report, "*These results suggest that genistein acts as an estrogen in the sexual differentiation of the brain and causes (female) defeminization….."*

2007, journal of *Neurotoxicology,* H. Patisaul et al report,*"Genistein demasculinized male AVPV volume…these results suggest that acute exposure to endocrine active compounds (genistein) during a critical development period can independently alter nuclear volumes of sexually dimorphic nuclei and their phenotypic profiles in a region specific manner."*

2008, *Neurotoxicology*, H. Patisaul et al reports*, "This study is a breakthrough in determining how these naturally occurring endocrine disrupting compounds can cause reproductive health problems….a region of the brain that …can be significantly altered by exposure to phytoestrogens or plant-produced chemicals that mimic hormones-during development. Specifically the study finds that the compounds alter the sex-specific organization of the hypothalamus……..these phytoestrogenic compounds cross the placental barrier in humans…."*

10. Soy-causation of neurotransmitter damage, related to autism- Estrogens, of which soy exudes biologically active plant-estrogens, are well-known to target the brain.

Neurotransmitters are neuron connective chemicals that communicate, relay, amplify, and modulate signals from one brain cell to the next. Neurotransmitter systems control brain functions that regulate: emotions, bonding, behavior, cognition, learning, attention, reward, sleep, memory, arousal, and motor control. There is confirming evidence that brain disorders such as autism are related to damage caused to one or more neurotransmitter systems.

Soy phyto-estrogens are reported throughout published studies to severely damage not one, but several neurotransmitter systems: vasopressin, oxytocin, serotonin, GABA, and cholinergic. Neurotransmitter system damage is repeatedly proven in the causation of: attention, hyperactive, learning and behavioral disorders, autism disorder, mental retardation, cerebral palsy, seizures, and such

2007, *Journal of Biomedical Science*, Y Jin et al report, *"Genistein and daidzein induce neurotoxicity at high concentrations in primary rat neuronal cultures. Isoflavones possess estrogen-like activity……isoflavones specifically genistein and daidzein are toxic to primary neuronal culture at high concentration."*

Journal of Psychopharmacology, one of many studies confirm, "*Vasopressin concentrations were significantly elevated in the soy diet group compared to controls."*

Department of Pharmacology and Toxicology, University of Utah, *"Soy an active estrogen, increases estradiol levels which has direct effects upon levels of brain hormone, oxytocin."*

2003, *Pharmacogenomics Journal*, C.A. Shively et al report, "*Soy and social stress affect serotonin neurotransmission in primates. Conjugated equine estrogens and soy phytoestrogen increased serotonin….."*

1995, *Journal of Neurochemistry*, D.J. Bare et al report, "*The tyrosine kinase inhibitor genistein increases endogenous dopamine release from normal…."*

Journal of Biomedical Science, Y Jin et al report, "*….the toxic effect of genistein and daidzein could be due to their inhibition of the GABA-A receptor resulting in further enhancement of excitation by glutamate and leading to cellular damage."*

A report in the *Proceedings of Society for Experimental Biology and Medicine* concludes, *"Choline acetyltransferase mRNA levels were significantly higher in the frontal cortex of estradiol and soy phytoestrogen-treated retired breeder rats….."*

2007, *Journal of Biomedical Science*, J Jin et al report, "*Genistein and daidzein induce neurotoxicity at high concentrations in primary rat neuronal cultures……isoflavones specifically genistein and daidzein are toxic to primary neuronal culture at high concentration."*

As well as damage to neurotransmitter systems, soy phyto-estrogens are also proven to damage mitochondria. Mitochondria is the power generator that converts

oxygen and nutrients into adenosine triphosphate (ATP), an energy supply found in all living cells that powers the metabolic cellular activities necessary in the processes of life.

2000, *British Journal of Pharmacology,* J Zheng and VD Ramirez report, "*In conclusion, the ATP synthase is a target for dietary (soy) phytochemcials. This pharmacological property of these phytochemicals should be included in the examination of their health benefits as well as potential cytotoxicity."*

11. Soy-causation of hypothyroidism, related to physiological and neurological damage (such as autism)- Endocrine disruptors interfere with the complex regulatory network of the thyroid hormone synthesis, metabolism, distribution, and action on the various levels of endocrine regulation and feedback control. Soy is reported to severely damage the thyroid causing hypothyroidism.

Journal of *Endocrinology,* C. de Ona Ruiz et al report, "*The fetal thyroid function is influenced by maternal hypothyroidism. Soy plant-estrogens are proven to cause maternal (as well as infant/child) hypothyroidism, with potential to cause irreversible brain damaging effects, including autism."*

2005, University of Texas Health Sciences Center, M.E. Shils et al report, "*Intrauterine deficits of thyroid hormones (as brief as 3 days) result in permanent alterations of cerebral cortical architecture reminiscent of those observed in brains of patients with autism. Some plant isoflavonoids (soy plant-estrogens) have profound effects on thyroid hormones and on the hypothalamus-pituitary axis."*

Endocrine disruptors and trypsin inhibitors are known to cause iodine deficiencies, soy contains both. Iodine affects every tissue in the body not *only* the thyroid. Soy endocrine disruptors have been reported to decrease iodide accumulation known to damage the thymus and thyroid. In fetus, infants, and children, if the thymus fails to develop the immune system will fail to develop. Damage to the thymus and/or thyroid contributes to neuro-endocrine (brain-hormone) damage and deficient immune system function.

2002, in the *Environmental Health Perspectives,* NIH scientists, Drs. Doerge and Chang report, "*This paper reviews the evidence in humans and animals for anti-thyroid effects of soy and its principal isoflavones, genistein and daidzein."*

Proper thyroid function is absolutely necessary for numerous developmental biological processes such as: proper organ functions, growth, development, and differentiation and maturation of the central nervous system. Endocrine disruptors such as soy, interferes on several levels of the hypothalamic-pituitary-thyroid axis. Most interestingly, normal thyroid development and function is essential for normal brain development and function. There is active and dynamic collaboration between both the thyroid and immune system, and the thyroid and brain development and functions.

Department of Physiology and Endocrinology, Medical College in Georgia confirms that "*There is a critical period for thyroid hormone mediated brain development that begins in utero and extend through 2-3 years of age in humans. Excessive or deficient hormone levels during this period can cause irreversible brain damage."*

2006, NIH, National Toxicology Program, Center for the Evaluation and Risks to Human Reproduction, reports, "*Soy formula- Significantly more children with thyroid disease received soy formula compared to healthy siblings and healthy unrelated controls. Infants with congenital hypothyroidism were fed soy formula (and) improved with discontinuation of soy formula."*

12. Leukemia: soy inhibits Topoisomerase II, and causes IL dysfunction- Soy is proven to inhibit DNA Topoisomerase II, an essential enzyme that resolves deformation problems during DNA replication transcription and recombination. Topoisomerases are involved in the regulation of DNA supercoiling and prevention of DNA distortion.

1994, journal, *Nutrition and Cancer*, National Cancer Institute, M.J. Messina reports, "*Soybeans are a unique dietary source of the isoflavone genistein, which possesses weak estrogenic activity….Genistein is also a specific inhibitor of protein tyrosine kinases; it also inhibits DNA topoisomerases and other critical enzymes involved in signal transduction."*

Soy is a scientifically known topoisomerase II poison. Damage caused to topoisomerase II contributes to the cause of leukemia and other cancers.

2002, *EXCLI Journal*, J.G. Hengstler et al report, "*Recently, some alarming topoisomerase II- poisons, including bioflavonoids such as genistein……may contribute to the development of infant leukemia……. In addition, the incidence of infant leukemia is almost 2-fold higher in several Asian cities…..than in Western countries. This difference might be explained by the high food intake of bioflavonoids in many regions of Asia, especially by consumption of soybeans and soybean products, (Strick et al, 2000). …..soy products and other foods containing high levels of topoisomerase II-poisons should not be consumed during pregnancy."*

Soy isoflavones are also reported to cause dysfunction to several interleukins (IL) (signaling molecules that secrete proteins) encouraging autoimmune disease, cancers, and cancer metastasis. Soy damage to Interleukin-6 (IL-6) is concluded in several studies to also cause and stimulate childhood leukemia.

2002 book titled, *Phytoestrogens and Health*, by G.S. Gilani and J.J.B. Anderson report, "*Feeding high isoflavone soy had been shown to increase IL-6 production…….negative effect of soy is the suggestion that isoflavones may cause a rare form of childhood leukemia and brain atrophy…."*

13. Soy-causation of cancers and metastasis- Soy Causation of Oxydative Stress is an imbalance between the production of reactive oxygen and biological ability to readily detoxify the reactive intermediates or easily repair the resulting damage. The major portion of long-term effects is inflicting DNA damage.

2004, journal *Biochemistry*, reported by the Department of Environmental Molecular Medicine, concludes, *"These findings suggest that oxidative DNA damage by*

(soy) isoflavone metabolites plays a role in tumor initiation and that cell proliferation by isoflavones via estrogen receptors, estrogen response element binding induces tumor promotion and/or progression resulting in cancer of estrogen-sensitive organs."

Endocrine disruptors such as soy estrogenic/antinutrient phyto-toxins are reported throughout several studies to increase the risk of cancers and cancer metastasis.

2005, journal of *Cancer Resources*, I Balk et al report, *"….hormones are strongly associated with stem cell potential in human umbilical cord blood and point to a potential mechanism that may mediate the relationship between in-utero exposure to hormones and cancer risk in offspring."*

1996, *Health Action Network Society* reports, "*Additionally genistein was found to stimulate breast cells to enter the breast cancer cycle.* S*oy products may increase breast cancer in pregnant women.….people also have much higher rates of cancer of the esophagus, stomach, liver, pancreas and thyroid particularly as soy causes these same types of cancer in laboratory rats."*

Several studies report the soy-causation of estrogen-sensitive tumor metastasis such as the following: 2008, journal of *Endocrine-Related Cancer*, R. Dip et al report, *"…..phytoestrogens, achievable through soy-rich diets, stimulate the proliferation of estrogen-sensitive tumor cells. …these phytochemicals contribute to a tumor-promoting transcriptional signature*."

Published studies report on the soy phyto-toxic influences on the following cancers: leukemia, breast, uterus, testicular, prostate, thyroid, bladder, pancreas, liver, kidney, throat, stomach, intestine, and colon.

In conclusion- Soy estrogenic and anti-nutrient levels qualifying as phyto-toxins, are not FDA required to be measured or revealed on product labeling. Without personal testing, people with endogenous high levels of soy plant-estrogens and/or soy anti-nutrients are not able to know who they are, while at greatest risk for soy phyto-toxicity and consequential ill-health to themselves and their children. It is certain that in comparison to adults, the more vulnerable fetus, infant, and child are at highest risk for soy phyto-toxic ill-health effects.

The FDA has not established safety exposure levels for soy phytoestrogens and anti-nutrients. However, it is well-known that there is zero tolerance for developmental endocrine disruptor contamination, yet it is unknown as to why extensively recognized soy phyto-toxic endocrine disruptor effects remain FDA muted.

Soy products are explosive developmental cocktails of which literally several hundred scientific studies report as the cause of an assortment of physiological and neurological health-damaging effects including: allergies (and encourages peanut allergies), asthma, headache, nausea, gastrointestinal distress, liver, kidney, and pancreatic disorders and diseases, diabetes, extensive reproductive damage, hypothyroidism, immune deficiency diseases, leukemia, cancers, cancer metastasis, and extensive irreversible neurological disorders, such as autism.

Throughout the past few decades, it is evident that increasing availability and consumption of soy phyto-toxic chemicals precisely coincides with increases in

children's disorders and diseases. This soy-connection must not be regarded as merely coincidence, but as the cause.

Although there will be a NIH "Genistein Toxicity" meeting with special focus on "soy-based infant formulas," to be scheduled (as I am told by Dr. Shelby) "by the end of year,"……..what are the chances that the FDA will allow public notification that soy phyto-estrogens are scientifically established endocrine-disrupting-phyto-toxins, and as all estrogens are overwhelmingly concluded as especially damaging to exposed fetus, infants, and children?

Soy product WARNINGS, especially alerting of developmental dangers are past due. All soy-based infant formulas must be WITHDRAWN or to the least, based upon ethical physician responsibility become prescribed with careful documented follow-up as equal to all active estrogens.

Most urgently important, the American public deserves the right-to-know the truth about the extensive published study evidence concluding soy phyto-toxic contamination of their children, until the FDA is able to prove otherwise.

Gail Elbek
[Redacted]

SOY ENDOCRINE DISRUPTORS

ARE PROVEN TO CAUSE

IRREVERSIBLE

PHYSIOLOGICAL and NEUROLOGICAL

DEVELOPMENTAL DAMAGE

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July 24, 2009

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Soy Endocrine Disruptors and Antinutrients Cause Irreversible Developmental Health Damage:

"Knowledge not communicated almost invariably is knowledge wasted, and if the information can help better protect and promote the health of our public, the waste is intolerable," former Commissioner, Food and Drug Administration (FDA) Andrew C. von Eschenbach.

Prescribed estrogen pharmaceuticals or estrogenic pollutants, all estrogens, including soy phyto-estrogens increase normal levels of anatomical estrogens, and are reported as especially health-damaging particularly during developmental timeframes. Excess estrogens, for all people and largely during development, are well-known to disrupt and damage the entire body's hormone system.

Contrary to public belief, neither soy phytoestrogens and/or the variety of soy antinutrients are proven as safe by the Food and Drug Administration, while in truth, soy phyto-chemical exposures are overwhelmingly documented as increasingly physiologically and neurologically threatening during most fragile fetal, infant, and child development.

Soybeans have a built in phyto-toxic defense system that protects the plant from attack by insects, birds, and animals. Phyto-estrogens mimic estrogenic hormones as nature's way to deliberately cause reproductive damage to predators, and encourage the cause of physiological and neurological damage as well.

While known that maternal consumption of soy exposes her fetus to potent soy phytoestrogens and antinutrients, as well as to her infant during breast feeding, it is also the soy-based infant formula as 100% of infant's dietary intake for several months that is also most alarming.

Proving inconsistencies, there are large fluctuations in vitamin, mineral, sodium, and sugar/corn syrup contents in infant formulas. Nutritionists confirm that there are no man-made formula substitutes that can match the uniqueness of necessary nutritional breast milk values to assure the infant's fullest physical, emotional, and intellectual development potential. Breast milk is alive with white blood cells, digestive enzymes, immune-fighting substances, etc., all that maximizes anatomical developmental potential.

Some countries worldwide require "prescription only" to purchase soy-estrogen-based formulas with close follow-up of the infants exposed, while other countries alarmingly dissuade from the use of soy-based infant formulas altogether.

2009 "Men's Health" magazine article by Jim Thornton reports, "*For now, at least, the United States is gambling that widespread use of soy formula won't lead to long-term consequences. In 2005, Israel's health ministry recommended that soy products be limited in young children and, if possible, avoided altogether in infants. In issuing such a caution, Israel joined France, New Zealand, and Australia in officially embracing a better-safe-than-sorry approach for the next generation."*

Soy is alive with multiple hormone disrupting phytoestrogens and antinutrients and is described throughout hundreds of published studies as soy phyto-toxins that place at risk an assortment of adverse physiological and neurological health effects particularly during most sensitive developmental timeframes.

FDA researchers, Ph.D. Doerge and Sheehan confirm that "*Development is recognized as the most sensitive life stage for estrogen toxicity because of the indisputable evidence of a very wide variety of frank malformations and serious*

functional deficits in experimental animals and humans……there is abundant evidence that some of the isoflavones found in soy…..demonstrate toxicity…..”

Soy is scientifically and NIH concluded as an estrogenic “endocrine disruptor” of which the greatest risk for adverse phytotoxic effects may be caused by soy-based infant formulas. It is most often not realized that the majority of milk-based infant formulas also contain varying levels of soy phytotoxins.

While not approved as safe, the FDA concludes, “*FDA has not found it necessary to conduct prior marketing or routine safety reviews of whole foods derived from plants. FDA currently does not have a regulation for soy isoflavones and the regulatory status of soy isoflavones has not been determined.”*

FDA Consumer Safety Officer for the Center for Food Safety explains, “*From a regulatory perspective, the soybean itself is considered a food and hence would not be regulated. Infant formula is a food. The FDA does not approve infant formulas before they can be marketed. The FDA currently does not have a regulation for soy isoflavones and the regulatory status of soy isoflavones has not been determined.”*

FDA Center for Food Safety and Applied Nutrition (CFSAN): “*No, FDA does not approve infant formulas before they can be marketed. All formulas must meet federal nutrient requirements and manufacturers must notify the FDA prior to marketing a new formula.”*

Rarely if ever does the CFSAN monitor infant formula manufacturing nutrient requirements, and the soy estrogenic phytoestrogens and antinutrient levels are not investigated. Soy phytotoxins can largely fluctuate among resulting soy products.

“Endocrinology,” The Center for Biotechnology and Department of Medical Nutrition reports, *“In summary, while the estrogenic potency of industrial-derived estrogenic chemicals (environmental pollutants) is very limited, the estrogenic potency of phytoestrogens is significant…and may trigger many of the biological responses that are evoked by the physiological estrogens.”*

The Federal Food, Drug and Cosmetic Act *“puts responsibility for food safety on the manufacturer and also gives the FDA the authority to intervene if a food is unsafe.”*

The FDA CFSAN states, *“Substances used in infant formulas must be safe and lawful.”*

In the USA, without proving soy-based infant formula safety, the FDA has also never implemented any clinical data analysis or reporting system to carefully document reported adverse effects caused to fetus, infants, or children who swallow soy phyto-estrogens and soy antinutrients.

2004, Epidemiology Branch, National Institute of Environmental Health Sciences (NIEHS) confirms: “*Soy infant formulas are widely used but few studies have evaluated long-term safety or examined specific forms of toxicity, such as to the endocrine or immune systems. We conclude that more clinical and epidemiological study is warranted.”*

While at this same time the FDA confirms, “*If a safety or usage issue exists to which consumers must be alerted, consumers must be informed by appropriate labeling. It is against the law when foods are misbranded, or when labeling is false and misleading.”*

The FDA recognizes soybeans as an active plant-estrogen, a known allergen, and although infants may seem to be allergic to milk formulas or diagnosed as lactose intolerant, they may instead be more likely to be allergic to soy phytochemicals.

November 2005, Section 555.250, *"Statement of Policy for Labeling and Preventing Cross-contact of Common Food Allergens,"* the FDA reports, *"Each year the FDA receives reports of consumers who experienced adverse reactions following exposure to an allergenic substance in foods. Food allergies are abnormal responses of the immune system……Frequently such reactions occur because the presence of the allergenic substances in the foods is not declared on the food label. To combat this problem, the agency issued a letter titled 'Notice to Manufacturers,' dated June 10, 1996……FDA believes there is scientific consensus that the following foods can cause serious allergic reactions in some individuals and account for more than 90% of all food allergies. Peanuts, Soybeans, Milk, Eggs……..……..Manufacturers are responsible for ensuring that food is not adulterated or misbranded as a result of the presence of undeclared allergens."*

Studies also confirm that soybean allergens contribute to the causation of peanut allergies. Most people do not know that soybeans are FDA classified as allergens, and that soy phyto-estrogen endocrine disruptors and antinutrients are overwhelmingly proven to cause an assortment of severe health disorders resulting in sickness and disease, as revealed in detail throughout this report.

Resulting in the failure to alert the American public with appropriate WARNING labels, the following review of published studies along with NIH testimony details the severity of soy "misbranding."

This in-depth published study review confirms with certainty that it is detrimental that soy foods, beverages, and infant formulas will be clearly posted with appropriate WARNING labels as known phytochemicals proven as anatomically toxic to humans especially during most sensitive fetal, infant, and child developmental exposures.

National Institute of Environmental Health Sciences (NIEHS) NEWS- Journal "Environmental Health Perspectives," Volume 110, Number 6, June 2002, "*Increasingly, new research is questioning the purported health benefits of soy in adults, as well as raising concerns about adverse effects in children. Researchers are debating the relative safety and risk to infants of consuming soy- a source of environmental hormones- in formula. Soy formula is available off the shelf in the United States, but available only by prescription in Europe. NIEHS researcher Retha Newbold's concern is based in part on findings from a recent study published in the June 2001 issue of 'Cancer Research' in which she and her colleagues demonstrate that genistein (soy phytoestrogen) can trigger reproductive tract abnormalities in aged mice, including uterine adenocarcinoma, a rare form of cancer. In this study, newborn mice were given subcutaneous injections of genistein at a daily dosage of 50 mg/kg. The researchers indicate that although this dosage is higher than the daily amount that infants receive from soy formula (which they estimate at up to 11mg/kg) it is within an order of magnitude. …. 'I think it's a lot better to be checking this out in an experimental system than testing it on kids' she says. New information from Newbold's lab (published in Biology of Reproduction), shows that the ovary in particular is a target for the developmental effects of genistein…..and are consistent with early reproductive aging. Researchers agree that a biologic response to*

phytoestrogens in infants and young children is likely and that a lack of data hinders its characterization. (In regards to infants raised on soy formula), Newbold says, 'I hope I'm wrong, but in case I'm not, experimental animals are telling us this is something to worry about.'"

National Institute of Health- Freedom of Information (FOI), "Adverse Events Reporting System- Related to Soy Infant Formula 09/09/2008"-

Most people, most parents are not aware of an existing- "*Voluntary soy infant formula adverse event reporting system,"* containing reports of adverse health effects caused to their children due to soy consumption. Parents also complain that there exists a great deal of difficulty knowing who to contact, and how to file adverse soy health reports. The collection of soy damaging fetal and infant "adverse health events" are not publicized to the American people, unless filing a Freedom of Information request:

FOI disclosure, dated *"January 2000 to August 2008; Soy infant formula adverse effects include: Developed Severe Allergic Reaction, Skin Redness, Skin Rash, Hives, Diarrhea, Bloody Stools, Nausea, Vomiting, Severe Vomiting and Coughing, Change in Body Temperature, Fever, Fatigue, Weakness, Gastric Distress, Attention Deficit Disorder, Change in Activity Level, Hyperactivity, Listless, Weakness, Early Puberty, Depression, Severe Tension Disorder, Migraine Headaches, Fibromylagia (chronic widespread musculoskeletal pain, suffer from sleep disturbances, cognitive difficulties, anxiety and depression), Chronic Fatigue Syndrome, Thyroid Disorders, Fussy Behavior, Sick, Frothing at the mouth, Irritability, Yellow Eyes, Dark Urine, Constipation, Refusal to Eat, Uncharacteristic Spitting Up, Difficulty Breathing, Serious Gastric Distress, Inconsolable Crying, Ill with Fever, Change In Body Temperature, Fussiness, Repeated Colic, Gastric Reflux, Severe Vomiting, Severe Constipation, Shaking and then Motionless, Lethargic, Salmonella Poisoning, Baby Fails to Thrive, Refuses to Drink, Made Allergies Worse, Neurological Symptoms, Baby Became Blind- optic nerve was compressed, soy formula was discontinued Baby returned to normal in 24 hours except for damaged muscles of the eye, Baby now has one dominant eye. Pediatric Ophthalmologist reportedly believes baby suffers from a formula deficiency in vitamins or nutrients. The Ophthalmologist had a second baby patient with the same symptoms. Baby was on the same soy formula, and also experienced blindness and severe optical nerve compression. It was found that the vitamin B in soy was not absorbable."*

Adequate nutritional intake during the first three years of a child's life (and hereafter), is especially paramount for maximal physiological and neurological development. Soy antinutrients, compounded with soy-encouraged estrogenic hormonal disruptions during most important developmental stages, with particular concern regarding neurological development, can be identified in the cause of several irreversible physiological and neurological developmental health disorders and diseases.

SOY'S ACTIVE and UNPREDICTABLE ESTROGENIC ISOFLAVONES-

Soy isoflavones are unrestricted dietary plant-estrogens proven to have biological estrogenic effects in the cell cultures of humans and animals. Soybeans contain estrogenic phytoestrogens as bioactive agents that disrupt normal endogenous hormone functions, and to the developing fetus, infants, and children exposed, these hormone changes are reported to result in a host of damaging health effects.

FDA, "Poisonous Plant Database" includes, "soy bean" on the list, while stating, "This database contains references to the scientific literature describing studies of the toxic properties and effects of plants and plant parts." In addition to, "soy bean" the FDA named soy phyto-estrogens, "genistein, daidzein, and equol" are also individually listed on the FDA "Poisonous Plants Database," while also concluding that soy phyto-estrogen glycitein is the lower level estrogen of which equipment may not qualify to measure.

Soybeans contain an abundance of phytoestrogens: genistein, daidzein, and glycitein, all of which are highly active estrogenic chemicals found in soy foods, soy beverages, including soy-based infant formulas. Phytoestrogens are capable of disrupting and damaging a variety of biological processes of which are detailed throughout this report. During a most sensitive period of life for induction of toxicity; the fetus, infants, and children being fed soy phytoestrogens are ingesting high levels of hormone-active estrogenic chemicals.

Research scientists from the FDA Division of Biochemical Toxicology, Drs. Doerge and Sheehan report, "*Soy is known to produce estrogenic isoflavones. Here, we briefly review the evidence for binding of isoflavones to estrogen receptor, in vivo estrogenicity and developmental toxicity. Although safety testing natural products, including soy products is not required, the possibility that widely consumed soy products may cause harm in human population via either or both estrogenic and goiterogenic activities is of concern. …..genistein and other isoflavones can have adverse effects in a variety of species, including humans.*"

2003, "Handbook of Fermented Functional Foods," Edward Farnworth reports, "C*onsumption of soybean foods increased blood isoflavone concentrations to several orders of magnitude higher that those of physiologic estrogens.*"

The book, "Handbook of Plant and Fungal Toxicants" by J. B. D'Mello concludes, "*Isoflavonoids have potent effects on cell growth and estrogen-dependent processes. Plant concentrations result in biologically significant levels in human and animal circulation. Both beneficial and adverse effects have been reported in mammals……..implicating isoflavonoids in both health and disease.*"

Centers for Disease Control (CDC) reports, "*Generally, phytoestrogens are much less potent than endogenously produced estrogens, but phytoestrogens can be present in much greater quantities, 100 to 1000 times the concentration of endogenous estrogens.*"

Soy-based infant formulas are a spoken "***concern***" of the National Institute of Health (NIH) and FDA, as Janice Oliver, Deputy Director, FDA Center for Food Safety and Applied Nutrition (CFSAN) confirms, "*FDA acknowledges that 'concerns' have been voiced about possible effects of isoflavones in soy infant formulas on sexual development, neurobehavioral development, immune function and thyroid disease. Infant formula manufacturer must provide FDA with notification about the proposed infant formula, of which notification must contain: detailed information about the formulation, nutritional and manufacturing assurances. Manufacturer must provide assurance that formula will provide adequate nutrition for infants to thrive, that the formula will be manufactured under current good manufacturing practices, and that every batch of formula will meet all of the nutrient requirements.*"

2005, "International Immunopharmacology," JH Zhao, "*Soy isoflavones, which are phytoestrogens present in large quantities in soy and soy-derived products have estrogenic activity, …….and exert other effects in the human body. Thus the recent*

spread of soy consumption in Western populations emphasizes the need to more fully understand the potential effects in the body……"

In combination with estrogen-active soy isoflavones, soy also contains several antinutrients as nature's plan to protect soybean longevity while proving toxic to grazing wildlife. Soy is proven to cause extensive hormone disruptions in animals and humans throughout anatomical hormone systems, resulting in phytotoxicity that encourages: underdevelopment, infertility as well as extensive reproductive damage, organ failure, hypothyroidism, neurological disorders such as: ADHD, autism, mental retardation, and a host of potentially fatal adverse health effects such as leukemia, and/or diabetes as a multitude of published literature conclude, and is specifically outlined throughout this report.

1998, "American Journal of Clinical Nutrition," KD Setchell reports, "*….it is recognized that there are many plant-derived bioactive nonnutrients…..Among these phytochemicals is the broad class of nonsteroidal estrogens called phytoestrogens, and in the past decade there has been considerable interest in the role of isoflavones because of their relatively high concentrations in soy protein. The isoflavones in modest amounts of ingested soy protein are biotransformed by intestinal microflora, are absorbed, undergo enterohepatic recycling, and reach circulating concentrations that exceed by several orders of magnitude the amounts of endogenous estrogens. These phytoestrogens and their metabolites have many potent hormonal and nonhormonal activities that may explain some of the biological effects……..in phytoestrogens."*

Levels of fluctuating soy phytoestrogens and antinutrients are the result of: varying soybean plants, soy processing, type of soy food, cooking procedures, rate of individual bioavailability, longevity of soy consumption, and age at time of exposure. Among each person consuming soy products there is a high rate of "interindividual variability," again contributing to extreme fluctuations among individual capabilities to metabolize, absorb, and eliminate chemically active soy isoflavones. Most problematic, extreme levels of soy hormone disruptors as well as soy antinutients of which each individual is exogenously consuming, and endogenously accumulating, is unknown. Certainly, these multiple unknowns should not be so simply considered as developmentally safe, but instead, as anatomically contaminating.

2000, "The Journal of AOAC International," Y Nakamura et al report, "*The contents and composition of the isoflavonoids in the 11 soybeans varied by species and country of origin. The level of isoflavonoids found in the processed foods varies by manufacturing method or ingredients."*

2002, "Journal of Nutrition," N Tsunoda et al report, "*….absorption of isoflavones varies substantially among individuals."*

2002, "Journal of Nutrition," M Richelle et al report, "Individual isoflavones do not have the same absorptions and body retentions."

1998, "American Journal of Clinical Nutrition," L Coward et al report, "*Chemical modification of isoflavones in soyfoods during cooking and processing- extraction of isoflavones from soyfoods and the effects of commercial processing procedures and of cooking on isoflavone concentrations and composition. Soymilk and tofu consisted almost entirely of beta-glucoside conjugates.……Isolated soy protein and textured vegetable protein consisted of a mixture of all 3 types of isoflavone conjugates….baking of soy flour in cookies did not alter total isoflavone content, but there was a steady increase in beta-*

glucoside conjugates….. The isoflavones in foods should be taken into consideration when evaluating their availability for absorption from the diet."

2007, "Journal of the Science of Food and Agriculture," E Koh, and AE Mitchell report, "*The consumption of soybean paste resulted in significantly higher urinary excretion of both daidzein and genistein as compared with soy flour."*

A multi-University, Cancer Epidemiology Study confirms, "*Intake of soy foods correlates significantly with urinary Genistein and Daidzein. Soy foods are the primary contributors to isoflavone intake, however, additional 'hidden sources' of soy may also contribute to exposure. Isoflavonoid excretion was correlated positively with intake of high-fat and processed meats. Isoflavones are highly concentrated in soybeans and soy products."*

2002, "Journal of Agriculture and Food Chemistry," MI Genovese and FM Lajolo report, "*Total isoflavone content varied significantly among products, from 2 to 100mg/100 g. with the lowest content being found for soy-based enteral/oral diets and the highest found for textured soy proteins. For soy beverages isoflavone content varied from 12 to 83 mg/L. Soy sauce, miso, and tofu had isoflavone contents of 5.7 mg/L, 20 mg/100g, and 7mg/100g, respectively. The beta-glycosides were the predominant form of the isoflavones in the products analyzed, except for miso, shoyu, and 'diet Shake' in which the aglycones were present in the highest proportions. On the basis of these data, the daily intake of isoflavone from soy products was estimated: the highest values were found for infants fed soy-based formulas, from 1.6 to 6.6 mg/kg of body weight."*

Health Action Network Society reports, "*100 grams of soy protein….can contain almost 600 mg of isoflavones."*

May 2006, Federal Register/Vol 71, No.94…. Dept. of Health and Human Services, National Toxicology Program; Center for the Evaluation of Risks to Human Reproduction (CERHR). Notices- Background; *"Genistein is a phytoestrogen found in some legumes, especially soybeans. Phytoestrogens are non-steroidal, estrogenic compounds ……...In plants, nearly all genistein is linked to a sugar molecule and this genistein-sugar complex is called genistein. Genistein and genistin are found in many food 'products' especially soy-based foods such as tofu, soymilk, and soy infant formula, and in….supplements. CERHR selected genistein and soy formula for expert panel evaluation because of (1)* ***the availability of reproductive and developmental toxicity studies in laboratory animals and humans, (2) the availability of information on exposures in infants and women of reproductive age, and (3) public concern for effects on infant or child development."***

2003, "American Journal of clinical Nutrition," W Miltyk et al report, "……*it (genistein) causes genetic damage in cultured human cells."*

In 2001, The Division of Biochemical Toxicology, a division of the FDA reports; "*Genistein is a naturally occurring isoflavone that interacts with estrogen receptors and multiple other molecular targets. Human exposure to genistein is predominantly through consumption of soy products including soy based infant formula and dietary supplements."* A summary of this report concludes: "*Genistein treated rat dams showed litter birth weight was depressed, decreased prostate weight, higher pituitary gland to body weight ratio, hyperplasia of mammary gland in both sexes, abnormal vaginal maturation, abnormal ovarian follicles, delayed spermatogenesis, deficit of sperm, increase in severity of renal tubal mineralization. Dietary genistein thus produced effects*

in multiple estrogen-sensitive tissues in males and females. These effects occurred within exposure ranges achievable in humans."

This published study from Germany confirms, "*Soy isoflavones exert genotoxic (cell damage/DNA damage) actions*."

A 2004 study in Japan proved that *"Estrogenic activity in a water sample resulted from the presence of Genistein an isoflavone compound of plant origin*." Concluding that, *"Detection of Genistein (soy) as an estrogenic contaminant of river water in Osaka."*

2007, "Food Chemistry Toxicology" RM McClain et al report, "*Concern has been raised…of potential adverse effects due to the estrogenic and other activities of the isoflavones and thus a comprehensive series of safety studies was performed with genistein. To assess the teratogenic and fetal toxic potential of genistein, several studies were conducted. Genistein was tested in an in vitro rat whole embryo culture assay (WEC) which is a preliminary screen for fetotoxic and teratogenic potential, over a concentration range of from 1 to 100 microgram and at 100 microg/mL, all embryos were malformed. A slight maternal toxicity at 1000 mg/kg/day was observed as indicated by decreased body weight and food consumption and at this does, adverse effects in the pups were observed including increased pup mortality, poor general condition, reduced pup body weights and reduced pup milk uptake. At the low dose of 20mg/kg/day and increased mortality, reduced milk uptake, a decreased % of male sex ratio, and decreased body weights during lactation were observed. In an oral prenatal developmental safety study…. At 500 mg/kg maternal body weight and food consumption were markedly reduced. Fetal body weights were also reduced. It is concluded that genistein has no teratogenic potential in vivo at very high doses of up to 1000mg/kg/day in the embryo-fetal toxicity pilot study or up to 500 mg/kg/day by dietary admix in the prenatal developmental study even thought these doses were maternally toxic and fetal-toxic."*

Published in "Toxicological Sciences" NV Soucy et al, reports, "*Diets high in soy-based products are well known for their estrogenic activity. Genistein the predominant phytoestrogen present in soy, is known to interact with estrogen receptors alpha and beta and elicits reproductive effects in developing rodents. It is critical to understand the delivery of free and conjugated genistein across the placenta to the fetus following maternal genistein exposure such that the potential fetal exposure to free genistein can be assessed. Genistein 4 or 40 mg/kg was administered to pregnant rats daily from gestation day 5 through 19. High placental concentrations of genistein indicate the placenta is a potential target organ for genistein action during gestation."*

2005, Developmental Endocrinology and Endocrine Disrupter Section, Laboratory of Molecular Toxicology, National Institute of Environmental Health Sciences, D. Doerge et al report, "*Exposures of Sprague-Dawley rats to the soy isoflavone, genistein throughout the entire lifespan have produced a number of effects on reproductive tissues, immune function, neuroendocrine function and behavior."*

2007, "Toxicology and Applied Pharmacology" CB Klein and AA King report, "*Genistein genotoxicity: critical considerations of in vitro exposure dose- Although here is increasing popularity of dietary phytoestrogen…… diets among adolescents and adults, concerns about potential detrimental or other genotoxic effects persist. ….a variety of genotoxic effects of phytoestrogens have been reported in vitro…..this review focuses on in vitro studies of the most abundant soy phytoestrogen, genistein, critically*

examining dose as a crucial determinant of cellular effects. Recent cellular, epigenetic and microarray studies are beginning to decipher genistein effects that occur at dietary relevant low concentrations. In toxicology, the well accepted principle of 'the dose defines the poison' applies to many toxicants and can be invoked, as herein, to distinguish genotoxic…..in vitro effects of natural dietary products such as genistein."

2004, "Plant Foods and Human Nutrition," T Mebrahtu et al report, "*Thirty-one soybean genotypes from maturity groups III to VI were grown at Randolph Research Farm of Virginia State University, Petersburg, Virginia, during 3 years. The genotypes were harvested at immature green pod stage and analyzed for isoflavone contents. Significant differences among the genotypes were found for genistein, daidzein, glycitein, and total isoflavones. The genotype x year interactions were also significant for the seed traits analyzed, indicating that the performance of the genotype changes from year to year. However, genotypes Pella and Aoda consistently showed with higher means than the overall means for all the seed traits throughout the 3 years. Maturity groups differences were also observed for genistein, daidzein and total isoflavone content. Low to moderate-heritability estimates of 54, 45, 58, and 64% were observed for genistein, daidzein, glycitein and total isoflavone content, respectively, suggesting that the seed traits are equally influenced by environments and genetic variations."*

2004, "Journal of Agriculture and Food Chemistry," JO Bennett et al report, "*Accumulation of genistein and daidzein…..is significantly elevated by irrigation-Methanol extracts of seed harvested from different planting dates when analyzed by high-performance liquid chromatography showed striking differences in isoflavone content. Dependent upon the variety, total isoflavone content was increased as much as 1.3-fold in early-planted soybeans. Irrigation enhanced the isoflavone content of both early-and late-planted soybeans as much as 2.5-fold. Accumulation of individual isoflavones, daidzein and genistein was also elevated by irrigation."*

Alarmingly the highest levels of isoflavones are found in soy-based infant formulas, of which these phytoestrogens are documented as highly active endocrine disruptors. Soy-based formulas are infant-consumed as 100% of dietary intake, and for the long-term. Extreme health risks as documented by highly acclaimed published studies are reviewed throughout this report.

Due to a variety of adverse events, the FDA is not able to establish fetal (due to maternal consumption), infant, child (or adult) thresholds for soy safety levels. Infants most often consume soy-based estrogenic isoflavone formulas as 100% of their dietary daily intake for long periods of time, without evidence of safety. In fact there are no health benefits for soy-exposed fetus, infants, children, adolescents, while multiple studies conclude adverse health risks. Also, published studies related to soy as a health benefit for adults are simply presumed as well as highly contradictory.

Stated in the Federal Register 64 FR 57699, 1999, the FDA recognizes- "*Many comments addressed concerns about the possible deleterious consequences of phytoestrogen effects of the soy isoflavones, genistein and daidzein."*

In 2000, the FDA "Consumer Magazine" public affairs staff writer John Henkel reports, "*What's known is that all foods, including soy, are complex collections of chemicals……(that) can be harmful to some people when used inappropriately. Recently raised concerns focus on specific components of soy, such as the soy isoflavones (plant estrogens) daidzein and genistein. The problem is that isoflavones are phytoestrogens, a*

weak form of estrogen that could have a drug-like effect in the body. It is a scientific conundrum…..that is causing some researchers to urge caution. (The FDA health claim about soy), does not extend to isoflavones genistein and daidzein."

NIH, National Center for Toxicological Research, Dr. Doerge reports, "*Current evidence for the beneficial effects of soy requires a full understanding of potential adverse effects as well."*

2005, "Food and Chemical Toxicology, Z Wu et al repot, "*Effects of subcutaneous administration of daidzein on blastocyst implantation in rats- The results revealed that high-dose (daidzein) treatment (150mg/kg body weight) significantly diminished the rate of blasctocyst implantation and serum levels of gonadotrophin-releasing hormone, progesterone, and endorphin increased significantly. The results of this study suggest that the anti-implantation effects of daidzein are probably caused by the interference of the hypothalamus-pituitary-gonadal axis……..."*

There are "hidden sources" of dietary estrogenic soy isoflavones due to U.S. law that allows the addition of soy as food fillers that are not always specified in product ingredients. During the past 8 years manufacturers actively marketed nearly 2,700 additional soy estrogenic-active foods and beverages, including soy-based infant formulas. From 1992 to 2006 soy foods and beverage sales increased from $300 million to over $3.9 billion.

1999, "Cancer Epidemiology Biomarkers & Prevention," confirms, *"Hidden sources of isoflavones appeared to contribute significantly to isoflavone exposure in this U. S. population."*

2002, "Journal of Nutrition," T Nobuyo et al report, "*…….small amounts of (soy isoflavones) were measured in…...…..subjects after the control or washout phase. These individuals claimed to have avoided legumes but it might have reflected the widespread use of soy protein processed foods."*

1999, "Journal of Nutrition," Y Zhang et al report, "*Glycitein metabolism was compared with other isoflavones to begin to understand the effect of this compound. The average 48 hour urinary excretion of glycitein, daidzein and genistein was ~55, 46, and 29% of the dose ingested, respectively, which was significantly different from each other in men and women. At the high glycitein dose (soygerm), plasma concentration at 24 hours after dosing suggested a modest gender difference in glycitein bioavailability."*

1999, "Journal of Agricultural and Food Chemistry" TT Song et al report, "*Glycitein accounts for 5-10% of the total isoflavones in soy food products. The biological activity of this compound has not been reported to date, although numerous studies have been performed with the other soy isoflavones, daidzein and genistein. These data indicated that glycitein has weak estrogen activity, comparable to that of the other soy isoflavones, but much lower than that of DES and 17beta-estradiol."*

The most active soy phytoestrogens are: genistein, daidzein and glycitein. Genistein is proven as a highly active estrogenic isoflavone, while studies report that equol binds with greater affinity to estrogen receptors than daidzein from which equol is derived. Adding to the challenges of determining levels of soy toxicity, individual: adult, adolescent, child, infant, and fetal bioavailability of soy phytoestrogens varies significantly depending upon intestinal bacteria responsible for metabolism of daidzein to the higher estrogenic equol, and/or to estrogenic O-DMA.

Besides soy isoflavone genistein exhibiting a high level of estrogenic potency, women during pregnancy and then while breast feeding who are also capable of metabolizing daidzein to equol and/or to O-DMA, encourage the passage of highest levels of estrogenic endocrine disruptors to her fetus, and then again to her nursing infant.

Bioavailability of equol and O-MDA is exclusively dependent upon interindividual intestinal bacteria, some people are producers and some are not. Of deepest concern, it remains unknown as to which persons harbor O-DMA and equol-producing bacteria that increases soy-caused estrogenic bioavailability, while others do not. Studies report that between 30 to 50 percent of the human population can biotransform soy to the more estrogenic potent daidzein metabolite equol and about 70-90 percent to O-MDA. Studies report that high equol producers excreted around 200-fold more equol in urine than non-equol producers.

2006, "Journal of Nutrition," KD Setchell and SJ Cole report, "*The frequency of equol production varies among individuals and populations…..*"

2001, "FDA's National Center for Toxicological Research," confirms, "*Product # E0700701 Importance of Human Intestinal Microflora in Conversion of Phytoestrogens to Estrogenic Compounds- Objective(s): 1) To detect various metabolites of phytoestrogens, produced by the metabolism of these compounds by pure culture of bacteria typical of that isolated from human microflora, and elucidation of the metabolic pathways of phytoestrogens by human intestinal bacteria. 2) To assess the estrogenic effect of each phytoestrogen metabolite produced by intestinal bacteria. 3) To determine the bacterial species producing estrogenic metabolites from phytoestrogens and elucidation of enzymes involved in various steps of these metabolic processes. 4) To determine the effects of phytoestrogens and their metabolites on the population, composition, metabolic activity, and enzyme production of bacteria from the human gastrointestinal tract. FY 2000 Accomplishments: 1) Bacterial species from the human intestinal tract that are involved in the conversion of daidzein and genistein to more estrogenic compounds, daidzein and genistein, ere detected. 2) Intestinal anaerobic bacteria with demethylating enzymes wee used to produce estrogenic metabolites from natural isoflavonoids. 3) Anaerobic bacteria from the human intestinal tract involved in the reductive metabolism of daidzein and genistein were identified. FY Plans: 1) Detect specific bacteria from the human intestinal tract involved in the conversion of phytoestrogens (daidzein and genistein) to estrogenic and nonestrogenic end products.*"

Equol, a non-steroidal estrogen was first identified from pregnant mares urine in 1932 and was later identified in the urine of humans consuming soy products. Equol has a structure similar to the steroidal estrogen estradiol, and is also found in the estrogenic cocktail of prescribed hormone replacement therapy that displays warnings of extreme health risks.

Equol is a highly active and biologically potent soy-induced estrogenic phytochemical that stimulates gene transcription of both estrogen receptors, resulting in high levels of estrogenic potency in combination with genistein, and other phytoestrogens. Findings have shown that equol was the agent responsible for an infertility syndrome in sheep and other animals. Soy phytoestrogens are reported to cause a variety of human reproductive disorders as revealed later in this report. Alarmingly, no one knows without testing if they are the endocrine disrupting estrogenic soy equol (and O- MDA) producers, or are they not.

1997, "American Journal of Clinical Nutrition," SC Karr et al report, "*Soybeans contain isoflavones. The purpose of our study was to measure urinary isoflavonoid excretion in response to daily consumption of soy that contained 0-36mg isoflavones, a lower range that used in previous studies, and to compare urinary isoflavonoid excretion between equol excreters and nonexcreters. This randomized, double-blind, crossover study consisted of four 9-day diet treatment periods. During each treatment period participants consumed a low-phytoestrogen controlled diet and a beverage containing 0,5,10, or 20 grams soy protein. Urine collected on the last 3 days of each treatment period was analyzed for isoflavonoids (equol, ODMA, genistein, and daidzein)….contents…… There was a highly linear dose response of urinary isoflavone excretion to soy consumption which did not differ significantly between equol excreters and nonexcreters. Our results indicate that urinary isoflavonoid excretion is dose dependent in humans at low to moderate levels of soy consumption."*

2005, "Environmental Research," E Todaka et al report, "*Fetal exposure to phytoestrogens- the difference in phytoestrogen status between mother and fetus. It was found that phytoestrogens were transferred from mother to fetus. The detection rates of genistein, daidzein, equol,…….. were 100%, 80%, 35%,……. respectively. Levels of genistein and daidzein were higher in cord than in maternal serum……The correlations were significant between the concentrations levels of genistein and daidzein, genistein and equol, and genistein and daidzein plus equol in cord serum. Also in 8 of 10 cord serum samples, sulfate-conjugated genistein was detected…… This study demonstrates placental transfer of phytoestrogens from mother to fetus. …..and once phytoestrogens are transferred to the fetus, they tend to stay in the fetal side longer than in the maternal side…..these data suggest that the effects of fetal exposure to phytoestrogens should be studied further."*

1998, "American Journal of Clinical Nutrition, "JL Slavin et al report, "*Influence of soybean processing, habitual diet, and soy dose on urinary isoflavonoid excretion- In attempt to explain the wide individual variation seen in urinary isoflavonoid phytoestrogen excretion, we conducted a series of 3 human feeding studies: In women, equol excretion was associated with higher intake of dietary fiber and carbohydrate. Processing of soy affects isoflavone metabolism and must be considered in recommending exposure to isoflavones from soy foods. Phytoestrogens are plant compounds that have a wide range of biological effects, manly related to the close structural relation between phytoestrogens and endogenous reproductive hormones such as estrogens. Genistein, daidzein, and daidzein metabolites equol and O-desmethylangolensin (O-DMA) are compounds found in urine after consumption of foods containing isoflavones. An inverse relation between excretion of equol and O-DMA has been noted, suggesting preferential pathways for daidzein metabolism. These individual differences in isoflavonoid metabolism are potentially important because they may influence the biological effects of isoflavone consumption. Equol is known to be more estrogenic than both daidzein and O-DMA. Differences in excretion rates of these phytoestrogens have also been noted."*

Estrogen receptors exist as two subtypes: estrogen receptor-alpha (ER-a), and estrogen receptor beta, (ER-b), both responsive to soy phytoestrogens, and both displaying multiple effects upon multiple body systems.

2004, "Bioorganic & Medical Chemistry," RS Muthyala et al report, "*Equol is a metabolite produced in vivo from the soy phytoestrogen daidzein by the action of gut microflora. It is known to be estrogenic, so human exposure to equol could have significant biological effects. All equol isomers have higher affinity for both ERs……"*

2002, "Journal of Nutrition," KDR Stechell et al report, "*Equol is a nonsteroidal estrogen of the isoflavone class. It is exclusively a product of intestinal bacterial metabolism of dietary isoflavones and it possesses estrogenic activity, having affinity for both estrogen receptors, ERa and ERb."*

2006, "Medical Hypotheses," MF McCarty reports, "*S-equol, a bacterial metabolite of daidzein, has an affinity for ERbeta nearly as high as that of genistein…"*

1998, "Endocrinology" G Kuiper et al report, "*…we investigated the estrogenic activity of environmental chemicals and phytoestrogens in competition binding assays with ER-a or ER-b protein….In summary, while the estrogenic potency of industrial-derived estrogenic chemicals is very limited, the estrogenic potency of phytoestrogens is significant, especially for the ER-b and they may trigger many of the biological responses that are evoked by the physiological estrogens."*

2000, "Journal of Nutrition," S. Barnes et al report, "*It has been 50 years since it was first realized that isoflavones have a range of estrogen-like effects. However, they are not classical estrogens nor are their estrogenic effects consistent. The discovery of a second estrogen receptor ER-b (Kuiper et al 1996) a receptor for which genistein and the natural estrogen 17B-estradiol have approximately equal affinity, has provided a new perspective on the pleiotropic (influence on multiple characteristics) nature of the effects of genistein because ER-b is expressed in differing amounts and in different cells…..However, several other biological properties of the isoflavones also contribute to the complexity of understanding their actions….data suggest that genistein has its effects through transcriptional processes…."*

2001, From the, Department of Molecular and Cellular Biology, K. Morito et al report, *"Isoflavone glycoside binds weakly to both receptors and estrogen receptor-dependent transcriptional expression is poor. The aglycones (genistein and daidzein) bind more strongly to ER-b than to ER-a. The binding affinities of genistein, dihydrogenistein and equol are comparable to the binding affinity of 17beta-estradiol. Equol induces transcription most strongly with ER-a and ER-b. The concentration required for maximal gene expression is much higher than expected from the binding affinity of the compounds."*

The book, "Phytoestrogens and Health" Gilani and Anderson report, "*On the basis of in vivo and in vitro data these (soy) isoflavones are clearly within the concentration range to activate both estrogen receptors ER-a and ER-b. The plasma of soy-fed infants contains high concentrations of isoflavones (and probably other soy phytochemicals)."*

2002, "Endocrinology" H. Patisaul et al report, "*Genistein at a dietary concentration of 500ppm had differential activity through ER-a and ER-b in the hypothalamus. Genistein increased ER-b mRNA expression in the paraventricular nucleus of the hypothalamus by 24%....."*

Another 2002 study concludes that, "*Mice treated neonatally on days 1-5 with phytoestrogen genistein…. ..ER alpha expression was higher on day 5."*

2003, "Journal of Agricultural and Food Chemistry," D Kostelac et al report, "*Phytoestrogens modulate binding response of estrogen receptors alpha and beta to the estrogen response element- Binding of estrogen receptor (ER) to estrogen response element (ERE) induces gene activation and is an important step in estrogen-induced biological effects. Here we investigated the effects of some dietary phytoestrogens such as the isoflavones genistein and daidzein, and its metabolite equol and the coumesttane coumestrol on the binding rate of ERalpha and ERbeta to ERE……17beta- Estradiol and phytoestrogens induced an increase in ER binding to ERE in concentration- dependent manner. Regarding the efficacy of activation of ERalpha, from the most to the least....17beta-estradiol (0.03 microM)> coumestrol (0.2microM)> equol(3.5microM)> genistein (15 microM)> daidzein (>300microM) and for ERbeta 17beta-estradiol (0.01 microM)> Coumestrol (0.025 microM)> genistein (0.03 microM)> daidzein (0.35 microM)> Equol (0.4 microM). These ratios indicate that genistein and daidzein preferentially activate the binding of ERbeta to ERE. The endogenous hormone 17beta-estradiol as well as coumestrol and daidzein metabolite equol activate the binding of ERbeta to ERE only slightly more effectively than the binding of ERalpha to ERE. The effect of daidzein can be changed from a specific activator of ERbeta to an activator of both ER isotypes alpha and beta in human who are able to convert daidzein to equol. …there was a distinct difference between our results and the binding affinities of phytoestrogens for the ERbeta. This leads to the conclusion that phytoestrogens differ not only in their binding affinities for the ER, but also in the potential to increase the rate of receptor binding to the ERE."*

2004, "Toxicological Science," SO Mueller et al report, "*Phytoestrogens and their human metabolites show distinct agonistic and antagonistic properties on estrogen receptor alpha (ERalpha) and ERbeta in human cells- Phytoestrogens exert pleiotropic effects on cellular signaling…..due to activation/inhibition of the estrogen receptors ERalpha or ERbeta, these compounds may induce or inhibit estrogen action and therefore, have the potential to disrupt estrogen signaling. The soy-derived genistein, coumestrol, and equol displayed a preference for transactivation of ER beta compared to ERalpha and were (only) 10- to 100-fold less potent that diethylstilbestrol (DES). All other phytoestrogens tested including….human metabolites of daidzein….were weak ER agonists. Interestingly, the daidzein metabolites 3',4',7-isoflaveon and 4',6,7-isoflaveon were superagonists on ERalpha and ERbeta. All phytoestrogens tested showed reduced potencies to activate ERalpha and ERbeta compared to DES on the estrogen-responsive C3 promoter…...…indicating a degree of promoter dependency."*

2006, "The Journal of Nutrition," K Mitsuyoshi et al report, "*Bioavailability of isoflavones after Ingestion of Soy Beverages in Healthy Adults- It is unknown whether the bioavailability of isoflavones is affected by the concomitant ingestion of glucosides or aglycones. This study was designed to investigate the effects of soymilk-based beverages containing different types of isoflavones on their absorption, excretion, and metabolism. After the ingestion of soymilk, the total concentration of isoflavones in serum rose slowly…… However B-glucosidase-treated soymilk and fermented soymilk increased the serum isoflavone concentration significantly more quickly …..The urinary excretion of isoflavones after ingesting of these aglycone-enriched preparations was significantly greater than after consumption of untreated soymilk up to 8 hours after injection, but not thereafter…… However, in equol producers, the ingestion of enriched soymilks tended to*

increase urinary excretion of equol compared with the consumption of fermented soymilk ……and that the metabolism of isoflavones might be affected by the type of soymilk consumed. However, the bioavailability of aglycones and glucosides of soy isoflavones is controversial. Izumi et al found a greater bioavailability of (soy) aglycones, whereas Setchell et al reported a more efficient use of glucosides. It makes sense that isoflavone aglycones are absorbed faster than glucosides, because aglycones have greater hydrophobicity and smaller molecular weight, whereas glucosides have lower absorbability and must be converted to aglycones. The present study indicates that isoflavones in fermented soymilk (aglycone-enriched) are absorbed more efficiently by rats than those in unfermented soymilk (glucoside-enriched). Before subjects consumed the soymilk preparations, serum concentrations of isoflavones were undetectable. After ingestion of enriched soymilk and fermented soymilk, they increased rapidly. In equol producers the ingestion of enriched soymilk tended to increase urinary excretion of equol compared with fermented soymilk. …..Isoflavone aglycones may be absorbed faster than glucosides….The absorption of isoflavones differs between Japanese and Americans because intestinal microflora, dietary habits, and ethnic background all have an effect. ……the consumption of soy products has decreased in Japan…….."

2008, "American Journal of Clinical Nutrition," CE Rufer et al report, "*There are conflicting results in the literature on the bioavailability of isoflavones in the aglycone and the glucoside forms. Our results show that daidzein……..gluocoside exhibits a greater bioavailability than its aglycone when ingested as an isolated form."*

2001, "Journal of Nutrition," KDR Setchell et al report, "*This study demonstrates differences in the pharmacokinetics of isoflavone glycosides compared with their respective B-glycosides. Although all isoflavones are efficiently absorbed from the intestinal tract, there are striking differences in the fate of aglycones and B-glycosides. The apparent volume of distribution of isoflavones confirms extensive tissue distribution after absorption. Plasma genistein concentrations are consistently higher than daidzein when equal amounts of the two isoflavones are administered, and this is accounted for by the more extensive distribution of daidzein compared with genistein, and bioavailability of these isoflavones is greater when ingested as B-glycosides rather than aglycones……Biochanin A and formononetin, two isoflavones found in one phytoestrogen supplement, were rapidly and efficiently demethylated, resulting in high plasma genistein and daidzein concentrations typically observed after the ingestion of soy-containing foods……..…it cannot be assumed that all isoflavones are comparable in their pharmacokinetics and bioavailability. An analysis of 33 phytoestrogen supplements and extracts revealed considerable differences in the isoflavone content from that claimed by the manufacturers. There studies indicate a need for improvement in quality assurance and standardization of such products."*

As with toxicity warnings reported for soy supplements, soy foods and beverages can also result in phytoestrogen toxicity. The same for soy supplements holds true for the assortment of levels of phytoestrogens found in soy foods, beverages, most dangerously, soy-based infant formula especially based upon body weight ratio. Upon soy consumption, no one can be sure of phytoestrogen potency, availability of soy antinutrients, and individual bioavailability, all that encourage the cause of genotoxicity, with increasing health risks during fetal, infant, and child developmental timeframes.

2002, "Journal of Nutrition," T Nobuyo et al report, "*Absorption in Humans of Isoflavones from Soy and Red Clover Is Similar- The absorption of isoflavones varies substantially among individuals. It is unknown whether isoflavone absorption differs between those originating from soy and those from red clover, which contain different mixtures of isoflavones. The 24-hour excretions of isoflavones in urine were measured: ~25% of each isoflavone was recovered in urine, suggesting that similar amounts were absorbed irrespective of their glycoside/aglycone nature or the differing compositions of their sources (daidzein and genistein in soy and formononetin and biochanin in red clover). Thus, when isoflavones are consumed in moderate amounts over several weeks, modest differences in their composition or their conjugation status do not appear to affect the amounts that become bioavailable. After soy consumption, the daidzein: genistein ratio rose well above that in the food…….After red clover consumption all subjects showed some formononetin in the urine…….However, there had been considerable conversion from the two parent isoflavones to daidzein and genistein. Although there was little daidzein and genistin in the ingested red clover, the ratios in the urine showed far greater amounts of daidzein than of formononetin, and of genistein than of biochanin. The ratio of daidzein: genistein in the urine was 4.37, and that of formononetin: biochain in the food, 1.47. As in the present study, proportionately more daidzein than genistein was excreted for pharmacokinetic reasons that are not fully understood. The large standard deviations and the 25-75% ranges reflected the relatively large interindividual variability in excretion (and presumably in absorption) of isoflavones. However, there was a significant intraindividual correlation between the amounts excreted during the two test periods demonstrating that low and high excreters showed consistent metabolic responses to eating isoflavones……. the amounts excreted when subjects consumed the two sources of isoflavones were correlated."*

Warnings are clearly stated for women during pregnancy or breastfeeding to avoid ingesting Red Clover isoflavones, while actively hormone disrupting soy plant-estrogens do not display appropriate warnings during pregnancy or breastfeeding.

2005, "Fred Hutchinson Cancer Research Center," C Atkinson reports, "*Intestinal bacteria are involved in estrogen metabolism. One-third to one-half of the population harbors the yet-to-be-identified bacteria that metabolize daidzein, a soy isoflavone, to equol. Furthermore, equol-producers compared to non-producers, converted significantly more estrogen to estradiol…….These findings suggest differences may exist between equol-producers and non-producers in bacterial estrogen metabolism. However,…….the conversion of estrogen to estradiol could represent potentially….. detrimental pathways……..."*

2002, book, "Phytoestrogens and Health," Gilani and Anderson report, "*In that first study…..four subjects increased urinary equol excretion by 50- to 100-fold after soy consumption, whereas the other two were essentially incapable of production of equol. Subsequent studies in both men and women have repeatedly confirmed there are large interindividual variation in metabolite excretion….when consuming a soy diet, irrespective of gender. Substantial variations were also seen for O-DMA, daidzein and genistein excretion. Given the uniqueness of equol, there is growing interest in understanding why the variation occurs and whether it can be manipulated. Setchell et al first proposed that the variation (in equol excretors) could be due to factors that may be influenced by diet such as composition of the intestinal microflora, intestinal transit*

time, or the redox level in the large intestine. Some studies have shown higher consumption of carbohydrate and dietary fiber and lower consumption of fat in equol excretion……Further research is required to gain a better our understanding of equol and its effects on reproductive hormones….."

It is reported that the consumption of a variety of foods can also influence levels of dietary soy isoflavones, another reason added to the long list as to why individuals could never know they are consuming dangerously excessive levels.

2000, "Nutrition and Cancer," IR Rowland et al report, "*Interindividual variation in metabolism of soy isoflavones…..influence of habitual diet on equol production by gut microflora- It is suggested that the dietary fat intake decreases the capacity of gut microbial flora to synthesize equol. Interindividual variation in the urinary excretion of O-desmethyl-angolensin (O-DMA) was also apparent (76-fold after the high-isoflavone treatment period), but there was no relationship between equol excretion and O-DMA excretion."*

2007, "Vegetarian Journal," R Mangels reports, "*Vegetarians are more likely to produce equol…….People differ in how they metabolize soy products. Vegetarians were more than four times as likely to produce equol compared to non-vegetarians. Close to 60% of vegetarians produced equol."*

1995, "Nutrition and Cancer" LM Kirkman et al, *"….isoflavone (urinary) excretion was examined in 11 men and 9 women consuming four nine-day controlled experimental diets: … soy (tofu and textured vegetable protein product). Urinary excretion of the isoflavonoids equol, O-desmethylangolensin (O-MDA), daidzein, and genistein was higher when subjects consumed soy diets than when they consumed the other (vegetable) test diets."*

2005, "Journal of Nutrition," TE Hedlund et al report, "*Long-term dietary habits affect soy isoflavone metabolism and accumulation……in caucasian men- Participants then consumed a soy beverage daily for one week…. ….men who had consumed > or = 30 mg soy isoflavones/day for at least 2 years had 5.3-times the probability of producing equol than men who had consumed < or = 5mg/d. Additionally, those men who consumed animal meat regularly had 4.7-times the probability of producing equol than men who did not consume meat."*

2007, "Vegetarian Journal," R Mangels reports, "*A group of 41 adults, 29 of whom said they were vegetarian, was given a soymilk drink twice daily for 3 days. Vegetarians were more than four times as likely to produce equol compared to non-vegetarians. Close to 60% of vegetarians produced equol."*

2006, "Steroids," MC Hall et al report, "*Equol producer status, salivary estradiol profile and urinary excretion of isoflavones in Irish Caucasian women, following ingestion of soymilk- Following consumption of the soymilk, equol was detected in the urine of 18 (51%) of the volunteers (Irish women)…..5 hours after drinking soymilk. Salivary estradiol in most volunteers had decreased…..after drinking the soymilk. However, the salivary estradiol in 12 (34%) subjects increased from 33.76/13.4 pmol/L to 137.4/65.64 pmol/L over the same period. Volunteers who reported a first-degree link to breast cancer were more likely to…….be equol producers (71% compared to 51%). The results indicate a significant, distinctive variation in equol production, isoflavone excretion and salivary estradiol profile among individual volunteers following ingestion of soymilk."*

2006, The Institute for Preventative Medicine, Nutrition, and Cancer in Helsinki, SM Heinonen reports, *"Infants with underdeveloped gut microflora are unable to metabolize daidzein and genistein resulting in high isoflavone plasma levels if they are fed soy-based infant formulae. (There is) Marked interindividual variation in the bacterial metabolism of isoflavones regarding the capability to metabolize daidzein. Very little is known about the bacteria responsible for isoflavone metabolism…..Only few species of bacteria have been isolated, characterized, and studied. Further studies are needed to fully identify the bacteria associated with equol production."*

1998, "American Journal of clinical Nutrition," JL Slavin et al report, "*Daidzein, equol and total isoflavonoid excretion differed by diet treatment and increased significantly with increasing doses of soy. Genistein excretion differed significantly by soy treatment….O-DMA differed significantly by diet treatment and was significantly different among all diet treatments.…..The objective of this study was to determine what percentage of healthy humans excrete equol when given a soy challenge. Few data have been published on habitual dietary habits of equol excreters and nonexcreters…..equol excretion correlated positively with intake of total fat, meat consumption, and with the fat-to-fiber ratio. Individuals consuming more meat and fat were suggested to have the intestinal flora capable of producing equol from daidzein. Higher intakes of dietary fiber may promote the growth of bacterial populations responsible for equol production in the colon. The health implications of being an equol producer are not clear. Equol is thought to be more estrogenic than daidzein and O-DMA. Rates of urinary excretion of these compounds also vary, with daidzein and genistein concentrations returning more quickly to baseline concentrations than those of equol and O-DMA. The combination of equol's greater estrogenicity and longer time in circulation than daidzein or O-DMA may result in greater physiologic effects in equol excreters who regularly consume isoflavones. The bioavailability of isoflavones may be influenced by the form of soy consumed. Soy products vary considerably in isoflavone content depending on the initial isoflavone content of the ingredient soybeans and on the processing method. These variations in isoflavone content and bioavailability could limit the use of urinary isoflavonoid excretion as a biomarker of soy consumption. However, measurement of urinary isoflavonoid excretion may still be useful as an indicator of dietary isoflavone exposure. The chemical composition of soybean products was also found to affect sex hormone metabolism……For equol excreters, equol excretion differed significantly among all diet treatments. Individual variation in isoflavonoid excretion was high. O-DMA excretion was the most variable…..Variability in isoflavonoid excretion is probably due to individual differences in isoflavonoid absorption and degradation, which could be influenced by gut microflora and transit time. Contrary to other studies O-DMA was not lower in equol excreters than in nonexcreters. Joannou et al identified dihydrodaidzein, a daidzein metabolite and an intermediate in O-DMA formation in human urine. We did not measure this metabolite……. It also is not clear whether human subjects adapt to chronic consumption of soy or if the metabolic pathways for isoflavones change with exposure. Lu et al fed soymilk to male subjects and reported that chronic soy exposure……..did alter the time courses of daidzein and genistein excretion. The authors suggested that chronic exposure to soy might prolong the tissue exposure to the biologically active forms of isoflavones.……Our dose-response study suggests that the isoflavones in soy-protein isolate are bioavailable at amounts as low as 9mg/d, or about*

the amount found in 28.4 g tofu (1 oz, the standard serving size). Much more remains to be learned about isoflavones, including their metabolism, the bioavailability of isoflavones from different food sources, individual differences in isoflavone absorption and metabolism, and how these differences relate to disease risk, before specific amount of soy consumption can be recommended."

2004, "British Journal of Nutrition," L Hoey et al report- *"Influence of soya-based infant formula on consumption on isoflavone and gut microflora metabolite concentrations……and metabolic activity in infants and children- Urinary genistein, daidzein and glycitein were detected in all infants (4-6months) fed soya-based infant formula; O-DMA was detected in 75% of infants….equol was detected in…25%. In controls urinary isoflavonoids were very low or not detected. In older age groups (7 months-7 years), O-DMA was found in urine samples of 75% of the soya group and 50% of controls, after the soya challenge (soya yoghurt alternative product containing 4.8g soya protein on average 22 mg total isoflavones). Equol excretion was detected in 19% of the soya-group infants and children, and in only 5% of the controls."*

Maternal consumption of soy during pregnancy dangerously manipulates estrogenic exposure of developing fetus, with varying contamination occurring among the male and female gender. Postnatally, newborns that are fed soy-based formula isoflavone estrogenic endocrine disruptors as 100% of dietary intake are prone to overdose of phyto-chemicals and as published literature proves are again at increasing risk for adverse health effects. Which infants, and at what point in time do infants develop gut microflora thus increasing bioavailability of highly potent estrogenic equol as well as O-MDA while their dietary source is 100% soy-based formulas is not known without testing. It is also reported that infants with, or without developed microflora, in both cases have high levels of estrogenic isoflavones.

2004, "Toxicologist," E Todaka et al report, *"Fetal Exposure to Phytoestrogens……..Phytoestrogens are estrogen-like chemicals derived from plants mainly soy. As there is a concern if it is safe when human fetus is exposed to excess amount of phytoestrogens. Genistein was detected from 96% of maternal serum and 100% cord serum. Equol was detected from 37% of maternal serum and 35% of cord serum. Coumestrol was detected from only one maternal serum. Equol is a metabolite of daidzein and is reported to be more estrogenic than daidzein or genistein. Also, there was a tendency found that the endogenous estrogen level of newborns that were exposed to equol was lower than the newborns that were not exposed to equol. Furthermore, there was another tendency found that the concentration level of estraidol was lower in female than in male newborns when they were divided as equol exist group and non-exist group."*

Northern California Cancer Center study results indicate, "*Traditional soy-based foods were found to contain high levels of genistein and daidzein, as well as substantial amounts of coumestrol. A wide variety of 'hidden' sources of soy was observed."*

2003, "Food Standards Agency," University of Ulster and Kings College London report, "*Influence of human gut microflora on dietary soya isoflavone phytoestrogen bioavailability in adults and children- It is known that the microflora in the human gut strongly influence the absorption and metabolism of phytoestrogens in the body. The types of gut microflora will be analyzed and compared to those in adults and breast-fed infants. Results and findings- Around one third of adults have the gut microflora to*

convert daidzein to equol. Babies fed soya milk formula excreted isoflavones in urine. This shows that they can absorb phytoestrogens from the gastrointestinal tract. Young infants acquired the gut microflora to undertake metabolism of some phytoestrogens. But over time the composition of the gut microflora altered to allow additional metabolic reactions to take place. The type of infant formula consumed (i.e. soya or cows milk based formulas) influenced the composition and form of the infant gut microflora, which affected the metabolism of isoflavones."

2004, "British Journal of Nutrition," L Hoey et al report, "*The urinary excretion of soya isoflavones and gut microflora metabolites was investigated in infants and children who had been fed soya-based infant formulas in early infancy. These infants and children were compared with cows'-milk formula-fed controls, to determine at what age gut microflora metabolism of daidzein to equol and/or ODMA was established…….. Urinary genistein, daidzein, and glycitein were detected in all infants (4-6months) fed soya-based infant formula: O-DMA was detected in 75% of infants…… equol was detected in….25%. In the controls urinary isoflavonoids were very low or not detected. In older age groups (7 months-7years), O-DMA was found in the urine samples of 75% of soya group and 50% of controls……Equol excretion was detected in 20% of the soya-group infants and children……....only 5% of controls. The gut microflora in early childhood is very different to that in adulthood, therefore it is important to characterize developmental changes in isoflavone biotransformation in early life. The intestinal tract of the human fetus is sterile, but after birth it rapidly becomes colonized by bacterial microflora from the mother's faecal, vaginal and skin floras. Further bacterial types are then established in the gut from a variety of endogenous and exogenous sources including diet and the environment."*

Irvine et al (1998) report, "*Significant amounts of daidzein and genistein were excreted in the urine of soya-based infant formula-fed infants, but not cows' milk formula-fed infants (up to 4 months). Setchell et al (1997) reported significantly greater amounts of genistein and daidzein in the plasma of 4-month old soya-based infant formula-fed infants. The intake values for infants fed soya-based infant formulas are approximately four to five times that of adult soya consumers. In contrast, the infants fed cows'- milk formula had negligible isoflavone intake, with a maximum exposure to isoflavones of 0.03mg/kg per day, over 100-fold lower than that of soya-based infant formula-fed infants. Urinary excretion data indicate that the isoflavones are readily absorbed from the gut even in infants in the youngest (4-6month) age group. In this age group, isoflavones could not be detectable in the urine of the cows-milk formula-fed infants. Approximately equal amounts of daidzein and genistein were excreted in urine in the youngest infants…..consistent with the limited data available from a previous study. It is clear that the ability to convert daidzein to O-DMA is acquired at an early stage in development, because the metabolite was detected in the urine of 74% of the 4-6month-old soya-based infant formula fed infants. …..it has been shown that the metabolism of daidzein to equol by cultured human microflora can be influenced by the condition used. A high NSP content, which stimulates bacterial fermentation resulted in a rapid conversion of daidzein to equol…under conditions that mimicked low carbohydrate intake equol was not formed…..good equol producers consumed less fat compared with poor equol producers and more carbohydrates. ….women but not men who were good equol producers consumed a significantly higher percentage of energy as*

carbohydrate…..and they also consumed more plant protein and dietary fiber. The observed increase in the ability to produce equol and O-DMA with increase in gage, in the soya-group and control-group (following soya challenge) infants and children in the present study may thus be partly related to the increase, with increasing age, in the dietary fiber content of the diets……..

To evaluate the influence of soya-based infant-formula feeding on gut health-related, bacterial composition of the faecal flora and on certain aspects of bacterial metabolism, we focused on a subgroup of the infants aged 4-12 months old, which is a period when there are known to be major changes in the gut microflora. In this subgroup, the soya-based infant formula-fed infants had significantly lower total numbers of bacteria than the cow's milk fed infants and this difference was consistent across all the four main groups of bacteria (bifidobacteria, lactobacilli, enteroccoi, and SCFA) studied. There was a significant difference in bifidobacteria numbers, approximately 10-fold lower in the soya-based infant formula-fed infants compared with cows-milk formula fed infants. Bifidobacteria are considered to be of particular importance for gut health……..…an increase in B-glucosidase activity….observed in the soya-based infant formula-fed infants compared to the controls, in response to the considerable soya isoflavone glucoside consumption by the soya group. …..…the activities of faecal bacterial B-glucosidase and B-glucuronidase do appear to be higher in the soya-based infant formula-fed infants compared with controls suggesting that these enzymes were induced in some bacteria. As B-glucuronidase can additionally hydrolyse glucuronide conjugates of ingested toxicants, releasing potentially toxic aglycones in the colon, and similarly B-glucosidase can hydrolyse glucoside conjugates found in plants releasing biologically active phytochemicals that may be beneficial or harmful….greater B-glucuronidase activity could exert damaging effects on the host and thus have adverse health consequences. In conclusion, therefore, the present data have shown that infants aged 4-6 months fed soya-based infant formulas excreted considerable quantities of genistein, daidzein and glycitein in urine, indicating that the compounds are well absorbed. As the hyrolysis of isoflavone glucosides to aglycones by glucosidases is required for absorption, the results suggest that hydrolytic ability develops by or before 4-6 months of age. The majority of soya-based infant formula-fed infants (including those under 6-months) were capable of converting daidzein to O-DMA…..conversion of daidzein to equol was seen in few children.....soya-based infant-formula fed infants (4-12 months) having significantly lower total bacteria counts and bifidobactera counts, and bacteroide and clostridia counts than cow's milk formula fed infants in the same age group."

1995, "Proceedings of the Nutrition Society", Xu et al report, *"If an individual possesses bacteria that are not effective in isoflavone metabolism and degradation then more isoflavones would be absorbed, which would explain the positive association between high fecal isoflavones and greater total urinary recovery of isoflavones."*

2008, "Nutrition and Cancer," BM Halm et al report, "*Oral Antibiotics Decrease Urinary Isoflavonoid Excretion in Children After Soy Consumption- How oral antibiotics alter isoflavones in soy-consuming children is unknown. Urinary isoflavones were hypothesized to change after oral antibiotics due to intestinal microflora alterations. During oral antibiotics use….total isoflavones was reduced……In contrast, a trend toward more O-DMA production during oral antibiotics was observed. The reduction in*

urinary isoflavones appearance could be due to the changes of intestinal bacteria by oral antibiotics and/or due to processes related to the infection."

2006, Human Metabolome Database (Version 2.0) finds, "*O-Desmethylangolensin- It is unclear why some, but not all, persons harbor ODMA-producing bacteria. ODMA production is inversely associated with age, height, weight, and body mass index. In addition, Asians are less likely than whites to be ODMA producers, and former smokers were more likely than never smokers to be ODMA producers. Investigators have attempted to identify the bacteria involved in ODMA production, and several candidate bacteria were associated, but not definitely identified. ODMA production is correlated with the abundance of methanogens, indicating that the metabolic fate of daidzein may be related to intestinal H(2) metabolism."*

Intestinal measurements of H(2), methane, and nitric oxide gases may be used to monitor birth-related bacterial colonization in relation to postnatal age and maturation. In preterm infants, gaseous distension of the gut is common and may signal bacterial overgrowth. There may be a potential role for intestinal gas measurements as a diagnostic tool for intestinal disorders. Soy isoflavones can reportedly contribute to weight reduction that is related to preterm birth that is related to bacterial overgrowth of which more powerful daidzein metabolites may develop.

There are many, many variables dependent upon interindividual production of equol and O-DMA, indicating the extreme fluctuations of adverse health effects that soy plant-estrogens can have on the human body, particularly related to the developing fetus, infants, and children exposed. It is also reported in published studies that levels of estrogenic-active O-DMA in plasma and urine are higher in men than in women, with concern of even greater estrogenic-active isoflavone risks caused to males.

2004, American Journal of Clinical Nutrition," H Wiseman et al report, "*Influence of 10 week of soy consumption on plasma concentrations and excretion of isoflavonoids and on gut microflora metabolism in healthy adults- Concentrations of isoflavones and their gut microflora metabolites in the plasma, urine, and feces were significantly higher in the subjects who consumed the high-soy diet than in those who consumed the low-soy diet. Concentrations of O-DMA in plasma and urine were higher in the men than in the women. Fecal bacteria from subjects consuming both diets could convert daidzein to equol ex vivo. Fecal beta-glucosidase activity was significantly higher in the subjects who consumed the high-soy diet than in those who consumed the low-soy diet. Although interindividual variation in isoflavone metabolism was high, intraindividual variation was low…… concentrations of O-DMA in plasma urine appeared to be influenced by sex."*

Data indicate that cytosolic beta-glucosidase is a hepatocyte-specific enzyme, and support the hypothesis that cytosolic beta-glucosidase in the liver functions to hydrolyze small glucosides absorbed by the intestine. This suggests that acute increases in serum levels of cytosolic beta-glucosidase in animal models of liver injury may reflect direct injury of hepatocyts. Soy causation of significantly higher beta-glucosidase in fetus and infants warrants further investigation.

2002, "Toxicological Sciences," CA Lamartiniere et al report, "*Diets containing 0mg, 250mg (low dose), and 1000mg (high dose) daidzein/kg feed were fed to virgin female rats starting 2 weeks prior to breeding and continued until the offspring were 50 days postpartum. The serum daidzein concentrations in adult female rats fed the low and*

high daidzein-containing diets were determined to be 6- and 13-fold higher than serum daidzein concentrations of Asians eating a traditional diet high in soy. The high….daidzein dose resulted in reduced body weight….(in male and female offspring)….With the low dietary daidzein dose, total equol and daidzein concentrations in the blood of pregnant females, 7-day-old, 21-day-old, and 50 –day-old female offspring were 529 and 303nM, 1653 and 982nM, 1188 and 1359nM, and 3826 and 630nM respectively."

1998, "The Journal of Nutrition," S. Watanabe et al report, "*Pharmacokinetics of Soybean Isoflavones in Plasma, Urine and Feces of men after ingestion of 60g Baked Soybean Powder. The plasma concentration of genistein increase after 2 hours and reached its highest value 6 hours later. The plasma concentration of daidzein peaked at the same time, but it was always lower than that of genistein. Peak plasma concentration of O--desmethylangolensin (O-DMA) and equol appeared after the daidzein peak in four and two subjects respectively. The individual plasma and urinary concentrations of equol and O-DMA were quite variable….The high plasma concentration of isoflavones for at least several hours after a single ingestion of soy protein suggests that these compounds may interact with macromolecules and have biological effects…..the soy milk given to women contained much larger amounts of isoflavonoids, and the relative amount of daidzein was higher. Equol and O-DMA excretion in the urine may depend on the different composition of (individual) gut microflora. Our results demonstrated that O-DMA is a metabolite that appears slightly earlier than equol in the body. O-DMA is a major metabolite of daidzein and it has been suggested that equol is also a metabolite of genistein."*

As confirmed, gut microflora is necessary to convert daidzein to highly estrogenic equol and O-DMA and genistein conversions to dehydrogenistein and O-DMA, while studies report that "type of delivery (natural vs. cesarean) and feeding (breast vs bottle) also play dramatic roles in determining the gut microflora composition of the infant. Largely varying among adults and especially varying among infants, important gut bacteria converts plant-estrogens into an increasing number of active phytochemicals. There are varying levels of estrogenic soy components that vary in each soy product, as well as large differences in intestinal digestibility among fetus, infants, children and people of all ages

2008, "Intestinal Immune Health," DM Bier et al report, "*The fetal intestinal immune system is structurally intact from a very early gestational age. At birth the neonate is challenged with an extraordinary and variable bacterial challenge. Fortunately the neonate is armed with a multitude of protective mechanisms by which to ensure a productive microbiota in the setting of an intact mucosal surface. The intestinal epithelium orchestrates complex interactions and signaling…..the immunomodulartory capacity of breast milk which is increasingly implicated in the achievement of intestinal and immunologic health…..developmental expression of enzymes, pattern recognition, downstream signaling and dendritic cell interaction all contribute to intestinal homeostasis. These strategies lend insight into the establishment of tolerance so critical to neonatal health."*

2008, "Endocrine-Related Cancer," R Dip et al report, "*After extraction from soymilk, phytoestrogens were deconjugated and processed through reverse-and normal-phase cartridges. Analysis of mRNA on high density microarrays revealed that soy*

phytoestrogens induce a genomic fingerprint that is indistinguishable from the transcriptional effects of the endogenous hormone 17B-estradiol. Highly congruent responses were also observed by comparing the physiologic estradiol with daidzein, coumestrol,……each representing distinct phytoestrogen structures……in late-stage cancer cells lacking ERb, these phytochemicals contribute to a tumor-promoting transcriptional signature."

Coumestrol is biosynthetically related to isoflavones that is found in soybean sprouts. However the estrogenic activity of coumestrol is greater than that of the most potent isoflavones with respect to estrogen receptor levels. Coumestrol and genistein have been shown to be more potent than any other known phytoestrogens when their in-vitro estrogenic activity was compared with that of 17B estradiol. Soy isoflavones in the order of estrogenic levels of potency are: genistein, equol, daidzein, O-MDA and glycitein. Soy isoflavones mixed in combination with other known or unknown estrogenic influences (environmental pollutants, pesticides, estrogenic drugs, etc) encourages highest estrogenic levels.

The journal, "Endocrine Regulations" confirms, "*Soybeans contain an abundance of phytoestrogens such as genistein and daidzein…..The soybean extract……was positively identified as coumestrol."*

Varying levels of active soy plant-estrogen/antinutrients can be found in soybean products such as: soy-based infant formulas, soy powders, soy tofu, soy cheeses, soy butter, soy drinks, soy fiber, soy flour, soy meal, soy hot dogs, soy burgers, soy sausage links, soymilk, soy noodles, soy seeds/nuts/chips, soy sprouts, soy cheese, soy cereals, soy paste, soy protein, soybean chips, raw soybeans, soybean flakes, soy yogurts, soy lecithin, soy meal, soy food-fillers, natto, miso, tempeh, and soy supplements.

It is found that soybeans produced in different regions of the U.S. can contain extreme variations in the levels of active soybean phytoestrogens, antinutrients, protein composition and quality, amino acid levels, essential mineral content, heavy metal content, that are all largely influenced by soybean seed, soil conditions, fertilizers, germination, frequency of watering, climate changes, plant age at harvesting, soybean processing and packaging. It is also stated that soybeans harvested in different years present considerable variation in their composition and nutritional quality.

Certified Nutritional Advisor, Dr. R. Brouse reports, "*However, not all soybeans are created equal. Quality and amino acid content will vary based on soil conditions, and variable growing and harvest conditions. If one essential amino acid is missing, the immune system can be depressed 30%, and many important body functions are delayed or stopped."*

Measurements for the fluctuating levels of soy plant-estrogens and soy phyto-chemical anti-nutrients are not required by the FDA to be calculated or acknowledged as public information. There are no industry demands by the FDA to disclose toxic soy phytochemical warnings that are most urgently important during pregnancy and while breast feeding. There are no responsible soy-based infant formula warnings disclosing soy estrogenic/antinutrient contents as also health threatening during delicate infant physiological and neurological development.

No studies to date have investigated the impact of soy estrogenic/antinutrient contamination of sperm during conception.

NIH researchers, Drs. Daniel Doerge and Daniel Sheehan confirm, "*The health labeling of soy protein isolate for foods needs to be considered just as would the addition of any estrogen.....to foods, which are bad ideas. Patients are informed of (drug) risks and monitored by their physicians for evidence of toxicity. There are no similar safeguards in place for foods, so the public will be put at potential risk from soy isoflavones……without adequate warning and information."*

A study published in "Laboratory Animal Science" concludes, "*Phytoestrogens exert estrogenic effects on the central nervous system……and dietary phytoestrogens have the potential to alter results of studies of estrogenicity. Careful attention should be given to diet phytoestrogen content and their concentration should be reported."*

There are no proven safe levels of exposure to soy phytoestrogens for fetus, infants, and children. The tragedy remains: because soy estrogenic and antinutrient availability can fluctuate from plant-to-plant and person-to-person, no one can be sure what levels of active soy plant-estrogens and soy antinutrients each fetus, infant, child, adolescent, and adult are in fact exposed to.

A study published in the "Journal of Nutrition" reports, "*Potential Adverse Effects of Phytoestrogens- "Evaluation of the potential benefits and risks offered by naturally occurring plant estrogens requires investigation of their potency and sites of action when consumed at natural dietary concentrations. …. Findings illustrate the broad range of actions of these natural estrogens (coumestrol or commercial soy-based diet), and the variability in potency across endpoints. This variability argues for the important of fully characterizing each phytoestrogen in terms of its sites of action, balance of agonstic and antagonistic properties, natural potency, and short-term and long-term effects. Findings illustrate the broad range of actions of these natural estrogens and the variability in potency across endpoints. This variability argues for the importance of fully characterizing each phytoestrogen in terms of its sites of actions….potency and short-term and long-term effects."*

Veterinary journals report on the health dangers of phytoestrogens to dogs among countless other animals.

For pet safety the "American Journal of Veterinary Research" publicly reports that their, "*Objective- to identify and determine concentration of phytoestrogens in commercial dog foods. Dietary intake of phytoestrogens may have….deleterious health effects. Our results indicated that certain commercial dog foods contain phytoestrogens in amounts that could have biological effects when ingested long-term."*

2001 "Journal of Endocrinology" KS Weber, et al report, "*The present study describes the short-term effects of dietary phytoestrogens on regulatory behaviors, (food/water intake, locomotor activity and body weight), prostate weight…….After 5 weeks of consuming (approximately 600 microg/g isoflavones) these diets, plasma phytoestrogen levels were 35 times higher in animals fed the phytoestrogen-rich verses phytoestrogen-free diets. Body…… weights were significantly decreased in animals fed the phytoestrogen-rich diet….."*

2008, "Journal of Nutrition," I Torre-Villalvazo et al report, "*As a result, rats fed the soy diets gained less weight than those fed the casein diets……"*

Low fetal and infant birth weight is a proven cause of a number of adverse health effects.

2007, "Toxicity Report Series," National Toxicity Program- KB Delclos and R Newbold report, "*Genistein is a naturally occurring isoflavone that interacts with estrogen receptors and multiple other molecular targets. Human exposure to genistein is predominantly through consumption of soy products, including soy-based infant formula…..…..A series of short-term studies with genistein was conducted with two goals: 1) to obtain data necessary to establish dose levels for subsequent multigenerational reproductive and chronic toxicity studies and 2) to evaluate the effects of genistein on endpoints outside the reproductive tract. … ….data generated from these studies have been reported previously in the peer-reviewed literature or in technical reports. The present report focuses on the reproductive and general toxicology endpoints evaluated. Data obtained in separate evaluations of behavioral, neuroanatomical, neurochemical, and immunological endpoints……are also discussed to put in better perspective the selection of doses for the multigenerational and chronic studies. Genistein was administered ….to female Sprague-Dawley rats starting on gestation day 7 and continuing throughout pregnancy. Dietary exposure of the dams continued through lactation……Body weight and feed consumption of the treated dams prior to parturition showed decreasing trends with increasing dose. The most pronounced organ weight effects in the pups were decreased ventral prostate weight in males…..and a trend toward higher pituitary gland to body weight ratios in both sexes. Histopathologic examination of female pups revealed ductal/alveolar hyperplasia of the mammary glands at exposure concentrations greater than 250 ppm. Ductal/alveolar hyperplasia and hypertrophy also occurred in males with significant effects seen at exposure concentrations of 25 ppm or greater hypertrophy and 250ppm or greater for hyperplasia. Abnormal cellular maturation in the vagina was observed at 625ppm….and abnormal ovarian antral follicles were observed at 1250ppm. In males, aberrant or delayed spermatogenesis in the seminiferous tubules relative to controls was observed at 1250ppm. Histologic evaluation indicated a deficiency of sperm in the epididymis at 625ppm…Control females showed a high incidence of renal tubule mineralization, and the severity of this lesion was significantly increased at exposure concentrations of 250 ppm or greater. Males showed…renal tubule mineralization (with) severity increased with increasing exposure concentration at 250ppm and greater. These long-term studies were designed to address multiple aspects of the endocrine disruptor hypothesis…..that exposures of human and wildlife populations to endocrine-active compounds contribute to adverse reproductive tract effects and cancers of hormone-sensitive organs. …..long-term consequences of low dose exposures that may produce subtle initial effects. While ..... to significantly impair reproduction, the observation of significant effects at 250ppm together with the suggestion of subtle effects at this exposure concentration and less in the parallel immunotoxicity and neuroanatomical surveys, a high exposure concentration between 250 and 625ppm was deemed appropriate for the purposes of the multigeneration reproductive toxicology study and chronic study of genistein. A high exposure concentration for the multigenerational and chronic studies was thus set at 500ppm."*

2007, "Metabolism" M. Fujioka et al report, "… …*bone mineral density of the whole body and femur in the female daidzein group was significantly lower (during mice growth period) than that in the control group."*

2007, "Food and Chemistry Toxicology," RM McClain et al reports, "*Concern has been raised….of potential adverse effects (of genistein) due to the estrogenic and*

other activities of isoflavones and thus a comprehensive series of safety studies was performed with genistein. To assess the teratogenic and fetal toxic potential of genisteins several studies were conducted. (Genistein) Treatment related anomalies were observed at concentrations of > or = to 10 microg and at 100 microg/mL, all (rat) embryos were malformed. A slight maternal toxicity at 1000 mg/kg/day was observed as indicated by decreased body weight…adverse effects in the pups were observed including increased pup mortality, poor general condition, reduced pup weights, and reduced pup milk uptake. At ….1000mg/kg….some minor visceral and skeletal variations were observed. At low dose of 20mg/kg/day an increased mortality, reduced milk uptake a decreased % male sex ratio, and decreased body weights during lactation were observed. At 500mg/kg, maternal body weight and food consumption were markedly reduced. The incidence of resorptions was markedly increased with a corresponding decrease in the number of live fetuses per dam. Fetal body weights were also reduced. On the basis of the definitive prenatal development study the, no observed adverse effect level for maternal toxicity and adverse effects on embryonic development was considered to be 100 mg/kg/day when administered orally by dietary admix."

2008, The NIH, National Toxicology Program, reports, "*Genistein is a naturally occurring isoflavone that interacts with estrogen receptors and multiple other molecular targets. Human exposure to genistein is predominantly through consumption of soy products, including soy-based infant formula and dietary supplements. . ….concerns have also been raised regarding potential adverse effects of genistein, particularly with regard to reproductive toxicity and the induction or potentiation of carcinogenesis, due primarily to its weak estrogenic activity. Mean body weights of 500 ppm (rat) females were less than controls…..early onset of aberrant estrous cycles suggesting early reproductive senescence was observed….pituitary gland weights were significantly increased, significant positive trend in the incidences of mammary gland adenoma or adenocarcinoma…positive trends in incidences of adenoma or carcinoma in the pars distalis of the pituitary gland….In males a significant positive trend occurred in the incidences of combined adenoma or carcinoma of the pancreatic islets. There was some evidence of carcinogenic activity of genistein in female rats based on increased incidences of mammary gland adenoma or adenocarcinoma and pituitary gland neoplasms. The effects of genistein on estrous cycling and the incidences of common hormonally related spontaneous neoplasms of female rats are consistent with an estrogenic mechanism of toxicity."*

2001, "Mutation Research," Department of Pharmacology & Toxicology, BJ Boersma et al report, "*For genistein the major isoflavone in soy, reported mechanisms for biological activities are numerous and include regulations of estrogen-mediated events, inhibitions of tyrosine kinase and DNA topoisomerase activities synthesis and release of TGF beta and modulations of apoptosis. Genistein is extensively metabolized in vivo with only about 14-16% excreted in an unmodified form. Metabolism may also occur because of interaction between genistein and oxidants produced by inflammatory cells…..These react with genistein to form brominated, chlorinated, and/or nitrated genistein. Emerging evidence indicates that these modifications may substantially increase the biological activities of the parent compound. Future investigations of genistein.....must….. take into account metabolism at the tissue site."*

2008, "Endocrinology" E Grossini et al report, "*Intracoronary genistein acutely increases coronary blood flow in anesthetized pigs through beta-adrenergic mediated nitric oxide release and estrogenic receptors- In conclusion, genistein primarily caused coronary vasodilation the mechanism of which involved ERalpha/ERbeta and the release of nitric oxide through vasodilatory beta(2) adrenoreceptor effects."*

Increased maternal blood flow through the fetal umbilical artery can be associated with poor fetal/infant outcome while causing: abnormal placental circulation, increase resistance to blood flow in the umbilical artery, vascular problems, fetal distress, smaller birth size, intrauterine growth retardation, risk for breathing, and complications after birth such as impaired neurological development. It is proven that prenatal complications can slow down fetal growth enough to impair the development of the fetal brain.

Genistein is also reported to release nitric oxide, while sustained levels can cause tissue toxicity and contribute to vascular collapse associated with septic shock, whereas chronic expression of nitric oxide is associated with various carcinomas, and inflammatory conditions including juvenile diabetes, multiple sclerosis, arthritis and ulcerative colitis.

Numerous studies conclude that endocrine disrupting soy phytoestrogens are capable of manipulating estrogen receptor-alpha and estrogen receptor-beta. No obvious differences have been reported between females and males in regional distribution of the ER-a receptor, but there have been reports of gender differences in the distribution of the ER-b receptor. Estrogens, even in the short-term can alter neuronal activity as many studies are in agreement that the extent of soy estrogenic manipulations on the developing brain are underestimated, as extensively revealed later in this report.

As a fact, soybeans are proven as increasingly toxic particularly during specific timeframes of highly sensitive fetal, infant, and child development especially based upon the smaller, lighter body weight ratio. Developmental exposure, (prenatally and/or postnatally) to soy phytoestrogens and soy phytoestrogen-containing foods and beverages is capable of altering a wide range of hormone systems in both males and females. As expected, although estrogenic manipulations are considered genotoxic to females, estrogenic hormone manipulations are also reported with potential for even greater developmental toxicity of exposed males. Bioavailability of soy estrogenic isoflavones not only significantly varies interindividually, but the bioavailability of equivalent soy isoflavone potencies can also vary between male and female gender.

1998, "American Journal of Clinical Nutrition," LJ Lu and KE Anderson report, "*Sex and long-term soy diets affect the metabolism and excretion of soy isoflavones in humans-….isoflavones daidzein and genistein…are weakly estrogenic. During one month of daily soy ingestion….soymilk providing 80-210 mg of each isoflavone daily, women initially excreted more isoflavone conjugates in urine than did men. Recoveries of conjugates of genistein, daidzein, and equol were 24%, 66% and 28% of the amounts ingested in women, respectively and 15%, 47% and 15%, respectively of those in men. A progressive decrease in urinary excretion of genistein and daidzein was observed in women, but not in men during the study. At least 10% of ingested daidzein was excreted in urine as equol conjugate in one man and one woman after the first soy ingestion. Three more women but no more men developed the ability to produce and excrete large amounts of equol. The elimination rates (k(e) for genistein, daidzein, and equol were 0.1, 0.16, and 0.08 h(-1), respectively, in women, and 0.19, 0.25, and 0.13 h (-1) respectively,*

in men. Thus, the excretion half-life values of genistein were longer in women (7,4, and 9 h, respectively) than in men (4,3,and 5hour) respectively after the first soy ingestion. The excretion half-life shortened progressively in women but lengthened progressively in men over the study period. Thus, isoflavone metabolism and disposition were affected by the duration of soy ingestion and by sex."

2006, "Journal of Nutrition," A Cassidy et al report, "*Factors Affecting the Bioavailability of Soy Isoflavones in Humans after Ingestion of Physiologically Relevant Levels from Different Soy Foods- "The dose of (soy) isoflavones administered to each individual as a single bolus dose was 0.44 mg/kg body weight. Serum isoflavone concentrations in all individuals and groups increased rapidly after the ingestion of each soy food; as expected. Genistein concentration exceeded daidzein concentrations in serum. In this small study, gender differences in peak concentrations of daidzein were observed, with higher levels attained in women. However, soy milk was absorbed faster and peak levels of isoflavones were attained earlier than with the other soy foods….. 30% of the subjects were equol producers and no differences in equol production with age or gender were observed."*

Besides human consumption of soy isoflavone phytochemicals, livestock are regularly fed soy-based feed and eventually are sold at meat markets, contributing to dietary estrogenic exposure to consumers. Also, soy-infiltrated livestock manure is recycled throughout soils that are planted upon, thus absorbed into a variety of edible vegetable plants. More research needs to investigate the soybean contamination of groundwater of which studies conclude that increasing estrogenic residuals are causing the well-known deformities, infertility, and extinction of several reptiles.

It is known that a variety of highly active phytoestrogen endocrine disruptors are passed to fetus, infants, and children exposed to soy, of which estrogenic disruptions are largely multiplied in combination with the several other xenoestrogen estrogen disruptor chemicals, i.e. pollutants, pesticides, plastics etc.

2001, Pharmacology and Experimental Therapeutics, S. Belcher, and A Zsarnovszky repot, "*…xenoestrogens and phytoestrogens may have similar effects on rapid-signaling mechanisms that are normally regulated by endogenous estrogen."*

Compounding the dangers behind soy isoflavones as active endocrine disruptors, published literature also confirms a vast variety of soybean antinutrients as reviewed later in this report. Also described further in this report is that soy phytoestrogens are repeatedly documented throughout published literature as "active endocrine disruptors," proven to cause multiple adverse reproductive and developmental disorders.

Estrogenic genistein, daidzein, glycitein, and daidzein metabolites are active soy phytoestrogens that are normally not found in the human body, with the highest levels of exception being soy consumption. Soy phytoestrogens are compared to environmental pollutants as active estrogenic endocrine disruptors, demonstrates a structural similarity to the steroid nucleus of steroidal estradiol estrogen, and is compared to destructive similarities as DES, all proving the biologically active soybean endocrine disrupting estrogenic effects.

SOY PHYTOESTROGENS COMPARED TO DES ESTROGEN:

The consequences of DES treatment of pregnant women stands as the clearest example of the potential adverse effects of estrogen exposure to developing fetus.

The United States Environmental Protection Agency and National Center for Environmental Research confirms that DES synthetic estrogen and hormonally active exogenous factors (pesticides, plastics, etc), are comparable with the endocrine disruptions that is also caused by soy plant-estrogens. Larger levels of soy isoflavones, particularly genistein is comparable to synthetic estrogen DES.

Federal Register 64 FDA 57699, October 1999, the FDA reviews a 1991 study reporting neonatal injections of genistein compared to the higher estrogenic levels in DES. The FDA concludes, "*Soy isoflavones…are known to exert hormonal effects…..they are much less potent than synthetic estrogens such as DES. ……during pregnancy in humans, isoflavones could be a risk factor for abnormal brain and reproductive tract development.*"

1982, "Medical Hypostheses," S Seely reports, "*Phytoestrogens are estrogen mimics produced mainly by leguminous plants, like clover, Lucerne, and soya beans…. They are isoflavones and other plant-phenols…..somewhat similar to non-steroidal synthetic estrogens, like diethylstilbestrol. It is suggested that when consumed by lactating cows, the estrogenic substance appears in their milk and transferred to the human consumer, on whom the effect could be similar to that of diethylstilbestrol…...*"

Lactating mothers consuming soy are shown to transfer soy-estrogens to their child.

Also passing to fetus via the placenta, DES estrogen was proven (in 1975) to cause carcinogenic effects in children exposed. DES estrogen can reportedly cause: autoimmune disease, damaging cognitive function, male infertility, female menstrual cycle and reproductive dysfunction, and cancers that are not ruled out due to the increasing estrogen levels caused by soy isoflavones. Published studies have established soy plant-estrogen levels, commonly genistein in comparason to the higher DES.

Reported in "Experimental Biology and Medicine" 2004, "*Genistein more closely mimicked the low dose DES……*"

NIH researchers Drs. Doerge and Sheehan, "*First, calculations based on the literature, show that doses of soy protein isoflavones….demonstrated estrogenic effects as potent as low active doses of DES. Second, we have recently shown that estradiol shows no threshold….and we subsequently have found 31 dose-response curves for hormone-mimicking chemicals that also fail to show a threshold. Our conclusions are that no dose is without risk, the extent of risk is simply a function of dose. These two features support and extend the conclusion that it is inappropriate to allow health claims for soy protein isolate*"

2004, "Environmental Health Perspectives," JG Moggs et al report, "*The need to decide if all estrogens are intrinsically similar- We used gene expression profiling to investigate whether the molecular effects induced by estrogens of different provenance are intrinsically similar. In this article we show that the physiologic estrogens 17-beta-estradiol, the phytoestrogen genistein, and the synthetic estrogen diethylstilbestrol (DES) alter the expression of the same 179 genes in the intact immature mouse uterus…..We conclude that the case has yet to be made for regarding synthetic estrogens (DES) as presenting a 'unique' human hazard compared with phytoestrogens and physiologic estrogens.*"

1998, the Environmental Protection Agency concludes, "*…an increase of soy consumption in the North American diet has resulted in increased exposure to dietary*

estrogen mimics by reproductive-aged women, raising concern regarding possible effects on the fetus and neonate. The effects of genistein relative to the reference estrogen DES were examined…..our specific aims are to determine whether intake of dietary soy phytoestrogens by (rat) dams from mid-gestation throughout lactation to weaning will affect progeny by altering normal sexually dimorphic development of the central nervous system as reflected by changes in: 1. Brain 2. Neuroendocrine maturation at puberty 3. Ovarian versus neuroendocrine aging over life span. Exposure of the pregnant dam to the soy phytoestrogen genistein, alone or in combination with DES resulted in decreased birth body weights in both male and female progeny…….. Awaiting analysis of brain and reproductive organs."

National Center for Environmental Researcher, (NCER) 1996-1999 Final Report: *"Developmental Effects of Dietary Soy Phytoestrogens- there is widespread concern that developmental exposure to endocrine active chemicals (EACs) may adversely affect reproductive, neurobehavioral, and immunological development or predispose those exposed towards various cancers later in life. This study focused on the effects of DES at marginally effective doses and genistein at levels comparable to the upper range of potential dietary intake on some markers of sexual development in Long-Evans hooded rats. The experiment showed that the reference estrogen DES at low doses and the common dietary phytoestrogen genistein at levels comparable to the upper range of human exposure affect some, but not all, of the markers of sexual development that we assessed in Long-Evans hooded rats. The second study was performed to test our hypothesis that man-made chemicals and phyotestrogens can be quantified in human amniotic fluid during the second trimester. Overall, 46.4% and 60.7% of women had quantifiable levels of daidzein and genistein, respectively in their amniotic fluid. …..at this time, our demonstrations in effects of these EACs in an animal model at levels of exposure that mimic those found in humans in North America during sensitive timeframes; and exposures of the human fetus to pertinent quantities of these same EACs 'do' occur during biologically comparable sensitive timeframes, sustain concerns a out potential adverse health effects of developmental exposures to EACs for the human fetus/neonate. The major emphasis of our last phase of this work has focused on developmental effects of dietary soy phytoestrogen in target tissues in mice. Analyses of tissues obtained from these experiments are ongoing. For some of these endpoints, daidzein and genistein mimicked DES, however, unique or opposite responses were also evidence for each of the phytoestrogens including the low dose of genistein. Changes were evident for both male and female pups with in utero, lactational, and both exposures to all four treatments compared to the appropriate control group. ….in utero and lactational exposure often had different effects. Altered outcomes during sexual maturity indicated that treatment effects continued to be evidence after the end of the exposure window (birth or weaning). These data indicate that in utero and lactational exposure to isoflavones can influence reproductive development of mice. Therefore, exposure of human fetus and/or nursing baby to these isoflavones has the potential to influence immediate and future reproductive development. Conclusions 1. In addition to endogenous steroids, the human fetus is exposed to mixtures of naturally occurring and xenobiotic EACs. 2. Exposures to mixtures of EACs occur at times that are known to be critical developmental intervals for the human fetus. 3. Developmental exposure of*

rodents to some EACs at levels of exposure that mimic those found in humans in North America produces target tissue effects that indicate changes in cell function."

SOY PHYTOESTROGEN: ESTRADIOL MIMIC:

Estradiol plays an important role in the development, maturation and function of a wide variety of reproductive and nonreproductive tissues, including those of the nervous system. Estradiol is a most potent, active, and potentially the most dangerous estrogen. All estrogens, especially estradiol are known to interact with multiple body and brain functions. Undisturbed circulation of normal estradiol levels is most important for normal development and function of the body and brain. Estrogens in excess are health-damaging and potentially deadly.

Soy phytoestrogens are proven to contain highly active estrogenic compounds of which potency is often compared to estradiol, the most dangerously potent physiologic estrogen that directly and indirectly manipulates numerous tissue and organ systems including the brain. Soy phytoestrogens are proven to influence, manipulate, and disrupt normal estradiol levels, while acting as agonists or antagonists of estradiol. The same as endocrine disrupting environmental estrogens, soy disrupting plant-estrogens disrupt body and brain functions by damaging normal estrogen/estradiol mediated processes.

Estradiol plays a role in the maintenance of pregnancy, and freely circulates through the placenta and umbilical cord of the fetus. In both males and females it is repeatedly proven that estrogen, especially estradiol has a significant part to play in sex differentiation of the brain, both pre-natal and throughout life.

Phytochemicals as those found in the active estrogen mimics of hormone disrupting soy phytoestrogens, as all estrogens, are never proven as safe during fetal, infant, child, (or adolescent) developmental timeframes.

2007, "Journal of Medicinal Food," WO Song et al report, "*In recent years, isoflavones have increased in popularity as an alternative to estrogen therapy……(Soy) isoflavones are heterocyclic phenols with structural similarity to etsrogeniol-17beta and selective estrogen receptor modulators. Actions at the cellular level depend on the target tissue, receptor status of the tissue, and the level of endogenous estrogen. Soy products also alleviate menopausal symptoms……..In conclusion, isoflavones are biologically active compounds……..Large, long-term intervention studies examining adverse effects and disease outcomes are needed before definitive conclusion can be drawn."*

An unknown amount of soy plant-estrogens during critical periods of neurological and physiological development can manipulate normal estrogen levels specific to estrogenic responses and functions. During the most delicate timeframe of physiological and neurological development and function, underscores the importance of understanding that soy plant-estrogens are endocrine disruptors capable of causing irreversible disease pathology.

2008, "Menopause," North American Menopause Society reports, "*Soy isoflavones are natural products that could be used as an alternative to menopausal hormone therapy because they are structurally and functionally related to 17B-estradiol. Nonfermented soy foods, such as roasted soybeans and soy powder have two to three times more isoflavones than fermented foods such as miso and tempeh. However, the baking of soy flour does not alter soy content. Soy flour contains 5mg isoflavone per gram of protein…..Soy isoflavones are nonsteroidal molecules structurally and*

functionally related to 17B estradiol….major isoflavones found in soybeans….bind to estrogen receptors a and B….they may exert agonistic, antagonistic, or partially agonistic/antagonistic effects at the receptor. There are large interindividual differences in metabolism of isoflavones. Equol production is largely dependent on intestinal microflora. Some people can produce larger amounts of equol than others….. Metabolism of isoflavones is also influenced by other components of the diet. A diet rich in carbohydrates results in extensive biotransformation of isoflavones and leads to great amount of equol (a greater affinity to estrogen receptors than daidzein from which it is derived). In the presence of antibiotics that alter intestinal microflora, the metabolism of isoflavones is reduced. Isoflavones bind to both estrogen receptors…..(and) isoflavones also bind to androgen receptors, progesterone receptors, oxytocin receptors, and peroxisome proliferator activator receptors. Because soy isoflavones have estrogen-like activity, clinicians are often confounded about their safety. There are studies reporting infertility in sheep and cheetahs that were fed high-phytoestrogen diets, compromised follicular development and shortened luteal phase in ewes, cystic ovaries in cattle and reduced breeding in California quails. Unfer et al reported an increased occurrence of endometrial hyperplasia in women who received 150mg soy isoflavones daily for 5 years….Other potential problems may be (caused by) alterations in the sex steroid pathway and thyroid hormone production."

2009, "Men's Health" magazine, Jim Thornton reports, *" William Kraemer Ph.D says, 'There are also concerns that soy might ….increase his estradiol production, which we tend to associate with female hormone production."'*

Soy protein isolates as used most often in soy products as well as soy –based infant formulas and soy food fillers (lecithin) as unfermented soy, the most potent and actively disrupting form of estrogenic isoflavones for adults, with greatest increasing health risks occurring during developmentally exposed fetus, infants, and children.

2001, "Pharmacology And Experimental Therapeutics," S. Belcher and A. Zsarnovsky report, "…*with the hope of bringing attention at an area of study that until recently has received little consideration, we will briefly discuss phytoestrogens and suggest that these compounds have the potential to influence rapid 17B estradiol induced mechanisms in the nervous system in ways that may result in modified brain functions. Numerous studies have also demonstrated that 17B estradiol.….can rapidly (within seconds to a few minutes) influence cellular physiology in many different cell types of reproductive and nonreproductive tissues through the activation of a diverse array of intracellular signaling mechanisms. Estradiol also plays a significant role during normal development and in genderization of the mammalian central nervous system (CNS), and it has important neurotrophic and neuroprotective functions in the brain."*

Estradiol is the most potent and dangerous of all estrogens. Soy phytoestrogens influence physiological estrogenic activity, although weaker than estradiol, over time plant-estrogens reportedly surpass estradiol levels that are particularly toxic to the body and brain of developing fetus, infants, and children. A number of published studies prove that these smallest developing brains and bodies are most vulnerable to soy plant-estrogen disruptions. Soybean phytoestrogens are proven to disrupt the balance of multiple endocrine signaling systems capable of causing prenatal and postnatal toxicity.

Department of Clinical Neuroscience in Sweden reports, "*Estrogen Receptor Gene Expression in Relation to Neuropsychiatric Disorders; Compelling evidence now*

exists for estrogen's involvement in the regulation of mood and cognitive functions. Serum estrogen levels have been shown to play an important role in the expression of psychiatric disorders…..The role of estradiol can also be examined in regard to its relationship to other neurotransmitter systems known to be linked to specific psychiatric disorders. Estradiol has been show to regulate neurotransmitters such as serotonin…..which has been strongly implicated in affective disorders. Overall the discrete anatomical organization of estradiol could modulate mood and thus underlie the neuropathology of psychiatric disorders."

Some reports compare prenatal exposure and then infant consumption of soy plant-estrogens as similar to ingesting 'prescribed' estradiol-containing birth control drugs. Soy plant-estrogens are reported to increase estradiol levels, without prescription.

It is reported that 100 grams of soy isoflavones is equal in comparison to the estrogen level of one contraceptive pill. Birth control pill contamination of fetus during pregnancy is alarming. Feeding birth control drugs to infants and small children is a criminal offense. Soy plant-estrogens are reportedly compared to causing the relevant damaging effects of estrogenic birth control pills.

FDA recognizes that prolonged consumption of soy protein elevates levels of plasma estradiol and progesterone, "*(Plasma) serum concentrations of the isoflavones genistein and daidzein increased in the soy group (of adults) at 14 days. Progesterone receptor expression increased significantly in the soy group. A number of studies report reduced fertility in animals exposed to phytoestrogens."*

The Federal Register 64, the FDA reviews several studies confirming, "*….findings are consistent with the conclusion that dietary estrogens (soy isoflavones) at low concentrations do not act as antiestrogens, but act like estradiol."*

The FDA reviews the study published by Harrison et al that concludes, "*Pregnant Rhesus monkeys fed genistein had serum estradiol levels 50 to 100% higher than the controls in three different areas of the maternal circulation. …… fetuses of genistein fed monkeys had a 70% higher serum estradiol level than did the controls. Significant differences in estradiol levels were noted at delivery in maternal blood, uterine veins, ovarian veins, and the fetus, and in maternal blood during pregnancy."*

Brown University Center for Healthcare Research confirms, "*Phytoestrogens are a group of plant-derived substances that are structurally or functionally similar to estradiol"*

Division of Biological Sciences, Missouri reports, *"Low (maternal) phyto-estrogen levels increase fetal serum estradiol."*

Active estrogenic endocrine disrupting soy isoflavones commonly contaminate fetus, infants, and children in varying levels on a daily basis, without prescription for estrogen-active chemicals, and without public knowledge.

2007, "Journal of Medicinal Food," WO Song et al report, "*Isoflavones are heterocyclic phenols with structural similarity to estradiol-17 beta and selective estrogen receptor modulators. Actions at the cellular level depend on the target tissue, receptor status of the tissue, and level of endogenous estrogen. Soy products also alleviate menopausal symptoms…..isoflavones are biologically active compounds. Long-term intervention studies examining long-term adverse effects and disease outcomes are needed before definitive (adverse effect) conclusions can be drawn."*

Center for Biotechnology and Department of Medical Nutrition. "*The estrogenic potency of phytoestrogens is significant, especially for estradiol and may trigger many of the biological responses that are evoked by physiological estrogens."*

Division of Biological Sciences, Missouri confirms, "*In fetuses whose mothers consumed the low-phyto-estrogen feed we found a paradoxical significant elevation in endogenous serum estradiol, which was associated postnatally with adverse reproductive outcomes referred to as the 'fetal estrogenization syndrome.' Estradiol acted at extremely low doses in the low part per trillion range. This is important since estradiol is the reference hormone against which estrogenic endocrine disruptors are compared for potency. Most estrogenic endocrine disruptors of concern appear to be within the range of 1,000-10,000 times weaker than estradiol. Recent evidence suggests that chemicals that appear weak in cell culture experiments or when tested in adults can have very potent effects in fetuses. Estrogenic chemicals….such as genistein…. found in plants such as soy had been shown to produce effects in the defined low dose range."*

Estradiol plays an important role in the development, maturation, and function of a wide variety of reproductive and nonreproductive tissues, including those of the nervous system (controlling brain functions). The actions of estrogens at target tissues can rapidly within seconds to minutes influence cellular physiology in many different cell types resulting in long-term actions mediated by intracellular estrogen receptor-induced changes in gene expression and actions that modulate a diverse array of intracellular cascading signaling effects.

2007, "Experimental Biology and Medicine," B Jurjevi et al report, "*Like the estradiol treatment, the higher doses of genistein and daidzein increased the total triglycerides levels in both rat models by more than 50%."*

"Journal of Steroid Biochemistry and Molecular Biology," ED Lephart et al reports, "*Phytoestrogens derived from plants (especially soy products) are molecules structurally and functionally similar to estradiol. Phytoestrogen rich fed animals displayed total serum phytoestrogen levels 37- fold higher compared to phyto-free values. In summary, consumption of dietary phytoestrogens (estrogen mimics) can alter hormone-sensitive hypothalamic brain volumes in rodents……"*

2006, "European Journal of Neuroscience," V Martinez-Cerdeno et al report, "*17-b-Estradiol (E2) is present in the adult and developing mammalian brain, and plays an important role in the central nervous system processes such as neuronal differentiation, survival, and plasticity. We show that aromatase, the E2 synthesizing enzyme, is present in the embryonic neocortex, that estrogen receptor-a is present in progenitor cells during cortical neurogenesis, that in vitro E2 administration rapidly promotes proliferation, and that in utero blockade of estrogen receptors decreases the proliferation of embryonic cortical progenitor cells. Furthermore…..E2 differentially influences the proliferation of these cortical progenitor cells types, (radial glial cells and proginator cells). These findings demonstrate a new functional role for E2 as a proliferative agent during critical stages of cerebral cortex development."*

Soy isoflavones are proven agonists of 17b estradiol, manipulating potent estrogenic effects that are especially health-threatening to fetus, infants, and children.

1998, KDR Setchell, PhD, reports, "*Isoflavones represent one of the classes of the so-called 'phytoestrogens.' These bioactive non-nutrients are strikingly similar in chemical structure to estradiol, the main female hormone……one can superimpose*

almost exactly the structures of estradiol and isoflavones so they become indistinguishable, and therefore they fit beautifully into the pocket representing the binding domain of the estrogen receptor. It is not surprising that isoflavones are many of the properties of endogenous estrogens. Isoflavones have the ability to behave as estrogen mimics, but also have other important non-hormonal properties…..The chemical form in which isoflavones occur is an important consideration since it can dramatically influence the biological activity, the bioavailability, and therefore the physiological effects. The extent of metabolism appears to be highly variable among individuals and is influenced by other components of the diet. A high carbohydrate milieu, which causes increased intestinal fermentation, results in more extensive biotransformation of phytoestrogens, with greatly increased formation of equol a mammalian isoflavone metabolite……the estrogenic potency of equol is an order of magnitude higher than that of its plant precursor, daidzein. Like estradiol, isoflavones are found in plasma mostly in the form of glucuronide conjugates, and to a lesser extent as sulfates…..Consequently, adherence to a soy-containing diet will ultimately lead to high steady-state plasma concentrations. Plasma concentrations of 50-800 ng/mL are achieved for daidzein, genistein, and equol in adults consuming modest quantities of soy-foods containing in the region of 50mg/day of total isoflavones. Infants fed soy formulas plasma concentrations are higher. Overall, when soy is consumed on a regular basis levels far exceed normal plasma estradiol concentrations which in men and women generally range between 40-80 pg/mL. …….led us to the hypothesis that with such disproportional levels one could anticipate hormonal effects from phytoestrogens. In summary, considerable knowledge of the metabolism and absorption of phytoestrogens was gained during the course of their discovery, however……..the optimal dose of isoflavone required to have clinical effects remains to be established."

2007, "Journal of Nutrition," JM Hamilton-Reeves et al report, *"Specific estrogen metabolites may initiate and promote hormone related cancers. Although soy supplementation has been shown to increase the ratio 16alpha-hydroxyestrogen in women, no studies to our knowledge have investigated the effects of soy supplementation on estrogen metabolism in men. The objective of this randomized controlled trial was to determine the effects of soy protein isolate (SPI) consumption on estrogen metabolism in men…….. Both soy groups had higher estradiol secretion than the milk protein isolate (MPI) group at 3 and 6 months. After 6 mo. of supplementation, the SPI+ group had a significantly higher urinary 16alpha-hydroxyestrogen ratio than the MPI group. Increased urinary estradiol excretion and 16alpha-hydroxyestrone ratio in men consuming soy protein isolate are consistent with studies in postmenopausal women……"*

Department of Food Science and Nutrition, C. Wang et al report, *"….genistein and coumestrol enhanced estradiol induced DNA synthesis….tamoxifen enhanced genistein-induced DNA synthesis, and genistein enhanced insulin and epidermal growth factor-induced DNA synthesis. At higher concentrations, inhibition was observed. Similar effects were seen with coumestrol. In conclusion, the effects of phytoestrogens in the presence of estradiol or growth factors are concentration dependent and variable. At low concentrations, genistein and coumestrol significantly enhanced estradiol induced and tyrosine kinase-mediated DNA synthesis; at high concentrations, inhibition was*

observed. The variable effects of phytoestrogens on DNA synthesis must be considered…"

Regulatory Toxicology and Pharmacology, UK, "*For soy-containing foods there has been concern that the phytoestrogen content of soy, which is composed of several isoflavones, could be a separate health issue, due to the estrogen-like activity of isoflavones. To address this, A method has been developed to estimate, relative to 17-beta estradiol, the activity of the common isoflavones present in soy phytoestrogens."*

Department of Molecular Genetics, University of Texas reports, "*Estradiol treatment in pregnant mice causes fetal wastage…….which in turn causes fetal death in midgestation. These findings indicate (estradiol) plays a crucial roll in estrogen toxicity during pregnancy."*

The fact that soy is compared to higher estrogenic powers of estradiol, puts damaging soy health effects into perspective as if a particular dosage of estradiol-containing birth control pills were approved for fetal, infant, and child consumption.

Proceedings of the Society for Experimental Biology and Medicine, N.Y. "*Effect of Genistein on Steroid hormone production in the Pregnant Monkey: Genistein is a phytoestrogen found is soy beans. Phytoestrogens have been reported to cause reproductive problems in sheep and rats. This research was conducted to determine the effects of Genistein fed to monkeys during pregnancy. Estradiol levels were higher in the four areas studies at delivery and in the maternal blood with advancing gestation. Additionally estrogen levels tended to increase more rapidly in the maternal blood of monkeys receiving Genistein than in untreated controls, suggesting that Genistein may stimulate the estrone in the gut thus allowing its re-absorption into the peripheral circulation and conversion to estradiol."*

SOY PHYTOTOXICITY: "ACTIVE ENDOCRINE DISRUPTORS"

Endocrine disruptors are natural or synthetic chemicals especially capable of causing adverse health effects by disrupting normal endocrine functions. Adverse health effects are caused because endocrine disruptors mimic or antagonize the action of normal endogenous estrogens that is largely associated with reproductive disorders as well as an assortment of anatomical diseases including carcinogenesis and autoimmune diseases in both animals and humans. Endocrine disruptors disrupt complex hormone activities of several biological systems. Endocrine disruptors damage hormone chemical messengers throughout the bloodstream that further disrupt specific hormone receptors of multiple target organ systems, and triggers disruptive biological effects that are proven to cause a large range of biochemical disruptions resulting in a huge assortment of cascading adverse health effects.

2003, "Environmental Health Perspectives," WB Welshons et al reports, "*Large effects from small exposures. Mechanisms for endocrine-disrupting chemicals with estrogenic activity- ……..endocrine-disrupting chemicals with estrogenic activity (EEDCs) can be active at concentrations far below those currently being tested in toxicological studies. Exogenous estrogens modulate a system that is physiologically active and thus is already above threshold……"*

It is overwhelmingly documented that during most sensitive developmental timeframes, endocrine disruptors are scientifically proven to cause the highest degree of physiological and neurological toxicity to exposed fetus, infant, and child. Endocrine

disruptors alter cell DNA, cause chromosome damage resulting in catastrophic insult of highest degree during body and brain development (as identified later in this report).

Endocrine disruptors are reported to accumulate in living tissue at much higher concentrations than natural hormones causing increasing health-damage for a lifetime. Endocrine disruptors can be transmitted to fetus and infant from exposed mother during pregnancy and breast feeding. Endocrine disruptors can be carried by contaminated male sperm should fertilized egg not spontaneously abort as expected.

The EPA confirms endocrine disruptors as the cause of children's diseases, such as "*autism, asthma, neurodevelopmental disorders.*" There is an ongoing list of adverse effects caused by endocrine disruptors. The EPA confirms, "*…approved last year-(2000) recognizes the potential for adverse impact on human health….associated with exposure to endocrine disruptors. The position also states that endocrine disruption is a mode of action that has the potential to lead to adverse effects, which may include carcinogenicity, reproductive and developmental effects, and learning and behavioral effects."*

Hundreds of published studies along with the NIH all confirm soy isoflavones as an active *"endocrine disruptor"* with the worst health effects caused to fetus, infants, and children. Little FDA and NIH attention has been directed to the multitude of potential consequences of such exposure.

Endocrine disruptors are well-known to cause disorders and diseases, while compromising the entire hormonal endocrine system involving the: hypothalamus, pineal, pituitary gland, thyroid, parathyroid, thymus, adrenal gland, kidney, stomach, pancreas, duodenum, gastrointestinal system, ovaries or testes as well as the entire reproductive system.

2007 book, "When Puberty is Precocious Scientific and Clinical Aspects," the chapter on, *"The Role of Endocrine Disruptors in Pubertal Development*," Ora Pescovitz and Emily Walvoord report, "*Endocrine disruptors may result in an altered hormonal status through interference with cell signaling pathways or altering the action of hormone receptors as coactivators or corepressors. Several agents have been classified as endocrine disruptors, including phytoestrogens, topical and natural estrogens, pesticides, industrial chemicals and phthalates."*

There is no evidence that fetus, infants, and/or child that are fed endocrine disruptors, can normally survive. Soy phytoestrogens are in fact classified as active estrogenic endocrine disruptors along with: pesticides, plastics, steroidal estrogens (such as estradiol), DES estrogen, and more that are particularly dangerous during developmental timeframes. The accumulation of multiple endocrine disruptors is the greatest threat to health. Scientists are finding that endocrine disruptors can be "transgenerational" or genetically passed from one generation to the next.

2006, "Journal of Health Science," S Ikegami et al report, "*Possible Adverse Effects of Soy Isoflavone Mixture on Pregnant and Lactating Rats and their Suckling Pups- However, isoflavones are well known as endocrine-disrupting chemicals. The possibility that soy foods might adversely affect the reproductive system of mothers and infants should be considered. We found that the dietary soy isoflavone mixture decreased the dam body weights in a dose-dependent manner and that the number of pups also tended to decrease. Genistein and daidzein were detected in the blood of the dams and the stomach contents of the suckling pups. We also found the transfer of isoflavones to*

the fetus. Our experiments suggested that soy isoflavones have the possibility of inducing adverse effects on endocrinic functions……..”

1999, “Toxicology Letters,” L Strauss et al report, “*….the possible adverse effects of phytoestrogens have not been evaluated. It is plausible that phytoestrogens, as any exogenous hormonally active agent, might also cause adverse effects in the endocrine system, i.e. act as endocrine disrupters.”*

2005, “ILAR Journal,” ED Lephart et al report, “*Behavioral effects of endocrine-disrupting substances: phytoestrogens- …phytoestrogens (isoflavones) are known endocrine disruptors. The isoflavones genistein and daidzein have similar molecular weights and structural characteristics to that of 17-beta estradiol….daidzein can be further metabolized to the potent and abundant molecule equol……”*

2006, “Allergy: European Journal of Allergy and Clinical Immunology,” M Chalubinski and M Kowalski report, “*Endocrine disrupters (ED’s) are environmental pollutants of industrial or agricultural origin that may influence health of wildlife and human. Endocrine-disrupting effect is obtained by mimicking the action of the steroid hormones and has been associated with several reproductive disorders as well as cancerogenesis both in animals and humans. ED’s can also influence synthesis of cytokines, immunoglobulins, and cell mediators as well as immune cell activation and survival. The aim of this review was to summarize data indication a potential effect of ED’s exposure on the immune system and allergic responses.”*

Soy phyto-estrogens are confirmed active endocrine disruptors capable of causing an vast assortment of damaging health effects, while binding to estrogen receptors and dangerously disrupting the normal actions of hormone functions. Even small dosages of soy phytochemicals cause disruptions to the endocrine system particularly during fetal and infant physiological and neurological development that is proven to cause irreversible adverse health effects involving: behavior, learning, cognition, attention, anxiety, excitement, etc.

Maternal exposure to endocrine disruptors is known to contaminate the fetus, and/or contaminate the infant while breast feeding. Soy-based infant formulas and soy products are another potent source of infant/child exposure to endocrine disruptors.

2004, “Toxicologist” G Orphanides et al report, “*The xenoestrogens group of endocrine disruptors have the potential to cause reproductive and developmental effects through stimulation or disruption of estrogen receptor signaling. Phytoestrogens have attracted attention due to opportunities for dietary exposure (e.g. soy) and their higher affinity for estrogen receptor (ER) beta, which has been proposed to antagonize the effects of ER alpha. Our data…suggest that genistein is capable of modulating the full spectrum of biological processes association with the action of 17b-estradiol in the uterus. Furthermore, we have identified a novel class of estrogen-regulated transcription factors included by both (genistein and estradiol) chemicals that appear to be direct targets of the estrogen receptors and whose function may be linked to the timing of cell cycle progression and proliferation.”*

2002, Environmental Health Perspectives, SH Safe et al report, “*Problems for risk assessment of endocrine-active estrogenic compounds- The results show that synthetic (estrogens) and phytoestrogens are weakly estrogenic but induce distinct patterns of ER agonist/antagonist activities that are cell contexts-and promoter-dependent, suggesting*

that these compounds will induce tissue-specific (in vivo) ER agonist or antagonist activities."

The 2000 NCER also concludes, "*The major emphasis of our ongoing work is now focused on developmental effects of dietary soy phytoestrogens in target tissues in mice. Soy isoflavones are chemicals in soy that can act similar to the female hormone, estrogen. Increased use of soy in the U.S. diet continues, younger women who may be pregnant or lactating will consume isoflavones in their diets. Development of the human fetus and newborn can be altered in adverse ways by exposure to other estrogens, such as DES. Because isoflavones also have estrogenic properties, it is important to determine whether these compounds can have similar developmental effects. Although human fetal effects have not yet been assessed, the measured concentrations and receptor-binding affinities of the Endocrine Active Chemicals relative to those of endogenous sex steroids suggest that target tissue effects are likely."*

Powerful estrogenic soy phytochemicals are described by the National Institute of Health as "*active endocrine disruptors*," meaning soy causation of DNA damage and cell mutations.

National Institute of Environmental Health Sciences (NIEHS) confirms that "*Endocrine Disruptors intervene with the endocrine system and produce adverse effects in humans. Cancer arises because endocrine disrupting chemicals are shown to have adverse effects in low levels. Health effects are increased by the fact that people are typically exposed to multiple endocrine disruptors simultaneously. Endocrine disruptors are naturally occurring compounds that may interfere with the production or activity of hormones of the endocrine system leading to adverse health effects linked with developmental reproductive, neural, immune and other problems. Some scientists think endocrine disruptors are adversely affecting human health in similar ways resulting in declined fertility and increased incidences or progression of some diseases including cancers. Endocrine active compounds with estrogenic activity are probably the most well studied. The endocrine system is one of the body's main communication networks and is responsible for controlling and coordination numerous body functions. Hormones are first produced by the endocrine tissues, such as the ovaries, testes, pituitary, thyroid and pancreas and then secreted into the blood to act as the body's chemical messengers where they direct communication among the tissues throughout the body. Endocrine disrupting chemicals may interfere with the body's own hormone signals because of their structure and activity. Endocrine disruptors can mimic naturally occurring hormones in the body like estrogens, potentially producing over stimulation, the normal signal then fails to occur and the body fails to respond properly. Phytoestrogen, genistein and daidzein can be found in soy derived products. People are exposed to endocrine disruptors through the food and beverages they consume. Research shows that endocrine disruptors may pose the greatest risk during prenatal and early postnatal development when organ and neural (brain) systems are developing. In animals adverse consequences such as subfertility, early puberty, premature reproductive senescence and caner are linked to early exposure, but may not be apparent until much later in life. NTP has found that there was 'credible evidence' that some hormone –like chemicals can affect test animals' bodily functions at very low levels, well below the 'no effect' levels determined by traditional testing. Data showing exposure to endocrine disrupting chemicals with estrogenic activity may have effects on obesity and diabetes. Endocrine*

disruptors may affect not just the offspring of mothers exposed during pregnancy, but the future offspring as well. Endocrine disruptors may be able to reprogram or change the expression of genes without mutating DNA."

2004, "Toxicologist," PM Schlosser et al report, "*Phytoestrogens such as genistein are endocrine-active compounds produced naturally by plants. High concentrations of genistein occur in soy products such as tofu and soy infant formula. Genistein is associated with a range of effects….observed reductions in weight and anogenital distances of rodents at birth. To estimate circulating levels of genistein during health-effects studies, physiologically based pharmacokinetic models for genistein in rats are being developed. Tissue concentration data were obtained in rats does with 4mg/kg of 14C genistein…….These data show a terminal half life of ~1hour for elimination from the blood….and rapid appearance in the blood after oral dosing (peak by 30 minutes). After oral dosing, total activity in gastro-intestinal tissue was 1-2 orders of magnitude greater than any other tissue……We also observed biphasic elimination of genistein from serum after IV administration and found that it could be described if binding of genistein to serum proteins was included. Experimental evidence already exists for binding to serum proteins….."*

2000, Canada's National Occupational Health & Safety Resource reports, "*Certain substances, both naturally-occurring and man-made, can affect the endocrine system. Some chemicals in plants (phytoestrogens) have estrogen-like effects. Certain drugs and environmental pollutants can (also) either mimic or block actions of some hormones. When there is interference with normal communication between the 'messenger' hormone and the cell receptors, the chemical message is misinterpreted and an abnormal response is generated in the body…..many of the complex activities of the human body are controlled by the endocrine system. Substances can disrupt the normal function of endocrine systems in 3 different ways: 1. Mimic a natural hormone and lock onto a receptor. The disruptor may give a signal stronger than the natural hormone, or a signal occurs at the wrong time, 2. Bind to a receptor within a cell and thus prevent the correct hormone from binding. The normal signal then fails to occur and the body fails to respond properly. 3. The disruptors can interfere or block the way natural hormones and receptors are made or controlled. If the endocrine disruptor stimulates or inhibits the endocrine system then increased or decreased amounts of hormone may be produced. …even very small amounts of a disruptor may have detectable effects.*

Natural substances such as sex hormones or phytoestrogens (plant chemicals having estrogen-like effects), can become concentrated in industrial, agricultural and municipal wastes. Exposure to these wastes may produce reactions in human, wildlife, fish or birds……endocrine disruptors may reach humans and animals in a variety of ways."

2000, "Neurotoxicology" S Ferguson et al, "*Developmental neurotoxicity of endocrine disruptors: focus on estrogens- Many of these (endocrine disruptors) have estrogenic effects in vitro and/or in vivo. Recent reviews have focused attention on the need for assessing the neurotoxicity of these compounds following developmental exposure. This attention comes in part from the literature on the effects of developmental exposure to exogenous estrogen on later behavioral and neuropathological alterations. A review of the ongoing neurobehavioral and neuropathological studies at the National Center for Toxicological Research on four such estrogen mimics, (genistein,*

methoxychlor, nonylphenol and ethinyl estradiol) is presented indicating that intake of a sodium solution is sensitive to these estrogenic mimics."

Confirming soy as an endocrine disruptor, the National Institute of Health repeatedly concludes soy as an endocrine disruptor. Endocrine disruptors are not proven as safe, and are repeatedly proven as especially anatomically dangerous during most sensitive developmental timeframes as expected. The implications of perturbing the hormonal milieu during fetal and infant development results in lifelong irreversible adverse health effects that are many times proven as risk factors due to consumption of soy plant-estrogen endocrine disruptors.

2005, NIH, Dr. Doerge et al conclude, "*Soy isoflavone genistein …….. produced a number of effects on reproductive tissues, immune function, neuroendocrine function and behavior."*

2004, "Toxicological Sciences," FDA Division of Neurotoxicology, A. Scallet et al report, "*Endocrine disruptors (EDs) may also alter brain development by mimicry or modulation of endogenous hormone systems. Two EDs that have recently been studied in protocols involving lifespan exposures are the phytoestrogen genistein and the weakly estrogenic compound para-nonylphernol, which is used in the production of many surfactants and plastics."*

2006, "Reproductive Biology and Endocrinology," EJ Hong et al report, *"Identification of estrogen-regulated genes by microarray analysis of the uterus of immature rats exposed to endocrine disrupting chemicals- We investigated the altered gene expression by estrogen and endocrine disruptors…in the uterus of immature rats….genes were enhanced by more that two-fold following treatment with estradiol(E2), suggesting that direct or rapid response to E2 is widespread at the mRNA levels (in specific genes). In addition, elevated expression levels of the genes (over 2-fold) were observed by diethylstilbestrol (DES; 9.01%) octyl-phenol (8.81%), nonyl-phenol (9.51), bisphenol-A (BPA;8.26%), (last three are environmental pollutants) or genistein (9.97%) in the uterus of immature rats. In addition, the mRNA levels of these genes….were increased at follicular phase when E2 level was elevated during estrous cycle of adult female rats. In conclusion, these results indicate distinct altered expression of responsive genes following exposure to E2 and estrogenic compounds and implicate distinct effects of endogenous E2 and environmental (pollutants and soy plant-estrogen genistein) endocrine disrupting chemicals in the uterus of immature rats."*

Studies confirm that exposure to estrogenic endocrine disruptors such as soy phytoestrogens during critical periods in prenatal and postnatal life can alter the development of reproductive organs, the neuroendocrine (brain) system, and irreversibly cause an assortment of anatomically toxic effects.

Numerous studies conclude that the soy phytoestrogens exert damaging effects that are twice and more compounded by soy's variety of antinutrients that each and worst together, cause biochemical cascading of irreversible developmental adverse effects.

NIH, National Toxicology Program reports- "*Genistein, Related: ENDOCRINE DISRUPTER. Known Uses: GROWTH INHIBITOR, NATURALLY–OCCURRING PHYTOESTROGEN FOUND IN SEVERAL PLANTS INCLUDING SOY PRODUCTS. NUTRITIONAL AND PHARMACEUTICAL APPLICATIONS. Organ Systems Toxicity-180 Days Immunotoxicity. GENISTEIN (ENDOCRINE DISRUPTOR). Long-Term Carcinogenicity- 2-YEAR (Dosed-Feed)-In Utero and continuing for 2 years: Female*

Rats = Some Evidence. In Utero and continuing for 20 weeks: Female Rats = Eqivocal Evidence. In Utero and continuing for Post Natal Day 21: Female Rats = Equivocal Evidence. Toxicology and Carcinogenesis Study of Genistein (CAS No. 446-72-0) in Sprague-Dawley Rats (Feed Study) Abstract- Genistein is a naturally occurring isoflavone that interacts with estrogen receptors and multiple other molecular targets. Human exposure to genistein is predominantly through consumption of soy products, including soy-based infant formula and dietary supplements. …..concerns have also been raised regarding potential adverse effects of genistein, particularly with regard to reproductive toxicity and induction or potentiation of carcinogenesis, due primarily to its weak estrogenic activity. The animals in this study were exposed to genistein during various phases of their lives from conception until termination at 2 years, and the ingested doses varied over the course of the study. During pregnancy, the ingested doses of the dams were approximately 0, 0.5, 9, or 45 mg/kg body weight per day. During lactation, the dams' ingested doses were 0, 0.7, 15, or 75mg/kg per day. In females of all study arms….an early onset of aberrant estrous cycles, suggesting early reproductive senescence, was observed in the 500 ppm groups. In the F3TT21 arm, there were also significant effects on the onset of aberrant estrous cycles in the 5 and 100ppm groups. Pituitary gland weights were significantly increased in females in the 500 ppm groups of the F1C and F1T140 study arms and in the 100 ppm group of the F3T21 arm. In F1C females, there was a significant positive trend in the incidences of mammary gland adenoma or adenocarcinoma….and the incidence in the 500 ppm group was significantly great than in the control group.

In F1C males, a significant positive trend occurred in the incidences of combined adenoma or carcinoma of the pancreatic islets…… the incidence in the 500 ppm group was elevated relative to that in the control group…….. CONCLUSIONS Under the condition of this 2-year feed study with continuous exposure to test compound from conception through terminations there was: some evidence of carcinogenic activity of genistein in female Sprague-Dawley rats based on increased incidences of mammary gland adenoma or adenocarcinoma and pituitary gland neoplasms. Exposure to genistein was also shown to accelerate the onset of aberrant estrous cycles in female Sprague-Dawley rats whether exposures were continuous or trunicated at PND 140 or at weaning. The effects of genistein on estrous cycling and the incidences of common hormonally related spontaneous neoplasm of female Sprague-Dawley rats are consistent with an estrogenic mechanism of toxicity."

Based upon the conclusions of an assortment of published literature as revealed throughout this report the exposure to estrogenic soy isoflavones as confirmed endocrine disruptors, and in addition to soy's multiple antinutrients, prove the causation of several irreversible physiological and neurological disorders, particularly during most sensitive exposure timeframes of fetal, infant, and child development.

Both the FDA and NIH report in agreement that soy plant-estrogens are ***"active endocrine disruptors,"*** well known to be toxic to the body and brain that without any doubt are the cause of extreme health risks during fetal, infant, and child development. As with all estrogens, there is no known safe level for endocrine disrupting soy phytoestrogen exposure of fetus, infants, and children.

2000, "Neurotoxicology," US Food and Drug Administration B. Schwetz reports, "*Developmental neurotoxicity of endocrine disruptors: focus on estrogens- Chemicals*

with estrogenic activity can affect the development and function of neural tissues through several different mechanisms…..Experimental approaches to detect neurotoxic effects of estrogenic chemicals include neurobehavioral, neuropathological, and neurochemical endpoints such as a) measures of physical activity, b) social behaviors, c) taste preferences, d) sexually dimorphic brain structures and e) neurotransmitter and steroid receptor regulation. A series of studies is planned or in progress at the FDA's National center for Toxicological Research on chemicals representing a range of hormonal potency as endocrine disruptors. Genistein, a naturally occurring estrogen mimic found in soy beans and soy products, and nonylphenol (plastics) a chemical intermediate with estrogenic properties are two chemicals on which multigenerational studies are in progress. These studies will compare toxicity in neural, immune, and reproductive systems and in some cases will evaluate potential carcinogenicity. At dose levels that (genistein and nonylphenol decreased maternal and offspring body weight, there were subtle alterations in some sexually dimorphic behaviors…..Moderate doses of either agent also decreased the volume of the sexually dimorphic nucleus of the hypothalamus n male offspring. The role of the hormonal activity of weak estrogens (genistein and nonylphenol) in the overall toxicity profile of chemicals to which humans are exposed is very important in order that regulatory agencies such as the FDA may conduct sound, scientifically based risk assessments."

National Institute of Environmental Health Sciences (NIEHS) a division of the NIH reports; "*Endocrine disruptors are chemicals that may interfere with the body's endocrine system and produce adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife. Research shows that endocrine disruptors may pose the greatest risk during prenatal and early postnatal development when organ and neural (brain) systems are forming……leading to adverse health effects linked with developmental reproductive, neural, immune, and other problems."*

NIEHS includes soy isoflavones within their stated list of toxic Endocrine Disruptors: "*Genistein and daidzein, plastic bottles, food containers, epoxy resin, metal food cans, detergents, flame retardants, foods, toys, cosmetics, pesticides (including DDT, dioxin), DES estrogen, natural human estrogen-estradiol, or the environmental estrogen bisphenol A (component of plastic)."*

The book, "Endocrine Disruptors" 2005 Second Edition, confirms; "*….these (phytoestrogens) may have a profound impact on developmental processes, particularly in the brain where hormones are critical. Both phytoestrogens and synthetic endocrine disruptors (industrial chemicals, pesticides, plastics) have been found to impair similar reproductive and neuroendocrine (brain hormone) endpoints……"*

Hormone disruption causes genotoxic (DNA damage), and cytotoxic (cell toxicity) effects of an otherwise precisely orchestrated endocrine gland system. The endocrine gland system includes the: brain, (particularly involving; pituitary, hypothalamus, hippocampus, amygdala), thyroid, parathyroid, thymus, pancreas, adrenals, ovaries, and testes. These endocrine glands influence hormone signaling between many organ systems by releasing precise levels of hormones into the bloodstream that act and interact as chemical messengers throughout the body and brain.

"JAMA" 2005 study titled, "*Endocrine-Disrupting chemicals Probed as Potential Pathways to Illness",* R. Trubo reports, "*Accumulating evidence that some of these widely used chemicals may have hormone-like effects on the body is heightening*

concerns about their potential long-term health risks, particularly when developing fetuses and neonates are exposed. At a day-long symposium….leading investigators shared the latest findings on the effects of synthetic chemicals- as well as naturally occurring substances such as phytoestrogens- that have been reported to have hormone-like activity and may be associated with an increased susceptibility to disease and dysfunction. The potential danger is greatest for the 'fragile fetus.'"

Besides soy plant-estrogens, DES, dioxin, PCB's (plastics), DDT, pesticides, herbicides, insecticides, fumigants, fungicides, and many pharmaceuticals are all examples of FDA classified estrogenic endocrine disruptors. While more often environmental estrogens are commonly labeled with warnings for public information, warnings for endocrine disrupting soy plant-estrogens continue as sorely deficient of appropriate and urgently necessary public warning labels.

In several published studies, soy phyto-estrogens are referred to as; soy phyto-estrogens.….or *"natural harmful substances of plants."*

Most active soy plant-estrogens; genistein, daidzein, glycitein, equol, or O-DMA, that are documented as active endocrine disruptors are *"not assessed for toxicity*" prior to FDA approval of soy products that includes soy-based infant formulas. Follow-up on exposed children is also disregarded, while estrogen-active soy is fed to infants as 100% of their dietary intake every few hours of a day, 24/7, during several months of early life….. and hereafter.

2000, FDA- Division of Neurotoxicology and Division of Biochemical Toxicology, K. Flynn et al report, "*The phytoestrogen genistein, the principal isoflavone in soybeans, has adverse effects on animal reproduction. As adult physiology and behavior are sensitive to perturbation by developmental estrogens, exposure to genistein during development may produce behavioral alterations as well. These results indicate that developmental genistein treatment, at levels that decrease maternal and offspring body weight, causes subtle alterations in some sexually dimorphic behaviors."*

2003, journal of "Maturitas" W. Wuttke, et al report, "*The question whether soy and red clover products…..are endocrine disrupters or may fulfill the criteria of the so-called phyto-SERMS will be discussed. Experimental and clinical evidence suggest that soy and red clover and their isoflavones do not fulfill the criteria of an ideal SERM. Furthermore, they seem to stimulate uterine growth and mammary epithelial proliferation….(resulting in endocrine disruption)."*

2005, "Human Fertility" M.C. West et al report, "*These non-steroidal estrogens of plant origin are potent endocrine disruptors that modulate normal physiological functions. Phytoestrogens have become a major component in the typical Western fast food diet over the last few decades. Soy formula….. is another common source of phytoestrogens now used increasingly as an alternative to breast or cow's milk for infants…..this use is of particular concern since the most vulnerable periods for estrogenic insult are thought to be the pre-and neonatal periods when irreversible damage can be inflicted……."*

2006, journal of "Hormonal Behavior" BC Ryan et al report, *"Humans and wildlife are exposed to numerous anthropogenic drugs and pollutants. Many of these compounds are hormonally active, and …..evidence suggests that the presence of these endocrine disruptors permanently alters normal development and physiology in a variety of vertebrate species. Here we report on the effects of developmental exposure to two*

common estrogenic pollutants…..…..Developmental exposure …was found to masculinize behavior in all of the rat assays used, …...and (increase) anxiety. ……..behavior is sensitive to endocrine disruption. These experiments suggest that both humans and wildlife are being exposed to levels of these endocrine disrupting compounds that are sufficient to disrupt the development of the nervous system and that may have permanent consequences on sexually dimorphic(male and female) behaviors."

2004, "Toxicology Pathology," JM Naciff et al report, "*Public concerns have been raised in recent years over the possible adverse effects that may result from exposure to ….endocrine disrupters. Regulations have been established that require the testing of pesticides used in food crops and drinking water contaminants for estrogenicity and other hormonal activities. …...The U.S. EPA proposed the endocrine Disrupter Screening Program to identify chemicals capable of interacting with various hormonal systems…...we identify 2 main problems with this approach: (1) The fact that developmental stages most susceptible to endocrine disruption are not represented…and (2 the expense to screen each chemical…..Thus, the need arises for an accurate, rapid and cost effective method for assessing the potential endocrine activity of multiple chemicals during development. We hypothesize that the largely latent developmental effects of some endocrine disruptors are preceded by immediate changes in gene expression in the embryo and fetus. Therefore, an approach to assess the potential estrogenic…...activity of different compounds is to identify those patterns of gene expression elicited in a tissue/organ exposed to these particular classes of chemicals. ……...the potential utility of such an approach for screening and better understanding of mechanism of action for specific chemicals with endocrine disrupter activities is presented using as an example (of) chemicals with estrogenic activity."*

2002 journal "Domesticated Animal Endocrinology," T Sweeney reports, "*….natural and synthetic environmental compounds disrupt normal hormonal actions. These compounds range from natural plant estrogens (e.g. genistein, coumesterol) and mycoestrogens to growth promoting pharmaceuticals to chemicals spread in water, sewage sludge, or the atmosphere such as detergents and surfactants, plastics, pesticides, and industrial chemicals. These compounds are commonly termed 'endocrine disrupting compounds' or 'endocrine disruptors' due to their ability to act as either hormone agonists or antagonists or the ability to disrupt hormone synthesis, storage or metabolism. …it is becoming clear that many compounds can directly or indirectly affect both the endocrine and immune systems. The susceptibility of target tissues is related to the stage of development, the cumulative exposure dose and the immune status of the individual. …...the possibility that effects that are observed in the adult may be due to exposure to endocrine disrupting compounds during fetal life."*

It is also proven that soy isoflavone endocrine disruptor genistein is capable of compounding toxic effects when bioavailability is combined with the frequent exposure to other estrogenic endocrine disruptors.

2002, "Toxicological Sciences" L You, et al report, "*Combined Effects of Dietary Phytoestrogen and Synthetic Endocrine-Active Compound on Reproductive Development in Sprague-Dawley Rats: Genistein and Methoxychlor (pesticide)- Humans and wildlife are frequently exposed to mixtures of endocrine active-compounds (EAC). The objective of the present study was to investigate the potential of the phytoestrogen genistein to influence the reproductive developmental toxicity of the endocrine-active pesticide*

methoxycholor. The estrogenic responses to genistein and methoxychlor administered together were apparently accumulative……genistein…..enhanced the effect of methoxychlor……. Data from this study indicate that phytoestrogens are capable of altering the toxicological behaviors of other EACs, and the interactions of these compounds may involve complexities that are difficult to predict based on their in vitro steroid receptor reactivities."

2001, "Pharmacology and Experimental Therapeutics," S. Belcher and A. Zsarnovszky report, "Estrogenic actions in the Brain: Estrogen, Phytoestrogens, and Rapid Intracellular Signaling Mechanisms- *Compounds characterized as having estrogenic properties are typically divided into two general categories, the xenoestrogens and the phytoestrogens. Xenoestrogens are a diverse group of synthetic compounds that include pesticides, widespread industrial pollutants…biphenyls; synthetic estrogen diethylstilbestrol and many others. ……these compounds (xenoestrogens) are addressed here only in regard to their potential as estrogenic compounds to mediate effects in the brain similar to those of phytoestrogens. Because infants that are fed soy-based formula have especially high plasma concentrations of daidzein and genistein during critical periods of brain development (Setchell et al., 1998), understanding the normal actions of estradiol during perinatal development of the brain, the way phytoestrogens may influence these actions, and whether they exert long-term effects on neuronal function is extremely important"*

2003, "Journal of Urology" The Johns Hopkins School of Medicine: A.B. Wisniewski et al report, "*Exposure to genistein during gestation and lactation demasculinizes the reproductive system in rats- Exposure to (phytoestrogen) genistein resulted in temporary prepubertal urogenital abnormalities at postnatal days ….Males exposed to genistein had smaller anogenital distance and testis size, and delayed preputial separation. Perinatal exposure to genistein also caused long-term dysfunction in reproductive behavior, in which adult males exposed to genistein were less likely to mount, intromit and ejaculate during mating tests. Males exposed to genistein also had lower testosterone concentrations in adulthood. Preinatal genistein exposure results in transient and lasting alterations in masculinization of the reproductive system There results extend our knowledge of the effects of early genistein exposure on male development and may have implications for human health in terms of potential relationships of endocrine disrupters and urogenital abnormalities thought to be increasing in incidence in boys and men."*

2006, NIH, Developmental Endocrinology and Endocrine Disruptor Section, E Padilla-Banks et al report, "*Neonatal Exposure to the Phytoestrogen Genistein Alters Mammary Gland Growth and Developmental Programming of Hormone Receptor Levels- "….but mice treated with Genistein 5mg and Genistein 50mg exhibited altered morphology including reduced lobular alveolar development, dilated ducts, and focal areas of 'beaded' ducts lined with hyperplastic ductal epithelium. In summary, neonatal Genistein exposure altered mammary gland growth and development as well as hormone receptor levels at all doses examined; higher doses of Genistein led to permanent long-lasting morphological changes."*

2008, "Brain Research Reviews," HB Patisaul and EK Polston report, "*Influence of endocrine active compounds on the developing rodent brain- We further demonstrated that neonatal exposure to the endocrine-active compounds genistein and BPA can affect*

sexually dimorphic brain morphology and neuronal phenotypes……Finally, developmental endocrine-active compound exposure has been shown to affect a variety of sexually dimorphic behaviors including reproductive behavior. These effects are likely to have a broad impact as maladaptive behavior could translate to decreased fitness of entire populations. Collectively, these findings emphasize the need to employ a comprehensive approach that addresses anatomical, functional, and behavioral endpoints when evaluating the potential effects of (genistein) endocrine active compound exposure."

FDA REPORT: Soy Endocrine Disruptors Cause Neurotoxicity:

FDA report, published in the Medical Journal "Neurotoxicology 2000, Feb-Apr; 21(1-2):250, Dr. Schweiz Director- National Center for Toxicological Research, FDA Senior Advisor for Science, reports, *"Developmental Neurotoxicity Of Endocrine Disruptors: Focus On Estrogens- Chemicals with estrogenic activity can affect the development and function of neural tissues through several different mechanisms, some receptor mediated and others not, such as effects on cell membrane properties. Experimental approaches to detect neurotoxic effects of estrogenic chemicals include neurobehavioral, neuropathologies, and neurochemical endpoints such as…..social behaviors…..sexually dimorphic brain structures, and neurotransmitter and steroid receptor regulation. A series of studies is planned or in progress at the FDA's National Center for Toxicological Research on chemicals representing a range of hormonal potency as ED's (endocrine disruptors). Genistein, a naturally occurring estrogen mimic found in soy beans and soy products, and nonylphenol,(a chemical intermediate with estrogenic properties used in the manufacture of latex coatings, adhesives, paper products, agricultural chemicals, cosmetics, medical devices and drugs), are two chemicals on which multigenerational studies are in progress. These studies will compare toxicity in neural, immune, and reproductive systems and in some cases will evaluate potential carcinogenicity….rats were given 1250ppm genistein or 2000ppm nonphenol from gestation day 7 of the dams until postnatal day 77 of their offspring. At dose levels that decreased maternal and offspring body weight, there were subtle alterations in some sexually dimorphic behaviors…..Moderate doses of either agent also decreased the volume of the sexually dimorphic nucleus of the hypothalamus in male offspring. The role of the hormonal activity of weak estrogens in the overall toxicity profile of chemicals to which humans are exposed is very important in order that regulatory agencies such as the FDA may conduct sound, scientifically based risk assessments."*

Health Action Network Society reports, *"Endocrine-disrupting isoflavones, genistein and daidzein are goitrogenic components found in soy."*

2007, NIH, National Toxicology Program- Toxicity Report: *"Reproductive Dose Range-Finding Study of Genistein reports, "Body weight and feed consumption of the treated (rat) dams prior to parturition showed decreasing trends with increasing dose…..A significant exposure concentration related effect on litter birth weight was observed….Pups in the 1,250 ppm group had significantly decreased body weights….(male and female). The most pronounced organ weight effects in the pups were decreased ventral prostate weight in males….and a trend toward higher pituitary gland to body weight ratios in both sexes. ….examination of female pups revealed*

ductal/alveolar hyperplasia of the mammary glands at exposure concentrations greater than 250ppm. Ductal/alveolar hyperplasia and hypertrophy also occurred in males, with significant effects seen at exposure concentrations of 25ppm or greater for hypertrophy and 250 ppm or greater for hyperplasia. Abnormal cellular maturation in the vagina was observed….and abnormal ovarian antral follicles were observed….In males aberrant or delayed spermatogenesis…was observed. …severity of …renal tubule mineralization and the severity of this lesion was significantly increased at exposure concentrations of 250 ppm or greater. These long-term studies were designed to address multiple aspects of the endocrine disruptor hypothesis, that is the hypothesis that exposures of human and wildlife populations to endocrine-active compounds (genistein) contribute to adverse reproductive tract effects and cancers of hormone-sensitive organs..…..the observation of significant effects at 250 ppm (hyperplasia in mammary gland of both sexes) together with the suggestion of subtle effects at this exposure concentration and less in the parallel immunotoxicity and neuroanatomical surveys, a high exposure concentration between 250ppm and 625ppm was deemed appropriate for the purpose (cause) of the multigenerational (effects across generations) reproductive toxicology study and the chronic study of genistein."

2004, CRISP Data Base, NIH- TL Guo reports, "*Genistein, a soy isoflavone has been suggested to mediate its biological function mainly as an endocrine disruptor….there are concerns about the long-term effects of this compound on human health, especially that of infants and young children."*

Potency content of estrogenic soy isoflavones can largely vary plant-to plant, as well as determined by individual status: estrogenic bioavailabilty, gastrointestinal functions, and elimination. Most frightening, each person can never know the levels of potency in estrogenic dosage one is actually receiving while consuming soy due to soy's continuing fluctuations in estrogenic endocrine disrupting potencies, as well as interindividual digestive capabilities.

Repeat consumption of soy plant-estrogen endocrine disruptors is stated to cause overall toxicity that is especially proven to contaminate fetal, infant, and child hormone systems. Soy isoflavone endocrine disruption orchestrates destructive alterations to an array of organ systems including the limbic/pituitary/hypothalamus/hippocampus brain regions that are most related to irreversibly severe disruptions in human brain functions.

During fetal, infant, and child brain development, brain toxicity caused by estrogenic chemicals, including soy plant-estrogens are proven to cause abnormal neurological hormone manipulations, thus solving an important missing link in the enigma behind several brain damaging disorders, including autism in children.

Unbelievably, there are no epidemiologic studies and no organized surveillance methods by health organizations to monitor soy phytotoxic adverse health effects of fetus, infants, children, adolescents, (or to adults), as caused by exposure(s) to estrogenic soy endocrine disruptors and/or the vast assortment of dangerous soybean antinutrients, (as also reviewed later in this report).

While soy plant-estrogens are proven as capable of causing extensive physiological and neurological damaging effects, especially during fetal, infant, and child development, those exposed, are in fact unknowingly participating in an undocumented soy plant-estrogen endocrine disrupting experiment.

June 13, 2007 epidemiology evidence reported by William Grant, PhD and Connie Soles reports, "*The autism rates determined in Japan and other Asian countries were considerably higher than those determined in primarily white countries….*"

January 2008, "Journal of Child Neurology" the first ever "Epidemiological Study of Autism Spectrum Disorder in China" reported by VCN Wong et al report, "*The estimated incidence of autism spectrum disorder was 5.49 per 10,000. The prevalence was 16.1 per 10,000 for children less than 15 years old for the same period. (1986 to 2005 . The male to female ratio was 6.58:1. This is the first reported epidemiologic study of autism spectrum disorder in Chinese children. The incidence rate is similar to those reported in Australia and North America……..*"

It is well-known that autism disorder has become an epidemic in the USA that precisely parallels the increasingly enormous marketing and population consumption of soy foods, beverages, and infant formulas.

MATERNAL CONSUMPTION OF SOY ENDOCRINE DISRUPTORS CONTAMINATES FETUS-

2006, "Journal of Health Science," (Japan) S Ikegami et al report, "*….isoflavones are well known as endocrine-disrupting chemicals. The possibility that soy foods might adversely affect the reproductive system of mothers and infants should be considered. Genistein and daidzein were detected in the blood of the dams and the stomach contents of the suckling pups. The concentrations of daidzein were higher than those of genistein. We also found the transfer of isoflavones to the fetus. Our experiments suggested that soy isoflavones have the possibility of inducing adverse effects on endocrinic functions and others in animal studies at very high doses.*"

Concentrations of isoflavonoids genistein, daidzein, and daidzein metabolites 0-DMA, and equol are found in umbilical cord plasma, and amniotic fluid at the time of delivery. Without public notification there exist an overwhelming number of important medical studies that conclude maternal consumption of soy foods and beverages during particular stages of pregnancy can result in fetal soy phytotoxicity and the cause of a variety of irreversible developmental adverse health effects.

Department of Environmental Medical Science, Chiba University reports; "*Fetal Hormonal Condition is Affected by Phytoestrogen Transferred From Mother; Phytoestrogens are estrogen-like chemicals. One concern is that exposure to phytoestrogens may pose a developmental hazard to infants and fetuses. To study whether the exposure to phytoestrogens had any influence on human fetuses, we investigated feto-maternal relationship between the serum concentrations of phytoestrogens and relationship between phytoestrogens and hormonal condition of fetuses. We detected that the concentrations of Genistein and Daidzein were significantly higher in cord serum than in maternal serum. These data suggest that the phytoestrogen affected the hormonal condition of human fetuses, and the response to the phytoestrogen of the fetuses was different from the adults.*"

Maternal consumption of soy isoflavones during pregnancy saturates her developing fetus with soy isoflavone: endocrine disrupting plant-estrogen neurotoxins, soy antinutrients, inhibition of essential minerals, heavy metal contamination, damaging interleukin effects, cause multiple neurotransmitter interruptions, all contributing to

damaging developmental body and brain dysfunctions as valid reasons to especially prohibit maternal soy consumption during pregnancy, as well as while breast feeding.

2001, "Reproductive Toxicology," U.S. FDA Division of Biochemical Toxicology, DR Doerge et al report, *"Genistein, the principal soy isoflavone, has estrogenic activity….The goal of the present study was to measure placental transfer of genistein in rats as possible route of developmental exposure. Fetal brain contained predominately genistein aglycone at levels similar to those in the maternal brain. These studies show that genistein aglycone crosses the rat placenta and can reach fetal brain from maternal serum genistein levels that are relevant to those observed in humans."*

2005, NIH- National Institute of Environmental Health Sciences, D. Doerge et al report, "…..*disposition of genistein during adult and fetal periods and this study describes the internal exposures of post-natal day 10 rat pups due to lactational transfer of genistein. These results suggest that developmental effects attributable to genistein exposure in our chronic and multi-generations studies are more likely to result from fetal exposures because of the higher levels of the active estrogenic aglycone form of genistein in utero, although the possibility of neonatal responses cannot be excluded."*

NIH- National Center for Toxicological Research confirms, *"No chemical regulated by the FDA has been tested for developmental toxicity in pregnant women."*

NIH Toxicologists D. Sheehan and D. Doerge report, "….*health labeling of SPI (soy protein isolate) for foods need to be considered just as would the addition of any estrogen….to foods, which are bad ideas. Estrogenic.….drugs are regulated by the FDA and are taken under a physician's care. Patients are informed of risks, and are monitored by their physicians for evidence of toxicity. No similar safeguards are in place for (estrogenic) foods, so the public will be put at potential risk from soy isoflavones in SPI without adequate warning information."*

What is dangerous for adults is of paramount danger for developing fetus, infants and children exposed. Focusing upon teratogens (avoidable chemicals causing birth defects to exposed fetus during pregnancy), the NCTR includes estrogens and estrogen-mimics in this category. Soy plant-estrogens are estrogen-mimics, either as agonistic or antagonistic. Studies prove that women who consume soy once a week, or once a month have significantly higher urinary excretion of estrogenic isoflavones than women who do not consume soy.

Maternal consumption of soy isoflavones during pregnancy are proven to cause high levels of active plant-estrogen transfer to fetus of: genistein, daidzein, glycitein, and possibly equol, O-MDA, and coumestrol. Soy's estrogenic transfer is proven as capable of causing developmental physiological and neurological toxicity to fetus. There are also a number of soy antinutrients (as reported further in this report) proving damaging health effects to developing fetus as well.

Cancer Prevention Research Program, Dr. C. Atkinson et al report, "*Dietary isoflavones are biologically active in humans. These studies show that genistein …..…crosses the rat placenta and can reach fetal brain from maternal serum…"*

Centers for Disease Control (CDC) reports *"Results of chronic feeding studies in pregnant animals suggest that high doses of phytoestrogens alter the fetal hormonal environment."*

FDA reports, "*Soy isoflavones and other dietary phytoestrogens are known to exert hormonal effects. There is considerable variability from person to person in the*

absorption, metabolism, and disposition of the soy isoflavones, genistein and daidzein."

2005 study published in "Environmental Research," E. Todaka et al, reports, "*The goal of this study was to investigate fetal exposure to phytoestrogens, estrogenic compounds derived from plants, by measuring serum concentrations of phytoestrogens in maternal and cord blood. The correlations were significant between the concentrations level s of Genistein and Daidzein, Genistein and Equol, Genistein and Daidzein plus Equol in cord serum. This study demonstrates placental transfer of phytoestrogens from mother to fetus. It is suggested that the metabolic and/or excretion rates of phytoestrogens are different between mother and fetus and once phytoestrogens are transferred to the fetus they tend to stay in the fetal side longer than in the maternal side."*

2005- National Center for Toxicological Research CE Hotchkiss et al report, "*High dose of genistein throughout the lifespan (rats) resulted in decreased bone size which may reduce the force required to break the bone."*

2006 report from the "Department of Epidemiology & Preventative Medicine" reports, *"High correlations were observed for isoflavone levels between maternal samples and umbilical cord blood indicating that isoflavone can be transferred from maternal to the fetal compartment."*

Because of their smallness; fetus, infants, and children are exposed to highest dosages of soy plant-estrogens, multiplied by their developing anatomical system that is too premature for adequate metabolism and elimination resulting in estrogenic accumulation, saturation, and contamination.

It is scientifically recognized that maternal consumption of soy isoflavones passes through the placenta (transplacental transfer) exposing estrogenic chemicals into the body and brain system of her developing fetus.

2001, "Journal of Pediatric Gastroenterology and Nutrition," reports, *"Phytoestrogens in maternal blood, cord plasma, and amniotic fluid in seven women at delivery show that isoflavonoids are indeed transferred from maternal to fetal compartment."*

Published in the "Archives of Toxicology" from University Dortmund, Germany reports, "The data shows that daidzein is transferred across the placenta of Han rats to fetuses. This is indicative of a rapid transfer from the mother to the fetus, but also that the efficient hepatic extraction of daidzein from the maternal blood occurs. Since dietary phytoestrogens account for a significant proportion of human exposure to potential endocrine modulations, and since the placenta does not represent a barrier to daidzein or related estrogenic isoflavones, the consequences of these exposures early in life should be examined and monitored carefully."

2008, "Journal of Reproduction and Development" by I. Woclawek-Potocka et al, titled "Concentrations of Isoflavones and Their Metabolites in the Blood of Pregnant and Non-pregnant Heifers Fed Soy Bean," reports, *"We noticed significant increases of equol…..in the blood plasma of the early-pregnant heifers (when compared to lat-pregnant heifers). Physiological status (cyclicity or pregnancy) of females influenced the concentrations of isoflavone metabolites in the blood plasma of heifers. The stage of pregnancy affects isoflavone absorption, biotransformation and metabolism differently and results in higher concentrations of active metabolites of isoflavones during early pregnancy in comparison to their lower concentrations during late pregnancy."*

In adults, even a modest isoflavone consumption rate of around 20 to 30 mg/day is stated to provide a high range of soy bioavailability and the maternal passage of estrogenic endocrine disruptors to her developing fetus can be intensified if breast feeding. The fluctuating fetal and infant exposure to soy plant-estrogens as well as antinutrients is most often unpredictable.

2005, "European Journal of Clinical Nutrition," G, Maskarinec et al, concludes, "*The high urinary isoflavone excretion levels detected in girls as compared to adult women suggest less intestinal degradation and/or great absorption of isoflavones in nonadult populations.*"

It has also been repeatedly reported that boys experience equal or even greater hormone interruptions caused by soy plant-estrogens.

In 2002, "Toxicology Letters", a multidisciplinary forum for research in all areas of toxicology reports, "*There is widespread concern that fetal exposure to hormonally active chemicals may adversely affect development of the reproductive tract. Second trimester amniotic fluid contains quantifiable levels of dietary phytoestrogens and thus is a marker of mid pregnancy fetal exposure.*"

Consumption of soy isoflavones results in high plasma genistein, daidzein, and glycitein, and because of specific individual gut bacteria, diet, and/or glucosidase activity between 30-50% of people are able to metabolize daidzein into another estrogenic metabolite, equol (greater estrogenic activity than daidzein but less than genistein), while 80-90% of people produce estrogenic O-desmethylangolensin, (O-DMA). Plasma genistein concentrations and bioavailability are reported to be consistently higher than daidzein when equal amounts are administered, while there is more extensive distribution of daidzein compared with genistein.

"Journal of Nutrition," Dr. Shaw Watanabe et al report, "*The individual plasma and urinary concentrations of equol and O-DMA were quite variable; subjects were classified as high and low metabolizers. The high plasma concentration of isoflavones for at least several hours after a single ingestion of soy protein suggests that these compounds may interact with macromolecules and have biological effects.*"

"American Journal of Clinical Nutrition," Dr. K. Setchell explains, "*The isoflavones in modest amounts of ingested soy protein are biotransformed by intestinal microflora, are absorbed, undergo enterohepatic recycling, and reach circulating concentrations that exceed by several orders of magnitude the amounts of endogenous estrogens. These phytoestrogens and their metabolites have many potent hormonal and nonhormonal activities that may explain some of the biological effects of diets rich in phytoestrogens.*"

A study by Xu et al, reports, "*If an individual possesses bacteria that are not effective in isoflavone metabolism and degradation then more isoflavones would be absorbed….*"

Even in low levels, maternal consumption of soy isoflavones exposes her developing fetus to increasing levels of estrogenic soy isoflavones that exceed fetal levels of endogenous estrogens and encourage the causation of irreversible developmental disturbances. This is also factual information related to maternal consumption of plant-estrogens while breast feeding infants, and exposure to soy-based infant formulas as well.

The FDA National Center for Toxicological Research (NCTR) reports that "*No chemical regulated by the FDA has been tested for developmental toxicity in pregnant*

women. Estrogens are etiological agents in female reproductive tract toxicity, a major human health problem. Estrogens are studied both with respect to their varying pharmacological and toxicological properties and their common mechanism of action. The division (FDA) is constructing an estrogen knowledge base to predict hormonal activity of untested xenobiotics (chemicals foreign to an entire biological system; to include dioxin and PCB's) and to help generate hypotheses identifying gaps in regulatory data."

The FDA NCTR confirms, "*The availability of natural and synthetic estrogens….. (each with toxicological properties) provides opportunities for development of methods and mechanistic approaches to predict risk. Estrogens are etiological (causation) agents in female reproductive tract toxicity, a major human health problem. Infants consuming soy formula are exposed to highest doses. Hyperactivity, mental retardation, and other neurological birth defects are another major public health concern. Since pregnant women are exposed to neuroactive xenobiotics (chemical pollutants particularly estrogen mimics) the FDA is responsible for assuring safety."*

Division of Biochemical Toxicology, NCTR FDA in 2005 concludes…."*These results suggest that developmental effects attributable to genistein exposure in our chronic and multi-generation studies are more likely to result from fetal exposure because of the higher levels of the active estrogenic form of genistein in utero, although possibility of neonatal responses cannot be excluded."*

Researchers, Drs. Sheehan and Doerge report, *"During pregnancy in humans, isoflavones per se could be a risk factor for abnormal brain and reproductive tract development."*

1999, "Proceedings of the Society for the Experimental Biology and Medicine," R. Harrison et al report, "*Effect of Genistein on Steroid Hormone Production in the Pregnant Rhesus Monkey- Phytoestrogens have been reported to cause reproductive problems in sheep and rats. This research was conducted to determine the effects of genistein fed to rhesus monkeys during pregnancy, with specific interest on fetal growth and steroidogenesis in the maternal-fetoplacental unit. Genistein-treated monkeys revealed…...estradiol levels were higher in the four areas studied at delivery and in the maternal blood with advancing gestation. Additionally, estrone levels tended to increase more rapidly n the maternal blood of monkeys receiving genistein than in untreated controls, suggesting that genistein may stimulate the deconjugation of estrogen in the gut, thus allowing its reabsorption into the peripheral circulation and conversion to estradiol."*

2005, "Neurotoxicology and Teratology," LA Becker et al report, "*Effects of dietary phytoestrogen exposure during perinatal period (second week of rat pregnancy to postnatal day 21)- There was a significant effect of phytoestrogen treatment on USV (tool used for emotion, behavioral motivation research in rats), for all male and female offspring. These results are the first demonstration of phytoestrogens affecting USVs and underscore the complexity of the effects of these substances on biobehavioral development."*

Department of Psychology and also Child Neurology, 2004 report concludes, *"Developmental effects of phytoestrogens were studies in offspring from pregnant rats who received a diet of genistein and daidzein. There was a significant effects of phytoestrogens treatment on ultrasonic vocalizations. There results…..underscore the*

complexity of the effects of these substances on biobehavioral (cognitive, learning, emotion, social, physical behaviors) development."

2004 "Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology" R Zhao et al report, "*Daidzein was added to the (duck) diet….yolk/albumen ratio decreased significantly. Ducklings hatched from daidzein-treated eggs were significantly smaller at hatching…….at 4 weeks of age an obvious down-regulation of hypolalamic GnRH mRNA expression was detected in ducklings maternally exposed to daidzein. Our results provide evidence that maternal exposure to daidzein affects post-hatch growth in the duck with accompanying changes in the secretion of metabolic hormones and expression of growth-related genes…..the long-term effect of maternal daidzein on reproductive function is not to be ignored and awaits further investigation."*

MATERNAL CONSUMPTION OF SOY ENDOCRINE DISRUPTORS WHILE BREAST FEEDING: Without public notification there is an overwhelming percent of important medical studies that conclude maternal consumption of soy products while breast feeding contaminates infant(s) resulting in the potential for a variety of damaging irreversible developmental infant health effects. Whether pre- or postnatal, the mother's consumption of soy products continues to transfer estrogenic isoflavones to her offspring.

Caused by maternal consumption of soy, the bioavailability of soy plant-estrogens found in mother's breast milk can vary not only between women but within each individual woman over the course of a day. Just 5 grams of soybeans is reported to increase estrogenic isoflavone genistein and daidzein levels in breast milk, while the levels of estrogenic equol and/or coumestrol are not calculated.

Although isoflavone levels are somewhat higher among infants who are directly fed soy-based formulas, bioavailable plant-estrogens are also transferred through breast milk to infants after mothers consume soy products as proven by infant plasma and urine analysis. It is confirmed that higher levels of plant-estrogens appear in infants than in the mothers who are consuming the soy. Infants and children have higher metabolic rates and absorb nutrients faster than adults, resulting in greater exposure to soy phyto-toxins and the immature capabilities to detoxify and excrete endocrine disruptor toxins.

Maternal consumption of soy endocrine disrupting isoflavones particularly during pregnancy, and/or while breast feeding is proven as capable of causing a variety of serious health risks as reported throughout a multitude of published studies.

2006, study published in "American Journal of Clinical Nutrition" concludes, "*The bioavailability of isoflavones in children after soy exposure is uncertain. Results: …isoflavone values increased significantly from baseline after mothers ate soy: in maternal urine…. and in breast milk…. and in infant urine. Tofu-fed infants had much higher mean isoflavone values in plasma. Statistically significant correlations were observed between the types of fluids (plasma/urine)investigated within mothers, between mothers and infants, and within infants."*

"Clinical Chemistry," Franke et al, report, "*Analysis of human breast milk has detected conjugates of genistein and daidzein following the consumption of roasted soyabeans…..Concentrations of daidzein and genistein ….have been found in a subject who naturally consumed a diet rich in soyabean products and from another subject following a soyabean challenge. A preferential excretion of main(daidzein) metabolites*

equol and O-DMA over the parent compounds was observed(in breast milk)…..This may be due to the higher isoflavone metabolite found in plasma compared with urine and feces."

2004 published study by the "Department of Medical and Scientific Services," reports, "*In utero and lactational exposure to estrogenic (isoflavone) agents has been shown to influence morphological and functional development of reproductive tissues. Consumption of dietary phytoestrogens such as isoflavones during pregnancy and lactation could influence important periods of development, when the fetus and neonate are more sensitive to estrogen exposure."*

"Toxicological Sciences", 2008 report states, "*Genistein is an efficient estrogen in the whole-body throughout mouse development. Genistein passed from the lactating mother to the suckling offspring at levels sufficient to activate gene expression in reproductive and nonreproductive tissues. Prolonged exposure (15 days) to genistein affects organs of mice in a dose and time depended manner at all developmental ages."*

The 2006 NTP CERHR Report confirms, "*Equol (the more potent soy estrogen component of daidzein) was detected in 7 of 9 human milk samples. A >10 fold increase in milk isoflavone levels was observed following ingestion of 30mg isoflavones in the form of 10g toasted soy nuts."*

It is scientifically documented that soy plant-estrogens profoundly exert physiological and neurological insult particularly during fetal and infant cell development. Soy plant-estrogens are proven to contribute to the cause of prenatal and postnatal developmental toxicity.

2001 study published in the journal, "Endocrinology" reports: *"…a variety of phytoestrogens, including genistein and daidzein activate estrogen-dependent gene transcription……even soy-based infant formulas contain at least the two most common phytoestrogens, genistein and daidzein in addition to several others. Multiple studies have shown that human plasma, urine, and breast milk…contain many different phytoestrogens making it necessary and imperative to study the combined effects of these compounds……."*

"Journal of Nutrition," reports, "*Developmental actions were examined by neonatal exposure of pups(infant rats) through milk of rat dams fed a coumestrol, control or commercial soy-based diet during the critical period of the first 10 postnatal days or throughout the 21 days of lactation. …the 21 day treatment produced a persistent estrus state in coumestrol-treated females….the 10-day coumestrol treatments produced significant deficits in the sexual behavior of male offspring. These findings illustrate the broad range of actions of these natural estrogens and the variability in potency across endpoints…..this variability argues for the importance of fully characterizing each phytoestrogen in terms of its sties of action…..and short-term and long-term effects."*

2005 study from Japan, T Kishida et al report, *"Analysis of Profile of Neurotransmitter in Hypothalamus and Blood Signals for Mechanism of Decreasing Food Intake of Rats Fed Soy Isoflavones- We speculated that the effect of daidzein could not simply be related to estrogenic effect of isoflavones. Leptin is one of the major food intake decreasing signal agents in blood…we observed that daidzein administration rather decreased serum leptin concentration."*

Leptin is a protein hormone that plays a key role in regulating energy intake and energy expenditure, including appetite and metabolism. Leptin is one of the most

important adipose derived hormones that interacts with receptors present in a number of hypothalamic nuclei. Circulating leptin levels give the brain input regarding energy storage so it can regulate appetite and metabolism. Leptin deficiency can cause destruction in NPY neurons involved in anorexia.

Leptin is also strongly linked with angiogenesis, or the process involving the growth of new blood vessels from pre-existing vessels, and the normal process in growth and development as well as wound healing. Leptin is linked with increasing vascular endothelial growth factor, involving important signaling proteins involved in the beginning embryonic circulatory system, an organ system that moves nutrients, gases, and wastes to and from cells, helps fight diseases and helps stabilize body temperature and PH to maintain homeostasis. Main components of the human circulatory system are the heart, blood, blood vessels, pulmonary circulation, a loop through the lungs where blood is oxygenated and through the rest of the body, providing oxygenated blood. Digestive system works with the circulatory system to provide the nutrients the system needs to keep the heart pumping. Critically necessary, leptin is decreased by soy isoflavone, daidzein.

It is well established as scientific knowledge, that increasing estrogenic saturation of fetus, and infant as caused by soy consumption during pregnancy and breast feeding is capable of causing irreversible biological damaging health effects for a lifetime.

SOY-BASED ENDOCRINE DISRUPTOR INFANT FORMULAS:

Infant nutrition is crucial to ensure adequate body and brain growth, development, function, and all around good health. During this most sensitive timeframe for infant body and brain development there is an extremely high dependence upon infant formulas, and the usage of soy-based infant formulas are extremely rare in Asian countries as well as most countries around the world, with largest exception found is in the U.S.A.

Feeding infants soy-based formulas and feeding children soy products is promoting the saturation of soy estrogenic and anti-nutrient endocrine disruptors, of which crucial role of timing, duration of exposure, and repeat exposures are well-known as increasingly phyto-toxic.

1998, National Center for Toxicological Research, FDA, Dr. DM Sheehan reports, "*These considerations suggest that much closer study in experimental animals and human populations exposed to phytoestrogen-containing products, and particularly soy-based foods, is necessary. Among human exposures, infant soy formula exposure appears to provide the highest of all phytoestrogen doses and this occurs during development, often the most sensitive life-stage for induction of toxicity. Large carefully controlled studies in this exposed infant population are a high priority.*"

Eleven years later, the FDA themselves, have done nothing to encourage controlled soy phytotoxic studies, while continuing to conceal evidence of several hundred other scientific studies proving drastic soy-risks particularly caused to children. It is established that soy-based infant formulas contain highly active estrogenic endocrine disruptors as well as a large variety of dangerous anti-nutrients. Individually, and together these damaging soy phytochemicals are proven as highly dangerous especially exposures during the fragility of developmental time-frames.

2007, University of Maryland Medical Center reports, "*Soy foods and soy-based infant formula are widely used in children, but there are no clinical studies that have*

determined whether isolated soy protein or isoflavone supplements are useful or safe in this population. Therefore, isolated soy products are not recommended for use with children at this time."

2002, "Journal of Agriculture and Food Chemistry," MI Genovese, and FM Lajolo report, "*On the basis of these data, the daily intake of isoflavone from soy products was estimated: the highest values were found for infants fed soy-based formulas, from 1.6 to 6.6 mg/kg of body weight."*

2007, "Current Opinion in Clinical Nutrition and Metabolic Care," D Turck reports, "*Concerns have recently been raised regarding potential risks with soy protein formula, in particular regarding their high phytoestrognic isoflavone content. Recent data are insufficient to draw definitive conclusions on safety……Soy protein formula……..have no nutritional advantages over cow's milk protein formula. Soy protein formulas have no role in preventing allergy or management of nonspecific gastrointestinal symptoms. They should not be used in preterm infants or infants with food allergy before age 6 months."*

Animal Sciences Group in New Zealand confirms, "*Exposure to estrogenic compounds may pose a developmental hazard to infants. Soy products which contain the phytoestrogens, genistein and daidzein are becoming increasingly popular as infant foods. We measured total genistein and daidzein contents of commercially available soy-based infant formulas, infant cereals, and dinners. Soy formulas provide the infant with a daily dose rate of total isoflavones, (genistein + daidzein) of approximately 3mg/kg body weight, which is maintained at fairly constant level between 0-4 months. The diet of 4-month-old infants with a single daily serving of soy cereal can increase their isoflavone intake by over 25%, depending on brand. This rate of isoflavone intake is much greater than that shown in adult humans to alter reproductive (estrogen) hormones. Since neonates are generally more susceptible than adults to perturbations of the sex steroid (estrogen) milieu, it would be highly desirable to study the effects of soy on steroid-dependent developmental processes in human babies."*

Institute of Clinical Science, Queens University in England reports, "*Soy formula now used increasingly as an alternative to breast or cow's milk for infants is of particular concern since the most vulnerable periods for estrogenic insult are the pre-and neonatal periods when irreversible damage can be inflicted on developing germinal epithelium (early stage organ tissue)."*

Scientists from the Epidemiology Branch of NIEHS confirm that infants consuming soy infant formulas show serum/plasma concentrations for genistein that exceed the concentration seen in laboratory studies using doses that are pharmacologically or toxicologically active in animals. Without evidence of safety, the reported FDA recommendation amount of isoflavones for adults is 24mg, 0.40mg per Kg body weight. Infants fed soy-based formulas are exposed to 22-45mg of estrogenic isoflavones per day, averaging 6.25mg per Kg body weight. Babies on soy formula are found to have levels of serum estrogens at 13,000 to 22,000 times higher than plasma estradiol concentrations in early life, and higher than babies who are breast fed or fed milk-based formulas. Continual soy exposure during gestation, and infants continued on a soy-fed diet, contributes to increasing estrogenic hormone disrupting levels.

Weston A Price Foundation reports that 10mg provides the estrogenic equivalent of a contraceptive pill to a baby of 6Kg. The average amount taken in by a child on soy-based formula provides the estrogenic equivalent of at least 4 birth control pills.

In 2005 the Department of Health and Human Services, National Toxicology Program; Center for the Evaluation of Risks to Human Reproduction (CERHR), (Michael Shelby Director) "*Announcement of the Genistein and soy formula 'Expert Panel' meeting: To reach conclusions regarding whether exposure to Genistein or soy formula is a hazard to human development or reproduction. Genistein is a phytoestrogen found in some legumes, such as soybeans and clover, or in products obtained from animals ingesting Genistein-containing feed. Phytoestrogens are estrogenic compounds that occur naturally in plant products. Genistein is found in food and is the primary phytoestrogen in soy formula. Soy formula is administered to infants …..*" CERHR selected Genistein and soy formula for 'Expert Panel' evaluation because of the availability of numerous reproductive and developmental toxicity studies in laboratory animals and humans."

1998, "American Journal of Clinical Nutrition," CH Irvine et al report, "*Soy-based formulas provided a mean daily dose of isoflavones (genistein plus daidzein) of 3.2-/-0.2 mg/kg body weight, which remained fairly constant regardless of age < or = 16 weeks. Isoflavones were measurable in all samples from soy-fed infants but not from the urine from dairy-fed infants. Daily isoflavone excretion rates varied little among infants and did not change with age. The mean percentage of the daily intake recovered in the urine of soy-fed infants was 38+/-4% for daidzein and 13+/-3 for genistein and remained constant with age. These values are similar to those for adults and indicate that young infants are able to digest, absorb, and excrete genistein and daidzein from soy-based formulas……*"

Soy protein isolate is industry produced non-milk used in soy-based infant formulas. Soy supplements are also made from soy protein isolate and heavily marketed to body builders, while published literature increasingly warns adults about numerous adverse health effects, while proven soy protein isolate damaging health effects to developing fetus, infants, and children remain silenced.

2003, "Journal of Family Health Care," The British Dietetic Association reports, "*Breast feeding should be strongly encourages as providing the safest, most nutritionally adequate form of feeding for most infants. Dietitians should discourage the use of soya protein in children with atopy or cow's milk allergy in the first six months of life to avoid sensitization to soya protein and exposure to phytoestrogens while organ systems remain at their most vulnerable. This would included soy infant formula and soya products……..…..When a soy-based infant formula is used, parents should be informed of current findings relating to phytoestrogens……Any parent choosing to refuse soya for their infant should be supported in their decision.*"

Soy-based infant formula made from powdered or liquefied soybeans undergoes an acid wash in large aluminum tanks (that can leach aluminum into the final soy-based product), is processed through high temperatures, then mixed in a caustic alkaline soaking solution producing lysinealine, and nitrosamines from spray drying, both of which are noted carcinogens, and of noted FDA concern. Remaining soybean curds are spray-dried at high temperatures to produce a protein powder used for soy-based infant formula. High temperature heating does not remove several of the soy-based

antinutrients, or endocrine disrupting estrogenic isoflavones, while heating has been proven to lower levels of protein nutrients and several essential minerals that are most necessary during body and brain development.

2007, "Federal Institute for Risk Assessment," I. Lukassowitz reports, "*Soybeans contain high concentrations of isoflavones. Furthermore, soybeans may also contain higher amounts of the plant component, phytate. Dr. Andreas Hensel President of the Federal Institute for Risk Assessment comments, 'Infant formula and follow-up formula made from soy protein should only be administered on medical grounds and then only under medical supervision.' This is because soy contains plant substances which may have hormone-like effects, the so-called phyto-estrogens. They have a similar chemical structure to the female hormone estrogens. Hence far higher isoflavone concentrations were found in the blood of infants given soy than infants given cow's milk formula or breast milk. Besides isoflavones, soy formula may also contain phytate. This natural plant component can influence the intake of minerals and trace elements. In animal experiments there were signs that elevated isoflavone intake affects the development of reproductive organs, the immune system and the thyroid gland. Soy formula for infants is not intended for administration to healthy infants. Soy protein itself can trigger allergic reaction and does not prevent allergic disorders."*

2006, "Journal of Pediatric Gatroenterology and Nutrition," C Agostoni et al report, "*Soy is a sourced of protein that is inferior to cow's milk, with a lower digestibility and bioavailability as well as a lower methionine content. Soy protein formula can be used for feeding term infants, but they have no nutritional advantage over cow's milk protein formula and contain high concentrations of phytate, aluminum, and phytoestrogens (isoflavones), which might have untoward effects. Soy protein formulas have no role in the prevention of allergic diseases, and should not be used in infants with food allergy during the first 6 months of life. …after the age of 6 months….tolerance to soy protein should first be established by clinical challenge. There is no evidence supporting the use of soy protein formula for the prevention or management of infantile colic, regurgitation, or prolonged crying."*

Other applications of soy proteins are listed to include: adhesives, asphalts, resins, cleaning materials, cosmetics, inks, paints, paper coatings, pesticides/fungicides, plastics, polyesters, and textile fibers.

Novasoy, among the many manufactures of soy-based infant formula, foods and supplements brag that "isoflavone contents of ….Soybeans (dry) - Genistein 738mg/kg and Daidzein 466mg/kg, (as extremely high estrogenic plant-isoflavones), relieve menopausal symptoms," while confirming soy estrogenic endocrine disrupting effects on adults, yet remaining mute as to the cause of outrageous endocrine disrupting effects to the developing fetus, infants, and children exposed.

1997, "Lancet," KD Setchell et al report, "*Exposure of infants to phyto-oestrogens from soy-based infant formula- The isoflavones genistein, daidzein, and their glycosides, found in high concentrations in soybeans and soy-protein foods……....Because these bioactive phyto-oestrogens possess a wide range of hormonal and non-hormonal activities it has been suggested that adverse effects may occur in infants fed soy-based formulas. All of the soy formulas contains mainly glycosides of genistein and daidzein and the total isoflavone content was similar among the 5 formulas analyzed and was related to the proportion of soy isolate used in their manufacture. From the*

concentrations of isoflavones in these formulas (means 32-47micrograms/mL), the typical daily volume of milk consumed, and average bodyweight, a 4-month old infant fed soy formula would be exposed to 28-47 per day, or about 4.5-8.0 mg/kg bodyweight per day, of total isoflavones. Mean (SD) plasma concentrations of genistein and daidzein in the seven infants fed soy-based formulas were 684 (443) ng/mL and 295 (60) ng/mL, respectively, which was significantly greater than in the infants fed either cow-milk formulas or human breast-milk and an order of magnitude higher per bodyweight than typical plasma concentrations of adults consuming soy foods. INTERPRETATION: The daily exposure of infants to isoflavones in soy infant-formulas is 6-11- fold higher on a bodyweight basis than the dose that has hormonal effects in adults consuming soy foods. Circulating concentrations of isoflavones in the seven infants fed soy-based formula were 13,000-22,000 times higher than plasma oestradiol concentrations in early life, and may be sufficient to exert biological effects, whereas the contribution of isoflavones from breast-milk and cow-milk is negligible."

1998, "American Journal of Clinical Nutrition," Setchell et al report, "*Isoflavone content of infant formulas and the metabolic fate of these phytoestrogens in early life- Soy-based infant formulas…..are manufactured from soy protein isolates and contain significant amounts of phytoestrogens of the isoflavone class. Genistein, found predominantly in the form of glycosidic conjugates, accounts for greater than 65% of the isoflavones in soy-based formulas. Total isoflavone concentrations of soy-based formulas prepared for infant feeding range from 32-47 mg/L, whereas isoflavone concentrations in human breast milk are….5.6+/-4/4 microg/L. Infants fed soy-based infant formulas are therefore exposed to 22-45mg isoflavones/d, whereas the intake of these phytoestrogens from human milk is negligible (less than 0.01mg/d). Plasma isoflavone concentrations reported previously for 4-mo old infants fed soy0based formula were 654-1775 microg/L, significantly higher than plasma concentrations of infants fed either cow-milk formula or human breast milk (4.7+/-1.3microg/L), (non dietary maternal consumption). The high steady state plasma concentration of isoflavone in infants fed soy- based formula is……..maintained by constant daily exposure from frequent feeding. Isoflavones circulate at concentrations that are 13,000-22,000-fold higher than plasma estradiol concentrations in early life."*

2000, "Journal of Nutrition," KDR Setchell reports, "*Absorption and metabolism of Soy Isoflavones- from Food to Dietary Supplements and Adults to Infants- Soy foods made from whole soybeans or isolated and purified soy proteins all contain relatively high concentrations of isoflavones, primarily in the form of various B-glycoside conjugates. When ingested, these conjugated isoflavones undergo hydrolysis by B-glucosidases in the jejunum, releasing the principal bioactive aglycones, daidzein and genistein……..there is adequate B-glucosidase activity to make isoflavones bioavailable to infants consuming soy formulas. Furthermore, it is the aglycones that show an affinity for estrogen receptors and have other nonhormonal effects on the cell machinery. Concerns have been express that too much isoflavones in the diet may have negative effects. On the basis of the pharmacokinetics of soy isoflavones……high steady-state plasma concentrations will be achieved by a regular intake particularly if phytoestrogens are ingested throughout the day."*

It is reported that soy-based formulas, as 100% of infant's daily diet, as well as ingested over long periods during most delicate developmental timeframes results in

excessive soy estrogenic (and antinutrient) exposures of which have been compared to feeding babies estrogenic birth control hormone drugs.

Bulletin De L'Office Federal de la Sante Publique, No 28, July 20, 1992, "*Babies on soy formula receive the estrogenic equivalent of at least 5 birth control pills per day.*"

In 2001 FDA Division of Biochemical Toxicology researchers Drs. Doerge and Sheehan, report, "*Genistein is a naturally occurring isoflavone that interacts with estrogen receptors and multiple other molecular targets. Human exposure to genistein is predominantly through consumption of soy products, including soy-based infant formula and dietary supplements. Dietary exposure to pregnant rat dams continued through lactation to postnatal day 50. (Rat) pups of both sexes had significantly decreased body weights…..decreased prostate weight….trend toward higher pituitary gland to body weight ratios. Female pups revealed ductal/alveolar hyperplasia on mammary glands …..with ductal hyperplasia and hypertrophy also occurring in males with significant effects seen at 25ppm and above. (In females) abnormal cellular maturation in the vagina was observed and abnormal ovarian follicles….and abnormal ovarian antral follicles were observed. In males…delayed spermatogenesis was observed….and deficit of sperm relative to controls. Both sexes showed increase in incidence and/or severity of renal tubal mineralization……..Dietary genistein thus produced effects in multiple estrogen-sensitive tissues in males and females that are generally consistent with estrogenic activity. These effects occurred within exposure ranges achievable in humans.*"

July 2008, Epidemiology Branch of the NIEHS confirms, "*Urinary concentrations of genistein and daidzein were about 500 times higher in the soy formula-fed infants than in the cow milk formula-fed infants.*"

2005, "Toxicology Sciences," A Hierlihy et al report, "*Phytoestrogens have been implicated both as agonists and antagonists of estrogen dependent cancers. These naturally occurring compounds have been shown to have estrogenic properties. The major human dietary source of isoflavones is obtained from soy foods. In addition to the purported health benefits of phytoestrogens, possible concerns exist in their actions as endocrine disrupters. Particularly in populations where exposure is high, such as in infants consuming soy-based milk formulas. In this study, the effect of dietary soy and isoflavones on gene expression and protein levels in female rat liver was examined at days 28 and 70. Results: isoflavones are known estrogen mimics; as a result the effects isoflavones on known estrogen targets were assesses. Increases in estrogen receptor alpha/beta and progesterone receptor A (PR-A) (2-fold) were detected at day 28…..Data comparing the effects of control vs high isoflavone diets on female liver from day 28 show greater than 2-fold increases in gene expression in several metallothion genes. Decreased gene expression (> 2-fold) was observed in genes involved in fatty acid metabolism. Conclusion: Temporal expression of estrogen-responsive receptors was observed. In addition, metallothionine-related genes, which are known to respond to oxidative stress were upregulated…. …..Furthermore, downregulation of several genes involved in fatty acid metabolism may have serious consequences.*"

An overwhelming problem is that the total soy plant-estrogenic isoflavone and antinutrient content of soybeans used in soy-based infant formulas and soy foods can largely vary between harvested soybean plants, processing, and brands.

When compared to infant body weight, soy-based infant formula can result in an estrogenic endocrine disrupting overdose. Studies such as those also reported in 1996 by toxicologist Michael Fitzpatrick PhD, concurs exposure to soy formulas as equating to the infant swallowing birth control pills.

Weston A Price Foundation reports, "*FDA recommended amount of estrogenic isoflavones for adults per day is24mg, or 0.40mg intake body weight and for children it is 38mg, or 6.25mg per Kg of body weight. Although avoiding consumer warnings the FDA has no evidence that soy-based infant formulas are safe and without subtle or extreme health risk."*

As stated earlier, soy-based infant formulas, due to soybean classification as agricultural, are frightfully exempt from the FDA approval process.

1997, Switzerland journal, "Mit Aus Dem Geb Der Leb Und Hyg" B Zimmerli, and J Schlatter report, *"Occurrence and significance of the isoflavones daidzein and genistein in infant formulas- The exposure levels of newborns and infants with the isoflavones genistein and daidzein are reviewed as well as their metabolism, biological effects, and potential health hazard. The isoflavones were analyzed in 3 soy-based infant formulas…..Feeding of newborns exclusively with such formulas would result in a mean daily intake of isoflavones of up to 20mg/kg/body mass. This dose is up to 25 times higher than the dose which was shown to prolong slightly the menstrual cycle in women. ……....possible adverse health effects of isoflavone exposure in newborns and infants, it is demanded that soy-based infant formulas containing isoflavones should be used only under strict medical indications and a lack of alternative products."*

2007, "Clinical Pediatrics," J.Teitelbaum and J. Lagmay report, "*To assess the familiarity of pediatricians with commercially available formulas….a list of formulas was generated by visiting several grocery stores. Pediatricians were asked to indicate their familiarity with these and other 'specialized' formulas…..these data suggest that pediatricians have a poor understanding of the content and appropriate use of neonatal and infant formulas."*

2006, "Journal of Pediatric Gastroenterology and Nutrition", European Society for Paediatric Gastroenterology Hepatology and Nutrition, as reported by C. Agostoni et al, *"Soy is a source of protein that is inferior to cows' milk, with lower digestibility and bioavailability as well as lower methionine(essential amino-acid) content. Soy protein formulae…..have no nutritional advantage over cows' milk protein formulae and contain high concentrations of phytate, aluminum, and phytoestrogens (isoflavones), which might have untoward effects. There are no data to support the use of soy formulae in preterm infants. Soy protein formulae have no role in the prevention of allergic diseases, and should not be used in infants with food allergy during the first 6 months of life. If soy protein formulae are considered for therapeutic use in food allergy after …6 months because of lower cost….tolerance to soy protein should first be established by clinical challenge. There is no evidence supporting the use of soy protein formulae for the prevention or management of infantile colic, regurgitation, or prolonged crying."*

2006, "Cambridge Journals," BH Halm et al report, "*Isoflavones from soy foods are more bioavailable in children than adults. The purpose of this present study was to determine whether children experience a higher systemic exposure to isoflavonoids when consuming a body weight adjusted dose of soy compared with adults. (Results)- Children, compared to adults showed a statistically significant higher urinary isoflavone*

excretion rate for daidzein, genistein, all non-metabolites…..and total isoflavonoids. Isoflavones are more bioavailable in children versus adults."

2003, "Journal of Paediatrics and Child Health," PG Tuohy reports, "*Soy infant formula contains high levels of the isoflavones, genistein and daidzein, which are commonly referred to as phytoestrogens. Infants consuming soy formula have high levels of circulating isoflavones. These are an order of magnitude greater than the levels of isoflavones which have been shown to produce physiological effects in adult women consuming a high soy diet. ……there is very little research on the effects of consumption of soy phytoestrogens by human neonates. ……there is an increasing number of recent reports that suggest that in experimental animals phytoestrogens have adverse effects with respect to carcinogenesis, reproductive function, immune function and thyroid disease. Despite the absence of adequate scientific research that quantifies the level of risk to infants, most would argue for a precautionary approach to be taken in situations where there are potential developmental effects from the consumption of pharmacologically active compounds in infancy and childhood."*

Book, "Endocrine Disruptors" by Rajesh Naz, "*Ever since soy-based formulas were introduced there have been health problems associated with them. Soy protein higher isoflavone content than soy flour expose infants to exogenous estrogens."*

"American Journal of Clinical Nutrition" reports, "**….***Young infants are able to digest, absorb, and excrete (estrogenic)genistein and daidzein from soy-based formulas."*

2001, Archives of Pediatrics, A. Bocquet et al report, "*There is no evidence that soy bean-based formulas (SBBF) have any efficiency in infant colic. SBBF have no indication in prevention of allergy, or in premature infants' nutrition. Studies have shown that SBBF contain large quantities of phytoestrogens, particularly isoflavone. Because of experimental data suggesting a possible deleterious effect of phytoestrogens on the neuroendocrine maturation, the reduction of their content in SBBF must be considered."*

Along with International Journal of Food Sciences and Nutrition, multiple studies confirm that levels of soy plant-estrogens are, *"likely to be exceeded in groups who have preferably consumed high phytoestrogen-containing foods such as soy-protein-based infant formula….."*

High soy isoflavone levels detected in blood, urine, and feces of infants prove estrogenic bioavailability. Bisphenol-A (BPA) used in plastic baby bottles also contaminate formulas. Endocrine disruptors; soy-based formulas with plastic bottles doubles the added estrogenic chemical contents even further when exposed to heat.

American Academy of Pediatrics reports, *"Because an infant formula provides the largest, if not sole, source of nutrition for an extended interval, the nutritional adequacy of the formula must be confirmed and indications for its use well understood. Full nutritional value of soybean protein is achieved only after heat has been applied. Subsequent studies confirmed the presence of a number of heat-labile factors with biological activity I soybean-based products. There also are heat-stable factors that remain in the soy protein isolate, including the low-molecular-weight fibers, phytates, saponins, (antinutrients) and phytoestrogens. …..the infants potential intake of phytoestrogen from isolated soy protein-based formula is higher than that demonstrated to influence the menstrual cycle of humans. Preterm infants….fed methionine-supplemented soy protein-based formulas demonstrated significantly less weight gain,*

less length gain, and lower serum aluminum levels that that achieved with cow milk-based formulas. Serum phosphorus levels were lower in preterm infants fed soy protein-based formula and when measured the alkaline phosphatase levels were higher. …the osteopenia of prematurity is reportedly increased in low birth weight infants receiving soy protein based formulas (even with added supplements)….and reduced bone mineralization. Severe gastrointestinal reactions to soy protein formula have been described for >30 years…..Small-bowel injury, and failure to thrive has been documented in at least four studies. Severe enterocolitis manifested by bloody diarrhea, ulcerations, and histologic features of acute and chronic inflammatory bowel disease also has been well described in infants receiving soy protein-based formulas. Two large studies of infants with atopic dermatitis addressed the frequency with which a double-blind, placebo controlled challenge with soy protein was positive. Prospective studies of high-risk infants suggest that soy protein based formula has no relative value over cow milk formula in the prophylaxis or prevention of allergic disease. Soy protein-based formulas have not demonstrated a significant benefit for colicky discomfort."

Besides plant-estrogens endocrine disruption, there are multiple soy anti-nutrients of which infants and children can react differently to, depending upon a large assortment of developmental factors to include; plant levels of isoflavones and antinutrients, in utero exposure, infant exposure, sexual gender, birth weight, developmental physiological functions, exposure to environmental contaminants, and more. Minimal exposure to potentially harmful soy phytochemicals and/or soy antinutrients can cause infant toxicity and a host of irreversible adverse developmental effects as multiple studies conclude.

2004, "Annual Review of Nutrition," L Chen and W Rogan from the NIH-National Institute of Environmental Health Sciences report, "*Isoflavones In Soy Infant Formula: A Review of Evidence for Endocrine and Other Activity in Infants- soy infant formulas are widely used, but few studies have evaluated long-term safety or examined specific forms of toxicity, such as to the endocrine or immune systems. This review focuses on newer experimental studies of the effects on estrogen activity, immune function and thyroid economy of genistein and daidzein two isoflavones in soy infant formula, and existing human studies of soy formula use. ….we examined the doses and the resulting serum or plasma concentrations seen in soy-fed infants. We also summarized the estimates of the potency of the isoflavone compounds relative to estradiol. Given the substantial laboratory evidence of hormonal and other activity at doses relevant to the soy-fed infant, we conclude that more……..study is warranted."*

Urinary excretion of isoflavones has been thoroughly investigated. Infants fed soy-based infant formulas are found to excrete considerable amounts of genistein, daidzein, and glycitein in urine, indicating that these estrogenic compounds are well absorbed. 75% of soy-based formula-fed infants are also able to convert daidzein to the estrogenic O-DMA, and 25% of infants produce equol, the higher estrogenic metabolite of daidzein, but less estrogenic than genistein.

High sugar and corn syrup content of soy is reported to lessen the capabilities of colonic bacteria to ferment carbohydrates, increasing the cause of gastrointestinal disorders found in soy-based formula fed infants. These poorly digestible carbohydrates are reported to stimulate the higher daidzein estrogenic production of equol.

The FDA 1996- 1997 report concludes: "*Estrogens are etiological agents in female reproductive tract toxicity, a major human health problem. Infants consuming soy*

formula are exposed to the highest doses (of phytoestrogen exposures). Estrogens are studied both with respect to the varying pharmacological and toxicological properties and their common mechanism of action. The division (FDA) is constructing an estrogen knowledge base to predict hormonal activity….and to help generate hypotheses identifying gaps in regulatory data."

In relation to their small developing bodies, babies fed soy-based plant-estrogen formulas are exposed to highest dosages of estrogenic compounds. Soy-based formulas (foods and beverages) contain significant amounts of active isoflavones that are proven to produce estrogenic toxicity to infants and small children.

The NTP CERHR reports under the heading, "*Toxicokinetics and Metabolism: Infants are able to absorb isoflavones and infants fed soy formula were demonstrated to have plasma isoflavone blood levels exceeding those of Japanese adults several-fold. Higher concentrations in infants are postulated to result from lower body weight, frequent feedings and reduced metabolism."*

2003, "Neuroscience Letter," E. Lephart et al report, "*Body weights (of exposed rats) were significantly decreased in phytoestrogen-rich fed animals compared to phytoestrogen-free values."*

Fetal and infant low body weight carries a host of dangerous adverse health effects, ranging from minor to irreversibly severe.

The NTP Center for Evaluation of Risks to Human Reproduction (CERHE) reports that "*Isoflavone levels in Infant soy formulas from different countries: US- 15 brands analyzed for total isoflavones= 25-281.4 mg per liter (L) formula as fed, Australia 4 brands analyze/total isoflavones = 18-21mg/L, and UK 6 brands analyzed =18-41mg/L."*

2008, "American Academy of Pediatrics (AAP)," J Bhatia et al report, "*This report reviews the limited indications and contraindications of soy formulas. It will also review the potential harmful effects of soy protein-based formulas and the phytoestrogens contained in these formulas.*

This statement updates the 1998 review of soy protein-based formulas and addresses the ongoing concern of phytoestrogens in soy formulas. In formulas, carbohydrate sources are corn maltodextrin, corn syrup solids, and sucrose with content raging from 10.26 to 10.95 g per 100 kcal or 6.9 to 7.4 g/dL…….soy protein isolate formulas still contain 1.5% phytates and up to 30% of the total phosphorous is phytate bound……soy phytates also bind iron and zinc…… the phytoestrogens are of particular interest in human health. Concerns raised in relation to phytoestrogen/isoflavones include their potential negative effects on sexual development and reproduction, neurobehavioral development, immune function, and thyroid function.

The structural similarity of phytoestrogens with 17-estradiol has prompted studies on the possible effects of soy isoflavones on reproductive function and growth. Numerous toxicity studies in rats have demonstrated some effects on estrogen-related tissues……..A recent study of the isoflavone genistein demonstrated adverse consequences of neonatal exposure in mice…..Soy diets were reported to stimulate growth of estrogen-dependent mammary tumors in mice in a dose-dependent manner. In humans, very limited data to date suggest that soy phytoestrogens have a low affinity for human postnatal estrogen receptors and low potency in bioassays. The absorption, distribution, metabolism and excretion of soy isoflavones vary, depending on age, and gender and among cultural

groups; interindividual variability has been documented in several studies. Analysis of maternal and cord plasma and amniotic fluid indicates placental transfer of these compounds after soy consumption……..the concentration of isoflavones in human milk reflects maternal diet with omnivores demonstrating considerably lower concentrations of isoflavones compared with vegans. Setchell and Casssidy estimated that the amount of isoflavones ingested by infants fed soy-based formula on a body weight basis exceeded those reported to increase the length of the menstrual cycle in adult women. In young adults 20 to 34 years of age who participated in a controlled feeding study of soy formula as infants demonstrated a longer duration of menstrual bleeding had greater discomfort in women exposed to soy as infants.

Although the aluminum content of human milk is 4 to 65ng/mL, that of soy protein-based formula is 600 to 1300ng/mL. The toxicity of aluminum is traced to increased deposition in bone and in the central nervous system, particularly in the presence of reduced renal function….and renal failure.

Consumption of soy products by infants with congenital hypothyroidism complicates their management, as evidence by a prolonged increase in thyroid-stimulating hormone when compared with infant not fed soy formula……As anticipated from observations, the degree of osteopenia is increased in infants with low birth weigh receiving soy protein-based formulas. Even with supplemental calcium and Vitamin D, radiographic evidence of significant osteopenia was present in 32% of 125 preterm infants fed soy-protein-based formula.

The cow milk protein-based formulas designed for preterm infants are clearly superior to soy protein-based formula……..Severe gastrointestinal reactions to soy protein-based formula have been described for >40 years…….30% to 64% of infants had concomitant soy-induced enterocolitis, with enterocolitis manifested by bloody diarrhea, ulcerations, and histologic features of acute and chronic inflammatory bowel disease. Eosinophilic proctocolitis a more benign variant of enterocolitis, also has been reported in infants receiving soy protein-based formula.

In a recent meta-analysis of 5 randomized studies, the authors concluded that feeding with soy formula should not recommended for the prevention of atopy in infants at high risk of developing allergy…..isolated soy protein-based formula has no advantage over cow milk-based formula for supplementing the diet of a breastfed infant. Regarding soy proteins and other food allergies…..feeding of soy milk for soy-protein-based formula was associated with the development of peanut allergy…..there are few indications for their (soy-based formula) use in place of cow milk-based formula. The routine use of isolated soy protein-based formula has not proven value in the prevention or management of infantile colic or fussiness."

Reported by the Division of Biological Science, soy plant-estrogens are shown to produce estrogenic effects in the defined "low-dose" range…for adults. Within the anatomy of each adult, child, infant, and fetus, there is "inter-individual variations" of soy isoflavone bioavailability that is dependent upon individual capability to metabolize, absorb, eliminate, and actually resist soy plant-estrogen/antinutrient contamination.

1977, "Rev Farm Bioquim," TM Filisetti et al report, "*Antinutritional factors in commercial soy products- Trypsin inhibitors were found in high amounts in raw bean protein concentrates and isolates…..Hemagglutinin was more resistant to thermal*

processing and was found inn all the products. In soy bean milks, tasted flour and protein isolates there are factors which can depress….rat thyroid by 30%."

Besides the antinutrients mentioned above soybeans contain a large variety of antinutrients such as: phytic acid, saponins, lectins, nitrates, and furan, inhibition of tyrosine kinase, inhibition of topoisomerase II, multiple heavy metal contents, and more as outlined further in this report. Soy antinutrients cause a large variety of direct and indirect adverse health effects that are especially damaging during fetal, infant, and child neurological and physiological development.

National Toxicology Program (NTP), January 2006, report, "*Toxicity of Soy Formula: Infants are abet to absorb isoflavones, and infants fed soy formula were demonstrated to have plasma isoflavone blood levels exceeding those of Japanese adults several-fold. Higher concentrations in infants are postulated to result from lower body weight, frequent feedings, and reduced metabolism."*

April 2006 another NTP report titled, "*Toxicity of Genistein*" confirms, "*Plasma isoflavone (estrogen) levels in infants fed soy formula were also higher than for adults ingesting similar levels of isoflavones from soy-based foods….."*

1997- Clinical Mass Spectrometry Center, in Ohio reports, *" The high steady state plasma concentrations of isoflavones in infants fed soy-based formula is explained by reduced intestinal biotransformation…and is maintained by constant daily exposure from frequent feedings. The daily exposure of infants to isoflavone in soy infant formulas is 6-11 fold higher on a bodyweight basis than the dose that has hormonal effects in adults consuming soy foods."*

While the "Journal of Pediatric Gastroenterology and Nutrition" references a 1994 study from the "American Journal of Clinical Nutrition," reporting "*When adjusted for body weight, studies show that infants exclusively fed soy-based formulas are exposed to a daily intake of (estrogenic) isoflavones that is 4 to 13 fold higher than the 0.7mg/kg intake shown to exert significant physiologic effects on hormonal regulation of women's menstrual cycles."*

On a bodyweight basis, infants fed soy-based infant formulas have circulating concentrations of hormones reported to be much higher than adults eating a diet rich in soy foods. Soy-based infant formula actively disrupts hormone levels, and worth repeating, soy estrogenic endocrine disruptors are for several months the entire source of infant dietary intake.

Reported in NIEHS News, Vol 110, June 2002, *"NIEHS researcher Retha Newbold, states that "Even low blood levels of bioactive genistein can produce significant accumulation in endocrine –responsive tissues. According to NIEHS researcher Walter Rogan, "Infants fed soy formula are at the highest end of human phytoestrogen exposure because all of their calories are derived from soy. Newbold says, 'Someone asked me, do you really think that soy infant formula is really harmful to kids?' My answer was another question: 'do you really think excess estrogens are harmful to kids?'"*

Ministry of Health, New Zealand reports, "*Soy infant formula contains high levels of the isoflavones, genistein and daidzein- These are chemicals with structural similarities to estrogen. Infants consuming soy formula have high levels of circulating isoflavones. These are an order of magnitude greater than the levels of isoflavones*

which have been shown to produce physiological effects in adult women consuming a high soy diet."

National Toxicology Program (NTP) reports that absorption for both daidzein and genistein is 1-3 hours following intake of soy isoflavones, and genistein and daidzein equivalents are reported to peak at 6-8 hours following ingestion of soy isoflavones.

NTP report, "Toxicity of Genistein," Table 4: "*Estimated Isoflavone Intake by Infants Consuming U.S. Soy Formulas: Formula isoflavone intake measures 22.5 to 24.8 mg/day by age 1 week, 31.5 to 36.0 mg/day in one month, and 41 to 45mg/day at 4 months."*

April 2006 NTP, "*Toxicity of Genistein"* reports, "*Cytotoxicity (toxic effect on cells) occurred in mice at genistein concentrations 6.8mg."*

A published study from Switzerland reports, "*Occurrence and significance of the isoflavones daidzein and genistein in infant formulas: Feeding newborns exclusively with (soy infant) formulas would result in a mean daily intake of isoflavones of up to 20 mg/kg body mass. This dose is up to 25 times higher than the dose which was shown to prolong the menstrual cycle in women."*

A more recent study demonstrated that small amounts of soy formula providing just 1.6mg to 3.5 mg isoflavone/kg/day can have damaging physiologic hormone effects in monkeys.

The NIEHS confirms, "*Soy infant formula contains large amounts of isoflavones (plant-estrogens) that can occupy estrogen receptors and act as estrogens in the laboratory. A food substance with estrogen activity might prolong the effect of maternal hormones or interfere with hormonal homeostasis in the child. We conclude that more clinical and epidemiological study is warranted."*

Active isoflavone estrogenic potency varies among soy: cereals, snacks, foods, beverages, including soymilks depending upon harvesting conditions related to: geographic location, season, climate, soil, and processing. FDA confirms that soy food and beverages including infant formulas contain unknown amounts of estrogenic isoflavones.

2004, "The American Society for Nutritional Sciences," AC Chen and SM Donovan report, *"U.S. infants are fed soy formulas containing up to 47mg/L of isoflavones (>65% as genistein + genistein); Little attention has been focused on genistein's impact on developing intestine. The concentration of total isoflavones in soy infant formulas ranges from 32 to 47 mgL….a 4-month-old, soy-formula-fed infant consumes 28-47mg (or 6-9mg/kg body weight/d) of isoflavones each day. This dose is 6 to 11 fold higher than the dose found to have physiological effects in adult humans. Thus, a biphasic effect of genistein was seen with a low dose stimulating intestinal cell proliferation through the estrogen receptor, whereas a high dose of genistein inhibited intestinal cell proliferation and altered cell cycle dynamics. A high dose of genistein may potentially compromise intestinal growth. Previous studies also have shown that genistein influences intestinal cell dynamics. The ability of genistein to stimulate and inhibit intestinal cell proliferation may have implications for soy formulas on intestinal growth."*

The FDA Center for Food Safety does not label varying levels of estrogenic availability of soy foods or soy-based formulas. And unlike the USA, countries worldwide restrict soy plant-estrogen infant formulas as "prescription only," and while

under strict physician supervision careful follow-up and reporting of adverse effects is required.

Confirming that infants are participating in a long-term experiment without parental knowledge, in 2000 FDA John Henkel concludes, "*The NIH is sponsoring a long-term follow-up study on the safety of soy infant formula. (Those consuming soy infant formula) will be evaluated for any adverse effects from infancy into childbearing years. Published in 1997in the medical journal 'The Lancet' showed that infants consuming soy formula had 5-10 times higher levels of isoflavones (estrogens) in their blood serum than women receiving soy supplements who show menstrual disturbances. These levels may cause toxicological effects. Infants receive higher doses of soy and isoflavones than anybody because it is their only food and they are consuming it all the time. "*

Promised nine years ago……an FDA evaluation of (a few thousand) published soy studies confirming damaging health effects, remains non-existent.

The greatest challenges confirmed by study results involving endocrine disruptors including estrogenic chemicals, is the long held conviction by many toxicologists that "the dose makes the poison." Safety levels of soybean endocrine disruptors consumed by all humans, but particularly exposure to fetus, infants, and children have not been FDA established. Clearly there are no known safety limits for what is not proven as safe, none for soy estrogenic compounds, and none for soy antinutrients.

2008, Journal of Exposure Science and Environmental Epidemiology," YA Cao et al report, "*……few studies report isoflavone levels in infants. Urinary concentrations of genistein and daidzein were about 500 times higher in the soy formula-fed infants than in the cow milk formula-fed infants. Concentrations of equol were detectable in a few urine samples."*

Health Action Network Society reports, "*Problems in both sexes associated with soy-based infant formula later in life also include extreme emotional behavior, immune system problems, pituitary insufficiency…thyroid disorders including thyroid problems in babies and infantile leukemia."*

(Thyroid disorders and leukemia are individually addressed later in this report.)

1998, "American Journal of Clinical Nutrition," AA Franke et al report, "*Isoflavones in human breast milk and other biological fluids- The HPLC method was also used to measure concentrations of isoflavones and their glucoside conjugates in various soy-based infant formulas. Total isoflavone concentrations varied between 155 and 281 mg/kg. ….a moderate challenge with 20g roasted soybeans (equivalent to 37mg isoflavones), we detected mean total isoflavone concentrations of approximately 2.0 micromol/L in plasma, 0.2micormol/L in breast milk, and 3.0micromol/h in urine. According to our measurements, with adjustment for body weight, isoflavonoid exposure is 4-6 times higher in infants fed soy-based formula than in adults eating a diet rich in soyfoods."*

NTP reports: "*Postnatal exposure to genistein (soy estrogens) with regard to neurodevelopmental endpoints, assessment of alterations with prenatal exposures, animal studies including effects on weight, reproductive and developmental outcomes, human longitudinal studies from prenatal exposure to age 18 to evaluate neurodevelopmental outcomes, and case control studies of congenital malformations to assess developmental risks. In comparisons to controls showed elevations of total genistein in all tissues in*

males and females fed 100 and 500 part pre million genistein. Brain genistein was elevated in the 500 ppm group/ and 5ppm in females increased ovarian, uterine, and liver total genistein concentrations compared to controls. There is increase in genistein in mammary gland. A number of statistically significant effects on hematology (blood and blood producing organs) and clinical chemistry parameters were observed. Significant organ weight effects considered to be treatment related at 26 to 52 weeks (of genistein study) were increased relative weights of adrenal, spleen, prostate, testis, ovary, uterus. Study authors reported an increase in osteoporosis (disorder characterized by increasing bone density). Other significant organ weight effects occurred but the study authors concluded that those effect resulted from reduced body weight. Following 24-hour treatment period, toxic effects on cells was determined using a staining method, and cell toxicity was determined at genistein concentrations of 6.8 mg/L. Concerns about soy-induced thyroid toxicity arose in the 1930's. In the 1950's and 1960's cases of altered thyroid function were reported in infants fed soy formula."

Health Action Network Society reports, "*Problems in both sexes associated with soy-based infant formula later in life also include….irritable bowel syndrome, asthma, …early maturation in girls….Infertility, reproductive problems, thyroid and liver disease due to dietary intake of isoflavones have been observed for several specials of animals."*

1986, "Archives of Pediatrics & Adolescent Medicine" L. W. Freni-Titulaer et al report, "*In subjects with onset of premature thelarche (breast development) before 2 years of age, significant positive associations were found with a maternal history of ovarian cysts, consumption of soy-based formula, and consumption of various meat products."*

2004, Mothering Magazine, Kaayla Daniel reports, "*Indeed thousands of studies link soy to malnutrition, digestive distress, immune-system breakdown, thyroid dysfunction, cognitive decline, reproductive disorders and infertility- even cancer and heart disease. In short, there is no historical precedent for eating the large amounts of soy food now being consumed by infants fed soy formula. Rural poor in China have never seen let alone feasted on soy……or other newfangled soy products that have infiltrated the American marketplace. ..neither soy milk nor soy infant formula is traditional in Asia. Soy in the West has been a product of the industrial revolution- an opportunity for technologists to develop cheap meat substitutes….the Federation of American Societies for Experimental Biology decreed in 1979 that the only safe use for soy protein isolates was for sealers for cardboard packages." (Soy was originally introduced to the market as a cardboard glue….the only place it may be safe).*

Soy estrogenic and soy antinutrient exposure, especially during fetal and infant body and brain developmental stages are overwhelmingly proven to cause a host of health risks; diseases and disorders, to be increasingly revealed throughout this report.

SOY CAUSES EXTENISVE REPRODUCTIVE DISORDERS & DISEASE-

Scientists have indicated since the 1940's and along with consistent scientific evidence to this day, soy phytoestrogens are repeatedly proven throughout a multitude of published studies to cause a vast assortment of irreversible reproductive defects to both males and females. Repeat confirmation of soybean estrogenic damage caused to wildlife, laboratory animals, and to the human reproductive tract confirms soybean status

as an actively dangerous "endocrine disruptor" particularly during reproductive system development.

U.S. Environmental Protection Agency refers to soy phytoestrogens, as "*active estrogens.*"

2006, The National Toxicity Program meeting is to: *"1. Interpret the strength of scientific evidence that genistein is a reproductive or developmental toxicant based upon data from animal or human studies. 2. Assess scientific evidence that adverse reproductive/developmental health effects may be associated with such exposures."*

NTP concludes in their 2006 meeting that over 4 million American infants younger than one year of age are fed soy-based formulas, resulting in extreme soy phytoestrogen levels, with evidence of a vast assortment of reproductive abnormalities in male and female mice and other experimental animals.

Studies prove, without any doubt that soy phytoestrogens are active estrogenic phytochemicals capable of causing complex endocrine disrupting changes resulting in extreme damaging health effects, with highest risks resulting during most sensitive fetal, infant, and child developmental timeframes. Estrogens, especially excess estrogens are well-known to cause a vast assortment of male and female reproductive abnormalities, including sexual differentiation damage particularly when intrinsic hormone balance is disrupted during gestation and/or infancy.

Studies also confirm that soy phytoestrogens and antinutrients are increasingly dangerous to health when in combination with other (unavoidable) estrogenic contaminants such as: pesticides, herbicides, pollutants, plastics (PBC's) etc., etc.

FDA Deputy Director Janice Oliver, Center for Food Safety and Applied Nutrition states, "*FDA acknowledges that concerns have been voiced about possible effects of isoflavones in soy infant formulas on sexual development, neurobehavioral development, immune function and thyroid disease. The Food and Drug and Cosmetic Act requires that foods must be properly labeled. While FFDCA does not include a specific provision for warning statements, it does give FDA the authority to require information on the label of a food to prevent the food from being misbranded. Section 403(a)- food is deemed to be misbranded if its labeling is false or misleading. Section 201(n) determines whether labeling or advertising of a food is misleading. FDA could establish requirements of a warning statement if it had evidence that information about the use of a food product was material information needed for consumers. FDA could require a waning statement on the product label based on valid scientific data. We would have to be provided valid scientific information that show for whom soy isoflavones are unsafe, why, and how they are unsafe for the target population."*

2001, FDA's National Center for Toxicological Research, reports, "*Project # E0212213- ADDEND: A Pilot Study to Assess the Effect of Developmental Genistein Exposure on Sexually dimorphic Behaviors- FY 2000 Accomplishments: Manuscript published describing the behavioral alterations resulting from developmental and chronic dietary genistein exposure. This manuscript was the first published from the NTP-supported endocrine disruptors studies here at NCTR and provides baseline data for future genistein studies as well as a basis for the current multi-generational studies.*

Project # E0213213 ADDEND: The Effects of Developmental/Chronic Genistein Exposure over Multiple Generations on Maternal, Play, Mating/Reproductive Behaviors and Neurochemical Measures- Objective(s): To determine whether chronic exposure of

rats over multiple generations to genistein a compound with potential estrogenic properties, will alter maternal behavior, play behavior of either sex, the female lordosis response, male mating behavior, or the amphetamine-induced release of striatal dopamine, which is known to be estrogen-modulated. FY 2000 Accomplishments: Two manuscripts in press. One described the effects of dietary genistein exposure on maternal behavior and the importance of examining maternal behavior in studies of endocrine disruptors with estrogenic actions. The other manuscript reviews the developmental neurotoxicity of endocrine disruptors.

Project # E0212215 ADDEND: Neuortoxicological Effects of Exposure to Estrogenic Compounds during Development: II. Genistein. Objective(s): 1) To determine whether developmental exposure to genistein may modify the sexually dimorphic areas of the adult rodent brain. 2) To compare neurochemical and neurohistological biomakers of genistein exposure for their relative sensitivity and concordance. FY 2000 Accomplishments: 1) Genistein was identified as one of a family of estrogenic compounds that interfered with normal sexual differentiation by feminizing the development of the genetically male rat brain. 2) A mathematical dose-response model for comparing and predicting the effects of genistein with those of other estrogenic compounds was developed. These models should have predictive value for determining the risk for this type of neurotoxic outcome as a result of exposure to various other estrogenic compounds.

Project # E0213215 ADDEND: Multigenerational Exposure to Estrogenic Compounds: I. Genistein Effect on Volume of Sexually Dimorphic Nucleus- Objective(s): To evaluate the hypothesis that multigenerational exposure to genistein may produce a reduction in the volume of the male sexually dimorphic nucleus of the medial preoptic area of the hypothalamus. FY 2001 Plans: Complete the Image Analysis of the male brains in order to see if this second experiment on genistein also shows that it can feminize the sexual differentiation of genetically male rats, as was observed in a previous experiment.

Project # X00050- Preinatal Biomarkers of Exposure in Genistein: Effects on Testosterone and Neuronal Estrogen Receptor Legation during Development- Objective(s): 1) To develop a dosing regimen with genistein and measure the resulting blood levels of genistein and testosterone in perinatal-aged male rats. 2) To locate estrogen receptors and aromatase, within the brains of perinatal-aged rodents exposed to genistein. 3) To evaluate the rate of neuronal apoptosis and proliferation in the sexually dimorphic hypothalamic nuclei (DSN) of perinatal-aged rats exposed to genistein. 4) To explain the bimodal dose-response curve previously observed for chronic dietary exposure to genistein and other endocrine disruptors. 5) To expand does-response comparisons for the three primary endpoints to other endocrine disrupting compounds; nonylphenol and ethinyl estradiol. FY 2000 Accomplishments: The protocol has been extended to add a consideration of the effects of very small amounts of estrogenic compounds on both testosterone levels as well as the binding of these agents to estrogen receptors located in the developing hypothalamus. The additional biomarkers should comprise a very useful screening system to identify compounds that may provide similar hazards for the normal sexual differentiation of the brain.

Project# E0213601, Transgenic Mouse Evaluations of Genistein: 28-day and 36-week Studies- Objective(s): The phytoestrogen genistein is a primary component of a

high soy diet. There is currently widespread interest in the impact of a high soy diet on human health. Where there is some indication that phytoestrogen may improve health in per-and postmenopausal women, there is concern that these compounds may have the potential to be carcinogens. The study is being conducted to investigate this possibility. Specific goals for the project are: 1) To determine the toxicity of genistein in the C57B16/J strain and to select doses for the 36 week studies. 2) To identify the potential carcinogenicity of genistein in the p53 transgenic mouse model. 3) To determine if the potential carcinogenicity of genistein relates to changes in the rates of cell death and cell proliferation. 4) To determine if exposure to genistein results in an increase in the mutant frequency in a reported gene, (Hprt), in the splenic lymphocytes of the p53 mouse. FY 2000 Accomplishments: 1) Protocol approved in FY 2000 YF 2001 Plans: 1) Conduct the 14-day dose-range-finding study. 2) Initiate 9-month chronic study."

Estrogenic endocrine disruptors are not confined to causing adverse effects of the reproductive tract, but are proven as capable of causing irreversible damaging effects to multiple endocrine-sensitive organ systems, including massive disruptions during neurological development, as revealed later in this report. The soy isoflavone cause of multiple cancers as well and promoting cancer proliferation is also exposed later in this report.

July 2008, online by "Neurotoxicology" H. Patisaul et al, "*Two hormone-like compounds liked to the consumption of soy-based food can cause irreversible changes in the structure of the brain resulting in early–onset puberty……in research animals, according to a new study by researchers at North Carolina State University. The study is a breakthrough in determining how these naturally occurring endocrine disrupting compounds can cause reproductive health problems…… a region of the brain that is important for female reproduction can be significantly altered by exposure to phytoestrogens or plant-produced chemicals that mimic hormone – during development. Specifically, the study finds that the compounds alter the sex-specific organization of the hypothalamus, a brain region that is essential to the regulation of puberty and ovulation. The study also shows that the phytoestrogens could cause long-term effects on the female reproductive system. …the affected 'circuitry' of the brain is similar in both rats and humans…...the changes in brain structure cannot be reversed. ……ascertaining the effects of phytoestrogens on developing fetuses and newborns …these phytoestrogenic compounds cross the placental barrier in humans and that, while many people are concerned about the effects of man-made compound on human health it is important to note that some naturally occurring substances can have similar effects. The study shows that both genistein and equol result in the early disruption of the rat's estrus cycle…...the study also showed that genistein caused the early onset of puberty. The disruption of the estrus cycle could stem from problems with the brain or ovaries…Patisual explains that the brains of both female rats and female humans have a region that regulates ovulation. That part of the brain is organized by hormones during development – the neonatal stage for rats and during gestation for humans. Patisaul says the new study shows that the female brain is 'critically sensitive' to genistein and equol during this (gestational) stage of development- and that this may indicate that the brain is also especially sensitive during this period to all phytoestrogens and possibly other man-made (estrogenic) chemicals such as bisphenol-A."*

As concluded throughout reproductive and neurological developmental studies, the female gender is highly sensitive to endocrine disrupting soy phytoestrogens, while it is proven that the male gender reacts with even higher sensitivity to soy estrogenic phytotoxicity. Autism and other brain disorders, although diagnosed in both genders, the more frequent diagnosis of neurological disorders in male gender should not be regarded as purely coincidental.

2004, "Toxicological Sciences," A C Scallet et al report, "*Endocrine disruptors (ED) may alter brain development, by mimicry or modulation of endogenous hormone systems. Sexually dimorphic nucleus (SDN) of the medial preoptic hypothalamus becomes larger in adult males than females, but its final volume may also reflect the hormonal conditions prevailing during development. Two EDs have recently been studies in protocols involving lifespan exposures are the phytoestrogen genistein and the weakly estrogenic compound para-nonylphernol (surfactants and plastics). The NTP has established an interagency agreement between the NIEHS and the NCTR designed to evaluate the effects of a range of does of endocrine disrupters on hormone-sensitive tissues over 'multiple generations' in Sprague-Dawley rats. Among the compounds selected were genistein…..Genistein is a phytoestrogen found in 'many' soy products consumed by humans. It is known that SDN structure may be altered following perinatal exposure to either estrogens or androgens….An irreversible syndrome then follows estrogen exposure during a critical perinatal period. The typical pattern of development of ER (estrogen receptor)-containing neurons of the SDN is altered, and a distinctive pattern of neurobehavioral changes takes place. Suspension or reduction of this process (in female rat hypothalamus) of programmed cell death, such as may occur with exposure to estrogen, or testosterone, results in the male pattern of hypothalamic development. Under more extraordinary or experimental circumstances, the structure of the genetic female hypothalamus may become masculinized. A masculinized female SDN may result from perinatal exposure to testosterone by excessive levels of estrogen or by moderate amounts of any estrogenic compound……*

The male rat hypothalamus maintains a large population of SDN neurons throughout development. … aromatase, converts the testosterone to estrogen. In…male rats, their hypothalamic neuronal ERs then remain liganded with estrogen produced by the aromatization of their circulating testosterone. …….bind to nuclear estrogen response elements, which can then promote the synthesis of nerve growth factors) and/or their 'trk-A' family tyrosine kinase receptors, which result in the down regulation of apoptosis.

The occurrence of a "feminized" SDN in genetic male may likewise occur insufficient testosterone may be available, aromatase activity may be suppressed…..Finally, 'hypermasculinized' genetic males both behaviorally and neurologically have been observed to occur when excessive estrogenic compounds are present during development in songbirds.

Changes in the reproductive function and behavior of rats who have undergone masculinization or feminization of the SDN have also been reported. Masculinization of genetic female rats results in delayed….sexual receptivity. Feminization of genetic male rats may slow or prevent them from mounting a stimulus female rat."

2007, "Neurotoxicology," H.B. Patisaul and al, report, "*Changes in the volumes f sexually dimorphic brain nuclei are often used as a biomarker for developmental*

disruption by endocrine-active compounds (EACs). In present experiments, we used a more comprehensive approach to assess whether postnatal exposure to the EAC genistein……affected the development of two sexually dimorphic brain regions in male rats: the anteroventral periventricular nucleus of the hypothalamus (AVPV) and the sexually dimorphic nucleus of the preoptic area (SDN). ….we also measured the number of immunopositive calbindin neurons in the SDN and ….gonadotropin0relasing hormone neurons, a neuronal population that is functionally linked to AVPV. We hypothesized that exposure to genistein during this critical period (neonatal) could disrupt brain sexual differentiation. …. …the number of calbindin neurons in the SDN was significantly increased by genistein. Genistein demasculinized male AVPV volume…..These results suggest that acute exposure to EAC (genistein) during a critical development period can independently alter nuclear volumes of sexually dimorphic nuclei and their phenotypic profiles in a region specific manner."

Journal, "Proceedings of the Society for Experimental Biology and Medicine" K. Weber et al reports, "*The purpose of this study was to examine the short-term effects of phytoestrogens in the diet on regulatory behaviors…….and brain androgen metabolizing enzyme activity levels in adult male rats. Significant alterations in the MBH-POA (Medial Basal Hypothalamic-Preoptic Area: regions of hypothalamus) and amygdale 5a-reductase activities were detected in animals receiving the phytoestrogen-containing versus the phytoestrogen-free diets."*

As reported earlier in this report, according to numerous studies the metabolism of soy daidzein to the estrogenic O-DMA or O-desmethylangolensin, while increasing the levels of endogenous estradiol, is gender selective towards the male sex, and most prevalent in males, and that males have higher risk for neurological disorders is not coincidence.

2007, "Cancer Epidemiology Biomarkers & Prevention," YL Low et al report, "*Phytoestrogen exposure is associated with circulating sex hormone levels….Results showed that phytoestrogens were positively associated with plasma sex hormone-binding globulin (SHBG- inhibits the function of testosterone and estradiol) levels are negatively associated with plasma testosterone…….. O-desmethylangolensin was positively associated with plasma estradiol level…… There were significant phytoestrogen interactions with polymorphisms in ESR 1 (ER-alpha) and NR112 genes in affecting estrone levels. We conclude that phytoestrogens modulate sex hormone and SHBG levels…….and interact with gene variants involved in estrogen signaling. Such phytoestrogen-gene interactions may explain the conflicting literature on hormonal effects of phytoestrogens."*

ESR1 is a gene that encodes an estrogen receptor, having affects on cellular proliferation and differentiation in target tissues.

2003, "Journal of Steroid Biochemistry and Molecular Biology" ED Lephart et al report, "*Estrogens and phytoestrogens: brain plasticity of sexually dimorphic brain volumes. Sexually dimorphic brain volumes (sexually dimorphic nucleus of the preoptic area (SDN-POA) and anteroventral periventricular (AVPV) nucleus are influenced by estrogens. Phytoestrogens, derived from plants (especially soy products) are molecules structurally and functionally similar to estradiol. In summary, consumption of dietary phytoestrogens (estrogen mimics) can alter hormone-sensitive hypothalamic brain (sexually dimorphic) volumes in rodents…"*

Suppression of body weight in fetus and infants as caused by soy phytoestrogens is a known cause of several damaging health effects. Encouraging low body weight of females, and more often to males, is again evidence that the male is most sensitive to the endocrine disruptions caused by soy phytoestrogens, and that the male gender is also diagnosed more often with brain disorders is not merely coincidence, as this report continues to prove.

2008, "Biomedical and Environmental Sciences," L Guan et al report, "*Developmental and reproductive toxicity of soybean isoflavones to immature SD rats-Oral administration of soybean isoflavone extracts (SIE) had no effect on food intake but decreased food efficiency ratio. Suppression on body weight gain by SIE was dos-dependent, and the effect was greater on male than on female rats. SIE at high doses exhibited hepatotoxicity by increasing a relative liver weight, and also caused a smaller uterus……in female rats, while leading to larger relative testis and epididymis in male rats. SIE could decrease progesterone concentrations in female rats, whereas in male rats it reduced not only total testosterone level but also sperm count compared with the control group."*

Decades ago, numerous studies began reporting that phytoestrogens cause fertility disorders among animals: cows, sheep, rabbits, cheetahs, guinea pigs, birds, mice, frogs, fish etc. To date, it is also proven by a library of published literature that humans, (fetus, infants, adolescents, and adults) exposed to estrogenic endocrine disruptor, such as soy isoflavones, are also at risk for an assortment of anatomical hormone disruptor disorders involving a variety of organs systems.

2001, "Reproductive Toxicology," KB Delclos et al report, "*Genistein is a naturally occurring isoflavone that interacts with estrogen receptors and multiple other molecular targets. Human exposure to genistein is predominantly through consumption of soy products, including soy-based infant formula and dietary supplements. A dose rang-finding study was conducted as a prelude to a multigeneration bioassay to assess potential toxicities associated with genistein consumption. Genistein was administered……to pregnant dams starting on gestation day 7 and continuing throughout pregnancy. Dietary exposure of the dams continued through lactation, and pups were maintained on the same dosed feed as their mother after weaning until sacrifice at Postnatal day 50. Body weight and feed consumption of the treated dams prior to parturition showed a decreasing trend with a significant reduction at the highest dose. Litter birth weight was depressed in the 1250ppm dose group, and pups of both sexes in that dose group had significantly decreasing body weights relive to controls…..The most pronounced organ weight effects in the pups were decreased ventral prostate weight in males at the 1250 ppm dose and a trend toward higher pituitary gland to body weight ratios in both sexes. Histopathologic examination of female pups revealed ductal/alveolar hyperplasia of the mammary glands at 250 to 1250 ppm. Ductal/alveolar hyperplasia and hypertrophy also occurred in males, with significant effects seen at 25 ppm and above. Abnormal cellular maturation in the vagina was observed at 625 and 1250 ppm, and abnormal ovarian antral follicles were observed at 1250 ppm. In males, aberrant or delayed spermatogenesis in the seminiferous tubules relative to controls was observed at 1250 ppm. There was a deficit of sperm in the epididymis at 625 and 1250 ppm relative to controls……Both sexes showed an increase in the incidence and/or severity of renal tubal mineralizations at doses of 250 ppm and*

above. Dietary genistein thus produced effects in multiple estrogen-sensitive tissues in males and females that are generally consistent with its estrogenic activity. These effects occurred within exposure ranges achievable in humans."

2008, the NIH, National Toxicology Program- "Toxicity Report of Reproductive Dose Range-Finding Study of Genistein," again confirms, "*….concerns have also been raised concerning potential adverse effects of genistein, particularly with regard to reproductive toxicity and the induction of potentiation of carcinogenesis, due primarily to its weak estrogenic activity. Because of these concerns, genistein was selected….to be examined in a protocol utilizing Sprague-Dawley rats to evaluate the effects of multigenerational and long-term exposures to doses of estrogenic agents that produce subtle reproductive tract lesions in developmentally exposed…rat pups. ….genistein reduced body weights….postweaning body weights were reduced in all 100 ppm…groups…both sexes showed depressed body weight…..Male pup preweaning body weight gains were also depressed in the 5ppm groups…. In the unexposed generation, pup birth weights in all exposed groups of both sexes were significantly lower than those in controls. Significant organ weight effects in both sexes were largely confined to single exposed groups in single generations…..Exposure-related microscopic lesions were confined to males with mammary gland and kidney affected…..both developmental and adult exposures contribute to the maintenance of this effect into adulthood. Statistically significant effects of genistein on the incidences of generally minimal to mild kidney lesions….were confined to the continuously exposed generations. Incidences of renal tubule mineralizations were significantly increased….and incidences of inflammation and renal tubule regeneration were significantly increased…..In addition to the results reported above, ancillary studies were conducted with (rat) pups….these results have been reported elsewhere…..Of particular importance are the data on blood and tissue genistein concentrations obtained from adult animals….from dams and fetuses….and from dams and nursing pups. These data provide measures of the internal dose resulting from the dietary exposure concentrations used in the current study and indicate that while fetal and adult exposures to genistein were at concentrations relevant to the full range of human exposures…..very low exposures were achieved during the early neonatal period when the pups were receiving exposures exclusively from the milk. The minimal exposure to genistein during this critical developmental period must be considered in the interpretation of the data derived from the current study. There were 'few' clear, overtly toxic effects that carried over across directly exposed generations or appeared to be imprinted to carry over into unexposed descendents under the conditions of exposure in this study."*

2008, another NIH, National Toxicology Program reports, *"NTP Toxicology and Carcinogenesis Studies of Genistein in Sprague-Dawley Rats- Results from the 2-year study are reported here, and results from the mutigenerational reproductive toxicology feed study are reported separately. The animals in this study were exposed to genistein during various phases of their lives from conception until termination at 2 years, and ingested doses varied over the course of the study. During pregnancy….during lactation….the dams ingested (genistein) doses…..per day. Multigenerational reproductive toxicology study indicated minimal transfer of genistein to pups via the dams' milk. Mean body weights …were less than those of the controls throughout the study…..In females of all study arms….an early onset of aberrant estrous cycles,*

suggesting early reproductive senescence was observed…..Pituitary gland weights were significantly increased…..there was a significant positive trend in the incidences of mammary gland adenoma or adenocarcinoma……There were positive trends in the incidences of adenoma or carcinoma in the pars distalis of the pituitary gland…..a significant positive trend occurred in the incidences of combined adenoma or carcinoma of the pancreatic islets. CONCLUSIONS: There was some evidence of carcinogenic activity of genistein in ..…rat s based on increased incidences of mammary gland adenoma or adenocarcinoma and pituitary gland neoplasms. There was equivocal evidence of carcinogenic activity of genistein in…rats based on marginally increased incidences of pituitary gland neoplasms. There was equivocal evidence of carcinogenic activity of genistein…based on increased incidences of mammary gland adenoma or adenocarcinoma……Exposure to genistein was also shown to accelerate the onset of aberrant estrous cycles in female rats whether exposures were continuous or trunicated at postnatal day140 or at weaning. The effects of genistein on estrous cycling and the incidences of common hormonally related spontaneous neoplasms of……rats are consistent with an estrogenic mechanism of toxicity."

2000, "Fertility and Sterility," SA Whitehead and M. Lacey report, "*The toxic effects of genistein on sexual development and reproduction may be attributed not only to its estrogenic action but also to its action as a protein tyrosine kinase inhibitor."*

Damaging effects caused by soy phytoestrogen inhibition of tyrosine kinase protein during developmental timeframes is described in detail later in this report.

2001, "Toxicological Sciences," M. Cotroneo and C. Lamartiniere report, "*Pharmacologic….Genistein Supports Endometriosis in a Rat Model- To assess estrogenic actions of genistein, we measured uterine estrogen receptor alpha (ER-a) and progesterone receptor (PR) isoforms A and B…..Injections of estrogen or genistein significantly reduced uterine ER-a……PR (B) was significantly increased by all injected doses of genistein or estrogen and by the higher dietary dose…..PR(A) was significantly increased by injected doses of genistein. We conclude that pharmacologic injections ….of genistein support surgically induced endometriosis in rats. Our results suggest a critical role for PR modulation and genistein bioavailability……..."*

2002, Environmental Toxicology Program, NIEHS, WN Jefferson reports, "*Biology of Reproduction- Neonatal exposure to genistein induces estrogen receptor (ER) alpha expression and multioocyte follicles in the maturing mouse ovary: evidence for ERbeta-mediated and nonestrogen actions- A statistically significant increase in the number of ovulated oocytes was observed with the lowest (genistein) dose, whereas a decrease was observed with the two higher doses. This increase in ovulatory capacity with the low dose coincided with higher ER-alpha expression. Histological evaluation on day 19 reveals a dose-related increase in multioocyte follicles in genistein-treated mice. These data taken together demonstrate alterations in the ovary following g neonatal exposure to genistein. Given that human infants are exposed to high levels of genistein in soy-based foods, this study indicates that the effects of such exposure on the developing reproductive tract warrant further investigation."*

It is proven that a percentage of adult patterns of sexual dimorphism and cerebral asymmetries are present at birth with continual development postnatally and hereafter. A large number of published studies conclude that fetus, infants, and children are most sensitive to soy's endocrine disrupting phytoestrogens and soy antinutrients during

developmental timeframes. As with all biologically active estrogens, soy phytoestrogens are proven to cause hormone interruptions in the sexually dimorphic nucleus, confirming soy endocrine disrupting capabilities with further potential to cause anatomical, (such as neurological) disruptions as well.

2006, "Food and Chemistry Toxicology" M. McClain et al report, "*The main hematological findings (in rats) were decreased red blood cell parameters at 500mg/kg/day (with genistein) with a compensatory increase in reticulocytes. …with the exception of a slight increase in gamma glutamyl transferase (liver enzyme) in male and female rats at the high dose, there were a number of other minor changes considered not toxicologically significant. ….in the 52 week (genistein study) dilation of the uterus with fluid at the high dose and cysts of the ovaries in treated animals were observed. Organ weight changes in male rats at the high dose of 500 mg/kg/day (genistein) included increased kidney, spleen, adrenal and testes weights and for females included, increased liver, kidney, spleen, ovary and uterus weights. After26 and 52 weeks of (genistein) treatment, histological changes were seen in the female reproductive organs (ovaries and uterus) and in males (male reproductive-epididymides and prostate) and bone, kidneys heart, liver, and spleen in both sexes. After 52 weeks of (genistein) treatment of males vacuolation of the epididymal epithelium at 500 mg/kg/day and inflammation of the prostate were recorded at a higher incidence at 50 and 500 mg/kg/day. In females, cytological changes in the uterus, squamous metaplasia at 50 and 500 mg/kg/day. Osteopetrosis (hyperostosis, musculoskeletal bone disorder) was observed in male and female rats at 50 and 500 mg/kg/day along with a compensatory increase in extramedullary hemopoiesis (cause organs to substantially increase in size) in the spleen; females were more affected than males. Hepatocellular hypertrophy and minimal bile duct proliferation were recorded at a higher incidence in animals at 500mg/kg/day. It is concluded that almost all of the treatment related findings in these studies are related to the estrogenic properties of genistein as a phytoestrogen. The increased incidence of minimal bile duct proliferation and slightly increased gamma glutamyl transferase (liver enzyme) are indicative of a mild hepatic effect at the high dose of 500mg/kg/day. The no observed adverse effect level of genistein is considered to be 50mg/kg/day based on the presence of mild hepatic effects….the no observed effect level is considered to be 5mg/kg/day based on the hormonally induced functional changes at higher doses."*

NTP, CERHR Soy Formula also reports, *"…onset of premature thelarche (breast development) before 2 years of age….Other significant factors included maternal ovarian cysts……..Association between maternal vegetarianism and hypospadias (birth defect in boys when urinary tract opening is not at the tip of the penis), may be due to estrogenic constituents of soy….alternative explanation….greater exposure of vegetarian women to pesticides used on food plants…..(such as soy)."*

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1998, U.S. Environmental Protection Agency, "National Center for Environmental Research," CL Hughes et al report, "*Previous studies have shown adverse effects on sexual dimorphic development in rat pups treated parenterally with the phytoestrogens genistein and coumestrol during the prenatal and neonatal intervals. Our preliminary study is focused on the effects of genistein, at levels comparable to the upper range of human exposure on fetal and neonatal development. The effects of genistein relative to the reference estrogen DES were examined using the developmental markers anogenital distance, at onset of puberty and initial estrous cyclicity in Long-Evans hooded rats. Male pups within all estrogen-treated groups (DES or Genistein phytoestrogen) had an earlier onset of puberty than the control animals."*

Reproductive damage specific to females-

Laboratory of Molecular Toxicology at North Carolina State University reports, "*Adverse effects on female development and reproduction following neonatal exposure to phytoestrogen Genistein (soy). Females treated with Genistein showed statistically significant decreases in number of live pups over time with increasing dose. Mice treated with stronger dosage of Genistein did not deliver live pups. Pregnancy in Genistein treated mice could not maintain pregnancy" (compared to controls).*

1998, "Fertility and Sterility" CA Awoniyi reports, " *After in utero and lactational dietary exposure to genistein- The weight of the ovaries and uterus and serum levels of estradiol and progesterone in genistein-exposed rats on day 21 were significantly reduced compared with control rats. Our data indicate that in utero and lactational exposure to dietary genistein adversely affects reproductive processes in the adult female rat."*

2000 "Biofactors" S. Watanabe et al report, "*Effects of the isoflavone supplement on hormonal states in young premenopausal women were studied……tablets contained 43.5 mg daidzein, 6.0 mg genistein, 24.0 mg glycitein….caused a prolonged menstruation in 60% of young women, shortened menstruation in 20%, 17% unchanged and 3% because irregular. SHBG significantly increased about 10% in three women. DEAS, androstendione and testosterone showed different responses according to the follicular or luteal phase. T3 and T4 increased as a result of isoflavone tablet administration in the follicular phase, but it decreased in the luteal phase. These changes suggest that isoflavones influence not only estrogen receptor-related functions but the hypothalamo-hypophysis (pituitary gland)-gonadal axis."*

2004, "Hormones and Behavior," HB Patisaul et al report, "*A soy supplement and tamoxifen inhibit sexual behavior in female rats- Proceptive, receptive, and paced mating behaviors are all regulated by, and sensitive to, estrogen and progesterone, suggesting that compounds capable of disrupting these critical hormones may also perturb the display of female sexual behavior. Similarly, the hopping and darting rate was also significantly depressed in both the soy- and the tamoxifen -treated animals compared to the estradiol benxoate (EB 10 pg) and progesterone (P, 500 pg)-treated controls, with the soy-treated animals showing significantly less proceptive behavior than the tamoxifen–treated animals. Finally, soy but not tamoxifen significantly attenuated paced mating behavior in animals compared to the EB-and P –treated controls."*

2006, "Biology of Reproduction", W. Jefferson et al report, "*….genistein exposure during development alters ovarian differentiation by inhibiting oocyte nest breakdown and attenuation oocyte cell death."*

2007, "Molecular Nutrition & Food Research", WN Jefferson et al report, "*Studies in our laboratory have shown that exposure to genistein causes deleterious effect on the developing female reproductive system. Mice treated neonatally on days 1-5 by subcutaneous injection of genistein (0.5-50 mg/kg) exhibited altered ovarian differentiation leading to multioocyte follicles at 2 months of age. Ovarian function and estrous cyclicity were also disrupted by neonatal exposure to genistein with increasing severity observed over time. Reduced fertility was observed in mice treated with genistein (0.5, 5, or 25mg//kg) and infertility was observed at 50mg/kg. Mammary gland and behavioral endpoints were also affected by neonatal genistein treatment. Further, transgenerational effects were observed: female offspring obtained from breeding genistein treated females (25mg/kg) to control males had increased mutioocte follicles. Thus neonatal treatment with genistein at environmentally relevant doses caused adverse consequences on female development which is manifested in adulthood. ….we have shown many effects obtained from feeding genistein, the glycosolated form of genistein found in soy formula are similar to those obtained from injecting genistein."*

2006, "Toxicological Sciences," MG Soni and GJ Nohynek report, "*In recent years, decreased sperm count and increased breast cancer rates have claimed to be associated with man-made and dietary (phyto)-estrogens. Several additives used in foods and other consumer products, such as isoflavones, UV screens, certain alkylphenols, bisphenol A, some parabens and certain phthalates have been shown to be weakly estrogenic in in vitro or in vivo assays. Recent finding on the presence of parabens in human breast cancer tissue samples have ignited the debate on the role of estrogenic food additives in the development of cancer and reproductive toxicity. The current risk assessment of estrogenic substances as food additives is performed individually and combined effects of these substances in the diet are not known. As these substances share a common mechanism of action, an aggregate risk assessment for each chemical in the group and a cumulative risk assessment is needed. Should the estrogenic substances be added to foods/consumer products and if so at what levels?"*

Journal "Hormones and Behavior" by Tom Kouki et al, reports, "*These results suggest that genistein acts as an estrogen in the sexual differentiation of the brain and causes defeminization of the brain in regulating lordosis and the estrous cycle in rats. In addition, neonatal daidzein also has some influence on ovarian function."*

In "Reproductive Toxicology" it is reported that, "*Mice treated neonatally by injection of genistein exhibit altered ovarian differentiation leading to multi-oocyte follicles. Ovarian function and cyclicity were disrupted in genistein treated mice with increasing severity over time. Reduced fertility was observed in mice treated with genistein…..and these effects can be transmitted to subsequent generations. Neonatal treatment with genistein at relevant doses caused adverse consequences on reproduction in adulthood."*

Reproductive damage specific to males-

2005, "Physiology & Behavior," AB Wisniewski et al report, "*Exposure to endocrine disrupting chemicals adversely affects reproductive development and behavior in males. Female C57BL/6 mice were fed a….diet supplemented with 5 or 300 mg/kg of genistein throughout gestation and lactation. Exposure to genistein resulted in smaller anogenital distance and reduced body mass, with the low-dose diet exerting a greater effect. ….defensive behaviors were increased, in males that receive the low-dose genistin*

diet. Exposure to genistein during critical periods of sex differentiation results in concurrent and persistent demasculinization in male mice. Phenotypic and behavioral abnormalities induced by genistein showed a non-monotonic response, where treatment with a low dose exerted a greater effect than treatment with a high dose of genistein. Given the popularity of soy infant formula, the influence isoflavone exposure on reproductive and behavioral health in boys and men should be considered."

1993, "Lancet," RM Sharpe and NE Skakkebaek report, "*The incidence of disorders of development of the male reproductive tract has more than doubled in the past 30-50 years while sperm counts have declined by about half. Similar abnormalities occur in the sons of women exposed to DES during pregnancy and can be induced in animals by brief exposure to exogenous estrogen/DES during pregnancy. We argue that the increasing incidence of reproductive abnormalities in the human male may be related to increase estrogen exposure in utero, and identify mechanisms by which this exposure could occur."*

2001, "International Journal of Toxicology" Division of Neurotoxicology, National Center for Toxicological Research/FDA W Slikker Jr et al report, "*In a series of initial range-finding studies in rats conducted at the NCTR, the effects of dietary exposure to the weak estrogen genistein have been assess using a number of techniques with validated gender-related outcome measures. The findings indicated that dose-related alterations of the volume of the sexually dimorphic nucleus of the medial preoptic area were observed in genistein-exposed male rats…..Additional studies…are necessary to further predict the effect(s) of genistein on human gender-based development."*

2007, "Current Opinion in Obstetrics & Gynecology," MC West reports, "*Time of exposure is crucial, as is interaction with other dietary components. Phytoestrogens are still a current research topic in reproduction and fertility. …..…..with evidence that it (genistein) may cause DNA damage in sperm, depending on the concentration. The effects of phytoestrogen in the body are not limited to oestrogenic action."*

2006, "Human Reproduction," K.A. Tan et al report, "*Infant feeding (male marmoset monkeys) with soy formula milk …..alters testis size and cell composition, and there is consistent, if indirect evidence for possible 'compensated Leydig cell failure'. Similar and perhaps larger changes likely occur in adult men who were fed Soy formula as infants."*

2001, "Environmental Toxicology and Pharmacology," S Wanichacheewa et al report, "*…we administered the extracts from seven kinds of plants to male rats. Treatments with these extracts resulted in a decrease in the number of sperm associated with decreased serum testosterone levels and an elevation of serum prolactin levels. ….some extract significantly decreased the lutenizing hormone levels. Thus the extracts may contain a biologically active substance such as phytoestrogens and lead to a hormonal imbalance."*

Deficiency in lutenizing hormone (LH) can result in hypogonadism resulting in reproductive abnormalities. LH plays a central role in the hypothalamic-pituitary-gonad axis located in the anterior pituitary gland. Once released into systemic circulation LH stimulates the gonads of females and males to release steroid hormones. LH is required for spermatogenesis. LH stimulates Leydig cells to convert cholesterol to testosterone that is responsible for spermatogenesis. LH forms during 16th to 20th week of gestation and are quiescent until puberty. Maternal consumption of soy phytoestrogens may cause

permanent reproductive fetal damage. There may also be infant reproductive damaging consequences during maternal soy consumption while breast feeding. Studies report damaging reproductive effects caused to female or male infants fed soy-based formulas

Story from BBC News, 2008 reports, "*A regular diet of even modest amounts of food containing soy may halve sperm concentrations, suggest scientists. Dr. Jorge Chavarro reports that the normal sperm concentration for a man is between 80 and 120 million per millilitre, and the average of men who ate on average a portion of soy-based food every other day was 41 million fewer.*"

2004, "Journal of Reproduction and Development," BJ Lee et al report, "*Genistein, a soybean-originated isoflavone is widely consumed by humans……its estrogenic activity may affect adversely the development of the male reproductive system. Twenty-one days old ICR mice weaned from dams fed with a casein-based AIN-76A diet during gestation and lactation were exposed to genistein (2.5 and 5.0 mg/kg/day, p.o.) for 5 weeks. Exposure to genistein caused hyperplasia of Leydig cells in testis and a slight increase of interstitial fibroblasts in the epididymis, while estradiol treatment caused severe damage to the testis and epididymis. These results suggest that dietary uptake of genistein during the juvenile period may affect male reproductive development, resulting in a slight decrease in sperm count……..*"

2007, "Food Chemistry Toxicology" RM McClain et al, " *Plasma testosterone and androstenedione levels were significantly lower in the animals fed the phytoestrogen-rich diet (600 microg/g) compared with animals fed the phytoestrogen-free diet. These results indicated that consumption of dietary phytoestrogens resulting in very high plasma isoflavone levels over a relatively short period can significantly alter body and prostate weight and plasma androgen hormone levels …..The findings of this study identify the biological actions of phytoestrogens on male reproductive endocrinology….*"

2004, "The Journal of Steroid Biochemistry and Molecular Biology," MJ McVey et al report, "*Altered testicular microsomal steroidogenic enzyme activities….with exposure to soy isoflavones- Previously, isoflavones have been shown to affect serum androgen levels and steroidogenic enzyme activities. ….exposure to dietary soy isoflavones on testicular microsomal steroidogenic enzyme activities were examined in the rat. F1 male rats were obtained from a multi-generational study where the parental generation was fed diets containing alcohol-washed soy protein supplemented with increasing amounts of Novasoy…..A control group was maintained on a soy-free casein protein-based diet. The diets were designed to approximate human consumption levels and ranged from 0 to 1046.6mg isoflavones/kg pellet feed encompassing exposures representative of North American and Asian diets as well as infant fed soy-based formula. Activities of testicular 3beta-hydroxysteroid dehydrogenase, P450c17 (CRP17), 17beta-hydroxysteroid dehydrogenase were assayed on post natal day (PND) 28, 70, 120, and 360 while 5alpha-reducatase was assayed on PND 28. At PND 28, 3-beta-HSD activity was elevated by approximately 50% in rats receiving 1046.6mg total isoflavones/kg feed compared to those on casein only diet. A similar increase in activity was observed for CYP17 in rats receiving 235.6 mg total isoflavones/kg feed, a level representative of infant exposure through formula, compared to those receiving 0mg isoflavones from the casein diet. These results demonstrate that rats fed a mixture of dietary soy isoflavones showed significantly altered enzyme activity profiles during*

development at PND 28 as a result of early exposure to isoflavones at levels obtainable by humans."

2004, "Urology," GB Srilatha et al report, "…white male rabbits were divided into control and treatment groups. …treatment groups were given estradiol or phytoestrogen daidzein daily for 12 weeks. Chronic treatment with estradiol and phytoestrogen significantly reduced the systemic total testosterone levels. …relaxant responses to acetylcholine, nitroglycerin, and nitergic transmission wee significantly attenuated compared with the control response. …both types of estrogen treatments significantly potentiated norepinephrine-induced antierectile contraction of the corpus cavernosum. These results indicate that estradiol treatment and chronic exposure of phytoestrogen may cause receptor-mediated pathophysiologic changes in erectile function leading to erectile dysfunction."

2005, "The Journal of Nutrition," B Dillingham et al report, "….*Serum collected on day 1, 29, and 57 of each treatment revealed the dihydrotestosterone (DHT) and DHT/testosterone were significantly decreased by the low isoflavone soy protein (Low-iso SPI), treatment group and the high isoflavone soy protein (high-iso SPI) group compared with milk protein isolate group…. Other significant effects included a decrease in testosterone by the low-iso SPI relative to the MPI (milk protein isolate) and high-iso SPI at day 29……and increases in estradiol and estrone by the low-iso SPI relative to the MPI at day 57. In conclusion soy protein, regardless of isoflavone content decreased DHT and DHT/testosterone with minor effects on other hormones providing evidence for some effects of soy protein on hormones.*

2004, Mothering Magazine, Kaayla Daniel reports, "…*soy lowers testosterone levels, …tofu has traditionally been used in monasteries to decrease the libido…Humans and animals appear to be the most vulnerable to the effects of soy estrogens and animals….most vulnerable to the effects of soy estrogens prenatally, during infancy, and puberty, during pregnancy and lactation, and during hormonal shifts of menopause. Infants on soy formula re at the highest risk because of their small size and developmental phase, and because formula is their main source of nutrient. A crucial time for the programming of the human reproduction system is right after birth, the very time when bottles of soy formula are given to many……..Normally during this period, the body surges with natural estrogens, testosterones and other hormones that are meant to program the baby's reproductive development from infancy through puberty and into adulthood."*

2005, "Journal of Nutrition," BL Dillingham et al, "…..dihydrotestosterone (DHT) and testosterone were significantly decreased by the low-isoflavone soy protein isolate…… compared to milk protein isolate. In conclusion, soy protein regardless of isoflavone content (low vs high) decreased DHT and DHT/testosterone with minor effects on other hormones providing evidence for some effects of soy protein on hormones."

Soy phytoestrogens as active endocrine disruptors also damage essential sperm binding functions necessary for fertilization.

2000, "Andrologia," KD Hinsch et al report, "*Sperm motility, binding of spermatozoa to the zona pellucida and induction of the acrosome reaction are prerequisites for successful oocyte fertilization. First observations indicate that genistein*

inhibits the induction of acrosomal exocytosis and binding of spermatozoa to the zona pellucida."

2008, "Human Reproduction," JE Chavarro et al report, "*These data suggest that higher intake of soy foods and soy isoflavones is associated with lower sperm concentration."*

2008, "Journal of Andrology," L Pan et al report, "*Exposure of juvenile rats to the phytoestrogen daidzein impairs erectile function in a dose-related manner in adulthood. When rats were examined in adulthood, we observed that those animals treated with a medium (20mg/kg or high (100mg/kg) dose of daidzein….showed lower plasma testosterone levels and attenuated erectile parameters, including apomorphine-induced erections and intracavernous pressure concomitant with markedly decreased expression of estrogen receptor beta in the corpora cavernosa. Thus these results suggested that exposure of juvenile rats to daidzein in a relatively large amount could adversely affect penile erection in adulthood."*

"The Journal of Urology, Volume 169, Issue 4, pages 1582-86, A Wisniewski et al report, "*Exposure to the phytoestrogen genistein can disrupt normal male sexual differentiation. Perinatal genistein exposure results in transient and lasting alterations in masculination of the reproductive system. These results extend our knowledge of the effects of early genistein exposure on male development and may have implications for human health in terms of potential relationship of endocrine disrupters and urogenital abnormalities thought to be increasing in incidence in boys and men."*

2002, "Molecular Medicine," SL Klein et al report, "*….testosterone concentrations were lower among genistein-exposed than genistein-free males. These data illustrate that exposure to genistein during pregnancy and lactation exerts long-lasting effects on the endocrine and immune systems in adulthood."*

2000, "Neurotoxicology" S Ferguson et al report, "*Volume of the sexually dimorphic nucleus of the medial preoptic area was reduced by genistein, nonylphenol, and ethinyl estradiol exposure in males."*

Soy formula severely interrupts hormone sexual development, gender differences, and fertility that is irreversibly damaging for a lifetime. Soy estrogenic isoflavones are also reported to cause hormone alterations in sex gland functions that may encourage sex reversal. Sexual behavior is reported to become confused in both males and females. Especially during fetal and infant development, balanced hormone levels are proven critical for sexual differentiation and determination.

2000, "British Journal of Urology Int," K North and J Golding report, "*A Maternal Vegetarian Diet in Pregnancy Is Associated with Hypospadias. This study assessment of nearly 8000 boys, found an association between a mother's vegetarian diet and the development of hypospadia (male developmental anomaly in which the urethra opens on the underside of the penis). The authors conclude that vegetarian mothers have greater exposure to isoflavones, and that these plant-estrogens may explain this developmental defect."*

2002, "Phytoestrogens and Health," GS Gilani and JJB Anderson report, "*……subcutaneous injections of genistein to pregnant rats at doses as low as 0.1mg/kg/bw/d during day 15 thought 20 gestation showed that the pups were more susceptible to the development of mammary gland cancer when later exposed to chemical carcinogens. Dietary exposure of dams to genistein at doses as low as 11mg/kg bw/day,*

from gestation day 7 through weaning…until postnatal day 50, resulted in microscopic changes in the mammary gland tissue and reproductive tissues of pups. ….ductal/alveolar hyperplasia and hypertrophy were observed….Additional histologic changes in female progeny at doses of 70mg/kg/bw/day and higher included abnormal cellular maturation in the vagina and abnormal antral follicles in the ovaries. In male progeny, delayed spermatogenesis was seen when dams had received doses > or equal to 70mg/kg bw/day. Both sexes showed developmental delays, such as late eye opening and ear unfolding….in greater detail….the findings showed that genistein in the dose range of 60-100mg/kg/bw/day can cause slight developmental delays or accelerations, minor weight changes to reproductive organs, and minor alterations to some sex-related behaviors. A major concern arising from the ingestion of isoflavones is the possibility of infertility. ….phytoestrogens have been observed to cause infertility in wildlife and laboratory animals. Feeding genistein to Sprague-Dawley rats from gestation day 7 through postnatal day 50 at doses of 250-1250 pg/g resulted in hyperplasia and hypertrophy of the ductal and alveolar mammary glands in male pups…..”

June 2009, “Men’s Health” magazine article by Jim Thornton reports, *But there may be a hidden dark side to soy, one that has the power to undermine everything it means to be male. James Price’s breasts had been painful and swollen. It looked as if gum balls were implanted underneath each nipple. The slightest touch triggered throbs. His breasts by this point resembled the buds of a pubescent girl. Price’s estrogen was so high, in fact, that the doctors were at a loss to explain it. Price explained that he’d…switch to soy milk exclusively. What’s more, studies of these phytoestrogens in leading peer-reviewed medical journals suggest that even lower doses-such as the amount of the 25-gram soy protein target cited by the FDA- have the potential to wreak hormonal havoc. William Kraemer, Ph D says, ‘There are also concerns that soy might decrease a man’s testosterone production and increase his estradiol production, which we tend to associate with female hormone production.’ In a Harvard study published last year in the journal ‘Human Reproduction’ Jorge Chavarro M.D., Sc. D., and colleagues found a strong association between consumption of soy foods and decreased sperm counts. The studies published in the ‘Journal of Andrology and Urology’ respectively looked at the effect of daidzein on the sexual function of male rats. Moderate doses of the phytoestrogen administered either in youth or adulthood significantly affected the quality of their erections…..produced less testosterone, had softer erections, and experienced biochemical changes to their penile tissues.”*

No levels of estrogenic endocrine disruptors, inclusive of soy phytoestrogen consumption, can be regarded as safe for developing fetus, infants, and children exposed. There exists a massive amount of published studies confirming soy phytotoxic cause of extreme and outrageous irreversible adverse reproductive damage to both genders. Evidence that soy phytotoxicity causes extensive damage to the entire reproductive tract also confirms soy phytotoxic capabilities to cause damage to multiple estrogen-sensitive organ systems, including the brain.

SOY PHYTO-TOXICITY CAUSES NEURO-TOXICITY:

Soy phyto-estrogens as all estrogens target the brain. It is overwhelmingly documented and accepted that estrogen hormones have multiple effects throughout development on estrogen responsive tissues in the brain. Multiple systems of the body

including the brain are estrogen targets, and estrogenic overdose especially during most sensitive timeframes of fetal, infant, and child exposure can, without question, result in irreversible adverse neurological effects. Besides soy phyto-estrogen endocrine disruptors, soy antinutrients compound soy phytotoxic nervous system destruction.

Autism diagnosis is reported as four times more prevalent in boys. This report describes in detail as to how endocrine disrupting soy phytoestrogens and multiple soy antinutrients cause irreversible neurological disorders leading to ADHD, mental retardation, and/or autism in females, and more often in males.

2001, "BioMed Central Neuroscience," TD Lund et al report, "*Visual spatial memory is ….inhibited in males by dietary soy phytoestrogens- In learning and memory tasks, requiring visual spatial memory (VSM,) males exhibit superior performance to females……This study examined the influence of phytoestrogens on VSM..….to examine varying aspects of memory. Furthermore, males fed the high phytoestrogen containing diet (Phyto-600) had significantly higher phytoestrogen concentrations in a number of brain regions, (frontal cortex, amygdala & cerebellum): in frontal cortex, expression of calbindin (CALB) decreased while COX-2 (cyclooxygenase-2 an inducible inflammatory factor prevalent in Alzheimer's disease) increased. Results suggest that dietary phytoestrogens significantly sex-reversed the normal sexually dimorphic expression of VSM…..in males VSM was inhibited by the same diet (Phyto-600). These findings suggest that dietary soy derived phytoestrogens can influence learning and memory and alter the expression of proteins involved in neural protection and inflammation in rats.*"

Soy isoflavones are phytochemical plant-estrogen-antinutrient-cocktails that target and disrupt most important areas of the developing brain that control cognition, moods, behavior, emotions, learning, language, memory, and the like. Phytoestrogen-caused hormone disruptions are known to cause irreversible destruction to several neurotransmitter systems while causing damage to neuronal connectors and functions.

Asperger's syndrome (an autistic disorder) is also associated with abnormalities in frontostriatal pathways resulting in defective sensorimotor gating that is characteristic of repetitive thoughts, speech, and actions. Those diagnosed with Asperger's syndrome have significantly less grey matter as well. Neuropathways connect frontal lobe regions with basal ganglia that mediate cognitive and behavioral programs within the brain. Grey matter, a major component of CNS consisting of neurons, glial cells, and short nerve cell extension processors (axons and dendrites) are all extensively manipulated by estrogenic influences, including endocrine disrupting soy phytoestrogens.

The frontostriatal circuit are neural pathways that connect frontal lobe regions with the basal ganglia that mediate motor, cognitive, and behavioral programs within the brain. Proper functioning of the frontostriatal pathways depends upon inputs from dopaminergic, serotonergic, noradrenergic, and cholinergic neurotransmitter cell groups that modulate information processing. Soy phytoestrogens indiscriminately disrupt each of these neurotransmitters as revealed in detail later in this report.

Proper development of the brain requires the precise integration of numerous temporally and spatially regulated stimuli. The brain is a chemically and functionally distinct organ that is highly sensitive to estrogenic manipulations. Studies report that estrogen directly influences brain function through estrogen receptors located on neurons in multiple areas of the brain, and also appears to have direct membrane-mediated effects on neurons.

2007, "Journal of Biomedical Science" Y. Jin et al report, "*Genistein and daidzein induce neurotoxicity at high concentrations in primary rat neuronal cultures. Isoflavones possess estrogen-like activity…… isoflavones specifically genistein and daidzein are toxic to primary neuronal culture at high concentration.*"

2003, "Journal of Anti-Aging Medicine" IW Goddard reports, "*Epidemiological research has demonstrated a positive correlation between tofu consumption and brain atrophy…..…recent in-vivo findings strengthen the case for a possible causal mechanism of soy-induced neurodegeneration In tissue cultures, genistein has been shown to suppress both DNA synthesis and the effects of brain derived neurotorphic Factor (BDNF) as well as to increase glutamate toxicity and glutamate induced peroxide accumulations. Recently the ability of dietary soy to suppress BDNF expression in the hippocampus and cerebral cortex has been demonstrated in male rats. Given that BDNF facilitates the survival of neurons and that its suppression is known to cause neural atrophy, such in-vivo findings clearly lend credence to hypothesis that soy may cause brain atrophy……some individuals may choose to adopt a policy of avoiding soy until it is proven safe rather than consuming it until it is proven unsafe….avoidance of soy also seems reasonable at the level of personal risk assessment and as such should not be discouraged as alarmist.*"

2002, "Journal of Neurochemicals," J Lee et al report, "*Evidence that brain-derived neurotophic factor (BDNF) is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis.……in the hippocampus of adult mice….BDNF signaling is important for proliferation of neural stem cells. The reduced neurogenesis in BDNF +/- mice was associated with a significant reduction in the volume of the dentate gyrus. These findings suggest that BDNF plays an important role in the regulation of the basal level of neurogenesis in the dentate gyrus of adult mice, and that by promoting the survival of newly generated neurons BDNF contributes to the enhancement of neurogenesis induced by dentate gyrus.*"

Studies prove soy phytoestrogens suppress BDNF to then suppress the dentate gyrus that is importantly involved in the trisynaptic loop of the hippocampus. Soy phytoestrogen/antinutrients are proven to cause biochemical cascading damaging effects.

2003, "Neuroscience Letters," SF File et al report, "*Soya phytoestrogens change cortical and hippocampal expression of BDNF mRNA in male rats- ….rats were fed a diet containing 150microg/g soya phytoestrogens or a soya-free diet for 18 days. This concentration of phytoestrogens should have been sufficient to occupy the oestrogen-beta, but not the oestrogen-alpha receptors. …. …..significant reductions were found in brain-derived neurotrophic factor (BDNF) mRNA expression in the CA3 and CA4 region of the hippocampus and in the cerebral cortex in the rats fed the diet containing phytoestrogens, compared with those on the soya-free diet. This suggests a role for oestrogen-beta receptors in regulating BDNF mRNA expression.*"

2008, "Neuropsychopharmacology," AJ Law et al report, "……*the negative results suggest that other features of mood disorder, such as decreased hippocampal volume and BDNF expression are related to different aspects of the pathophysiological process.*"

1997, "Brain Research and Molecular Brain Research," B Connor et al report, "*These results support and extend previous findings that BDNF mRNA is reduced in the*

human Alzheimer's disease hippocampus and temporal cortex, and suggest that a loss of BDNF may contribute to the progressive atrophy of neurons in Alzheimer's disease."

Estrogen hormones have multiple effects on estrogen responsive tissues throughout the body and brain. Soy phytoestrogens exhibit agonistic and antagonist effects upon the brain, causing irreversible endocrine disruptions that are proven as most damaging during prenatal and postnatal development

2000, "Brain Resources" ED Lephart et al report, *After approximately 5 weeks on the diets (P-600 or phytoestrogen 600microg/g vs. phytoestrogen free or P-free) the male rats were killed at 105 days, P-600 plasma phytoestrogen levels were 78-fold higher than the P-free values and the medial basal hypothalamic and preoptic area phytoestrogen content was 8-fold higher than the P-free group demonstrating the passage of phytoestrogens into the brain. …independent of brain site the abundance of calbindin from male P-600 rats was significantly lower than P-free animals. These data suggest that consumption of phytoestrogens via a soy diet for a relatively short interval can significantly: (1) elevate plasma and brain phytoestrogens levels and (2) decrease brain calcium-binding proteins……(while calcium-binding proteins are associated with protecting against neurodegenerative diseases)."*

The limbic system is an area of the brain located on top of the brainstem, underneath the thalamus and buried within the cerebral (cerebrum) cortex. The limbic brain system includes the amygdale, hippocampus, hypothalamus, and several other structures that are responsible for controlling: behavior; emotions, motivation, attention, awareness, thought, language, memory, sensory perception, motor function, stress, vision, and olfaction. The limbic system contains estrogen receptors and is highly sensitive to physiological modifications in estrogenic hormonal levels that can be rapidly manipulated by soy plant-estrogens that is especially dangerous during fetal and infant developmental timeframes.

Brain disorders, including autism are known to involve disturbances in the neuropathology of the limbic system. Soy isoflavones are reported to cause damaging effects to multiple areas of the brain and inducing irreversible neuronal cell toxicity.

2004, "Life Science" EJ Choi, and BH Lee report, "*Evidence for genistein mediated cytotoxicity and apoptosis in rat brain- The present study was undertaken to investigate the cytotoxic effects of chronic ingestion of genistein on rat brain in vivo and the observations were compared with results from in vitro studies with primary cultures of cortical neurons. The high dose genistein (20mg/day) significantly increased lactate dehyrogenase (LDH) in rat brain tissue homogenates, whereas the low dose of genistein (2mg/day) decreased LDH. In addition, DNA fragmentation was detected in homogenates of brain tissue from rats receiving either dose of genistein. There results are consistent with those of in vitro studies indication that high concentrations of genistin caused cytotoxicity and DNA ladder formation in primary cultures of cortical neurons. Genistein decreased the expression of the 32 kDa caspase-3 precursor and increased the levels of cleaved caaspase-3 (18 kDa) in both rat brain tissue homogenates and in primary cultures of cortical neurons. ….expression of poly (ADP-ribose) polymerase was also decreased in both experimental systems. There results suggest that chronic administration of genistein at high doses may induce cytotoxicity and apoptosis in the rat brain."*

2007, "Hippocampus" A. Contestabile et al report, *"Down syndrome the leading genetic cause of mental retardation is characterized by reduced number of cortical neurons and brain size. The occurrence of these defects starting from early life stages points at altered developmental neurogenesis as their major determinant. The goal of our study was to obtain comparative evidence for impaired neurogenesis in the hippocampal dentate gyrus of down syndrome fetuses…..We found that in the dentate gyrus of down syndrome fetuses the number of proliferating cells was notably reduce when compared with controls. Results provide novel evidence for proliferation impairment in the hippocampal dentate gyrus of the down syndrome fetal brain…."*

Further studies listed in this report commonly confirm soy isoflavones causes an assortment of brain cell toxicity, to include the reductions of cortical neurons, and impairment to the hippocampal dentate gyrus of which are reported evidence in the cause of downs syndrome and other irreversible neurological disorders.

Soy plant-estrogens are actively proven to mimic estrogenic functions and actions on the brain. During prenatal and postnatal development the brain is uniquely susceptible to estrogenic endocrine disruption, including disruptions caused by soy plant-estrogens as proven capable of altering and interrupting important neurological processes related to the dysfunction of: hormones, enzymes, amino acids, essential brain nutrients, resulting in damaging effects of brain neurotransmitters and electrical pathways

Journal of "Pharmacology and Experimental Therapeutics" S. Belcher and A Zsarnovszky report, "*Estrogenic Actions in the Brain: Estrogen, Phytoestrogens, and Rapid Intracellular Signaling Mechanisms- Because infants that are fed soy-based formula have especially high plasma concentrations of daidzein and genistein during critical periods of brain development, understanding the normal actions of estradiol during perinatal development of the brain the way phytoestrogens may influence these actions…...is extremely important…..xenoestrogens (estrogenic pollutants) and phytoestrogens may have similar effects on rapid-signaling (nervous system) mechanisms that are normally regulated by endogenous estrogen. Thus, it is anticipated that phytoestrogens may modify the normal activities of endogenous estrogens during critical periods in the developing brain that may influence the function of the mature adult brain. Transactivational potency of daidzein was nearly equivalent to that observed for the same concentration of estradiol……the transactivational potency of genistein at ER-a and ER-b is about 2-fold greater than a similarly high concentration of estradiol."*

Janice Oliver, Deputy Director, FDA Center for Food Safety and Applied Nutrition confirms, "*FDA acknowledges that concerns have been voiced about possible effects of isoflavones in soy infant formulas on sexual development, neurobehavioral development, immune function, and thyroid disease."*

"Neurobiological Perspectives on Autism," by Lauren Hellew reports, "*There is evidence that autism is associated with specific structural brain abnormalities. Dr. Eric Courchesne has found that certain areas of the cerebellum are distinctly underdeveloped in autistics. Thus certain characteristic features of autism…may be explained in terms of structural abnormalities in the cerebellum."*

Even in low levels, soy plant-estrogen endocrine disruptive activity in relation to the smallness and fragility of fetal and infant brain cell development are found to be neurologically destructive. Consumption of estrogens, including soy plant-estrogens during developmental timeframes; such as pregnancy, while breast feeding, or fed soy-

based formulas are proven to be especially capable of interrupting brain development and causing damaging effects in: neural function, behavioral patterns, and mental status.

"Neurotoxicology and Teratology," E Lephart, concludes, "*These results indicate that consumption of dietary phytoestrogens resulting in very high plasma isoflavone levels (in many cases over a relatively short interval of consumption…..) can significantly alter sexually dimorphic brain regions, anxiety, learning, and memory. …these studies identify the biological actions of phytoestrogens, specifically isoflavones and their metabolites, found in animal soy-containing diets on brain and behavior…."*

In a previous study, Lephart et al found that male rodent fed a phytoestrogen-rich diet resulted in apoptotic cells, (cell death) in the AVPV region of the brain. AVPV in the hypothalamus is essential for neural pathways mediating hormonal feedback particularly during brain development.

2007, "BMC Neuroscience" L. Bu et al reports, "*We observed a 22% reduction of ERbeta – positive cell numbers in AVPV (essential neural pathway) with consumption of soy isoflavones….these findings provide direct evidence that consumption of soy isoflavones…influences the loss of ERbeta-containing neurons…."*

2007, a study published in "Journal of Biomedical Science" titled, **"***Genistein and daidzein induce neurotoxicity at high concentrations in primary rat neuronal cultures," reports, "Since isoflavones possess estrogen-like activity….isoflavones, specifically genistein and daidzein are toxic to primary neuronal culture at high concentration. Treatment of neurons with ….genistein and daidzein for 24 hours increased the LDH (lactate deyhdrogenase, enzyme important in cell energy production) release by 90% and 67% respectively, indicating significant cellular damage."*

"Biochemical Biophysical Research Communications" P Wang et al report, "*Signaling mechanisms of daidzein-induced axonal outgrowth in hippocampal neurons."*

During varying timeframes of brain development the growth of neural circuitry and final integration into complex patterns of behavior are largely influenced by estrogens to include soy phytoestrogens. The effects of tofu on brain-causing dementia and brain damaging effects are well known.

1996, White et al, reports that vascular dementia prevalence in Hawaii and Japan are high while concluding, "*This group showed a significant dose-dependent risk for development of vascular dementia and brain atrophy from consumption of tofu soy product rich in isoflavones."*

2000 "Journal of the American college of Nutrition," L R White et al report, "*Brain Aging and Midlife Tofu Consumption…..higher midlife tofu consumption was independently associated with the indicators of cognitive impairment and brain atrophy in late life."*

Tofu is soybean curd made from coagulated soy "milk" (not truly a milk),or from soy protein isolate, the similar and same isolate used in soy protein-based infant formula.

2001, published in the "Journal, Biochemical Society of Transactions" reports, "*….ingestion of soy containing isoflavones was correlated with the suppression of neurodegeneration (progressive loss of structure or function of neurons including death of neurons) –relevant phosphorylation (cellular processes) of the microtubule-associated protein tau" (abundant in CNS neurons, but when misfolded can cause a number of neurodegenerative diseases).*

A September, 2005 Symposium titled: "Endocrine Active Compounds and Their Effects on Brain Development," unanimously confirms that, "*There is growing concern that low levels of endocrine-active compounds may exert toxicological effects in the brain.*"

2001, FDA Division of Biochemical Toxicology confirms, "*Fetal brain contained predominately genistein at levels similar to those in the maternal brain. These studies show that genistein crosses the rat placenta and can reach fetal brain from maternal serum genistein levels.*"

NIH, National Toxicological Program reports: "*Postnatal exposure to genistein (soy estrogens) with regard to neurodevelopmental endpoints, assessment of alterations with prenatal exposures, animal studies including effects on weight, reproductive and developmental outcomes, human longitudinal studies from prenatal exposure to age 18 to evaluate neurodevelopmental outcomes, and case control studies of congenital malformations to assess developmental risks. In comparisons to controls showed elevations of total genistein in all tissues in males and females fed 100 and 500 part pre million genistein. Brain genistein was elevated in the 500 ppm group and 5ppm in females increased ovarian, uterine, and liver total genistein concentrations compared to controls. There is increase in genistein in mammary gland*".

Study from the journal of "Biomedical Science" concludes, "*Genistein and daidzein induce neurotoxicity at high concentrations in primary rat neuronal cultures.*"

Reported in "Experimental Biology and Medicine- *The phytoestrogen coumestrol has estrogenic actions on peripheral reproductive tissues. Yet in the brain this compound has both estrogenic and anti-estrogenic effects.*"

2004 "Life Science" EJ. Choi and B.H Lee report, "*Evidence for genistein mediated cytotoxicity (toxicity of cells) and apoptosis in rat brain- The present study was undertaken to investigate the cytotoxic effects of chronic ingestion of genistein on rat brain in vivo…..rats were given 2 or 20 mg/day genistein for four weeks.*"

In a number of ways, numerous published studies prove that along with the neurological damaging effects as caused by soy endocrine disrupting phytoestrogens, soy's antinutrients again contribute to developmental brain disruptions, of which these multiple soy phytochemicals cause neurotoxicity during fetal, infant, and child exposure, questioning as to how it is possible for any child to survive soy's contaminating effects.

Published study from Department of Biological Sciences Bethlehem PA, and Department of Pathology/comparative Medicine, Wake Forest University, NC reports; "*Increased aggressive behavior and decreased affiliative behavior in adult male monkeys after long-term consumption of diets rich in soy protein and isoflavones. Results indicate that long-term consumption of a diet rich in soy isoflavones can have marked influences on patterns of aggressive and social behavior.*"

A published study from French scientists conclude, "*Studies have shown that soy bean-based formulas contain large quantities of phytoestrogens, particularly isoflavone. Because of experimental data suggesting a possible deleterious effect of phytoestrogens on the neuroendocrine maturation, the reduction of their content of soy formulas must be considered*".

2007, Department of Biomedical Science, University of Florida Atlantic, "*Isoflavones, specifically genistein and daidzein are toxic to primary neuronal culture…..*"

At the same time, Department of Clinical Neuroscience Stockholm, Sweden confirms: "*The human brain is mainly characterized by abundant estrogen receptor alpha messenger RNA expression in the amygdale, (complex structure involved in a wide range of behavioral function and psychiatric conditions associated with anxiety, phobia, panic, depression schizophrenia, fear, and autism) and hypothalamus-cerebral cortex, and hippocampus. Estrogen regulates distinct human amygdale-mediated functions. Estrogen receptor alpha messenger RNA is expressed in discrete areas of the human brain not only related to neuroendocrine function, but also to emotion, memory and cognition."*

During development the formation of both hypothalamic and pituitary structures are linked, and abnormalities of one can affect the other, while many hormones of the brain and body are most often interdependently linked.

For instance the Hypothalamic-Pituitary-Adrenocortical (HPA) axis plays a key role in the response to stress. Estrogens cause neuroendocrine HPA impairment of stress response as characteristic in autism disorder. Chronic stimulation of HPA activity alters ACTH (plasma adrenocorticotrophin) that controls stress response, a disorder of autism.

Estrogen is reported in 2007 "Journal of Neuroendocrinology" to *"cause dose-dependent increases in basal plasma ACTH and corticosterone concentrations but decrease the ACTH response to restraint stress."*

"Neuropsychopharmacy" reports, *"Low dose estradiol decreased the ACTH. …The physiological range of estradiol is an important inhibitory factor (of ACTH) in the HPA stress response of females"*…….and finding greater sensitivity in males.

2008, Department of Women and Child Health, Sweden, "Neuroendocrinology" reports, *"Transcriptional Analysis of Estrogen Effects in Human Embryonic Neurons and Glial Cells; Estrogen exerts many effects in the central nervous system….Estrogen treatment of the (neuron and glial) cell cultures during a 7-day culture period revealed a number of genes with significantly altered expression. Our results indicate that estrogen may influence developing human neurons and glia through regulating expression of genes that are important for the development of the nervous system."*

Glial cells are crucial in the development of the nervous system, while providing support and nutrition, maintain homeostasis, form myelin (axon insulation), and participate in signal transmissions in the nervous system. Glial cells largely outnumber neurons, and provide support and protection to neurons. They are partners to neurons, and glial cells have four main functions: surround neurons and hold them in place, supply nutrients and oxygen to neurons, insulate one neuron from another and to destroy pathogens and remove dead neurons. Glial cells modulate neurotransmission. Glial cells have important developmental roles, guiding migration of neurons in early development, and producing molecules that modify the growth of axons and dendrites. Glial cells are active participants in synaptic transmission, regulating clearance of neurotransmitter from the synaptic cleft, releasing factors such as ATP which modulate presynaptic function, and relax and release neurotransmitters themselves.

Estrogens are synthesized within the brain by glial cells, and studies report that estrogens have the capability to induce changes or deformities in glia neuron signaling.

2006, "Environmental Health Perspectives," Y Le Page et al report, "*The brain cytochrome P450 aromatase in zebrafish is expressed in radial glial cells and is strongly stimulated by estrogens (E2); thus, it can be used in vivo as a biomarker of xenoestrogen*

effects on the central nervous system. To investigate the impact of environmental estrogenic chemicals on distinct estrogen receptor activity, we developed a glial cell-based assay……analyses with ethynylestradiol, estrone, alpha-zeralenol, and genistein…..combination of these agents showed an additive effect according to the concept of concentration addition. This confirmed that the combined additive effect of the xenoestrogens leads to an enhancement of the estrogenic potency, even when each single agent might be present at low effect concentrations. In conclusion, we demonstrate that our bioassay provides a fast, reliable, sensitive, and efficient test for evaluating estrogenic potency of endocrine disruptors on ER subtypes in a glial context."

2003, "Neuroscience," TT Lam, and C Leranth report, "*Gonadal hormones act extrinsic to the hippocampus to influence the density of hippocampal astroglial processes- The important effects of estrogen on the morphology of hippocampal neurons are well established. This study addresses the possibility that estrogen-sensitive projections from the medial septum/diagonal band of Broca induced astroglial reactions. Rats that received estrogen-filled cannulae showed a lower density of glial processes in the hippocampal CA1 and CA3 subfields than animals of the control group. Two major conclusions can be drawn from these results. First, the data show that estrogen, in fact has an indirect influence on hippocampal cells….Furthermore, estradiol can have an indirect negative effect on hippocampal astrocytes, causing a reduction in the density of their processes."*

Researchers Drs. Bauman and Kemper have examined post-mortum brains of autistic individuals and have found the amygdale and the hippocampus to be underdeveloped. In particular, they have reported finding densely packed and unusually small neurons in the amygdale and hippocampus of autistic individuals.

Endocrine disrupting soy phytoestrogens are proven as an active estrogen (including estradiol) mimic that can cause damaging neurological effects as revealed in the cause of autism. Estrogens are known to have multiple effects throughout development on steroid responsive tissues in the brain, of which estrogenic soy can be included. As with soy phytoestrogens, gonadal steroids are implicated in the development of sexually dimorphic structures in the brain, in the control of physiological behaviors and functions.

There are Microglia that protect and support neurons of the CNS. Macroglia cells include: 1. Astrocytes- anchor neurons to their blood supply to the brain, and are the building blocks of the blood-brain barrier, and signal each other using calcium. 2. Oligodendrocytes- coat axons in the CNS and form the myelin sheath that provides insulation to the axon allowing electrical signals to propagate more efficiently. 3. Ependymal cells- create and secrete cerebrospinal fluid. 4. Radial Glia- in the developing nervous system function both as neuronal progenitors and as a scaffold upon which newborn neurons migrate, and in the mature brain the cerebellum and retina retain Radial Glia cells. 5. Schwann cells- provide myelination to axons in the peripheral nervous system. Satellite cells- line the exterior surface of the PNS neurons and help regulate PNS chemical environment.

Astrocyte are characteristic star-shaped glial cells in the brain and spinal cord and play a number of active roles in the brain, including the secretion or absorption of neural transmitters and maintenance of the blood-brain barrier. They perform many functions including: biochemical support of endothelial cells which form the blood-brain barrier,

the provision of nutrients to the nervous tissue and a principal role in the repair and scarring process in the brain. Astrocytes also promote the myelinating activity of oligodendrocytes.

2000, "Journal of Pediatric Endocrinology and Metabolism," JA Chowen et al report, "*Astroglia are targets for estrogens and testosterone and are apparently involved in the actions of sex steroids on the central nervous system. Sex hormones induce changes in the expression of glial fibrillary acidic protein, the growth of astrocytic processes and the extent to which neuronal membranes are covered by astroglial processes. These changes are linked to modifications in the number of synaptic inputs to neurons……"*

2002, "Journal of Comp Neurology," D Garcia-Ovejero et al report, "*In summary, these results suggest that reactive astrocytes and reactive microglia are a direct target for estrogens and androgens, respectively."*

2009, "Men's Health" magazine article by Jim Thornton reports, "*Eeef Hogervorst Ph.D of England's Loughborough University and other researchers published a study on soy products and dementia risk. Participants over age 68 who were regularly eating the most tofu had double the risk of dementia and memory impairment as those consuming a more moderate amount. 'We were very surprised by this at the time but a new consensus is starting to form now. Hormones and hormonelike products are not very good for people over 65.'"*

There is no available evidence proving that soy phytoestrogens are *NOT* causing damaging irreversible neurological effects to exposed fetus, infants, and children as estrogens are proven to target and damage brain functions.

2001, "Neurochemistry" Su Liao et al report, "P*roliferation of astrocytes is a common response of the CNS to injury and disease….the signaling pathways underlying glutamate-induced astrocyte proliferation are investigated. However, the tyrosine kinase inhibitors genistein……..inhibits the glutamate-induced proliferation (of astrocytes). These results suggest that glutamate induces astrocyte proliferation through a tyrosine kinase pathway."*

Soy as a well-known tyrosine kinase inhibitor and proven to cause damage to brain neurotransmitter functions, is clearly defined later in this report.

SOY Manipulates RET Manipulations of GLIAL BRAIN CELLS- RET is a member of the receptor tyrosine kinases superfamily that transduce signaling by glial cell line-derived neourotrophic factor (GDNF) and neurturin. RET is a tyrosine kinase receptor for GDNF. An established role of the RET signal transduction pathway is the development of the enteric nervous system. GDNF promotes the survival of enteric neuron system ENS as well as the survival, proliferation, and differentiation of multipotential ENS progenitors present in the gut of rat embryos.

Several studies conclude that estrogens directly influence glial cell line neurotrophic factor (GDNF) that is involved in the pathology of mood disorders. GDNF is a neurotrophic factor that plays a role in cell development and function of the limbic (brain) system. It is well established that the estrogenic influence upon GDNF expression in the developing hypothalamus, a critical part of the brain for receiving input and outputting instructions to the body, regulates numerous responsibilities: body temperature, hunger, response to pain, levels of pleasure, behavior functions; anxiety,

anger, aggression, and response to emotional situations. Also, GDNF cells exert a trophic action on dopamine neurons in the ventral midbrain.

Several studies conclude that estrogens modulate RET expression of which during developmental timeframes can cause damaging effects to several neural pathways.

2008, Scientists from Germany and England report in "European Psychiatry: *This proof of concept study supports previous findings of an alteration of the GDNF in patients with depressive disorders (DD)."*

1999, "Development," S Taraviras et al report, "*Our experiments show that a subpopulation of enteric neural crest (NC) undergoes apoptotic cell death specifically in the foregut of embryos lacking the RET receptor. We suggest that normal function of the RET RTK (receptor tyrosine kinase) is required in vivo during early stages of enteric nervous system (ENS) histogenesis for the survival of undifferentiated enteric neural crest and their derivatives."*

During embryonic development the RET gene is highly expressed in parts of the CNS, in the neural crest, and many of its derivatives including peripheral nervous system, and neuroendocrine cells such as C-cell of the thyroid, and chromaffin cells of the adrenal gland.

2007, "Journal of Neurochemistry," Y Hirata, K Kiuchi report, "*These results indicate that Ret, an important signal molecule in dopaminergic neurons, may be down-regulated in the early stages of neuronal degeneration caused by various neurotoxic substances……"*

Endocrine disruptor soy phytoestrogens as well as soy antinutrients are established neurotoxic substances particularly when exposed during fetal, infant, and child development.

2006, ""Developmental Neuroscience," L Li et al report, "*Here we demonstrate the involvement of Ret in the dopaminergic (DA) neuron development both in vitro and in vivo. Temporary blockade of Ret expression in embryos…….. in vivo led to reduced striatal DA content….. Taken together the data suggest the normal function of Ret is required in vivo for the maturation of dopaminergic neurons, in particular for cell survival and fiber innervation."*

2002, "Endocrinology," T Ivanova et al report, "*We conclude that 17-b estradiol is capable of influencing GDNF expression in the developing hypothalamus."*

Soy phytoestrogens are proven as a 17-b estradiol mimic.

1996, "Nature," P Durbec et al report, "*Our data strongly suggest that Ret is a functional receptor for GDNF, and that GDNF, in addition to its potential role in the differentiations and survival of central nervous system neurons, has profound effects on kidney organogenesis and the development of the peripheral nervous system."*

2008, "Journal of Neuroscience," F Ledda et al report, "*Glial cell line-derived neurotrophic factor (GDNF)/Ret signaling has potent trophic effects on ventral midbrain dopaminergic, motor, sensory, and sympathetic neurons."* Health Action Network Society reports, "*Problems in both sexes associated with soy-based infant formula later in life also include extreme emotional behavior, immune system problems, pituitary insufficiency…thyroid disorders including thyroid problems in babies and infantile leukemia."*

SOY CAUSATION OF METHIONINE (Essential Sulfur-Amino Acid) DEFICIENCY- Proteins are essential for body and brain development and repair. Studies report that the proteins in soy-based formulas may be limited due to several indispensable amino acids. Proteins are components of all living cells necessary for the proper functioning as well as maintenance. The basic structure of a protein is a chain of amino acids. The body requires a number of amino acids that are essential for human metabolism and body function for good health. Minus water, the body is 75% amino acids. The vast majority of important neurotransmitters are also composed of amino acids.

Researchers have asserted that soybean protein does not provide adequate methionine to meet dietary needs. This lack of methionine and other essential sulfur-amino acids limit or diminish the nutritional value of soy protein quality. Dietary intake of soy products along with a combination of other dietary foods may increase sulfur amino acids helpful for adjustment to soy's sulfur-amino acid deficiencies, but this adjustment is not possible when soy-based infant formulas are 100% of infant's dietary intake that largely limits nutritional protein value that is essential for fetal and infant body and brain development.

Methionine, the primary source of sulfur-amino acid that assures protein availability may be found in very low levels in soybeans, if at all, and levels can fluctuate between varied soy crops. Methionine must be added to soy-based infant formulas, and other soy products, but the appropriate level to assure protein quality per individual is not known.

Like soy proteins, the levels in essential amino acids, plant-estrogens, antinutrients, essential trace mineral content, heavy metals, and methionine as soy components can significantly fluctuate plant-to-plant.

The addition of methionine to soy-based infant formulas, if too much or too little, can cause toxic effects, while the precise amount of added methionine is not FDA regulated or investigated.

Sulfur-amino acids increase production of lecithin a major component of cell membranes (protect cells from oxidation and help develop protective sheath surrounding the brain), protects the kidneys, detoxify the liver, reduce bladder irritation, breaks down fats (preventing build-up), assists in digestion, and removes heavy metals from the body.

Sulfur containing amino acids are important for the body's production of glutathione, (GSH). GSH is one of the most important antioxidants found in the body and protects cells and serves to detoxify a variety of harmful compounds.

Although sulfur-amino acids perform a multitude of important functions, another primary function is related to the cellular respiration necessary in the oxidation-reduction reactions to help cells utilize oxygen that aids brain functions and all cell activity, as urgently important during brain development.

A study in "Journal of Food Science" concludes, "*The biological value of soy protein is increased by the addition of l-methionine to textured soy protein. This level of addition causes a minor problem in flavor of ensuing products and a noticeable disagreeable odor during cooking of some products. As in a previous investigation of parameters influencing in the PER (measuring system) of proteins, inconsistency in results between different laboratories on identical samples was encountered.*"

Low levels of methionine during pregnancy have shown to increase the risk of neural tube defects (NTDs) in the fetus. These defects are caused by the failure of the neural tube to close properly during the formation of the central nervous system in the developing embryo. NTD, is a serious birth defects with symptoms that range from mild to severe impairment, due to incomplete development of the brain, spinal cord and/or protective coverings.

Study from the University of Genova, Italy reports, *"A fast and reliable method for the determination of free amino acids in infant formulas was developed. The detected amounts of free taurine and methionine (necessary sulfur amino acids) were often lower than those listed by the manufacturers. In some samples significant amounts of free arginine, tyrosine and methionine were detected, although they had not been listed among the added ingredients."*

Nitrogen fertilizers are commonly used on soybeans to boost crop production. Nitrogen is also a natural chemical component in soybeans. Soybean decomposition increases nitrogen in the soil, and irrigation increases nitrogen levels even more. Nitrogen lowers sulfur amino acid content.

"Journal of Agriculture Food Chemistry" HB Kristnan et al reports, "*Nitrogen lowers the sulfur amino-acid content of soybean……Soybean protein quality could be significantly improved by increasing concentration of sulfur-containing amino acids, cysteine and methionine."*

Methionine is used by the body to manufacture SAMe (S-adenosyl-L-methione) that is found in every cell in the body and has been show effective as treatment for osteoarthritis, joint pain, stiffness and inflammation. SAMe has been shown to be beneficial for most types of depression, improves liver function, treatment of fibromyalgia, myelopathy and ADHD.

SAMe manufactured by methionine assists the body in producing a wide range of compounds, including neurotransmitters such as serotonin and dopamine. Therefore methionine deficiency is related to numerous disease syndromes. Children require about 1600 to 2,000 mg per day of SAMe, and infants require five times that amount.

"American Journal of Clinical Nutrition" reports, "*The results suggest that normal infants fed a formula providing 2.25/100Kcal of a soy protein isolate not fortified with methionine performed less well during the first 6 weeks of life than did breast-fed infants and infants fed milk-based formulas or other soy isolate-based formulas fortified with methionine. The limiting nutrient appears to have been methionine."*

Book, "Chemical Induction of Cancer" by Joseph Arcos et al, "*Deficiency or excess of L-methionine may enhance or inhibit carcinogenesis. Soybean protein diets are methionine deficient….and deficiency of methionine in soybean protein may influence tumor development."*

There is a fine line for adequate intake of sulfur-amino acids. Too much methionine is dangerous. As with so many unknowns about plant contents of each and every soybean crop, it is reported: "*Archives of Toxicology- Since methionine administration caused a rapid increase of the cysteine (sulfur-amino acid), which functioned as a predominant carrier in methylmercury transport in the maternal plasma, newly synthesized cysteine seemed to accelerate the mercury uptake."*

Methylmercury is a form of mercury that easily bioaccumulates and causes neurotoxicity, a poisoning of the brain and nervous system, and thought to cause neurological disorders including cerebral palsy.

Reported in "Journal of Nutritional Science and Vitaminology- *Excess methionine diets (in pregnant rats) resulted in complete loss of fetuses. The weights of fetuses in the excess amino acid groups were significantly lower than those in respective pair-fed controls. Excess aromatic amino acids caused growth retardation of fetal brain. The levels of not only the excess amino acids but also of other amino acids in fetal brain were appreciably elevated by these (maternally fed amino acid) diets. These findings suggest that the blood-brain barrier is immature and that the synthesis of proteins in fetal brain is impaired by excess amino acids in the mothers. The importance of experiments on diets with excess of single amino acids in pregnant animals is discussed in connection with studies on inborn error of amino acid metabolism."*

The Rowett Research Institute, reports, "*Animal studies show that the balance of methionine relative to other amino acids in the maternal diet is critical, as fetal growth is not only retarded by diets that are deficient but also by those containing excess. (Maternal) diets with an inappropriate balance of methionine can adversely affect both short-term reproductive function and the long-term physiology of the offspring."*

Methionine sulfur-amino acids added to soy products can result in too much…..or too little, with damaging health effects.

TRYPTOPHAN DEFICIENCY- is an essential amino acid having both metabolic and behavioral effects in infants. Human milk is a rich source of tryptophan, while lacking in soy-based infant formulas.

2001, "Plant Foods for Human Nutrition," G. Sarwar et al reports, "*Powder and liquid concentrate forms of soy-based infant formulas from four manufacturers were tested. The tryptophan contents of the test soy-based formulas were considerably lower compared to those of human milk……further research (is needed) to investigate the influence of tryptophan supplementation of soy-based infant formulas on tryptophan metabolites and their potential related effects on sleep latency and neurobehavioral developments in infants."*

There remain a multitude of published studies confirming estrogens, including soy phytoestrogens target the nervous system (brain, spinal cord, nerve cell functions) and exert complex effects on brain structure, function, and behavior. It is detrimental that naturally essential estrogenic hormone levels are not unnaturally soybean manipulated and disrupted, particularly during delicate developmental life stages. Soy plant-estrogen hormone disruptor capabilities are proven to cause damaging physiological and neurological effects to fetus and infants exposed.

The FDA pays little attention to prenatal and postnatal exposure to toxic developmental-behavioral chemicals such as soy estrogen-active phytoestrogen foods, beverages, and soy-based infant formulas while the CFSAN meets every few years to discuss, "Soy Toxicity" or "Toxicity of Genistein."

SOY ENDOCRINE DISRUPTORS DAMAGE SEVERAL NEUROTRANSMITTERS: THE CAUSE OF IRREVERSIBLE BRAIN DAMAGE, INCLUDING AUTISM: On genome.gov, the NIH, National Human

Genome Research Institute reports, *"Researchers have identified a number of genes associated with autism. Studies of people with autism have found irregularities in several regions of the brain. Other studies suggest that people with autism have abnormal levels of serotonin or other neurotransmitters in the brain. These abnormalities indicate that autism usually results from the disruption of normal brain development early in fetal development caused by defects in genes that control brain growth and that regulate how neurons communicate with each other."*

Estrogens target the brain, and overwhelmingly, soy plant-estrogen endocrine disruptors are (as expected) scientifically proven to damage several regions of the brain and disrupt several neurotransmitter systems as the stated cause of neurological disorders such as autism.

Neurotransmitters are neuron connective chemicals that through neuron synapse relay, amplify, and modulate signals from one neuron to the next. There are many neurotransmitter systems that are responsible for transferring information across the neural synaptic gap that control brain functions. Dysfunction of any one of these neurotransmitter systems (inhibitory or excitatory) can cause the dysfunction of the opposing neurotransmitter. Soy is proven to damage several neurotransmitter systems.

Neuroendocrine cells are cells that receive nerve cell input from the neurotransmitters and as a consequence of this input, release message molecules (hormones) to the blood. In this way three is integration between the nervous system and the endocrine system, known as neuroendocrine integration. The major center of neuroendocrine integration in the body is the hypothalamus and the pituitary gland. This is also the location targeted by estrogenic endocrine disruptors such as soy phytoestrogens, as well as the established brain area most involved in neurological developmental disorders.

Direct action of neurotransmitters is to activate complex metabolic neuronal pathways. Important neurotransmitter functions regulate: emotions, bonding, behavior, cognition, learning, attention, reward, sleep, memory, arousal, and motor control. Neurotransmitters must be broken down once reaching the postsynaptic cell to prevent further excitatory or inhibitory signal transduction.

During brain development neurons migrate to various areas of the brain and brain disorders occur when neuron interconnectivity become defective due to failure of neurotransmitter instruction and communications. Developmental brain disorders are caused when neurons are unable to normally migrate to specific brain areas particularly in the hippocampus of the limbic system that is buried deep within the cerebral cortex.

The hippocampal formation has several functional modules that contribute differentially to behavior both in infancy and adulthood while experiencing varying rates of maturation. Especially during sensitive fetal and infant developmental timeframes, and in fact throughout life, the hippocampus is known to be directly affected by estrogenic compounds, such as qualifying soy plant-estrogens that are proven capable of causing damaging effects to multiple neurotransmitters resulting in damaged brain cell development and functions as involved in: mental illnesses, depression, bipolar disorder, seizures, and a host of brain disorders, including autism.

The irreversible soy phytoestrogen disruption of several neurotransmitters is most neurologically-damaging during fetal, infant, and child brain-developmental timeframes.

"Journal of Antiaging Medicine," I.W. Goddard reports, *"….research has demonstrated a positive correlation between tofu consumption and brain atrophy in men. While it has been shown that the soy phytoestrogen genistein inhibits neuroprotective functions in cell cultures, recent in vivo findings strengthen the case for a possible causal mechanism of soy-induced neurodegeneration."*

In 2000 the National Institute of Aging of the NIH, White et al report in the "Journal of the American College of Nutrition- *Poor cognitive test performance, enlargement of ventricles and low brain weight were each significantly and independently associated with higher midlife tofu consumption."*

Tofu is made by coagulating the protein from soy milk, of which soy-based infant formula is also made from.

2001, "Journal of the American Pharmaceutical Association," JE Shepherd reports, "*…..areas of the brain involved in emotion are rich in estrogen receptors and estrogen directly influences synaptic concentrations of neurotransmitters."*

2009, "Medical News Today," reports on The National Institute of Aging, Susan Resnick conclusion that,….. "*brain scans showed small but significant losses in volume in the frontal lobe and hippocampus…in women who had taken (estrogen/progestin) hormones."*

Soy plant-estrogens are a confirmed highly active endocrine disrupting estrogenic agonist.

The in-depth WHI study confirms in 2002 that, "Estrogens increase dementia."

"Psycheducation" reports, "*The hippocampus is known to be directly affected by estrogen."*

2003, "New Brain Research, Implications for Autism" Sue Bennett reports, "*One area of the brain implicated in playing an important part in all these diseases (Autism, Parkinson's, Alzheimer's) is the hippocampus."*

2007, "Developmental Neuroscience" P. Lavenex et al report, "*The hippocampal formation is a multicomponent region of medial temporal lobe involved in declarative and relational memory processing. Behavioral studies have suggested a protracted functional maturation of these structures in primates, and postnatal developmental abnormalities in the hippocampal formation are thought to contribute to neurodevelopmental disorders, such as autism, schizophrenia, epilepsy and Down syndrome."*

Estrogen actions, to include soy plant-estrogens, can also deregulate neurotrophins (proteins that induce development, survival, and function of neurons) and growth factors, as well as neuronal structure and synapse brain cell signaling junctions.

Focusing upon the highly sensitive timeframe of fetal and infant brain cell development, numerous published studies specifically conclude that endocrine disrupting soy plant-estrogens target and profoundly damage hypothalamic production of a number of brain neurotransmitters such as: Vasopressin, Oxytocin, Serotonin, Dopamine, GABA and more. Not one, but several neurotransmitters are profoundly disturbed by estrogens, including soy plant-estrogens.

VASOPRESSIN: Peptides such as vasopressin and oxytocin are primary neurotransmitters in the hypothalamus. These peptides are far more potent than other neurotransmitters requiring only very *small* amounts to produce profound effects.

Increase in vasopressin brain-hormone levels is proven to cause negative behavior effects related to: learning, anxiety, communication, emotions, and stress. Elevated vasopressin levels cause damaging effects on the central nervous system (brain and spinal cord), cardiovascular system, and alter blood pressure. Soy plant-estrogens are proven to significantly increase vasopressin levels resulting in damaging neurological effects.

Published study in the, Journal of Psychopharmacology states, *"Isoflavones form one of the main classes of phytoestrogens. Effects have not been limited to reproductive behavior but include effects on learning and anxiety and actions on the hypothalamo-pituitary axis. It is therefore possible that soy content of diet could have significant effects on brain and behaviour. Vasopressin concentrations were significantly elevated in the soy diet group compared to controls. Major changes in behavioural measures of anxiety and in stress hormones can result from soy content of rat diet."*

Duke University Medical Center confirms, "*In extrapolating findings in the developing rat brain to man, it is important to note that the first 10 days of postnatal life in the rat represent stages of neurodevelopment corresponding to the last trimester of gestation in humans."*

2003, an official journal of the Society of Toxicology reports, *"Genistein is a plant-derived estrogenic isoflavone commonly found in soy-based products. It has been reported that exposure to 17 beta-estradiol or DES increased the vasopressin content of the hypothalamus. Vasopressin levels were significantly elevated in the genistein group."*

Division of Neurotoxicology, National Center for Toxicological Research in Arkansas, *"Dietary Exposure to Genistein Increases Vasopressin in the Rat Hypothalamus: Vasopressin is a neurosecretory neuropeptide synthesized primarily in neurons of the hypothalamus and secreted into the bloodstream from the posterior lobe of the pituitary. It has been reported that exposure to 17-beta estradiol and DES (estrogens reportedly in relation to soy plant-estrogens) increase the vasopressin content of the hypothalamus and that estradiol selectively damages hypothalamic beta-endorphin-containing neurons. Since little was known of the potential effects of estrogenic endocrine disruptor compounds on hypothalamic neuropeptides, we fed rat fetuses from day 7 utero until postnatal day 77 with Genistein (soy). Vasopressin levels were significantly elevated in the Genistein group. Elevated vasopressin levels may (also) be associated with fluid balance, altered blood pressure and cardiovascular effects. These data are consistent with the known actions of estradiol that may serve to explain our finding in a previous (genistein estrogen endocrine disruptor) study."*

Proceedings of the National Academy of Sciences (PNAS) reports, "*Vasopressin has the ability to influence social processes, particularly those related to emotional social communication. Our results thus support the possibility that variations in the vasopressin system could be related to individual differences in human sociality, particularly aggressive tendencies, and possibly even to the abnormalities in emotional communications observed in some cases of autism."*

Department of Psychiatry, University of Iowa College of Medicine confirms, *"Vasopressin and genes in the vasopressin system remain strong candidates for involvement in autism susceptibility…..…."*

2003, "Journal of Neuroscience" S. Somponpun et al agree that, "*The vasopressin magnocellular neurosecretory cells in the supraoptic and paraventricular nuclei are regulated by estrogen and exhibit robust expression of estrogen receptor, ER–b."*

Multiple studies conclude that soy plant estrogens can manipulate estrogen receptors ER-a and ER-b.

Published studies are in agreement that the appropriate balance of most important vasopressin and oxytocin neurological hormones are critical for neurological development related to: social behavior, social recognition, communications, emotional behavior, and bonding. Scientific evidence concludes that soy plant-estrogen endocrine disruptors are capable of causing profound interruptions and the imbalance in vasopressin and oxytocin neurological hormone systems that largely contribute to resulting brain damaging effects: aggression, anger, confusion, mood swings, behavioral changes, attention disorders, depression, and neurological damaging effects to include autism.

Department of Psychiatry and Behavioural Sciences, Emory University in Atlanta Georgia; "*Oxytocin and vasopressin contribute to a wide variety of social behaviors, including social recognition, communication, parental care, territorial aggression and social bonding. Neuropeptides, oxytocin and vasopressin play critical roles in modulating social behaviors…… and may contribute to variations in human social behavior including extremes outside the normal range of behavior and those found in autism spectrum disorders. Oxytocin and vasopressin are strong candidates for dysregulation in autism."*

OXYTOCIN: When in balance, oxytocin function is related to social cognition, trust, and bonding, and when out of balance the opposite occurs. Soy plant-estrogen influence upon brain hormone vasopressin is compounded by evidence that a second most important brain hormone neurotransmitter, oxytocin is also abnormally controlled by soy isoflavones. The same as vasopressin, oxytocin can be dangerously manipulated by soy plant-estrogen hormone disruptions that are particularly alarming during prenatal and postnatal neurological development.

Department of Pharmacology and Toxicology, University of Utah, "*Oxytocin receptors may be involved in adaptations of the brain oxytocin system during gestation, which are critical for systemic release of oxytocin during parturition and lactation. Estrogen treatment in animals resulted in increased oxytocin receptor binding. The oxytocin binding in the hypothalamus is increased during mid-and late-gestation, which may be mediated by increased estradiol. Soy an active estrogen, increases estradiol levels, which has direct effects upon levels of brain hormone, oxytocin."*

2005, "Biological Psychiatry" journal report by S. Wu et al, concludes, "*Previous research has suggested that the social impairments exhibited by individuals with autism are associated with changes in plasma oxytocin levels…..and numerous studies have implicated oxytocin in the regulation of social cognition and behavior. These data suggest an involvement of oxytocin in the susceptibility to autism…"*

Perinatal Research Center, University of Alberta, Canada reports, "*Estrogen stimulates oxytocin. Estrogen regulates oxytocin gene expression through a receptor-mediated mechanism in human fetal membranes. Estradiol physiological concentrations more than doubled the concentration of oxytocin."*

Department of Psychology, University of Utah, "*Oxytocin plays an important role in social-affiliative behaviors. Exposure to high levels of oxytocin at birth may increase*

susceptibility to autism by causing a down regulation of oxytocin receptor in the developing brain."

Primate Research Center, Atlanta, reports; "*Several lines of evidence support a role for oxytocin and vasopressin in complex social behaviors, including sex behavior, and aggression."* And Another study from PRC, reports; "*The authors review evidence from animal studies demonstrating that the nonapeptides, oxytocin and vasopressin have unique effects on normal expression of social behavior, communications and rituals. An abnormality in oxytocin and vasopressin neurotransmission may account for several features of autism."*

To date, an increasing number of published studies prove soy plant-estrogens can cause deleterious effects upon most important brain hormones: vasopressin and oxytocin. Regulation of oxytocin receptor expression is found in the ventromedial nucleus of the hypothalamus via an ER-a dependent mechanism, this ER-a estrogen receptor is reportedly influenced by soy phytoestrogens.

2003, "Cardiovascular Research," D. Wang et al, report, "*….genistein treatment increased estrogen receptor a (ERa) (2 to 3 fold)…..analysis revealed an increase of…. oxytocin receptor in the aorta of ovariectomized rats treated with genistein. Treatment with E2(estradiol) similarly to genistein increased oxytocin, oxytocin receptor, endothelial nitric oxide synthase, and ERa m RNA."*

Organization, "Autism Speaks" sponsored a meeting in Atlanta, consisting of a wide range of experts working on the chemistry of emotional regulation. The scientists reviewed recent discoveries confirming oxytocin and vasopressin regulation of complex social behavior of which Press Release states: "***Oxytocin and vasopressin are two peptide hormones found in the brain and shown to participate in social behavior, stress, anxiety, and affiliative behaviors including social communication. Panel discussions focused on translational opportunities including manipulation of oxytocin and vasopressin systems in the human brain. Oxytocin and vasopressin systems have been linked to social and emotional bonding and social cognitive behaviors in animal models, this system is of particular interest to autism research. Research presented by meeting organizer, Larry Young of Emory University focused on the social behaviors of animals that show small changes in the DNA sequence for the vasopressin receptor, which is related to different social behaviors. Other research findings focused on the role of oxytocin in anxiety, social interaction, and social preference."***

2007, "Journal of Neuroendocrinology" confirms, "*Oxytocin has central actions modulating behavioural and HPA axis responses during late pregnancy. Estradiol caused dose-dependent increases in basal plasma ACTH and corticosterone concentrations, but decreased the ACTH response to restraint stress. Present study demonstrates the converse effects of estradiol on basal and restraint stress-stimulated HPA axis activity, and that the ability of central oxytocin to inhibit HPA axis activity depends on the levels of circulating estradiol."*

Studies conclude that estrogenic activity interacts with oxytocin that interacts with ACTH activity to encourage impaired response to stress.

2007, journal of "Neuroscience Letter," S. Jacob et al reports, "*Association of the oxytocin receptor gene in Caucasian children and adolescents with autism. The haplotype test of association did not reveal excess (oxytocin) transmission form the*

parents to affected offspring. These findings provide support for association of oxytocin receptor gene with autism in a Caucasian population."

2001, "Neurotoxicology and Teratology" PL Whitten et al, "*These result suggest that isoflavonoid effects on the development and expression of sexual behavior might occur through ERalpha- and ERbeta-mediated effects on oxytocin and its receptor."*

Evidence that soy estrogenic isoflavones act as neurological toxins particularly during fetal and infant development due to the cause of delirious vasopressin and oxytocin effects, is again compounded by several additional ways that soy isoflavones encourage neuro-toxicity. A large assortment of published studies conclude that soy plant-estrogens disrupt multiple neurotransmitter systems of which can result in severe neurological damage during fetal, infant, and child brain development.

SEROTONIN- originates in the midbrain region and is distributed throughout the brain. Serotonin concentration in the brain is far more sensitive to effects of dietary intake than any other neurotransmitter. Serotonin performs broad neurological activities, and defects in serotonin transmissions are implicated in neurological diseases. Serotonin is involved with: anger, anxiety, aggression, mood, pain, appetite, sleep, depression, obsessive compulsive disorder, bipolar disorder, migraines, and body temperature. Estrogen cause of excessive serotonin levels as confirmed by published studies also encourages; feeling of sickness, loss of appetite, headaches and migraines.

Significant functional interactions between estrogen and serotonin are acknowledged. Studies confirm that estrogen increases the concentration of neurotransmitters such as serotonin, dopamine, and norepinephrine. It affects their release, reuptake, and enzymatic inactivation. It also increases the number of receptors for these neurotransmitters.

Soy isoflavones genistein and daidzein exert estrogenic effects of which during fetal, infant, and child development are especially involved in estrogen-induced changes in neurotransmission, binding, and metabolism in brain regions that are especially implicated in the regulation of mood, behavior, learning, focus, cognition, etc.

Serotonin is necessary for normal fetal brain development, of which soy phytoestrogens are proven to disrupt.

2003 "Pharmacogenomics Journal" C.A. Shively et al report, "*Soy and social stress affect serotonin neurotransmission in primates. Like conjugated equine estrogen, (CEE), soy phytoestrogen increased tryptophan hydroxylase (enzyme involved in synthesis of serotonin) protein levels. CEE and soy phytoestrogen increased serotonin….Thus, the hormone induced increase in SERT was accompanied by increase in serotonin 5-HT synthesis and neuronal firing….."*

2003, Journal of "Molecular Psychiatry," N.Z. Lu et al report, "*The serotonin reuptake transporter plays an important role in serotonin neurotransmission and in several psychopathological disorders such as depression and anxiety disorders. …there was a significant proliferation of immunofluorescent (serotoninergic axons) fibers in hormone-treated animals. In addition, estrogen and estrogen plus progesterone treatment increased serotonin uptake in the basal ganglia. These findings suggest that ovarian hormones regulate serotonin protein expression and distribution…..."*

Basal ganglia are a group of brain nuclei interconnected with cerebral cortex, thalamus, and brainstem, that is associated with a variety of brain functions.

Reported by Department of Clinical Neuroscience, Stockholm Sweden, "*Compelling evidence now exists for estrogen's involvement in the regulation of mood and cognitive functions. Estradiol has been shown to regulate serotonin system, which has been strongly implicated in affective disorders……Anatomical organization of the estrogen receptor in the human brain provide evidence as to the specific neuronal populations in which the actions of estrogen receptors could modulate mood and underlie the neuropathology of psychiatric disorders…..*"

Active soy phytoestrogens act as an estrogen mimic capable of modulating serotonin levels.

2003, "Pharmacogenomics Journal" CA Shively et al, reports, "*Soy and social stress affect serotonin neurotransmission in primates. Conjugated equine estrogen and soy phytoestrogen increased serotonin reuptake transporter.*"

The serotonin reuptake transporter plays an important role in serotonin neurotransmission and in several psychopathological disorders such as depression and anxiety disorders.

Utah Poison Control Center, Volume 4 2002 reports, "*(Abnormally) Elevated serotonin concentrations is termed 'Serotonin Syndrome.' Common cognitive behavioral, neuromuscular, and autonomic signs and symptoms associated with serotonin syndrome: confusion, agitation, irritability, unresponsive, anxiety hypomania, lethargy seizures, insomnia, hallucinations, dizziness……..*"

"Serotonin Syndrome" also referred to as serotonin toxicity is a dangerous adverse reaction caused by excessive serotonin activity in the central nervous system. Especially during prenatal and postnatal development, soy plant-estrogens encourage excessive serotonin levels that may lead to serotonin poisoning. Estrogens are proven to cause defects in serotonin transmission, and serotonin transporter function. Autistic children are stated as having elevations in whole blood serotonin levels.

Journal- "Molecular Endocrinology" reports, "*Estrogen can up-regulate the expression of the serotonin receptor.*"

2002, Web Report concludes, "*The effect of neurotransmitter serotonin on autistic symptoms. Serotonin levels are only one of autism's many contributing factors. ….abnormal levels of serotonin can be understood as a primary symptom…..Serotonin functions in a variety of ways and works in conjunction with other chemicals. Autistic children have abnormally high levels of serotonin and that high levels of serotonin in general cause more intense autistic symptoms.*"

Defective signaling of serotonin as potentially caused by soy plant-estrogens is being investigated as a root cause of sudden infant death syndrome. It can not be ignored that to date the investigative cause of SIDS may be due to one or more of the following: airway obstruction, breathing difficulties, immune system abnormalities, kidney disorder, bacterial or fungal toxicity, inflammation, low birth weight, seizures, gastrointestinal disease, abnormal serotonin levels…..of which each and all are reportedly capable of being caused by soy isoflavones.

DOPAMINE: has many functions in the brain including important roles in; mood, behavior, learning, cognition, attention, memory, bonding, excitability, hyperactivity, motor activity, motivation, problem solving, reward system, sleep, sociability, pain processing, noticeability of objects and events. Dopamine controls the

flow of information from other areas of the brain, and dopamine imbalance is associated with mood/behavioral disorders, psychosis, and schizophrenia.

Soy plant-estrogens are well known estrogenic endocrine disruptors capable of seriously disrupting dopamine release, (as does cocaine and amphetamines), proven to result in abnormal psychological effects involving: arousal, diminishing appetite, sleep deprivation, visual hallucinations, paranoid thinking, induction of vomiting, learning disabilities, compulsive and erratic behavior. The etiology of mental disorders can often be linked to dysfunction of dopamine. Soy plant-estrogens cause overexpression of dopamine, which is especially alarming during fetal and infant development.

2002, "Neurotoxicology and Teratology" SA Ferguson et al from the National Center for Toxicological Research/FDA report, "*Estrogen modulates baseline and amphetamine-stimulated dopamine (DA) release in the adult male rat striatum. The isoflavone found in soybeans, genistein, is a phytoestrogen and may have comparable effects on striatal dopamine levels. Similarly, the industrial intermediate and potential endocrine disrupter, para-nonylphenol, has estrogen-like effects. Here, Sprague-Dawley rats were continuously exposed to…..…genistein. Dietary Exposure to 500 ppm genistein significantly potentiated amphetamine-stimulated dopamine release in males and a similar trend was apparent…in females. These results suggest that dietary genistein exposure may act similarly to estradiol in augmenting amphetamine-stimulated dopamine release."*

1995, "Journal of Neurochemistry" DJ Bare et al report, "*The tyrosine kinase inhibitor genistein increases endogenous dopamine release from normal in weaver mutant mouse striatal (major input station of brain system interconnected with motor control, cognition, emotions, and learning) slices- Fractional release of dopamine was significantly increased over basal release levels by genistein (100 and 200 microM). The effect was concentration dependent and rapidly reversible on washout of the kinase inhibitor. "*

2003, journal "Sheng Li Xue Bao," XL Dong, and JX Xie report, "*Dopamine release from female ovariectomized rats increased significantly within 5 minutes after injection of soy isoflavones…… The above mentioned results suggest that endogenous estrogen may play an important role in regulating the activity of dopamine neurons in mid-limbic systems and that soy isoflavones exert an estrogen-like effect on the dopaminergic systems in the amygdala."*

2007, "Medical Hypotheses" publication concludes, "*Prenatal influences on brain dopamine and their relevance to the rising incidence of autism. ……the genesis of autism is characterized by a "hyperdopaminergic" state based on evidence from monkey and human behavioral studies, pharmacological studies in humans, and a left-hemispheric predominance of both dopamine and autistic-like symptoms. Chronically high maternal levels of dopamine may be especially significant epigenetic contributors to the recent autism rise."*

2000, "Journal of Neuroscience Research" C. Beyer et al report, "*Previous work form this laboratory indicates that the differentiation of mouse midbrain dopaminergic neurons is influence by estrogen. In addition estrogen exposure stimulated the phosphorylation of CREB in midbrain dopaminergic cells. These data …..demonstrate that estrogen can interact with membrane binding sites on dopaminergic neurons…..In conclusion, rapid 'nongenomic' estrogen signaling represent another mechanism, in*

addition to the activation of classical nuclear estrogens receptors, that is capable of influencing neuronal differentiation in the mammalian brain."

Dopamine release from the central amygdaloid (brain structure involved in a wide range of behavioral and psychiatric functions) is reportedly dose-dependent on serum concentrations of estrogen. Estrogens, to include soy plant-estrogens, manipulate and disrupt normal dopamine levels important for maintaining neuronal activity.

2002, "Journal of Neuroendocrinology," T Ivanova et al report, "*Rapid stimulation of the P13-kinase/Akt signaling pathway in developing midbrain neurons by estrogen- Estrogen promotes the differentiation of neurons in the CNS. In the rodent midbrain the maturation of dopaminergic neurons appears to be under estrogen control. This is supported by the fact that dopaminergic cells contain nuclear estrogen receptors-alpha/beta (ER). Second, aromatase is transiently expressed in the developing midbrain. In previous studies, we have shown that estrogen increases dopamine synthesis and plasticity of dopamine cells. Our study clearly indicates that estrogen can rapidly stimulate the P13-kinase/Akt signaling cascade in differentiating midbrain neurons. This effect requires the intermediate activation of calcium-dependent signaling pathways. In conclusion, estrogen effects in the developing midbrain appear to be connected with the P13-kiinase/Akt signaling mechanism."*

2002, journal, "Sheng Li Xue Bao, B Lu, and JX Xie report, "*Differential role of estrogen in dopamine metabolism in the amydgala- The results obtained imply that serum concentration of estrogen is one of the important factors which affect the dopamine metabolism and content in the amygdale of female rats….."*

2004, "Journal of Neuroscience" N. Chuhma et al report, "*Dopamine neurons mediate a fast excitatory signal via their glutamatergic synapses."*

2006, "Journal of Neurochemistry," Robert Hruska confirms, "*Elevation of Sriatal Dopamine Receptors by Estrogen…."*

Book- "Dispelling The Myths About Addiction," released by the Institute of Medicine, states, "*One must not perturb the dopaminergic pathway itself. Knockout mice display grossly aberrant excitatory behavior due to a persistent excess of synaptic dopamine."*

1986, "Neuroscience and Biobehavioral Reviews," C Van Hartesveldt and JN Joyce report, "*Effects of estrogen on the basal ganglia- …..estrogen regulates the activity of dopamine-sensitive cells in the basal ganglia. ….estrogens clearly affect behaviors mediated by the basal ganglia as illustrated in human patients suffering from extrapyramidal disorders. Both biochemical and behavioral research in animals has confirmed that estrogen modulates basal ganglia function…..The effects of estrogen on behaviors mediated by dopamine in the basal ganglia depend on the dose of estrogen administered, the time interval between estrogen treatment and testing, the behavior measured, and the part of the basal ganglia from which the behavior is elicited. A high dose of estrogen results in an initial suppression and later enhancement of dopamine-related behaviors……Even after low doses of estrogen, the latency to behavioral suppression varies depending upon the behavior measured. These varying latencies suggest that more than one mechanism is involved in the effects of estrogen on basal ganglia output. ….it has been demonstrated that estrogen can act directly on the striatum. These findings are related to the effects of estrogen on human extrapyramidal disorders."*

2001, "Proceedings of the National Academy of Sciences," NIH, National Institute of Neurological Disorders and Stroke, CK Hwang et al report, "*Dopamine receptor genes are under complex transcription control, determining their unique regional distribution in the brain. Designated dopamine receptor regulating factor (DRRF) itself can be regulated by manipulations of dopaminergic transmission. Mice treated with drugs that increase extracellular striatal dopamine levels (cocaine), block dopamine receptors, or destroy dopamine terminals, show significant alterations in DRRF mRNA. We conclude that DRRF is important for modulating dopaminergic transmission in the brain."*

Like cocaine, estrogens including soy phytoestrogens are proven to increase extracellular dopamine levels.

2000, "Journal of Neuroscience," WG Brake et al report, "*Obstetric complications involving anoxia or prolonged hypoxia are suspected to increase the risk for such mental disorders such as schizophrenia and attention deficit-hyperactivity disorder. In previous studies, we reported evidence of enhanced nucleus accumbens dopamine function in adult rats subjected to intrauterine anoxia during cesarean section birth. In this present study, we…….. investigate the possibility that this functional hyperactivity of the meso-NAcc (dopamine) system is attributable to loss of inhibitory control from the medial prefrontal cortex. In C-section +15 (additional 15 minute of intrauterine anoxia) animals, we observed a pronounced and persistent blunting of stress-induced dopamine release in the right prefrontal cortex. These findings suggest a mechanism by which perinatal complications….might contribute to the etiology of mental disorders that have been linked to disturbances in central dopamine transmission and lateralized prefrontal cortex dysfunction."*

Like prolonged hypoxia, soy plant-estrogens are linked to disturbances in dopamine transmission causing cortex dysfunction.

2005, "Endocrinology" KM Olesen et al report, "*Dopaminergic Activation of Estrogen Receptors in Neonatal Brain Alters Progestin Receptor Expression and Juvenile Social Play Behavior- (Estrogen) receptor activation in developing brain influences a variety of cellular processes that endure into adulthood, altering both behavior and physiology. Neonatal treatment with either estradiol or a dopamine D1 receptor agonist can increase the expression of an estrogen receptor-regulated gene (i.e. progestin receptors) and later juvenile social play. More importantly, increases in social play behavior induced by neonatal treatment with estradiol or a dopamine receptor agonist can be prevented by prior treatment with an estrogen receptor antagonist. This suggests that changes in dopamine transmission in developing brain can activate estrogen receptors in a ligand-independent manner to influence gene expression and have lasting consequences on social behavior."*

The same as estradiol estrogen, soy plant-estrogen is a dopamine receptor agonist resulting in causation of dopamine receptor changes in brain regions.

2004, "Neuropsychopharmacology" AM Barr et al report, "*A hyperdopaminergic state in humans has been hypothesized to contribute to the pathology of a number of psychiatric illnesses, including schizophrenia, bipolar disorder, and attention deficit hyperactivity disorder. These data indicate that …..chronic, elevated dopaminergic tone is present and contributes to abnormal behavior and sensorimotor gating deficits (in DAT KO mice."*

Soy plant-estrogens are proven to cause a hyperdopaminergic state.

GABA (gamma amino butyric acid): plays a fundamental role in controlling fear and anxiety. Amino acid GABA is a major inhibitory neurotransmitter in virtually every part of the brain that promotes communications between nerve cells critical for central nervous system function. In the cerebral cortex GABA-containing cells represent a subpopulation of interneurons that sustain the vitality of the CNS. GABA in dentate gyrus granule cells has been described as being the guardians of the hippocampus against an overpowering excitotoxicity. Preliminary findings point to the existence of granule cell-mediated synaptic GABA responses not only in CA3 pyramidal cells but also in interneurons.

Granule cells refer to tiny neurons found within the granular layer of the cerebellum; the dentate gyrus of the hippocampus having glutamatergic projection axons, and the olfactory bulb that are GABAergic and axonless. While anatomically similar, granule cells in different brain regions are functionally diverse.

2001, "FDA's National Center for Toxicological Research" reports, "*Project # E0704011 Validity of Developmental Cerebellar Stunting in the Rat as a Model for Attention Deficient Hyperactivity Disorder: Behavior and Neurochemistry- Objective(s): 1) To identify treatments which cause developmental cerebellar stunting, specifically those which decrease the granule cell population……2) To identify the neurochemical alterations in different brain regions resulting form the developmental insult."*

Soy phytoestrogens are proven to cause all of those.

A main purpose of GABA is to prevent the over-firing of the nerve cells by balancing the excitatory and inhibitory neurons. GABA effect on the bran neurons can be protective during hypoxia (oxygen deprivation) or ischemia (shortage of blood supply to an organ). Without GABA inhibition, protective effects upon hypoxia and ischemia mean the mismatch of blood supply and blood request for adequate oxygenation. Ischemia results in damaging effects due to the lack of oxygen and nutrients in a low blood supply that encourages cell, tissue, and organ death. Deficiency in GABA inhibition is a factor in seizure occurrence and the cause of anxiousness and excitability.

Many studies conclude that soy plant-estrogens cause GABA neurotransmitter deficiencies that are implicated in several debilitating neurological conditions such as: irritability, anxiety, sleep disturbances, muscle spasms, panic attacks, major depression, epileptic seizure disorder, ADHD (Attention deficit Hyperactivity Disorder), and even diabetes.

"Journal of Biomedical Science," Y. Jin et al conclude, "*…the toxic effect of genistein and daidzein could be due to their inhibition of the GABA-A receptor resulting in further enhancement of excitation by glutamate and leading to cellular damage."*

Reported from the UK, "Journal of Molecular and Cellular Neuroscience" concludes, "*Genistein inhibited in a noncompetitive manner GABA-activated currents…..daidzein also similarly inhibited responses to GABA……Inhibitors (genistein and daidzein) targeting the substrated binding site of tyrosine kinases, also inhibited the …..GABA receptors. The study concludes that tyrosine kinase inhibitors and their inactive controls can directly interact with GABA receptors completely independent of any effects on tyrosine kinases."*

1998, "Perspectives on Developmental Neurobiology" JL Barker et al report, *"GABAergic cells and signals in CNS development. ……GABAA receptor/C1-channel*

transcripts and encoded proteins emerge early and seemingly everywhere during CNS development, with their abundance closely paralleling neurogenesis and peaking before birth. There results indicate that in vitro GABA can affect embryogenesis of the CNS through effects on cell proliferation and migration."

2005, "Journal of Nutritional Biochemistry", Vol 16, Issue 11, *Soy Isoflavone and Cognitive Function,* by YB lee, HJ Lee and HS Sohn, concludes- "……*genistein treatment induces apoptosis (cell death) in neurons. Rats consuming large amounts of genistein showed a significant increase of LDH (Layered Double Hydroides) in rat brain tissue…...DNA fragmentation was detected in homogenates (uniform consistency) of brain tissue from rats receiving either (high or low) dose of genistein. Genistein also has recently been observed to inhibit superoxide (ion with more electrons in their nuclei) generation resulting from exposure of cerebral vessels to whole blood. Daidzein increases contraction activity in the basilar (region of brain) artery and increases contraction activity in the basilar arteries of male rats.*

Genistein decreases the expression of GABA receptors in plasma membrane of rat cerebellar granule cell bodies and dendrites (support neural action and release of neurotransmitters). It has also been reported that glycine (amino acid commonly found in proteins) receptors are inhibited by genistein."

2007 "Journal of Biomedical Science" published study by Y Jin, H Wu, et al, reports, "*It is surprising that….isoflavones, specifically genistein and daidzein are toxic to primary neuronal culture at high concentration. Both genistein and daidzein were found to have little effect on glutamate receptor binding, while the binding of (3H) muscimol to GABA(A) receptors was markedly inhibited……suggesting that the toxic effect of genistein and daidzein could be due to their inhibition of the GABA (A) receptor resulting in further enhancement of excitation by glutamate and leading to cellular damage."*

Damaging effects caused by soy plant-estrogens by decreasing GABA inhibitory neurotransmitter also severely interrupt retinal signal processing resulting in vision defects. Soy infant formulas have been reported to cause optic nerve compression and temporary or permanent vision defects or blindness.

2007, Department of Biomedical Science, Florida Atlantic University reports, "*Genistein and daidzein induce neurotoxicity at high concentrations in primary rat neuronal cultures……isoflavones, specifically genistein and daidzein are toxic to primary neuronal culture at high concentrations. Treatment of neurons with 50microM genistein and daidzein for 24 hours increased LDH release by 90% and 67% respectively, indicating significant cellular damage. …...toxic effects of genistein and daidzein could be due to their inhibition of the GABA-A receptor……and leading to cellular damage."*

GABAergic interneurons comprise the bulk of local inhibitory circuitry in brain, many of which contain the calcium binding protein, parvalbumin(PV).

2006, "Acta Pharmacological Sinica," IK. Hwang et al report, "*Soybean isoflavones alter paravalbumin in hippocampus (female and male rats)….AIM: to investigate the long-term effect of soybean isoflavones on changes in parvalbumin immunoreactivity in the hippocampus in normal female ….and normal male rats. RESULTS: Paravalbumin immunoreactivity and the number of parvalbumin immunoreactive neurons in all the groups (female and male rats) after isoflavone treatment were significantly changed in the hippocampal CA1 region and in the dentate*

gyrus…..…...Paravalbumin immunoreactivity and the number of paravalbumin neurons in all the isoflavone-treated groups decreased dose-dependently after isoflavone treatment. CONCLUSION: Long-term administration of isoflavones may induce a reduction of paravalbumin in interneurons in the hippocampal CA1 region and in the dentate gyrus. The reduction of paravalbumin in these regions suggests that the long-term administration of isoflavones may cause a change in calcium homeostasis in the hippocampal CA 1 region and in the dentate gyrus."

Parvalbumin interneurons reportedly determine hippocampal function and associated behavior. Parvalbumin influences the electrical properties and enzymatic machinery that modulates neuronal excitability and activity. The specific role of parvalbumin in GABA-containing cortical cells is related to controlling the effectiveness of inhibitory actions.

2006, "Endocrinology" Neurotoxicology Division, U.S. Environmental Protection Agency, M.E. Gilbert et al report, "*Thyroid Hormone Insufficiency During Brain Development Reduces Parvalbumin Immunoreactivity and Inhibitory Function in the Hippocampus-…..…..severe postnatal hypothyroidism reduces parvalbumin (PV) immunoreactivity in rat neocortex. These data demonstrate the moderate degrees of thyroid hormone insufficiency during the early postnatal period permanently alters interneuron expression of PV and compromises inhibitory function in the hippocampus."*

As caused by soy plant-estrogens, thyroid hormone insufficiency or (hypothyroidism) is overwhelmingly documented throughout published literature.

GABAergic transmission from the dentate gyrus to CA3 has major implications not only for information flow into the hippocampus but also for developmental and pathological processes involving the hippocampus. Soy causation of deficiencies in GABA inhibition reveals the further causation of multiple indirect neurological damaging effects.

2001, "Journal of Neuroscience Research," JD Su et al report, "*This study investigated the expression patterns of estrogen receptor-alpha (ER alpha) and –beta (ER beta) in the cultured hippocampal cells of neonatal rats……..immunoreactivity for either ER alpha or ER beta was observed to be localized in the majority of not only neurons but also astrocytes. The data also provide direct evidence for the expression of ER subtypes within GABAergic neurons in hippocampal cell cultures and suggest that estrogen's effect on the hippocampus may be mediated at least in part by its ER-containing GABAergic neurons."*

2006, "Cell and Tissue Research," M. Frotscher et al report, "*The axon terminals (mossy fibers of the hippocampal dentate granule cells form characteristic synaptic connection with large spines or excrescences of both hilar mossy cells and CA3 pyramidal neurons. Interneurons of the hilar region and area CA3 are also prominent targets of mossy fibers……the majority of mossy fiber synapses project to GABAergic inhibitory interneurons rather than to excitatory principals cells……the present review focuses on the contact formed between dentate granule cells and GABAergic interneurons…..there is an apparently convergent input of new mossy fibers onto GABA-immunoreactive interneurons dendrites that traverse the inner molecular layer. These mossy fiber-interneuron synapses in the dentate gyrus are observed in chronically epileptic rats and may be the structural correlate of granule cell hyperinhibition*

observed in these animals in vivo. Together, the findings reviewed here establish mossy fiber synapse as an important component of inhibitory circuits in the hippocampus."

2001, "Neuron" MC Walker et al report, "*GABAergic transmission from the dentate gyrus to CA3 has major implications not only for information flow into the hippocampus but also for developmental and pathological process involving the hippocampus."*

It is reported that CA3 pyramidal neurons can display a long-term hyperexcitability several months after insult resulting in a shift in the excitatory-inhibitory balance toward excitation that may constitute a substrate for the generation of epileptiform discharges in the hippocampus. Decrease in GABA inhibition as reportedly caused by soy products can result in CA3 hyperexcitabilty with potential to increasingly encourage migraine headaches and worse yet, seizures.

Soy causation of alterations in several neurotransmitter systems, including decreasing GABA inhibitory actions, greatly impairs trisynaptic circuitry that relays synaptic transmissions in the hippocampus and increases the risk of adverse neurological effects involving; memory, learning, and behavior.

Increasing evidence confirms that fetal, and continual infant hippocampal development and function involving extensive incoming and outgoing circuitry with a variety of cortical targets is highly sensitive to neurotoxic effects such as those caused by soy plant-estrogens, resulting in a variety of potential irreversible brain impairments.

The increase in autism and other behavioral disorders while male dominated, may be explained by gender differences in fetal and infant brain anatomy and greater sensitivity in males to soy plant-estrogens, antinutrients, heavy metals, etc.

2002, "Developmental Medicine & Child Neurology" ER Sowell et al report, "*Once the approximately 7% larger brain volume in males was controlled, only mesial temporal cortex, caudate, thalamus, and basomesial diencephalic structures showed sex effects with the females having greater relative volumes in these regions than the males."*

Book- "Principles of Gender-Specific Medicine" M Legato and J. Bilezikian report, "*The hippocampus, a brain region critical to the stress response, is a sexually differentiated structure."*

2005, "Neuroscience," S. Guidi et al report, "*Sex differences in the hilar mossy cells of the guinea-pig before puberty- Numerous sex differences have been detected in the morphology of the dentate and hippocampal neurons and hippocampus-dependent memory functions….differences favored females that had more proximal branches and a greater spine density on the distal dendrites than males. The results show that the mossy cells of the guinea-pig are sexually dimorphic prior to puberty.*

2007, "Journal of Biomedical Science," U. Ying et al report, "*Both genistein and daidzein at 50 uM, increased the intracellular calcium level (Ca2+) significantly….genistein and daidzein binding of (3H) muscinmol to GABAa receptors was markedly inhibited….suggesting that the toxic effects of genistein and daidzein could be due to inhibition of the GABAa receptor resulting in further enhancement of the excitation by glutamate and leading to cellular damage."*

It is well known that estrogenic compounds, including soy plant-estrogens are highly capable of damaging the hippocampal brain area throughout life, while causing highest neurotoxicity during fetal, infant, and child development. Estrogens damage several neurotransmitter systems, and cause brain shrinkage (fewer than normal brain

cells) of the hippocampus. Soybean causation of the malfunction of several neurotransmitters, as well as the estrogenic cause of smaller-sized hippocampus are each and all commonly diagnosed in a variety of neurological disorders, including autism.

SEIZURES- Several studies report that seizures in young children are associated with hippocampal neuron losses and derangement of mossy fiber sprouting during fascia dentate pre- and postnatal development. Studies report that these brain disruptions are capable of being caused by soy plant-estrogens. Soy decreases GABA inhibitory action resulting in excessive dentate gyrus excitability that may encourage or exacerbate seizures. Studies report that this decrease in GABA inhibition could contribute to neuronal circuit alterations and generate the epileptic condition.

Dentate gyrus granule cells communicate with their postsynaptic targets through distinct mossy fiber terminals. GABAergic cells are the major postsynaptic targets of mossy fibers that are involved in hippocampal formation or one of the few regions of the brain where neurogenesis or the birth of new neurons takes place. There is also a coexistence of excitatory and inhibitory amino acids in the same mossy fiber nerve terminals of the dentate gyrus.

Dentate gyrus contributes to the formation of memories, recognition of people and locations. Neurogenesis, (neuronal prenatal development and activity) in the dentate gyrus plays an important role in modulating symptoms of stress and depression. Mossy fibers are the sole excitatory projection from dentate gyrus granule cells to the hippocampus, forming part of the trisynaptic hippocampal circuit. This hippocampal pathology is reportedly involved in the cause and effects of seizures that originate in the temporal lobe. Soy plant-estrogens are confirmed to cause deficient GABA inhibition, a hippocampal dysfunction, resulting in unopposed granule cell hyper-excitability that is reported in the cause of seizures.

1994, "Annuals of Neurology," RS Sloviter reports, "*The functional organization of the hippocampal dentate gyrus and its relevance to the pathogenesis of temporal lobe epilepsy- Temporal lobe seizures are frequently associated with a characteristic pattern of hippocampal pathology (hippocampal sclerosis) as well as pathology in other temporal lobe structures……loss of dentate mossy cells may deafferent inhibitory neurons, render them 'dormant' and thereby disinhibit an enlarged expanse of the granule cell layer. The selective loss of neurons that normally govern lateral inhibition in the dentate gyrus may cause functional delamination of the granule cell layer and result in synchronous, multilamellar discharges in response to cortical stimuli. Thus hippocampal pathology may be both the cause and effect that originate in the temporal lobe."*

2001, "Journal of Neurophysiology," PR Patryol et al report, "*GABA uptake and heterotransport are impaired in the dentate gyrus of epileptic rats and humans with temporal lobe sclerosis. In vivo dialysis…….studies suggest that GABA uptake is altered in the dentate gyrus of human temporal lobe epileptics..…Concordantly, anatomical studies have shown that the pattern of GABA-transporter immunoreactivity is also altered in this region. This data suggest that the GABA transporter system is functionally compromised in both the forward and reverse directions in the dentate gyrus of chronically epileptic tissue …..*"

2007, "Progress in Brain Research" TP Sutula and FE Dudek report, *"…the overwhelmingly majority of sprouted synapses in the inner molecular layer of the dentate gyrus form recurrent excitatory connections and are thus likely to contribute to recurrent excitation and potentially to enhanced susceptibility to seizures."*

2001, National Center for Scientific Research, G. Chapouthier and P Venault report, *"Epilepsy is a pathological tendency to have convulsions, whose relation to a major inhibiting brain neurotransmitter, GABA, has long been known to scientists. It has been shown that anxiety is also related to GABA….researchers were able to show the correlation between epilepsy and anxiety."*

1992, "Epilepsy Research, Supplement" U Heinemann et al report, *"The dentate gyrus as a regulated gate for the propagation of epileptiform activity- Removing GABAergic inhibition…..caused the spread of seizure-like events from the entorhinal cortex to the dentate gyrus."*

STUTTERING-

2005, "Medical Hypotheses," P Movsessian reports, "…… *stuttering may involve the disrupt of the optimal balance between excitatory and inhibitory neurotransmission throughout the brain by inhibiting GABA receptors. The disruption of the optimal balance between excitatory and inhibitory neurotransmission can also cause dysfunction in whit matter fiber tracts such as those that connect the Broca's area to the motor cortex. This leads to a hyperexitation of the motor cortex which may mimic the motor cortex hyperexcitability that exists in developmental stuttering……..hyperdopaminergic state (also) exists in the brain of developmental stutterers……release of dopamine in the basal ganglia through the inhibition of adenosine and GABA receptors…….may also cause dysfunction in the basal ganglia similar in some ways to the dysfunction that exists in developmental stuttering. ……enhancement of dopaminergic neurotransmission ……..(has) been reported to cause stuttering in fluent individuals and to aggravate dysfluency in stutterers."*

Soy phytoestrogens inhibition of GABA neurotransmitters, and excessive release of dopamine is confirmed throughout numerous published studies.

GLUTAMATE- is a key molecule in cellular metabolism, and plays an important role in the body's disposal of excess or waste nitrogen. Glutamate is also the most abundant excitatory neurotransmitter in the mammalian nervous system. It is confirmed that the damaging soy-cause of inhibiting GABA inhibitory neurotransmitters, therefore causes dangerously high glutamate excitatory levels, of which both soy phytoestrogen actions are confirmed as neurotoxic.

In the opposing post-synaptic cell, glutamate receptors, such as the NMDA receptor, bind glutamate and are activated. Because of its role in synaptic plasticity, it is believe that glutamate is involved in cognitive brain functions, learning, and memory. Glutamate transporters are found in neuronal and glial membranes. Glutamate can accumulate outside cells causing calcium ions to enter cells via NMDA receptor channels, leading to neuronal damage and eventual cell death, called excitotoxicity. Mechanisms of cell death include: damage to mitochondria from excessively high intracellular Ca2+, and Clu/Ca2+-mediated promotion of transcription factors for pro-apoptotic genes, or down-regulation of transcription factors for anti-apoptotic genes.

Glutamate is the major excitatory neurotransmitter in the mammalian CNS. When the glutamate concentration around the synaptic cleft cannot be decreased or reaches highest levels, the neuron kills itself by a process called apoptosis. Increasing glutamate is neurotoxic and a buildup of glutamate further damages activation of glutamate receptors causing excitotoxicity in the brain.

Excitotoxiciy caused by excessive glutamate is associated with amyotrophic lateral sclerosis, lathyrism, autism, forms of mental retardation, multiple sclerosis, and Alzheimer's disease.

Glutamate amino acid has been implicated in epileptic seizures. Extracellular glutamate is reported to play an endocrine-like role as part of a larger homeostatic system. Glutamate also serves as the precursor for the synthesis of the inhibitory GABA in GABA-ergic neurons. This reaction is catalyzed by glutamic acid decarboxylase (GAD) which is most abundant in the cerebellum and pancreas. Stiff-man syndrome is a neuralgic disorder caused by anti-GAD antibodies leading to a decrease in GABA synthesis and therefore, impaired motor function such as muscle stiffness and spasm. Since the pancreas is also abundant for the enzyme GAD, a direct immunological destruction occurs in the pancreas and the patients will have diabetes mellitus.

Soy phytoestrogens cause increasing levels of glutamate, or excitotoxicity resulting in a biochemical cascade of adverse physiological and neurological effects.

2003, "Journal of Anti-Aging Medicine," IW Goddard reports, "*While it has been shown that the soy phytoestrogen genistein inhibits neuroprotective functions in cell cultures, recent in-vivo findings strengthen the case for a possible causal mechanism of soy-induced neurodegeneration. In tissue cultures, genistein has been shown to suppress both DNA synthesis and the effects of brain-derived neuotrophic factor (BDNF), as well as to increase glutamatic toxicity and glutamate-induced peroxide accumulation.*

Recently, the ability of dietary soy to suppress BDNF expression in the hippocampus and cerebral cortex has been demonstrated in male rats. Given that BDNF facilitates the survival of neurons and that its suppression is known to cause neural atrophy, such in-vivo findings clearly lend credence to a hypothesis that soy may cause brain atrophy……

……evidence raises questions about the safety of soy. ……it seems reasonable that some individuals may choose to adopt a policy of avoiding soy until it is proven safe rather than consuming it until it is proven unsafe……for those in positions of public health advocacy, avoidance of soy also seems reasonable at the level of personal risk assessment and as such should not be discouraged as alarmist."

2007, "Journal of Biomedical Science," Y Jin et al report, "*Genistein and daidzein induce neurotoxicity at high concentrations in primary rat neuronal cultures- Since isoflavones possess estrogen-like activity, it is of interest to determine whether isoflavones can also protect neuron from glutamate-induced neuronal injury. It is surprising that, contrary to estrogen, isoflavones, specifically genistein and daidzein are toxic to primary neuronal culture at high concentration. Treatment of neurons with 50 microM genistein and daidzein for 24 hour increased LDH (lactate dehydrogenase) release by 90% and 67% respectively, indicating a significant cellular damage. At 100 microM, both genistein and daidzein increased LDH release by 2.6- and 3-fold, respectively with a 30-min incubation. Furthermore, both genistein and daidzein at 50 microM increased the intracellular calcium levels, {Ca (2+)} (i), significantly. Both*

genistein and daidzein….while binding of {(3)H} muscimol to GABA(A) receptors was markedly inhibited. ……..suggesting that the toxic effect of genistein and daidzein could be due to their inhibition of the GABA (A) receptor resulting in further enhancement of excitation by glutamate and leading to cellular damage."

Excitotoxicity is the pathological process by which nerve cells are damaged and killed by glutamate and similar substances. This occurs when receptors for the excitatory neurotransmitter glutamate such as the NMDA receptor and AMPA receptor are overactivated. Excitotoxins like NMDA bind to these receptors, as well as pathologically high levels of glutamate causing excitotoxicity by allowing high levels of calcium ions (Ca2+-) to enter the cell. Ca2+- influx into cells activates a number of enzymes……..These enzymes go on to damage cell structures such as components of the cytoskeleton membrane, and DNA

1998, "Biofactors," DG Nicholls, SL Budd report, "*Chronic activation of NMDA receptors by glutamate is toxic to cultured neurons. The extensive Ca2+ entry accompanying receptors activation is largely accumulated by the intracellular mitochondria with resultant effects on mitochondrial membrane potential, ATP synthesis, glycolysis, reactive oxygen species generation and ultimately failure of cytoplasmic Ca2+ homeostasis and cell death. Each of these parameters is inter-related…..The conclusion is that mitochondrial Ca2+ accumulation is a key event in glutamate excitotoxicity…..*"

Effects of soy phytoestrogens/antinutrients are an unmatchable cause of biochemical cascading effects resulting in a host of irreversible damaging health, particularly during developmental timeframes.

1996, "Journal of Neuroscience," AF Schinder et al report, "*Mitochondrial dysfunction is a primary event in glutamate neurotoxicity- Excitotoxic neuronal death, associated with neurodegenerative disorders and hypoxic insults, results from excessive exposure to excitatory neurotransmitters. Glutamate neurotoxicity is triggered primarily by massive Ca2+ influx arising from overstimulation of the NMDA subtype of glutamate receptors. We have tested the hypothesis that mitochondria are primary targets in excitotoxicty by confocal imaging of intracellular Ca2+ ({Ca2+}i) and mitochondria membrane potential on cultured rat hippocampal neurons. Sustained activation of NMDA receptors (20 min) elicits reversible elevation of {Ca2+}i. Longer activation (50 min_ renders elevation of {Ca22+}I irreversible (Ca2+ overload). . Susceptibility to NMDA-induced Ca2+ overload ins increased when the 20 min stimuli are applied to neurons pretreated with electron transport chain inhibitor……These results suggest that early mitochondrial damage plays a key role in induction of glutamate neurotoxicity.*"

SOY DAMAGE OF MITOCHONDRIA- are considered the power generators of the cell, converting oxygen and nutrients into adenosine triphosphate (ATP). ATP is the chemical energy supply of all living cells that powers the metabolic cellular activities necessary in the processes of life. The ATP is produced in the miochondria using energy stored in food by a process of respiration, of which the use of oxygen generates cell energy. Mitochondrion may also be involved in controlling the concentration of calcium within the cell.

2007, "Journal of Neuroscience Research," DG Nicholls et al report, "*Bioenergetics of mitochondria in cultured neurons and their role in glutamate excitotoxicity- The pathologic activation of NMDA receptors by glutamate is a major contributor to neuronal cell death after stroke. Receptor activation causes a massive influx of calcium into the neuron that is accumulated by the mitrochondria. The favored hypothesis is that the calcium loaded mitochondria generate reactive oxygen species that damage and ultimately killed the neuron……..glutamate excitotoxicity suggests that enhanced reactive oxygen species are a consequence rather than a cause of failed cytoplasmic calcium homeostasis (delayed calcium deregulation {DCD}), but that prior oxidative damage facilitates DCD by damaging mitochondrial ATP generation."*

2005, "Journal of Carcinogenesis," Q Felty and D Roy report, "*Mitochondria are important targets of estrogen action. Therefore, an in-depth analysis of interaction between estrogen and mitochondria; and mitochondrial signaling to nucleus are pertinent to the development of new therapy strategies for the treatment of estrogen-dependent diseases related to mitochondrial disorders, including cancer. These findings suggest that in addition to estrogen mediated actions, other factor(s) must be involved in the stimulation of cell growth by estrogen. More recently, mitochondria have been implicated in the control of cell proliferation. For instance, the mitochondrial peripheral benzodiazepine receptor has been implicated in the regulation of human breast cancer cell proliferation. Similarly, we have demonstrated that mitochondria can modulate the expression nuclear cell cycle genes and human breast tumor growth. ….the growth of estrogen-dependent and estrogen-independent cells is inhibited by controlling mitochondrial biogenesis. In this paper, we critically review the role of mitochondria in the growth of estrogen-dependent cancer and non-cancer cells. The cross-talk between the cell nucleus and the mitochondria appears to control estrogen-induced signaling involved in the apoptosis, proliferation, and differentiation of both normal and malignant cells. The understanding of the regulation of mitochondrial biogenesis by estrogenic compounds would open a new way to better understand steroidal and non-steroidal estrogen action at the cellular level. Besides apoptosis, respiration, and oxidative phosphorylation; mitrochondral also control ion homeostasis, and the synthesis of heme, lipids, amino acids, and nucleotides. Steroidogenesis is also controlled by mitochondria. Estrogen biosynthesis-related enzymes, have been demonstrated in the mitochondria of ovarian tumor epithelial cells. Since mitochondria are enriched with lipids, the organelle has the ability to act as an estrogen-sink within the cell. The impact of estrogen on mitochondrial morphology has previously been reported in the human breast cancer cell line MCF7. These alterations in mitochondria structure were observed as early as 2 days after treatment with a physiologically relevant dose of estrogen….recent studies have identified ERa and ERb within the mitochondria implication its role in the regulation of mitochondrial genome transcription. More recently ERb was shown to be localized in the mitochondria of human lens epithelial cells, human heart, rat primary neuron and primary cardiomyocyte, and in a murine hippocampal cell line. Treatment of MCF7 with E2 (17-B-estradiol) significantly increased the mitochondrial level of ERa and ERb by 2.5-fold…..evidence has shown that mitochondrial transcription is enhanced by estrogen treatment. For instance, a 16-fold increase in cytochrome oxidase II mRNA is reported in the rat pituitary tumor cell line when treated fro 6 days withE2. Besides transcription of mitochondrial genes, estrogen has also been demonstrated to effect*

mitochondria at the protein level. Estrogen has been demonstrated in several studies to inhibit mitochondrial respiratory complex I II III, IV, and mitochondrial ATP syntheses. Several studies have reported estrogen specific inhibition of mitochondrial respiratory proteins……..Besides a direct interaction with mitochondrial proteins, estrogen may indirectly effect the electron transport chain through an increase of membrane fluidity. This effect is significant because estrogen-induced mitochondrial reactive oxygen species may participate in cell signaling. Human NADH dehydrogenase (complex 1) is the largest respiratory chain complex consisting of 7 mitochondrial genome encoded subunits and more than 41 subunits encoded from the nuclear genome. This integral membrane protein is located within the mitochondrial inner membrane and matrix. The researchers postulated that at relatively low doses, DES reversibly inhibits electron transfer at complex I…..Another class of compounds, phytoestrogens, which are found in our diet can also inhibit the activity of complex I. Genistein can inhibit FoF1-ATPase activity in rat brain mitochondria."

2000, "British Journal of Pharmacology," J Zheng and VD Ramirez report, *"Inhibition of mitochondrial proton FoFI-ATPase/ATP synthase by polyphenolic phytochemicals. In conclusion, the ATP synthase is a target for dietary phytochemicals. This pharmacological property of these phytochemicals should be included in the examination of their health benefits as well as potential cytotoxicity"*

2002, "Anticancer Resources," JH Choi et al reports, "*Overexpression of mitochondrial thioredoxin reductase and peroxiredoxin III hepatocellular carcinomas-Substantial evidence indicates that the alteration of cellular redox status is a critical factor involved in cell growth and death and results in tumorigenesis. These results suggest that alterations in cellular redox status……might be associated with the formation and development of hepatocellular carcinomas."*

2002, "Biochimica et Biophysica Acta," M Salvi et al report, "*Interaction of genistein with the mitochondrial electron transport chain results in opening of the membrane transition pore. Addition of genistein to isolated rat liver mitochondria induces swelling, loss of membrane potential, and release of accumulated Ca2+. Induction of the mitochondrial permeability transition by genistein is accompanied by oxidation of thiol groups and pyridine nucleotides…..thereby emphasizing that the effect of the isoflavone correlates with the mitochondrial redox state. Further analysis showed that genistein induces the mitochondrial permeability transition by the generation of reactive oxygen species due to its interaction with the respiratory chain at the level of mitochondrial complex III."*

Damaging results of excess calcium in the cytosol is the opening of the mitochondrial permeability transition pore, a pore in the membranes of mitochondria that opens when the organelles absorb too much calcium. Opening of the pore may cause mitochondria to swell and release proteins that can lead to apoptosis. The pore can also cause mitochondria to release more calcium. In addition, production of ATP may be stopped and ATP synthase may in fact begin hydrolyzing ATP instead of producing it.

Inadequate ATP can eliminate electrochemical gradients of certain ions. Glutamate transporters require the maintenance of these ion gradients in order to remove glutamate from the extracellular space. The loss of ion gradients results not only in the halting of glutamate uptake, but also in the reversal of the transporters, causing them to release glutamate from the extracellular space. This results in the buildup of glutamate

and further damaging activation of glutamate receptors. Excessive release of glutamate is the cause of excitotoxicty proven to result in damage to brain neurons.

2002, "Gynecological Endocrinology," F Massart et al report, "Dose-dependent inhibition of mitochondrial ATP synthase by 17 beta-estradiol- Mitochondria produce energy through oxidative phosphorylation. Estradiol could directly modulate mitochondrial ATP synthase activity through this subunit. In addition, intracellular ATP levels play a role in apoptotic death, which is an energy-dependent process requiring functioning mitochondria. Estradiol rapidly inhibited FOFI-ATP synthase activity in the physiological range. With 1 nmol/1 of estradiol, the inhibition was already significant…..In conclusion, we showed a new non-genomic effect of estradiol on a key mitochondrial enzyme, which thereby directly modulates cellular energy metabolism."

2005, "Journal of Carcinogens," Q Felty and D Roy report, "*Estrogen, mitochondria, and growth of cancer and non-cancer cells- Estrogen is considered to elicit different growth responses in various tissues and through binding to the estrogen receptor(ER)- a and ER-b. The estrogen responsive gene transcription by the ER is termed a 'genomic' action of estrogen. In contrast, 'non-genomic' effects of estrogen are characterized by a rapid onset of action within second to minutes after hormone exposure though post-translation modification of signaling proteins. ER-mediated signaling pathways are considered to support the growth of normal, preneoplastic and neoplastic cells. ….recent studies have shown evidence of rapid signaling pathway mediated by cell surface ERs and non-genomic estrogen-induced signal transduction pathways which contribute to cell proliferation. More recently, mitochondrial have been implicated in the control of cell proliferation. In this paper, we critically review the role of mitochondria in the growth of estrogen-dependent cancer and non-cancer cells. Mitochondria are important targets of estrogen action. The cross-talk between the cell nucleus and the mitochondria appears to control estrogen-induced signaling involved in the apoptosis, proliferation and differentiation of both normal and malignant cells. Mitochondria through its interaction with the cytoskeleton, export of cleaved signaling peptides or generation of ROS appears to transducer signals to the nucleus for the activation of transcription factors involved in the cell cycle progression of estrogen-dependent cells. The understanding of the regulation of mitochondrial biogenesis by estrogenic compounds would open a new way to better understand steroidal and non-steroidal estrogen action at the cellular level. Besides apoptosis, respiration, and oxidative phosphorylation, mitochondria also control ion homeostasis and the synthesis of heme, lipids, amino acids, and nucleotides. Although estrogen synthesis occurs in the mitochondria, exogenously added estrogen is also transported to this organelle. The impact of estrogen on mitochondrial morphology has previously been reported in the human breast cancer cell line MCF7. These alterations in mitochondria structure were observed as early as 2 days after treatment with a physiologically relevant dose of estrogen……recent studies have identified Era and ERb within the mitochondria implicating its role in the regulation of mitochondrial genome transcription. In summary, mitochondria are a major target of estrogen……interactions between estrogen and mitochondria merit further investigations."*

As previous studies confirm, endocrine disrupting soy phytoestrogens dangerously manipulate ER-a and ER-b, as well as the mitochondria, and all that is of greatest danger to developing fetus, infants and children.

CHOLINERGIC SYSTEM- is a system of nerve cells that uses acetylcholine in transmitting nerve impulses. The cholinergic system is a neurotransmitter system involved in the regulation of memory and learning. It is this system the degenerates in Alzheimer's disease. Acetylcholine tends to cause excitatory actions and is neurotransmitter in both the central nervous system and in the peripheral nervous system. Acetylcholine is one of many neurotransmitters in the autonomic nervous system and the only neurotransmitter used in the somatic nervous system associated with the voluntary control of body movements by sending brain signals for muscle contraction, and controls the reception of external stimuli such as; touch, hearing, and sight. It is also the neurotransmitter in all autonomic ganglia, which are clusters of neuronal cell bodies and their dendrites acting as a junction between autonomic nerves originating from the CNS and autonomic nerves innervating their target organs in the periphery.

In the PNS, acetylcholine is the transmitter that stimulates messages from the nerve to the muscles, including the muscles of the gastro-intestinal system. Acetylocholine is also found in sensory neurons, autonomic nervous system, (maintains homeostasis: heart rate, digestion, respiration rate, salivation, perspiration, diameter of the pupils, urination and sexual arousal) and has a part in scheduling REM (dream) sleep. In the CNS, acetylcholine is involved with arousal, learning tasks, and ability to use memory, etc. Acetylcholine is the only neurotransmitter used in the somatic nervous system, connecting brain signals with muscle contractions. Choline is a building block needed to produce the neurotransmitter acetylcholine.

The accumulation of acetylcholine causes over-stimulation of the acetylcholine receptor sites in both the central and peripheral nervous systems. High acetylcholine in the brain causes; sensory and behavioral disturbances, poor coordination, depressed memory, slow learning/cognition, and depressed respiration.

The FDA requires that infant formula not made from cow's milk be supplemented with choline, while it is proven that soy plant-estrogens already encourage excessive choline levels.

2008, "Annuals of N.Y. Academy of Science" reports, *"The present findings suggest that estrogens and phytoestrogens most likely stimulate catecholamine (neurotransmitter) synthesis via estrogen receptors in the plasma membrane….."*

"Proceedings of the Society for Experimental Biology and Medicine" reports, "*Choline acetyltransferase mRNA levels were significantly higher in the frontal cortex of estradiol and soy phytoestrogen-treated retired breeder rats…. Our data suggest that soy phytoestrogens may function as estrogen agonists in regulating choline acetyltransferase and nerve growth factor mRNAs in the brain…..*"

"Effects of Phytoestrogens on Acetylcholine….in rat aorta….." Yamaguchi et al reports, "*Theses results indicate that phytoestrogen, isoflavones, certainly possess estrogenic actions on the vasodilating responses caused by acetylcholine.…..*"

2001, "The Japanese Journal of Pharmacology" K Yamaguchi et al report, "*These results indicate that phytoestrogen, isoflavones, certainly possess estrogenic actions on the vasodilatory responses caused by acetylcholine and isoprenaline, as well as weaker uterotrophic effects.*"

Endocrine disruptors such as soy plant-estrogens, pesticides, etc, act as irreversible acetylcholinesterase inhibitors by binding cholinesterase so that the enzyme

cannot do its job and causing a build up, or over-accumulation of acetylcholine. Paraoxonase, is an enzyme that brakes down acetylcholinesterase inhibitors such as estrogen-mimics (pesticides, or soy plant-estrogens), before they bind to the cholinesterases, thus affording the human body some protection. However, not all people have the same levels of these paraoxonases. People with less paraoxonases are at higher risk of endocrine disruptor poisoning, causing neurotoxicity that damages the autonomic nervous system, and panic disorders may result. Certainly, fetus, infants, and children are far less likely to have adequate paraoxonases enzymes for protection.

SOY INCREASES CHOLECYSTOKININ- (CCK) is a group of similar proteins sharing specific hormonal activities in the digestive tract, and neurotransmitter functions in the central nervous system (CNS). The CCK hormones range in size from 4 to 55 amino acids involved in CNS/cognitive processes like anxiety, memory, and learning. CCK also functions by causing satiety, and is linked to eating disorders like anorexia nervosa. CCK in the bloodstream quickly travels to the CNS, stomach, liver, gallbladder and pancreas. CCK signals the liver to create more bile, for the pancreas to release digestive enzymes, signals the gallbladder to spasm to secrete bile into the small intestine, instructs the stomach to stop emptying, regulate gastrointestinal motility and induction of satiety, potentiate insulin secretion, regulate bowel motility, regulate food intake, and helps to facilitate the absorption of nutrients. Major biological actions of CCK are the reduction of food intake and the induction of anxiety-related behavior. A number of molecular forms of CCK have been identified in the brain, intestine, and blood. Studies confirm that soybeans increase CCK levels that lead to the causation of damaging body and brain disorders.

NIH Pubmed study titled, "Dietary regulation of rat intestinal cholecystokinin gene expression" by RA Liddle et al report, "*Next, as a means of stimulating CCK secretion, soybean trypsin inhibitor was perfused (in rats) for up to 24 hours. (Soy) trypsin inhibitor administration increased plasma CCK levels for 0.9+/-0.1 to approximately 5pmol/liter. In trypsin inhibitor-treated rats, a two-to threefold increase in transcriptional (CCK) activity was observed. ….stimulation of CCK secretion is associated with an increase in intestinal CCK mRNA content resulting from an increase in CCK gene transcription."*

2003, "Biochemical Molecular Actions of Nutrients" M Nishimukai et al report, *"The physiologic roles of dietary (soy)lecithin have not been clearly defined. These results demonstrate that oil containing (soybean) lecithin …..effects are associated in part with (increasing) CCK release."*

1989, "AJP- Gastrointestinal and Liver Physiology," S Rosewicz et al report, *"Pancreatic digestive enzyme gene expression: effects of CCK and soybean trypsin inhibitor- Plasma CCK levels were raised to levels comparable to physiological postprandial levels either by intraduodenal perfusion with soybean trypsin inhibitor or by continuous intravenous infusion with cholecystokinin octapeptide. These data suggested that soybean trypsin inhibitor (SBTI) acted via its ability to raise plasma CCK levels. The ability of SBTI infusion to increase plasma CCK accounts for its effects on pancreatic digestive enzyme mRNA levels."*

CCK is isolated from the gastrointestinal system and extensively and abundantly distributed within the central and peripheral nervous system. CCK receptor is of great

importance to human CNS functioning. It is reported that research finding increasing CCT levels are recognized as important to psychiatric neuroscience. CCK also interacts with dopamine-mediated behavior, and interrupts several neurotransmitter functions, increasing the risk of neurological disorders. The involvement of CCK in human anxiety and behavioral responses is well documented.

1992, "International Journal of Neuroscience" A Yamashita reports, "*Distribution of CCK immunoreactive structures was studies in various neocortical areas of macaque monkey during prenatal and postnatal development. The largest number of CCK cells was observed at embryonic day 140, and subsequently they decreased in number until postnatal day 60. These findings suggest that CCK may be involved in the development and special function of each neocortical areas of the primate."*

There is a regulatory system of CCK distribution during fetal and infant brain development of which is seriously disrupted by soy phytoestrogens and antinutrients. Soy disruption of CCK in the cortical area of the limbic system upsets the higher functions of sensory perception, generation of motor commands, spatial reasoning, conscious thought, and language, as involved in the cause of neurological disorders.

2001, "Scandinavian Journal of Clinical and Laboratory Investigation Supplementum" TV Hansen, and FC Nielsen report, "*Whereas intestinal CCK is involved in the release of pancreatic enzymes and the contraction of the gallbladder, cerebral CCK is implicated in a variety of functions, such as feeding behaviour, anxiety, and memory. The expression of CCK is developmentally regulated. Brain CCK mRNA levels are low before birth, but increase markedly shortly after birth and reach adult like patterns of expression three weeks after birth during the final maturation of the CNS. Recent studies have examined the signaling pathways, transcription factors and regulatory elements involved in cAMP, fibroblast growth factor-2 and calcium-induced DDK gene transcription in neuronal cells."*

Doubling up with the damaging effects to neurotransmitters caused by the plant-estrogen chemical component of soy isoflavones, several studies confirm that soybean trypsin inhibitors also interrupt the endocrine system to include the cholecystokinin hormone system. Soybeans abnormally increase CCK levels. Physiologically meaningful overexpression of CCK causing overexpression of soy plant-estrogen increased vasopressin and oxytocin levels (and disrupting other neurotransmitters) are reported in the causation of behavioral disorders, to include autism.

2001, "Neuropsychopharmacology" JL Abelson et al report, "*CCK neurotransmitter modulates hypothalamic-pituitary-adrenal (HPA) axis activity and may be involved in fear or anxiety states. Arginine vasopressin (AVP) also modulates HPA axis activity and may play a role in fear conditioning. Few human studies have examined interactions between CCK and AVP systems. AVP release appeared to increase with increasing doses of the CCK-B agonist. AVP release was significantly correlated with anxiety symptom responses. These findings suggest a possible role for the CCK-B receptor in AVP release, which may be at least partially separate from its role in modulation of the HPA axis."*

2002, "European Journal of Surgery," B Ohlsson et al report, "*Cholecystokinin stimulation leads to increased oxytocin secretion……..Oxytocin was secreted in response to endogenous as well as exogenous CCK stimulation."*

Besides serious disruptions in neurotransmitters, soybean causation of CCK overexpression also increases the risk of : loss of appetite of which is critical during fetal and infant developmental growth, kidney and pancreatic damage, with potential to encourage pancreatic cancer.

1990, " Science" A Weller et al report, "*Intragastric administration of soybean trypsin inhibitor, a procedure that releases CCK from the small intestine decreased the subsequent intake of test meal (in rat pups). Thus endogenous, small intestinal CCK can cause satiety in the neonatal rat and this effect involves CCK-A receptors."*

1996, "Present Knowledge in Nutrition" C Berdanier writes, "*Zinc is critical for control of genes expression CCK and uroguanylin. Zinc deficiency results in overproduction of these hormones. CCK affects pancreatic secretion and satiety. The overproduction of CCK may explain the compromised pancreatic function and anorexia associated with zinc deficiency."*

1992, "Cancer Research" RH Bell et al report, "*Cholecystokinin is a growth factor for normal pancreas. Numerous studies also suggest that CCK promotes pancreatic carcinogenesis in the rat…..growth of preneoplastic pancreatic foci was stimulated by CCK more than that of normal pancreas…."*

2008, "Transgenic Research" M. Aunapuu reports, "*Although cholecystokinin is a regulatory peptide with a predominant role in the brain and the gastrointestinal tract, there is an increasing evidence for its role in the kidney. The altered morphology of kidneys of mice with cholecystokinin overexpression was seen by all microscopic techniques used. ….renal tubules were thickened and the epithelial cells were damaged…cholecystokinin plays important role in renal structural formation and in functioning as different aspects of urine production in mice with cholecystokinin overexpression……"*

Soy phytoestrogens and antinutrients prove to cause overexpression of cholecystokinin, increasing risks of brain, kidney, pancreatic damage, and more.

(Soybean causation of CCK overexpression as the cause of pancreatic cancer is more closely reviewed later in this report.)

Conclusion-

Neuroimaging indicates that children with; attention-deficit disorders, impulsivity, hyperactivity, damaged fine motor skills, behavioral disorders including autism, prove that neurotransmitters are in fact "different" from that of healthy peers. Overwhelming evidence confirms that soy plant-estrogens and/or soy antinutrients are neurotoxic, while capable of damaging multiple neurotransmitters systems as concluded in the cause of irreversible neurological disorders such as autism.

SOY INHIBITION OF TYROSINE KINASE DAMAGES NEUROTRANMITTERS - Protein tyrosine kinases regulates normal cell processes, while having profound effects on cells. PTK are key enzymes in signal-transduction pathways for a wide range of cellular processes. PTK are highly expressed in the CNS, which is consistent with the importance of tyrosine phosphorylation in a variety of neuronal functions. Protein phosphorylation is known to be involved in the regulation of neurotransmitter receptors. PTK modify other proteins by chemically adding phosphate groups to them, called phosphorylation.

Kinases enzymes transfer phosphate groups that are important for the regulation of a majority of cellular signaling pathways and play major roles in the control of cell growth and transformation to tyrosine an amino acid used by cells to synthesize proteins. PTK are concentrated in the synapse or the junctions through which neurons signal to each other and to non-neuronal cells allowing neurons to form interconnected circuits within the central nervous system. Tyrosine kinases are involved in a number of signaling cascades, principally those involved in neurotransmitter signaling, and other signaling including that of the growth hormone. High levels of protein tyrosine kinases are reportedly found in the hippocampus, a brain region involved with learning and memory, while the soy inhibition of tyrosine kinase can have irreversible effects on the hippocampus and other areas of the brain. The brain uses amino acids such as tyrosine to synthesize neurotransmitters that are most vulnerable to soybean deregulation during fetal, infant and child development. Deficiencies in amino acids and interruption of protein synthesis can lead to the cause of countless ill-health disorders especially during developmental stages of life.

Protein kinases act on critical control points in many cellular processes, including cell growth and differentiation and are essential during fetal and infant development. Tyrosine functions as a receiver of phosphate groups that are transferred by way of protein kinases. Phosphorylation of the hydroxyl group changes the activity of the target proteins, and tyrosine phosphorylation is considered to be one of the key steps in signal transduction and regulation of enzymatic activity. Extracellular signal-regulated kinase signaling is important for neuronal synaptic plasticity including hippocampal long-term potentiation. .

The hippocampus (learning, behavioral, and memory brain region) utilizes tyrosine kinase and other important protein kinases, while soy inhibits normal production thus function of protein. kinases. Kinases are key precursors of neurotransmitter functions, while most important thyroid stimulating hormones T3 and T4 are also reduced by soy cause of kinase inhibition.

Estrogens, soy phytoestrogens, particularly genistein are well known to inhibit tyrosine kinase activity of which levels of inhibition fluctuate dependent upon the levels of soy intake. Soy inhibition of tyrosine kinase causes severe disruptions in neurotransmitter signaling and thyroid hormone functions of which individually, (and worse together) are reported to cause varying degrees of damaging neurological effects particularly during fetal and infant brain development. Deregulation of PTK is a frequent cause of diseases.

1998, "Teratology," TE Grafton and DK Hansen of the FDA-National Center for Toxicological Research report, *"This compound (genistein) is known to inhibit tyrosine protein kinases what are necessary for the function of epidermal growth factor. This suggests an antiproliferative effect and concern for potential developmental toxicity."*

The Book, "Phytoestrogens and Health, by GS Gilani and JJB Anderson report, "*In 1987 Akiyanna et al serendipitously discovered that genistein was a specific inhibitor of tyrosine protein kinases….."*

2001, Japan Journal of Physiology," F Okamoto et al report, "*Genistein a soybean-derived isoflavone with an inhibitory effect on protein tyrosine kinases has been shown to suppress osteoclastic bone resorption."*

2004, "The American Society for Nutritional Sciences" AC Chen and SM Donovan report, "*….U.S. infants are fed soy formulas containing up to 47mg/L of isoflavones (>65% as genistin+ genistein); thus, these infants' intestines are exposed to a high dose of genistein, a phytoestrogen and tyrosine kinase inhibitor. Little attention has been focused on genistein's impact on the developing intestine. A high dose of genistein may potentially compromise intestinal growth."*

2005, "International Immunopharmacology," JH Zhao et al report, "*Isoflavones, which are phytoestrogens present in large quantities in soy and soy-derived products have estrogenic activity, inhibit protein tyrosine kinase, and exert other effects in the human body. The soy diet exacerbated renal damage (in mice). These findings indicate that a soy diet in comparison with a casein diet, significantly exacerbates the clinical course of this autoimmune (lupus) disease."*

2000, "Brain Resources," A Quesada and AM Etgen report, "*These studies examined the functional interactions between adrenergic G-protein coupled receptors and protein tyrosine kinases in the preoptic area and hypothalamus brain regions….In hypothalamic slices genistein, a general tyrosine kinase inhibitor, enhances norepinephrine-stimulated cAMP synthesis……..Genistein appears to act by increasing beta-adrenoceptor signaling. At high norepinephrine concentrations, estradiol potentiates genistein enhancement of the cAMP response in hypothalamic slices….genistein enhances cAMP accumulation by modifying alpha(1) and/or alpha(2)-adrenoceptor ….signaling. Genistein amplification of norepinephrine-stimulated cAMP synthesis is not mediated by interactions with estrogen receptors. At the concentration used, genistein inhibits tyrosine phyophorylation in slices from both brain regions. These results suggest that protein tyrosine kinases regulate adrenergic responses in the hypothalamus and preoptic area."*

Catecholamines are chemical hormones derived from the amino acid tyrosine and released into the bloodstream by the adrenal glands in situations of stress and psychological stress or low blood sugar levels. Dopamine is the first catecholamine to be synthesized, norepinephrine and epinephrine in turn, are derived from further modification of dopamine.

The adrenergic receptors are a class of G protein-coupled receptors that are targets of the catecholamines. Many cells possess these receptors and affect heart rate to increase, pupils to dilate, energy will be mobilized and blood flow may be diverted from organs to skeletal muscle.

Soy is a tyrosine inhibitor. Norepinephrine is synthesized from tyrosine as a precursor, and affects parts of the brain where attention and responding actions are controlled. Along with epinephrine, norepinephrine also underlies the fight-or-flight response, directly increasing heart rate, triggering the release of glucose from energy stores and increasing blood flow to skeletal muscle. It is released from the adrenal medulla into the blood as a hormone and is also a neurotransmitter in the CNS and sympathetic nervous systems where it is released from noradrenergic neurons. Noradrenergic neurons project bilaterally sending signals to both sides of the brain to many locations, including the cerebral cortex, limbic system and the spinal cord, forming a neurotransmitter system.

Genistein inhibits the tyrosine kinases important to cardiac ion channels-

1998, "Circulation Research" LC Hool et al reports, "*Genistein increases the sensitivity of cardiac ion channels to beta-adrenergic receptor stimulation- The whole-cell patch-clamp technique was used to monitor the effects of genistein, a tyrosine kinase inhibitor…..daidzein, an analogue of genistein ….weakly inhibits tyrosine kinase activity. These results suggest that tyrosine kinase activity may play an important role in regulating beta-adrenergic responsiveness of the heart."*

2001, "Japan Journal of Physiology" F Okamoto et al report, "*Genistein, a soybean-derived isoflavone with an inhibitory effect on protein tyrosine kinases has been shown to suppress osteoclastic bone resorption. Daidzein….also showed a weak inhibitory effect on I(Kir)….Genistein-induced inhibition of I(Kir) would cause membrane depolarization, elevation of {Ca(2+)I, and inhibition of osteoclastic bone resorption."*

2007, Journal, "Seminars in Reproductive Medicine" concludes, "*It has been known for some time that estrogen can rapidly alter neuronal activity within seconds….In addition, estrogen can affect second messenger systems including calcium mobilization and a plethora of kinases (controlling cell behavior) to alter cell signaling. This review considers our current knowledge of rapid membrane-initiated and intracellular signaling by estrogens in the brain and the nature of receptors involved…..*"

Soy plant-estrogen manipulations of PTK is damaging to fetal and infant development, and when referring to brain development, these enzymes are involved in neurite outgrowth. Soy inhibition of tyrosine kinase inhibits neurite growth, therefore inhibiting neuron; axons, and dendrites, of which are all most critical during neurological development. Important nerve growth factors as well as tau proteins stimulate nerve cell axons and dendrites of which are indirectly inhibited by soy plant-estrogens.

2005 "Journal of Nutritional Biochemistry" study title: "Soy isoflavones and cognitive function," concludes, "*Estrogenic effects of soy isoflavones appear to be dose dependent…….another study found that high concentrations of genistein are toxic to neurons. Soy isoflavones can affect the viability of neurons and cognitive function……and they can also utilize differential distribution and regulation of ER-a (Estrogen Receptor-alpha) and ER-B (Estrogen Receptor- beta) in the brain. Genistein also affects ER-B but not ERa-dependent gene expression in the hypothalamus. ER-B modulates emotional and cognitive behavior. Genistein is known to inhibit tyrosine kinase (involved in various responses in the brain including neuroregeneration, synaptic plasticity) which is generally considered to be detrimental to a neuron. Protein tyrosine kinases are highly expressed in several brain regions, including the hippocampus and are reported to be involved in the induction of long-term potentiation (or LTP, the major cellular mechanisms that underlie learning and memory) in the hippocampus, which is crucial to learning and memory. Large amounts of genistein are needed to inhibit tyrosine kinases in the brain and suppress cognitive function in vivo.*

Conclusions- Genistein can have negative influences on cognitive function when it is present at a high level due to its action as a tyrosine kinase inhibitor, which enables it to block LTP and cognitive function."

Long-term potentiation (LTP) is the long-lasting improvement in communication between two neurons that results from stimulating them simultaneously. Neurons communicate via chemical synapses, and memories are believed to be stored within these

synapses. LTP is considered a major cellular mechanism that underlies learning and memory. Genistein can block LTP function.

"Nature" 1991 Volume 353, TJ O'Dell et al, report, "*…..data suggest that tyrosine kinase activity could be required postsynaptically for long-term synaptic plasticity in the hippocampus. Long-term potentiation in the hippocampus is blocked by tyrosine kinase inhibitors."*

Inhibition of PTK's are reported to depress intracellular CA2+ response and deregulate the whole-cell currents and function of the receptor, a subtype of the excitatory amino-acid receptor.

1994, "Journal of Allergy and Clinical Immunology," YT Wang et al report, *"PTKs and protein- tyrosine phyosphatases (PTP together with PTK regulate the phosphorylation state of many important signaling molecules) are key enzymes in signal-transduction pathways for a wide range of cellular processes. PTKs and PTPs are highly expressed in the CNS with is consistent with the importance of tyrosine phosphorylation in neuronal function. Protein phyosphorylation is known to be involved in the regulation of the neurotransmitter receptors but effects of PTP on neurotransmitter receptor function in the CNS are unknown. Here we present evidence that in mammalian central neurons tyrosine phosphoylation regulates the function of NMDA (N-methl-D-aspartate) receptor a subtype of excitatory amino-acid receptor. NMDA receptor-mediated whole-cell currents and intracellular Ca2+ responses are depressed by inhibition of PTKs. NMDA currents are also potentiated by intracellular administration of an inhibitor of PTK's . Protein-tyrosine phosphorylation is a new mechanism for regulating NMDA receptors and may be important in neuronal development, plasticity and toxicity."*

2004, "Journal of Neuroscience," A. Khan et al report, *"….Protein-tyrosine kinases (PTKs) participate in NMDA-R (receptor) signaling mechanisms….. we determined PTK involvement in lateral hypothalamic area mechanisms underlying both types of feeding stimulation through food intake and biochemical measurements……behavioral and biochemical results demonstrate that, although it is easier to suppress NMDA-elicited feeding by PTK inhibitors, food deprivation readily drives PTK activity in vivo."*

Soy plant-estrogens are known to inhibit PTKs involved in NMDA signaling. NMDA mimic the action of neurotransmitter glutamate on the NMDA receptor. NMDA is an excitotoxin; this trait has applications in behavioral neuroscience research while testing for the behavior of interest such as operant behavior. Glutamate, thus NMDA are believed to be involved in cognitive functions such as learning and memory. Soy isoflavones interrupts or inhibits normal PTK function, to then cause the deregulation of NMDA and glutamate neurotransmitter signaling.

2000, "The Journal of Neuroscience" M. Singh et al report, *"We have shown previously in the developing cerebral cortex that estrogen elicits the rapid and sustained activation of multiple signaling proteins within the mitogen-activated protein kinase cascade……"*

Soy phytoestrogens are known as estrogenic endocrine disrupting phytochemicals with biochemical cascading effects, and are well documented tyrosine kinas inhibitors.

1997, "Brain Research Cognitive Brain Research," RA Whitechurch et al report, "*Tyrosine kinase inhibitors impair long-term memory formation in day-old chicks- The involvement of protein kinases in numerous neuronal cellular processes, including*

learning and memory, has been well established, particularly regarding serine/threonine kinases…..the role of protein kinases in learning was further examined through an investigation of the inhibitors of tyrosine kinase activity on memory formation. The present findings reveal that the intracranial administration of the tyrosine kinase inhibitors genistein…..produced retention deficits in day-old chicks trained on a single-trial passive avoidance task. These deficits were not apparent until 90 minutes after the training episode and were not observed at all in chicks administered control substances. The possibility that the tyrosine phosphorylation disrupted by the presence of the inhibitors is related to NMDA glutamate receptor activation is considered."

In the adrenal gland, tyrosine kinase is converted to levodopa by the enzyme thyrosine dyroxylase (TH), and TH is also the rate-limiting enzyme involved in the synthesis of the catecholamine hormones; dopamine, norepinephrine, and epinephrine (adrenaline). These brain neurotransmitters are also involved in mood, alertness, and energy, of which are disrupted by soybean inhibition of tyrosine.

1995, "Journal of Cardiovascular Pharmacology" A Worku et al report, "*The (tyrosine kinase)inhibitory effects of genistein on norepinephrine induced contraction was observed both in the absence and presence of extracellular calcium, which produced phasic and tonic contractile responses respectively. The effect of genistein was more pronounced on the phasic contraction, suggesting that tyrosine kinases play a greater role in mediating the responses associated with the release of intracellular calcium."*

2004, "AJ P- Renal Physiology," M Salomonsson and W. Arendshorst report, "*High-dose Genistein inhibited the peak and plateau response to norepinephrine by 87 and 75% respectively, low-dose genistein attenuated both responses by ~20%. Genistein….abolished the immediate (Ca2+) mobilization response. Genistein…also inhibited by 60% the (Ca2+) response….indicating a direct interaction with voltage-sensitive, L-type Ca2+ entry channels. These results indicate that tyrosine phosphorylation is an important link in the chain of events leading to a-adrenoceptor-induced Ca2+ recruitment (both entry and release) in afferent arteriolar smooth muscle cells."*

1987, "Journal of Biological Chemistry," T Akiyama et al report, "*Tyrosine-specific protein kinase activity of the epidermal growth factor (EGF) receptor, pp60v-src and pp1 10gag-fes was inhibited in vitro by an isoflavone genistein. When the effect of genistein on the phosphorylation of the EGF receptor was examined in cultured A431 cells, EGF-stimulated serine, threonine, and tyrosine phosphorylation was decreased…….genistein inhibited the EGF stimulated increase in phosphotyrosine level……."*

Tyrosine enzymes are also crucial to the brain in a second way; in that it is needed for the body to develop thyroid hormones, another major physiological regulator of mammalian brain development. Thyroid hormones regulate the growth and migration of neurons including synaptic development and myelin formation in specific brain regions. Soy plant-estrogens and the soy cause of low blood levels of tyrosine are associated with an under-active thyroid gland, as you have read about previously in this report.

MET IDENTIFIED IN AUTISM DISORDER- The pleiotropic MET receptor tyrosine kinase when deficient has been identified in the cause of autism. Soybean

inhibition of tyrosine kinase disrupts and inhibits MET signaling that is involved in the causation of autism disorder. MET gene mutations are also associated with cancers.

2006, "National Academy of Sciences" DB Campbell et al report, *"MET signaling participates in neocortical and cerebellar growth and maturation, immune function, and gastrointestinal repair, consistent with reported medical complications in some children with autism. These data implicate reduced MET gene expression in autism susceptibility, providing evidence of a previously undescribed pathophysiological basis for this behaviorally and medically complex disorder."*

2007, "*Autism: It's Not Just in the Head,*" Jill Neimark writes, "*Levitt, (neuroscientist Pat Levitt director of the Vanderbilt Kennedy Center for Research on Human Develpement), and his colleagues recently discovered that a common variant gene called MET doubles the risk of autism. The finding was widely regarded as a breakthrough because MET modulates the nervous system, gut, and immune system- just the kind of finding that matches up with the emerging new view of autism."*

MET signaling controls cell growth and migration during embryogenesis and is essential for the generation of the hyperproliferative epithelium in skin wounds, a fundamental regeneration process in humans. MET-triggered signaling pathways regulate hepatocyte cell survival during embryogenesis, of which regulates multiple functions including endocrine secretions and alterations in cerebellar and cortical formations and functions. Many studies report that decreased expression of MET may lead to the cause of autism.

2006, Program on Neurogenetics, Departments of Child Psychiatry and Genetics, Yale University, Matthew W. State et al reports, *"The MET transcript codes for a receptor tyrosine kinase composed of a-and b-subunits, which form a homodimer capable of binding to the ligand, hepatocyte growth factor/scatter factor (HGF/SF). HGF binding results in phosphorylation of multiple tyrosine residues located within and outside the intracellular kinase domains. The downstream signaling cascade has been shown to involve a wide range of docking molecules, and MET activation results in pleotrophic effects…..decreased expression of MET mRNA may lead to autism spectrum disorders…….. Previous work has demonstrated abnormalities in brain development resulting from disrupted processing of the MET receptor's single known ligand, HGF/SF, leading to decreased MET signaling. The attendant alterations in cerebellar and cortical architecture bear a tantalizing resemblance to…..neuropathology of autism. However, the MET receptor is also highly pleiotropic and is known to serve as a docking site for multiple protein substrates that influence a wide range of biological processes, including immune function and gastrointestinal repair. ……there are some data suggesting increased difficulties in these areas in patients with autism. Finally, as the investigators elaborate the autism-related biology of the MET pathway, the prospect that these finding could identify novel molecular therapeutic targets offers an exciting glimpse of the next epoch in autism research."*

2007, "Annuals of Neurology" DB Campbell et al reports, "*Multiple genes contribute to autism spectrum disorder susceptibility. One particularly promising candidate is the MET gene, which encodes a receptor tyrosine kinase that mediates hepatocyte growth factor (HGF) signaling in the brain circuit formation, immune function, and gastrointestinal repair. The MET promoter variant rs1858830 allele "C" is strongly associated with the ASD and results in reduced gene transcription."*

SOY CAUSES HYPOTHYROIDISM THAT INCREASES RISK OF IMMUNE DEFICIENCY DISEASES AND NEUROTOXICITY: Soy endocrine disrupting phytoestrogens and soy antinutrients are proven to disrupt the endocrine system such as the thyroid gland, causing thyroid hormone deficiency or hypothyroidism. Thyroid hormones stimulate multiple biological processes controlling; immune system, growth, reproduction, development, and metabolism. The hypothalamic-pituitary-thyroid axis is a target of endocrine disrupting chemicals such as soy. Throughout all of life, and especially during fetal, infant, and child development normal thyroid function is critical for the healthy development of several organ systems.

Although all fetal developmental stages necessitate proper maternal thyroid function, scientists frequently refer to prenatal and postnatal timeframes as a critical period in which appropriate thyroid hormone levels are absolutely essential for anatomical normalcy. The physiologic function of thyroid hormones upon the brain is to provide a timing signal that leads to the induction of specific neurological programming during precise developmental stages.

Soybeans are accepted as "goitrogens" or substances that interfere with thyroid gland function. Soy phyto-estrogens are well-known to decreased thyroid function, hypothyroidism/

Soy-based formulas increase risk of estrogenic contamination that also encourages the development of infantile hypothyroidism.

2005, University of Texas Health Sciences Center at San Antonio, ME Shils et al report, *"Intrauterine deficits of thyroid hormones (as brief as 3 days) result in permanent alterations of cerebral cortical architecture reminiscent of those observed in brains of patients with autism. Some plant isoflavonoids (soy estrogen) have profound effects on thyroid hormones and on the hypothalamus-pituitary axis."*

Department of Physiology and Endocrinology, Medical College in Georgia, confirms that *"There is a critical period for thyroid hormone mediated brain development that begins in utero and extend through 2-3 years of age in humans. Excessive or deficient hormone levels during this period can cause irreversible brain damage."*

As far back as 1960, a New England Journal of Medicine study reports how well known it is that soybean isoflavones depress thyroid function and cause autoimmune thyroid disease particularly to the infants fed soy phytoestrogens.

It is reported that in 1999, FDA Dr. Daniel Sheehan, Director Division of Genetic and reproductive Toxicology, and FDA Dr. Daniel Doerge, Division of Biochemical Toxicology, verbally opposed FDA approval of soy while discussing abundant evidence that some of the isoflavones found in soy, including genistein and daidzein demonstrate toxicity in estrogen sensitive tissues and in the thyroid. This is true for a number of species including humans.

National Center for Toxicological Research, scientists Daniel Sheehan and Daniel Doerge report their study titled, "*Inactivation of thyroid peroxidase* (large family of important enzymes) *by Genistein and Daidzein: Mechanism for anti-Thyroid Activity of Soy."*

"Proceedings of the National Academy of Science"- U.S. A., study concludes "*Genistein injected at 8 mg per day produced serum genistein levels comparable to those*

reported in soy-fed human infants, and this dose caused significant thymic and immune changes in mice. Genistein, at concentrations that produced serum genistein levels substantially less than those in soy-fed infants produced marked thymic atrophy. Genistein concentrations found in soy-fed infants may be capable of producing thymic and immune abnormalities, as suggested by previous reported of immune impairments in soy-fed human infants."

Besides soy phytoestrogen toxicity of the thyroid gland, there is a critical relationship between iodine status and thyroid function. Studies prove significant soy-causation of iodine deficiency which causes anatomical inflammation, including inflammation of the brain. Because of soy causation of thyroid toxicity, the immune system is at risk as well. There remains no question that soy as a major cause of thyroid toxicity, also encourages extremely damaging fetal, infant, and child neurological development. Thyroid-pituitary-hypothalamic function is interrupted by soy saturation of fetus and of infants exposed.

Maternal soy consumption may cause iodine deficiency in mother, while further encouraging congenital hypothyroidism, a condition of thyroid hormone deficiency present at birth. Severe congenital hypothyroidism can lead to growth failure and permanent mental retardation.

From the Johns Hopkins Bloomberg School of Public Health in Baltimore, "*Early exposure to Genistein exerts long-lasting effects on the endocrine and immune systems in rats. These data illustrate that exposure to Genistein (main estrogenic component of soy) during pregnancy and lactation exerts long-lasting effects on the endocrine and immune systems in adulthood. Whether exposure to phytoestrogens during early development affects responses to infections, or autoimmune diseases, as well as cancers, later in life requires investigation."*

2008, Department of Cell and Molecular Biology- Karolinska Institutet in Sweden, Maria Sjogren reports, *"Lack of sufficient thyroid hormone during pregnancy and early postnatal development results in profound mental retardation and motor deficiencies, whereas altered thyroid status in the adult is associated with disturbed metabolic homeostasis and impaired cardiac function. The locomotor dysfunctions (caused by insufficient thyroid hormone) correlated with delayed or perturbed development of several brain regions. Notably, we report that specific GABAergic cells in the neocortex were affected: the appearance of parvalbumin-immunoreactive GABAergic interneurons was severely delayed……"*

Regulation of: brain-specific proteins, neuronal outgrowth, synapse formation, transcription of specific messenger RNAs, and alteration of gene expression, are some of the proposed mechanisms whereby thyroid hormones control brain development. Damage to the thyroid is proven to cause brain disorders such as autism.

2007, "The Journal of Neurological Sciences, GC Roman reports, *"Autism: Transient in Utero Hypothyroxinemia Related to Maternal Flavonoid Ingestion During Pregnancy - deficits of thyroid hormones (as brief as 3 days) result in permanent alterations of cerebral cortical architecture reminiscent of those observed in brain of patients with autism. …….early maternal hypothyroxinemia resulting in low T3 in the fetal brain during period of neuronal cell migration (weeks 8-12 of pregnancy) may produce morphological brain changes leading to autism. Plant isoflavonoids have profound effects on thyroid hormones and on the hypothalamus-pituitary axis."*

2007, The American Family Physician, AAFP, under the guideline source of American Academy of Pediatrics reports, "*Congenital hypothyroidism can cause mental retardation….Most infants with congenital hypothyroid ism appear unaffected at birth, probably because of placental transfer of thyroid hormone; infants whose mothers have hypothyroidism have significant impairment of neurointellectual development….*"

2000, the book, "Biology of Autistic Syndrome," by C Gilberg and M Coleman report, "*Infant hypothyroidism occurs in one out of every 639 live births. Autistic syndrome has been seen in babies with congenital hypothyroidism who have been diagnosed as autistic when as young as 6-9 months. Hypothyroidism is tied to autistic syndrome another way. Parents of autistic children are more prone to hypothyroidism. A comparison of parents with controls showed a statistically significant increase in hypothyroidism.*"

Published studies confirm that soy isoflavone causation of abnormal thyroid function can directly influence the cause of brain cognitive decline: "Journal Watch Psychiatry" reports, "*The association between low thyroid functioning and cognitive impairment is well established.*"

1990, "Journal of the American college of Nutrition," P Fort reports, "*There is a critical period for thyroid hormone mediated brain development that begins in utero and extend through 2-3 years of age in humans. Excessive or deficient hormone levels during this period can cause irreversible brain damage.*"

And again in 1990, "Journal of the American College of Nutrition" P Fort et al reports, "*The frequency of feedings with soy-based milk formulas in early life was significantly higher in children with autoimmune thyroid disease. This retrospective analysis documents the association of soy formula feedings in infancy with autoimmune thyroid disease.* "

A study published in "*Neurotoxicology*" concludes, "*Offspring of women with untreated hypothyroidism exhibit measurable neurological deficits despite (the infant) being euthyroid (normal thyroid gland function) at birth. Failure to identify and treat congenital hypothyroidism can lead to measurable (fetal) neurological deficits. This suggests that thyroid hormone of maternal origin plays a role in fetal brain development.*"

2000, "Molecular Brain Research," ALS Dowling and RT Zoeller report, "*Recent clinical studies indicate that thyroid hormone plays essential roles in fetal brain development. We recently identified several genes expressed in the fetal cortex show abundance is affected by thyroid hormone of maternal origin. We now report that the well-known thyroid hormone-responsive gene RC3/neurogranin is expressed in the fetal brain and is regulated by thyroid hormone of maternal origin. These findings support the concept that maternal thyroid hormone exert a direct action on expression of genes in the fetal brain that are important for normal neurological development.*"

1979, "European Journal of Biochemistry," A Fellows et al states "Thyroid Hormones and Neurotubule Assembly In Vitro During Brain Development-…. *These results implies that thyroid hormones are required briefly after birth…….. to allow intensive neurite growth during the critical period of brain development.*"

2007, "Endocrinology" Bertrand Saunier reports, "*How Low Can Maternal Thyroxin Go?-although normal brain development is strongly determined by genetic factors, seemingly minor environmental or congenital factors can interfere with its*

process and alter its conclusion. Goodman and Gilbert report that a neuronal ectopia had developed in the brain of young rats upon induction of a mild hypothyroidism starting the first week of gestation. Since then, congenital hypothyroidism resulted in cretinism, (severely stunted physical and mental growth). Studies have shown that maternal hypothyroidism…..in fact, greatly involved in neurodevelopmental disorders for her offspring. There is now evidence for fetal brain developmental abnormalities resulting from both early and late maternal hormonal deficits. Neuronal migration is impaired by a lack of thyroid hormones, the consequences of which greatly depend on developmental stages and regions of the feta brain. ….even if properly treated after birth congenital hypothyroidism will still result in impaired cognitive functions."

Book "Handbook of Developmental Cognitive Neuroscience" by Charles A. Nelson concludes, "*Brain development is severely compromised by hypothyroidism with particularly profound cognitive effects."*

2007, "Trends in Endocrinology & Metabolism" P. Berbel et al report, "*…maternal hypothyroxinemia,(low levels of T-4) which affects pregnant women even in apparently iodine-sufficient areas and often goes unnoticed….Even a mild hypothyroxinemia during pregnancy increases the risk of neurodevelopmental abnormalities, and experimental data clearly demonstrate that it damages the cortical cytoarchitecture of the fetal brain."*

1999 "The Journal of Clinical Endocrinology & Metabolism," AM Duncan et al report, "*Soy isoflavones Exert Modest Hormonal Effects….The high isoflavone diet decreased free T3 and dehydroepiandrosterone sulfate levels."*

Dehydroepiandrosterone (DHEA) is a multi-functional steroid that has been implicated in a broad range of biological effects in humans. DHEA is produced by the adrenal glands, but also synthesized in the brain. It is considered a neuroactive neurosteroid proving to be vulnerable to soy isoflavone deregulation.

T3 induces the enzyme tyrosine hydroxylase involved in catecholamine synthesis. Catecholamines are hormones released by the adrenal glands in situations of stress such as psychological stress or low blood sugar levels. Soy isoflavones decrease T3, decreasing catecholamines synthesis and therefore disrupting psychological reactions to stress. Soy isoflavone causation of hypothyroidism involves multiple damaging effects to many body systems.

1989, "Biology of the Neonate," PS Timiras and EU Nzekwe report, "*Thyroid hormones and nervous system development- Regulation by hormones of nervous system development is well recognized in humans….T4 and T3, the major thyroid hormones act on brain development and maturation by binding to T3 nuclear receptors. T-3 responsive genes have been identified with the T3 receptor as a superfamily of genes including cortisol and estrogens, necessary for adaptation and survival."*

It is overwhelmingly documented that estrogenic soy isoflavones, as active plant-estrogenic endocrine disruptors depress thyroid hormones that damage thyroid function while causing an under-active thyroid, or hypothyroidism, resulting in numerous biochemical cascading effects upon physiological/ neurological development. Hypothyroidism during critical periods of fetal, and/or infant neurological development is proven to severely impair neurological; structural development, organization, stability, and functions. Because of causation of thyroid damage, fetus, infants, and children

exposed to soy plant-estrogens (and multiple soy antinutrients) are increasingly at risk for neurotoxicity causing brain disorders, as well as goiter, and autoimmune diseases.

Thyroid hormones of maternal origin are essential for normal brain development during gestation. Maternal thyroid hormones cross the placenta to the fetus, unless she is thyroid deficient as caused by consumption of soy phytoestrogens, while unknowingly causing congenital hypothyroidism and impairing fetal brain development. Maternal hypothyroidism may also impair fetal growth and development. Lactating infants may also be exposed to (thyroid) hormone disruptors due to maternal consumption of soy products.

"Endocrinology," C de Ona Ruiz et al report, "*The fetal thyroid function is influence by maternal hypothyroidism. Soy plant-estrogens are proven to cause maternal (as well as infant/child) hypothyroidism, with potential to cause irreversible brain damaging effects, including autism."*

The hypothyroid child experiences neurological disorders in; behavior, practical reasoning, memory, hyperactivity, perceptomotor and visuomotor discrimination, spatiomotor skills, sensorineural hearing, language, comprehension, fine motor skills, and extrinsic motor eye movement. Hypothyroidism is highly relevant to all the same symptoms that are known in the diagnosis of neurological disorders including autism.

Soy plant-estrogens reduce thyroid hormone output by blocking activity of the thyroid peroxidase enzyme, and therefore causing iodine deficiency. Iodine is of utmost important for proper physiological and neurological development.

1997, "Biochemical Pharmacology," RL Divi et al report, "*Anti-thyroid isoflavones from soybeans……mechanisms of action- The soybean had been implicated in diet-induced goiter by many studies. It was observed that an acidic methanolic extract of soybeans contains compounds that inhibit thyroid peroxidase- (TPO) catalyzed reactions essential to thyroid hormone synthesis……..enzymatic assay of the soybean extract showed that the components responsible for inhibition of TPO-catalyzed reactions coeluted with daidzein and genistein. In the presence of iodide ion, genistein and daidzein blocked TPO catalyzed tyrosine iodination by acting as alternate substrates……Genistein also inhibited thyroxine synthesis using iodinated casein or human goiter thyroglobulin as substrates for the coupling reaction. The IC50 values for inhibition of TPO-catalyzed reactions by genistein and daidzein were ca.1-10 microM, concentrations that approach the total isoflavone levels previously measured in plasma from humans consuming soy products. Because inhibition thyroid hormone synthesis can induce goiter and thyroid neoplasia in rodents, delineation of anti-thyroid mechanisms of soy isoflavones may be important for extrapolating goiterogenic hazards identified in chronic rodent bioassays to humans consuming soy products."*

Japanese researchers report damaging effects on the thyroid by soybeans due to soy cause of significant increase in thyroid stimulating hormone which is produced by the brain's pituitary gland when thyroid hormones are too low. "*Excessive soybean ingestion might suppress thyroid function and cause goiters in healthy people."*

Thyroid peroxidase (TPO) is an enzyme that most importantly converts thyroid hormones to T-3 and T-4, and the soy inhibition of TPO is proven to cause a number of adverse health effects, including brain damaging effects to developing fetus, infants and children. Estrogens, including soy plant-estrogens reportedly interfere with thyroid hormones by increasing the risk of hypothyroidism, a functional failure of the thyroid

gland's ability to meet the body's crucial demands for thyroxine (T4) and triiodothyronine (T3). Together these molecular mechanisms cooperatively act in a carefully calculated timeframe to control thyroid hormone action that is detrimental during fetal, infant, and child brain development. Soy estrogenic and anti-nutrient interruptions of thyroid hormones disrupt an otherwise most important calculated function in thyroid hormone production and metabolism that more specifically is proven to impair the development of the central nervous system, (brain and spinal cord).

By 1997, NIH scientists from the National Center for Toxicological Research report that soy plant-estrogens genistein and daidzein "*…..inhibit thyroid peroxidase-catalyzed reactions essential to thyroid hormone synthesis.*"

2002, Scientists from the NIH- Division of Biochemical Toxicology, National Center for Toxicological Research, DR Doerge and HC Chang report, "*Inactivation of thyroid peroxidase by soy isoflavones in vitro and in vivo- ….studies of soy isoflavones in experimental animals suggest possible adverse effects as well (e.g. enhancement of reproductive organ cancer, modulation of endocrine function, anti-thyroid effects). This paper reviews the evidence in humans and animals for anti-thyroid effects of soy and its principal isoflavones, genistein and daidzein.*"

2002, "Environmental Health Perspectives," Division of Biochemical Toxicology NIH scientists D Doerge and D Sheehan report, "*Soy is known to produce estrogen isoflavones. Here we briefly review the evidence for binding of isoflavones to the estrogen receptor, in vivo estrogenicity and developmental toxicity, and estrogen developmental carcinogenesis in rats. Genistein the major soy isoflavone also has a frank estrogenic effect in women. Soy effects on the thyroid involve the critical relationship between iodine status and thyroid function. In rats consuming genistein-fortified diets, genistein was measured in the thyroid at levels that produced dose-dependent and significant inactivation of rat and human thyroid peroxidase (TPO). Furthermore, rat TPO activity was dose-dependently reduced by up to 80%. Additional factors appear necessary for soy to cause overt thyroid toxicity. These clearly include iodine deficiency, but may also include additional soy components, other defects of hormone synthesis, or additional goitrogenic dietary factors. …safety testing of natural products including soy products, is not required, the possibility that widely consumed soy products may cause harm in the human population via either or both estrogenic and goitrogenic activities is of concern.*"

Placing thyroid function in peril, plant-estrogens inhibit thyroid peroxidase (TPO), an enzyme with most important functions to convert thyroid hormones to T-3 and T-4. Damage to the thyroid as caused by plant-estrogens is multiplied by negative thyroid soy antinutrients effects, and proven blockage of iodine absorption, are all proven soy-causes of hypothyroidism. Results of prolonged TSH encourages the inability to produce T-3 and T-4 thyroid hormones as caused by soy effects on the thyroid while forcing an insufficient thyroid into excessive TSH production.

Thyroid gland hormones, T-3 and T-4 circulate in the bloodstream and help regulate metabolism or the rate at which the body uses fats and carbohydrates, and help to regulate production of proteins that are essential for body and brain development. The pituitary gland and hypothalamus control the rate at which thyroid-stimulating hormones (TSH) are produced and released depending on the amount of circulating T-3 and T-4 is

in the bloodstream. In turn the thyroid gland regulates production of hormones based on amount of TSH it receives from the pituitary gland.

2000, "Neurotoxicology" RT Zoeller reports, "*Thyroid Hormone of Maternal Origin Directly Affects Fetal Brain Development. Thyroid hormone clearly plays essential roles in brain development. This observation showed that thyroid hormone of maternal origin reaches the fetus. Second, it was found that fetal brain express thyroid hormone receptors before the onset of fetal thyroid function, and that these receptors are occupied by thyroid hormone. Most recently it was shown that pregnant women with undiagnosed hypothyroidism gave birth to children with measurable deficits in various neurological measures including 'IQ' and measures of attention. We have identified a number of genes expressed in the fetal cortex that are selectively regulated by thyroid hormone of maternal origin. The genes identified have provided the first clues about the developmental processes affected by thyroid hormone."*

2006, NTP CERHR "Soy Formula" report states, " *Significantly more children with thyroid disease received soy formula compared to healthy siblings and healthy unrelated controls. Infants with congenital hypothyroidism were fed soy formula (and) improved with discontinuation of soy formula."*

Hypothyroidism is difficult to recognize; growth becomes stunted and brain pathology is impaired. Prior to pregnancy women must also be careful to have a full functioning thyroid, and eliminate soy phytoestrogens from her diet throughout pregnancy. Iodine and selenium (but not excessive amounts) are two minerals critically important in the proper functioning of the thyroid.

Hypothyroidism also elevates LDH lactate dehydrogenase release, an enzyme important in energy production of cells of which elevation is reported in "Journal of Biomedical Science" that " genistein and daidzein increased LDH release….indicating cellular damage… …isoflavones specifically genistein and daidzein are toxic to primary neuronal culture at high concentration."

Elevated LDH release as again caused by hypothyroidism is toxic to the brain.

Referenced from a 1995 and 1996 study, U.S. Environmental Protection Agency reports, "*Endocrine Disruptor Research Initiative Federal Project Inventory: anti-thyroid Activity of Genistein and Daidzein- Soy products in infant food formulas and wide consumption of soy products demands an examination of the antithyroid activity. Extracts of soybean contain components identified as genistein and daidzein that inhibit thyroid peroxidase (TPO) the key enzyme in thyroid hormone synthesis. Both the presence and absence of iodide ion, inhibition of thyroid hormone synthesis by the soy isoflavones is predicted….."*

FDA, National Center for Toxicological Research concludes, "*Isoflavone genistein is a potent inhibitor of thyroid peroxidase that causes hypothyroidism, a thyroid disease."*

In 2002, from the FDA Division of Biochemical Toxicology, Drs. Daniel Doerge and Daniel Sheehan, experts on soy conclude, "*…..there is abundant evidence that some of the isoflavones found in soy, including genistein and equol, a metabolize of daidzein demonstrate toxicity in estrogen sensitive tissues and in the thyroid. Isoflavones are inhibitors of the thyroid peroxidase which makes T3 and T4 inhibition can be expected to generate thyroid abnormalities, including goiter (inflammation) and autoimmune thyroiditis. There are significant reports of goitrogenic effects from soy consumption in*

human infants (1959, 1960, 1960, 1965 1995) and adults (1933 and 1991). Soy effects on the thyroid involve the critical relationship between iodine status and thyroid function. In rats consuming genistein-fortified diets, genistein was measured in the thyroid at levels that produced significant inactivation of rat and human thyroid peroxidase (TPO) in vitro. Additional factors appear necessary for soy to cause overt components, other defects of hormone synthesis, or additional goitrogenic dietary factors. Safety testing of natural products, including soy products is not required. Possibility that widely consumed soy products may cause harm in human population via either or both estrogenic and goitrogenic activities is of concern."

Symptoms of goiter include: hypothyroidism, throat tightness, neck swelling, difficulty breathing, difficulty swallowing, hoarseness, coughing, neck vein distention, dizziness, rapid heartbeat, diarrhea, nausea, vomiting, fatigue, constipation. Goiter can interfere with swallowing and/or breathing, and to an infant goiter may be fatal.

Diagnosis of hypothyroidism is based on the biochemical measurements of thyroid hormones in low circulation, particularly T3 and T4. Soy isoflavones can cause low concentrations of these thyroid hormones resulting in inadequate brain function.

While stated to increase the risk of autism and neurological diseases, mercury, pollutants, pesticides, and soy plant-estrogens can also cause antithyroid effects or hypothyroidism.

Soy isoflavone inhibition of thyroid peroxidase increases the risk of autoimmune (thyroid) disease, and an insufficient immune system increases the risk of several diseases, including diabetes.

FDA Consumer magazine in 2000 states, *"A 1997 study in 'Biochemical Pharmacology' identified genistein and daidzein (estrogens of soy isoflavones) as inhibitors of thyroid peroxidase."* (An established cause of autoimmune disease).

Fort et al reported in 1986 and again in 1990, *"(There is) a doubling of risk for autoimmune thyroiditis in children who had received soy formulas as infants,"* when compared to infants receiving other forms of formula.

Department of Pediatrics, North Shore University Hospital in New York reports, "*….thyroid alterations are among the most frequently encountered autoimmune condition in children. ……feedings with soy-based formulas in early life was significantly higher in children with autoimmune thyroid disease…..*"

Autoimmune is defined by abnormal activity of the body's immune system whereas the body attacks healthy cells, hereby causing any of many severe diseases. The immune system overlaps with orchestrated functions of the brain's nervous system.

2001, JAMA report concludes: "*….children with autoimmune disease were significantly more likely to have received soy formula as infants than were healthy siblings or control subjects."*

2006, "Thyroid" M Messina and G Redmond report, "*….soy may be contraindicated for some subsets of the population. One concern is that soy may adversely affect thyroid function and interfere with the absorption of synthetic thyroid hormone. ….in individuals with compromised thyroid function and/or whose iodine intake is marginal soy foods may increase risk of developing clinical hypothyroidism."*

2006 "Clinical Chemistry Laboratory Medicine" J. Milerova et al report, *"Actual levels of soy phytoestrogens in children correlate with thyroid laboratory parameters-Since both (genistein and daidzein) phytoestrogens have been reported to inhibit thyroid*

hormone biosynthesis and in high concentrations to exert goitrogenic effects……Correlation analysis revealed a significant positive association of genistein with thyroiglobulin autoantibodies and a negative correlation with thyroid volume. Multiple regression analysis of the relationships between actual phytoestrogen levels and measured thyroid parameters revealed only a weak but significant association between genistein and thyroid variables. ….even small differences in soy phytoestrogen intake may influence thyroid function…..”

1990 “American College of Nutrition” P. Fort et al concludes, *“….frequency of feedings with soy-based formulas in early life was significantly higher in children with autoimmune thyroid disease.”*

Cerebellar hypoplasia is a developmental disorder characterized by the incomplete or underdevelopment of the cerebellum that is reportedly caused by thyroid abnormalities and/or estrogenic chemicals, (viral infections or stroke). In infancy, symptoms include developmental delay, hypotonia (manifestation of many different diseases and disorders that affect motor never control by the brain or muscle strength), ataxia (gross lack of muscle movements implying dysfunction of parts of nervous system such as cerebellum), seizures, mental retardation, and involuntary eye movements. Cerebellar hypoplasia may be associated with other disorders.

2007, “Endocrinology” J. Goodman, and M Gilbert report, *“An examination of Nissl-stained sections of the (rodent) brains from developmentally hypothyroid offspring sacrificed on PN23 (Postnatal day 23) revealed the presence of a….bilateral cellular malformation, a heterotopia, (displacement of organ or part of) positioned within the white matter of the corpus callosum of both hemispheres. …..this heterotopia primarily consist of neurons born between gestational days (GD) 17-19 and exhibits a dose-dependent increase in size with decreases in thyroid hormone levels. Importantly this structural abnormality is evidence at modest levels of maternal thyroid hormone insufficiency……Developmental exposure to …..goitrogen, also induced formation of this heterotopia……the presence of the heterotopia underscores the critical role thyroid hormone plays in brain development during the prenatal period and provides a new model in which to study mechanisms of cortical development and cortical dysplasia”*

Brain Resources, A. Rami et al report, *“Hypothyroidism also markedly impairs hippocampal growth, affected the calbindin D-28k content per hippocampus but not the calbindin D28k: protein ratio. This emphasizes the unique influence of thyroid hormone on brain development. The relative preservation of calbindin-D-29k in the hippocampal formation of animals lacking thyroid hormone suggests that calbindin D28k function may be crucial in this brain region.”*

Deregulation of Calbindin D28k as caused by soy plant-estrogens is involved in the cause of epilepsy and seizures as further described later in this report.

Hypothyroidism is also related to hearing loss.

1993, Department of Physiology and Endocrinology, Medical College of Georgia, S. Porterfiel and C. Hendrich describe, *“The Role of Thyroid Hormones in Prenatal and Neonatal Neurological Development-……..forebrain neuronal maturation, neurite outgrowth, synapse formation and myelination….all of these events are known to be dependent upon normal thyroid hormone levels…..Hearing loss is seen in rats rendered hypothyroid at birth.”*

There are a percent of children with brain disorders including autism that also experience hearing loss.

It is well known that soy plant-estrogens cause hypothyroidism and the many health disorders, most severely neurological damage that is directly related to hypothyroidism, while there remain no warnings to avoid soy consumption during pregnancy, nursing, or all the while healthy infants are fed a complete diet of soy-based formulas.

1987, Neuroendocrinology MJ Meaney et al report, "*Thyroid hormones influence the development of hippocampal glucocorticoid receptors in the rat- these data suggest that thyroid hormones mediate, in part at least, the development of glucocorticoid receptor concentrations in the hippocampus and that this effect occurs independently of their effects on corticosterone titers."*

The hippocampus is a neural structure primarily responsible for neuronal circuitry, a relay of synaptic transmission. Hippocampal dysfunction is related to memory loss, hyperactivity, learning disabilities, anxiety, and depressed olfaction or sense of smell.

Department of Pediatrics, Chicago, report, *"Soy formula complicates management of congenital hypothyroidism."*

Extensive published literature concludes that hypothyroidism as caused by soy especially during most sensitive fetal and/or infant development causes an assortment of damaging health effects such as neurological disorders that includes autism, as well as diseases related to autoimmune disorder. The thyroid interacts with brain development and functions that intercommunicate with the immune system. Estrogens, including soy phytoestrogens are proven to cause hypothyroidism, causing irreversible neurotoxicity and immune system dysfunction.

2000, even Novasoy manufacturers of soy infant formula and foods can not deny damaging thyroid conclusions when confirming, "And in fact, very recently, dietary genistein (the main soybean isoflavone) was found to inhibit thyroid peroxidase (TPO) by up to 60% in rats. TPO is the primary enzyme responsible for the synthesis of thyroid hormone. In conclusion, there is no reason to restrict soy consumption over 'concerns' about the impact on thyroid function."

2001, "Faculty of Pharmaceutical Sciences," K. Takahama et al report, "*There has been increasing evidence that sex hormones and thyroid hormones play important roles in the development of the brain. Thus it seems probable that perinatal exposure to endocrine disruptors, which may have an affect on biosynthesis, transport, action and metabolism of hormones, may disrupt brain development enough to impair the brain functions. (1)Perinatal exposure to relatively low concentrations of endocrine disruptors may cause an impairment of higher brain functions, such as sexual behavior and learning behavior, (2)There seems to be sexual difference about the impairment…(3) Endocrine disruptors may cause an increase in volume of some nuclei, such as…preoptic area (hypothalamus) and locus coeruleus (nucleus in the brain stem with physiological responses to emotional or physical threats, or panic) of the brain, (4) The disruptor might change the level of some substances that are considered to be involved in synaptic functions."*

Connection of the Thyroid to Neurons- PURKINJE CELLS- are a class of GABAergic neurons located in the cerebellar cortex, and are key elements in motor

learning and motor coordination. They are the largest neurons in the human brain, and send inhibitory projections to the deep cerebellar nuclei, constituting the sole output of all motor coordinates such as eye contact, smiling, facial expression, gestures and other signals of social intent.

Purkinje cells receive hundreds of thousands of both inhibitory and excitatory impulses while integrating information and the control of cerebellar function related to speech, learning, emotions, and attention. Cerebellar abnormalities explain aberrant motor activity, impaired cognitive abilities, and apparent lack of emotion that are characteristic of neurological disorders including autism.

Deficiencies in Purkinje cells are especially involved in the cause of cerebellar abnormalities related to; autoimmune diseases, genetic mutations, neurodegenerative diseases such as: ataxia, (lack coordination of muscle movements), tremors, hyperreactivity, inability to determine space and distance, emotion, attention, and behavioral disorders.

Estrogenic soy phytochemicals are proven to directly and indirectly inhibit Purkinje cell functions, of which this deficiency in Purkinje cells is also observed in many behavioral disorders, including autism. Deficiencies in Purkinje neuron cells cause chronic over-stimulation, or a neuron frenzy, resulting in disturbed mental capacities.

Soy phytoestrogens are well known to cause thyroid damage, or hypothyroidism with cascading effects that cause Purkinje cell alterations and destruction to several neurological processes involving brain signaling neurons that are responsible for the activation of intracellular signaling pathways throughout the developing cerebellum.

2001, Department of Pediatric and Adolescent Sciences in Italy, confirms, "*Thyroid hormone deficiency during nervous system development causes altered noble nervous cells, such as (involving the)….Purkinje cells.*"

1999, "Neurobiological Perspectives on Autism," L Hellew reports, "*There is also evidence that autistic individuals have dramatically reduced levels of Purkinje cells in the cerebellum.*"

Worsening these effects, multiple studies confirm that estrogenic soy phytochemicals decrease glial cell line derived neurotrophic factor (GDNF), the proteins that regulate and actively support Purkinje cells in the developing cerebellum.

American Journal of Psychiatry- "*Total Purkinje cell counts were significantly lower in the cerebellar hemisphere and vermis of each autistic subject than in the comparison subjects.*"

2007, "Journal of Neurological Sciences," G. Roman reports, "*Autism: Transient to utero hypothyroxinemia related to maternal flavonoid ingestion during pregnancy- Alterations of cortical neuronal migration and cerebellar Purkinje cells have been observed in autism. Neuronal migration requires T3 produced by deiodination of T4 by fetal brain deiodinases. Experimental animal models have shown that transient intrauterine deficits of thyroid hormones (as brief as 3 days) result in permanent alterations of cerebral cortical architecture reminiscent of those observed in brains of patients with autism. Maternal hypothyroxinemia resulting in low T3 in fetal brain during the period of neuronal cell migration weeks 8-12 of pregnancy) may produce morphological brain changes leading to autism. The most common causes include inhibition of deiodinases from maternal ingestion of dietary flavonoids, (soy) or from anti-thyroid environmental contaminants, (herbicides, PCB's perchlorates, mercury and*

coal derivatives). . Some plant isoflavonoids have profound effects on thyroid hormones and on the hypothalamus-pituitary axis. Genistein and daidzein from soy inhibit thyroperoxidase that catalyzes iodination and thyroid hormone biosynthesis. The current surge of autism could be related to transient maternal hypothyroxinemia resulting from dietary and/or environmental exposure to antithyroid agents."

Another study in "Journal of Neurological Sciences," as reported by G. Roman reports, *"Autism: …related to maternal flavonoid ingestion during pregnancy and to other environmental antithyroid agents. The most common causes (of antithyroid effects) could include inhibition of deiodinases D2 or D3 from maternal ingestion of dietary flavonoids or from antithyroid environmental contaminants. Some plant isoflavones have profound effects on thyroid hormones and on the hypothalamus-pituitary axis. Genistein and daidzein from soy inhibit thyroperoxidase that catalyzes iodination and thyroid hormone biosynthesis. Environmental contaminants interfere with thyroid function including 60% of all herbicides. Other antithyroid agents include PCBs, perchlorates, mercury, and coal derivatives. The current surge of autism could be related to transient maternal hypothyroxinemia resulting from dietary (isoflavones) and/or environmental exposure to antithyroid agents."*

Numerous studies of autistic patients have shown well-defined cerebellar anatomic abnormalities, particularly involving deficits in cerebellum Purkinje neuron cells while concluding….. *"Certain areas of the cerebellum are distinctly underdeveloped in autistics. The cerebellum lobes are significantly smaller in autistic individuals. Characteristic features of autism may be explained in terms of structural abnormalities in the cerebellum. There is also evidence that autistic individuals have dramatically reduced levels of Purkinje cells in the cerebellum These cells are rich in neurotransmitter serotonin, transmit inhibiting messages from the cerebellum to areas of the cerebral cortex explaining some of the cognitive deficits characteristic of autism."*

Cerebellar hypoplasia occurs when Purkinje cells either fail to developed in utero, or die off in utero prior to birth. Cerebellar hypoplasia is a developmental disorder characterized by the incomplete or underdevelopment of the cerebellum. Cerebellar hypoplasia may be caused by thyroid abnormalities, drugs and chemicals. Soy phytoestrogens cause thyroid abnormalities, and are compared to potent estrogenic endocrine disruption similar to drugs and chemical pollutants.

In infancy, symptoms of cerebellar hypoplasia include developmental delay, hypotonia, ataxia, seizures, mental retardation, and involuntary eye movements. At later ages, symptoms include headache, vertigo, imbalance, hearing impairment, and may be associated with several other disorders.

SOY PHYTOTOXIC DAMAGE TO THE THYMUS- Thymic or thymus is a hormone producing gland that stimulates the production of infection-fighting cells that are of central importance in the maturation of T-cells responsible for directing many facets of the immune system. The T-receptor of the T cells recognizes foreign antigens. In fetus and infants, if the thymus fails to develop and/or becomes nonfunctional the body's immune system fails to develop. The thymus continues to grow to an age of puberty then gradually decreases in size until it blends in with surrounding tissue in adulthood.

Studies report that soy plant-estrogens dangerously decrease thymic hormone and neuropeptide activity of which (again) contributes to neuroendocrine damage and immune system impairments.

June 2009, "Men's Health," magazine article by Jim Thornton reports, "*Paul Cooke, PhD, a reproductive biologist at the University if Illinois has studied mice raise on enough genistein to make their blood levels comparable to those of human infants fed soy formula. Among other worrisome findings, he discovered significant shrinkage of the thymus gland, a key part of the immune system. 'The thymus,' says Cooke, 'is like a finishing school for white blood cells- it's where they go to mature.'*"

Soy infant formula intake in the diet reportedly ranges from 15-200 mg/day. Genistein injected in mice at 8 mg/day produced serum genistein levels comparable to those reported in soy-fed human infants, and this dose caused significant thymic and immune changes in mice.

2002, "Proceedings of the National Academy of Sciences," S Yellayi et al report, "*Use of soy-based infant formulas and soy isoflavone supplements has aroused concern because of potential estrogenic effects of soy isoflavones genistein and daidzein. ….genistein injections in ovariectomized adult mice produced dose-responsive decreases in thymic weight of up to 80%. Genistein's thymic effects occurred through both estrogen receptor (ER) and non-ER- mediated mechanism……Genistein decreased thymocyte numbers up to 86% and doubled apoptosis, indicating that the mechanism of the genistein effect on loss of thymocytes is caused in part by increased apoptosis. Genistein injection caused decreases in relative percentages of thymic CD4(+)CD8(-) and double-positive CD4(+)CD8(+) thymocytes, providing evidence that genistein may affect early thymocyte maturation and the maturation of the CD4(+)CD8(-) helper T cell lineage. Decreases in the relative percentages of CD4(+)CD8(-) thymocytes were accompanied by decreases in relative percentages of splenic CD4(+)CD8(-) cells and systemic lymphocytopenia. In addition genistein produced suppression of humoral immunity. Genistein injected at 8mg/kg/per day produced serum genistein levels comparable to those reported in soy-fed human infants, and this dose caused significant thymic and immune changes in mice. Critically, dietary genistein at concentrations that produced serum genistein levels substantially less than those in soy-fed infants produced marked thymic atrophy. These results raise the possibility that serum genistein concentrations found in soy-fed infants may be capable of producing thymic and immune abnormalities, as suggested by previous reports of immune impairments in soy-fed human infants.*"

2002, "Molecular Medicine," SL Klein et al report, "*The primary goal of this study was to compare the effects of perinatal exposure with life-long exposure to genistein, an estrogenic compound in soy, on the endocrine and immune system in adulthood. Early exposure to genistein exerts long-lasting effects on the endocrine and immune systems in rats- Relative thymus masses were greater among males exposed to the high genistein diet than among males exposed to no genistein…..the percentages of CD4+CD8+ thymocytes, CD8+ splenocytes, and total T cells in the spleen were higher and the percentages of CD4-CD8- thymocytes were lower among males exposed to genistein than among males not exposed to genistein. Synthesis of interferon-gamma was marginally higher and testosterone concentrations were lower among genistein-*

exposed……These data illustrate that exposure to genistein during pregnancy and lactation exerts long-lasting effects on the endocrine and immune systems in adulthood."

Published in "The Journal of Nutrition" confirms, "*Estrogen regulates thymic development and immune function. Similarly, humans and animals are exposed to increasing amounts of the estrogenic soy isoflavone genistein in the diet….dietary administration to mice that produced serum genistein concentrations similar to those reported in human infants consuming soy formula also had demonstrable effects…….effects of estradiol and genistein on neonatal thymus indicated that estradiol affected genes involved in transcription, apoptosis, cell cycle and thymic development and function; genistein had similar effects on many estradiol target genes, but also had unique actions not replicated by estradiol."*

"Proceedings of the National Academy of Sciences," reveals, *"The phytoestrogen genistein induces thymic and immune changes: A human health concern? These results raise the possibility that serum genistein concentrations found in soy-fed infant s may be capable of producing thymic immune abnormalities, as suggested by previous reports of immune impairments in soy-fed human infants."*

1989, "Neuroendocrinology," N. Fabris et al report, "Thyroid-thymus interactions during development and aging- a *good body of experimental and clinical evidence suggests that biodirectional interactions do exist between the neuroendocrine system and the thymus activity. In particular thymic endocrine activity seems to be strongly influenced by neuroendocrine signals. …studies performed in hyper-and hypothyroid subjects and in the low T3 syndrome which affects premature infants, have clearly shown that thyroid hormones and in particular T3 physiologically modulate thymic peptide secretion."*

Soy plant-estrogens are confirmed in all of the above: causation of hypothyroidism, interruptions of neuroendocrine signals, decreasing T3 thyroid hormone.

2004, "Clinical & Experimental Immunology," EM Curran et al (supported by NIH) report, "*Consumption of soy products in dietary supplements and soy-based infant formula can result in serum levels of phytoestrogens that are actually higher than serum levels in Asian diets. Yellayi et al showed that injection of genistein into ovariectomized female mice resulted in dramatic reduction in the size of the thymus as well as the percentage of CD4, CD8 thymocytes. In this study, dietary supplementation of genistein produced significant decreases in thymic size……Together, our results and the studies listed above suggest that dietary oestrogens play a role in modulation of cell-mediated immunity and type 1 inflammatory responses and may be a factor in disease resistance and susceptibility."*

Department of Neuroscience reports, "*Marked hypothyroidism in rats, increase by about 100% the thymic content of oxytocin…."*

2009, Book, "Nutrigenomics and Proteomics in Health and Disease," Chapter Authors H. Fazlul et al report, "*Alteration in Gene Expression and Proteomic Profiles by Soy Isoflavone- Microarray analysis of the effects of genistein on neonatal thymus indicated that genistein affected genes involved and in the cell cycle transcription, thymic development, and immune functions (Cooke et al 2006). There results are consistent with the genistein individual inhibition of the NF-xB, one of the important mediators of immune function. Therefore, as Dr. Barnes indicated, isoflavone are much more than merely weak estrogens or thyrosine kinase inhibitors (Barnes 2004)."*

CYTOKINES DEFICIENCY- are a category of signaling proteins and glycoproteins that, like hormones and neurotransmitters are used extensively in cellular communication. While hormones are secreted from specific organs to the blood, and neurotransmitters are related to neuron activity, the cytokines are more diverse class of compounds in terms of origin and purpose. Cytokines are critical to the development and functioning of both the innate and adaptive immune response. They are often secreted by immune cells that have encountered a pathogen, thereby activating and recruiting further immune cells. Cytokines are also involved in several developmental processes during embryogenesis.

Cytokines play a crucial role in Natural Killer-cell activation. Cytokines are stress-molecules released by cells upon infection that signal the NK-cell of the presence of viral pathogens. Soy plant-estrogens reportedly decrease cytokine bioavailability that can be especially damaging during fetal and infant development.

1998 study published in, "Soy Protein Research" by Yagasaki Kazui et al, reports *"In contrast, productivity of (cytokines) TNF- ALPHA, interleukin -1, and nitric oxide (a fundamental compound in the field of neuroscience, physiology, and immunology) was significantly lower in the 20% soy protein isolate-fed animals, (rats), than in the casein fed ones when each diet was fed to hepatoma (liver cancer)-bearing rats for 14 days. Since cytokine productivity in macrophages (rid the body of worn-out cells and other debris in locations such as the lungs, liver, neural tissue, bone, spleen and connective tissue) is several times higher in the hepatoma-bearing state than in the normal state, soy protein isolate (soy infant formula/soy products) may be regarded as a depressant of enhanced cytokine production."*

Reported from Iowa State University, "Effect of Protein Source (Casein vs. Soy) on Growth in Antigen Exposed Pigs- *Genistein has been noted to reduce the production of cytokines in vitro through the inhibition of tyrosine kinase activity. The reduction in cytokine release, however, also may be associated with the lower production of lymphocytes and antibodies. This potentially could increase the pigs' susceptibility to secondary antigens……"*

2004, Serbian Journal, "Srp Arh Celok Lek" L. Markovic reports, "*Interaction involving the thymus and the hypothalamus-pituitary axis, immunomodulation by hormones- Perfectly projected and impeccably created, the endocrine system precisely regulates the most delicate immune processes……..there is active and dynamic collaboration of these (neuroendocrine and immune) systems in the execution of their designated functions. These interactions occur at many stages of embryonic and neonatal development and they are a continual part of normal homeostatic balance necessary to preserve health. There is communication between neuroendocrine and immune system via cytokines, neurotransmitters, and peptide hormones…..Endocrine influences appear to be a part of bidirectional circuitry, namely, thymic hormones also regulate the release of hormones from the pituitary gland. Physiologically, thymus is under neuroendocrine control. NK (natural killer) cells and T- lymphocytes activities have been decreased by the action of estrogens, as well as the release of thymus hormones."*

Soy plant-estrogens mimic the actions of estrogens thus dangerously interfering with thymic hormones as well as cytokine release.

SOY DAMAGE TO CHROMOSOMES:

Soybeans are a cause of chromosome damage and to all people and particularly developing child interfering with chromosomes is devastating. Chromosomal abnormalities are the leading cause of spontaneous abortion. Chromosome alterations caused to fetus, infants, or children have been linked with the incidence of leukemia and other congenital birth defects such as; neurological disorders, seizures, epilepsy, damage to organ systems, cancers, etc, etc.

2004, "Toxicology Letters" AL Di Virgilio et al report, "*Genotoxicity of the isoflavones genistein, daidzein and equol in V79 cells- Hormonally active chemicals in the human diet, such as man-made estrogenic chemicals or plant-derived compounds (phytoestrogens) have become a matter of public concern, A significant part of human exposure to phytoestrogens is attributable to soy isoflavones. Besides their estrogenic properties, soy isoflavones exert genotoxic actions. Genistein induced mostly anti-kinetochore (CREST) (-) micronuclei i.e. micronucleus (MN) chromosomal fragments, thus inductive of clastogenic (inducing chromosome disruptions or breaks) mode of action. MN induced by high concentrations of daidzein were partly CREST (+) and CREST(-) whilst equol induced mostly CREST (+) micronuclei indicative of an aneugenic action. These results point to a differential genotoxicity of phytoestrogens.*

"Cancer Genetics and Cytogenetics," Volume 186, Issue 2 pages 78-84, Y Kim et al report, "*Genistein is a major soy isoflavone with multiple properties. After 3 months of exposure to genistein, the cell line MCF-10A/G1 showed loss of a normal chromosome 8 and gain of an extra chromosome 20, as well as loss of a chromosomal segment on the short arm of chromosome 9, leading to a homozygous deletion of the tumor suppressor genes CDKN2A and CDKN2B. Our results suggest that long-term, low-concentration exposure to genistein may have the potential to induce chromosomal imbalances. These genotoxic effects may work in concert with other factors to induce genetic lesions that contribute to soy-and genistein-associated risk."*

An extra chromosome 20 can cause severe seizures, behavior disorders and mental retardation. Defect in gene 20 also causes severe iron overload in the liver that can lead to death. Iron overload can cause the heart, pancreas and/or other organs to fail. Loss of chromosome 9 can cause a wide variety of human tumors, particularly noted in urinary bladder cancer. There are also many genetic conditions related to alterations in chromosome 8, particularly associated with several types of cancer, severe intellectual disabilities, heart defects, underdeveloped kidneys, eye abnormalities, and abnormal muscle stiffness.

MALE TRANSFER OF DEFECTS IN SPERM DNA DURING FERTILIZATION OF EGG: Fetal, infant, and child developmental damage is stated to be caused by maternal consumption of soy phytotoxins, however men may be equally responsible for chromosomal injury to their offspring during fertilization.

Men with spermatozal DNA damage have difficulty fathering offspring. However sperm with abnormal DNA can fertilize an oocyte, which may progress to live birth and cause adverse health effects to offspring. Many studies report the same:

Center for Advanced Research in Human Reproduction, Cleveland Clinic Foundation, A. Agarwal and S. Allamaneni report, "*The quality of sperm DNA is very*

important in maintaining the reproductive potential of men. Sperm DNA is known to contribute one half of the genomic material to offspring. Normal sperm genetic material is required for fertilization, embryo and fetal development and postnatal child well being. Abnormal DNA can lead to derangements in any of these processes. Evidence now exists in the literature to show that sperm DNA damage influences the fertility outcome after ART (assisted reproductive techniques) procedures. Even is spermatozoa with abnormal DNA fertilize an oocyte and live birth occurs, there is a possibility of congenital abnormalities in the offspring."

2002 "Human Reproduction" I.D. Morris et al report, "*The integrity of sperm DNA is important for the success of natural or assisted fertilization as well as by normal development of the embryo, fetus and child. This study contributes to the evidence of DNA damage within sperm. As it is likely that sperm with DNA damage contributed to successful fertilization and in-vitro development, potential adverse effect remain to be clarified."*

SOY ENDOCRINE DISRUPTOR DAMAGE IS MULTIPLIED BY OTHER ENDOCRINE DISRUPTORS:

It is overwhelmingly proven that an endocrine disruptor in combination with other endocrine disruptors multiplies damaging health effects that are likely not escapable. For instance; an infant fed out of the warmed BPA plastic baby bottle that contains soy-based (plant-estrogen) formula, or the mother (possibly the father) surrounded by pesticides while also consuming soy endocrine disruptor products. The instances involving multiple endocrine disruptors is proven to multiply risk factors for irreversible health disorders.

2009, "Biology of Reproduction" A Muhlhauser et al report, "Bisphenol A Effects on the Growing Mouse Oocyte are Influenced by Diet," synopsis by Wendy Hessler – *"A study with mice finds that diet can modify the harmful effects of bisphenol A. Animal studies have shown that exposure to bisphenol A can cause abnormal patterns of chromosomal behavior in a female's eggs- called oocytes- leading to errors in cell division. The authors report three important conclusions. First, when exposed to bisphenol A, the daughters of mice maintained on a casein diet low in soy phytoestrogens develop errors in the cell division process, meiosis, that leads to formation of their eggs. Second, if instead fed a diet with high soy phytoestrogens, the BPA effect is reduced at a low BPA levels but increased at high. Third, even without BPA, the daughters of mice fed the soy phytoestrogen diet develop the same errors. Studies of human populations spanning several countries, including the United States, have found BPA in the bodies of virtually everyone tested. Because past results of how BPA may affect egg development varied, the paper's authors tested whether 'dietary estrogens were influencing the effect of BPA on the oocyte.' Female mice in this study were fed two different diets, one high in soy protein and the other not. Soy protein contains phytoestrogens, plant compounds such as the isoflavones daidzein and genistein that can act like estrogen. The abnormalities in the eggs of mothers fed the high soy diet were nearly 4 times greater than those fed the diet low in soy. However, the soy-rich diets appear to make the harmful effects of BPA worse, according to researchers. 'The results presented here provide evidence that diet influences one reported BPA induced effect, disturbances in meiotic spindle formation and chromosome alignment in the periovulatory oocyte,' the researchers conclude."*

SOY INHIBITION OF DNA TOPOISOMERASE II, A CAUSE OF LEUKEMIA-

Topoisomerases are essential enzymes that resolve topological problems during DNA replication transcription and recombination. They are involved in the regulation of DNA supercoiling and prevention of DNA distortion. Topoisomerases are nuclear enzymes inducing transient breaks in the DNA, allowing DNA strands or double helices to pass through each other. DNA topoisomerases fall into two major classes: topo type I, a DNA single-strand endonuclease and ligase that functions mainly during transcription, and topo type II represented by two isoforms (a and B) that are ATP-dependent DNA double-stranded endonucleases and ligases. Topo IIa is a major component of the chromosomal matrix that decatenates double-stranded DNA during replication. The expression of topo IIa is cell cycle regulated and proliferation dependent.

Soy phytoestrogens inhibit essential biosynthetic enzymes such as tyrosine kinases and topoisomerases involved in cell transformation and proliferation that are most important during fetal and infant brain and body development. Soy is confirmed as an inhibitor of topoisomerase IIa enzymes causing permanent double strand breaks leading to chromosomal aberrations that reportedly initiate leukemia by acting as a topoisomerase II poison.

2002, International Journal of Toxicology, Office of Preventive Oncology, National Cancer Institute reports, "*Genotoxicity and carcinogenicity studies of soy isoflavones-.....there remains a mechanistic concern associated with the ability of isoflavones (i.e., genistein) to inhibit topoisomerase, possibly leading to DNA strand breaks.*"

2002, book, "Phytoestrogens and Health," GS Gilani and JJB Anderson report, "*…..we found that genistein inhibited the topo II catalytic activity. Inhibition of topo II generally takes place by either stabilization of a transient reaction intermediate between the topo II and DNA (called the cleavable complex) or the hindering of its formation by interfering with the relegation step; on the basis of their mode of action, topo II inhibitors are distinguished into catalytic inhibitors or poisons, respectively. Because normal topo II activity is essential for chromosomal segregation, the catalytic inhibitors of top II are expected to cause abnormalities in sister chromatid segregation during the mitotic phase of the cell cycle. These abnormalities can result in chromosomal breakage and apoptosis. On the basis of this scenario, the formation of the cleavable complex by topo II poisons, (including genistein) can be dissociated from the downstream signals that lead to catastrophic DNA damage and apoptosis. Another possibility that must be considered in evaluating the interactions of genistein with top II is that sublethal doses of genistein may cause permanent genetic alterations. I these alterations involve key regulatory genes such as transcription factors, oncogenes, or tumor suppressor genes, carcinogenesis may be initiated. The carcinogenic effects of etoposide chemotherapy in the case of acute myeloid leukemia is an example of this delayed adverse effect of topo II poison-induced genetic toxicity…..certain tissues, accumulate higher levels of genistein…supports the possibility that genistein may cause delayed adverse effects by producing low levels of DNA damage either by stabilizing the interactions between DNA and topo II or by promoting abnormal chromosomal segregation.*"

1994, "Nutrition and Cancer," National Cancer Institute, MJ Messina reports, "*Soybeans are a unique dietary source of the isoflavone genistein, which possesses weak estrogenic activity…..Genistein is also a specific inhibitor of protein tyrosine kinases; it also inhibits DNA topoisomerases and other critical enzymes involved in signal transduction.*"

1999, "Journal of Nutrition," S JI et al report, "*The isoflavones, genistein and daidzein are cytotoxic in vitro (e.g., inhibition of cell proliferation), due in part to inhibition of protein tyrosine kinase and DNA topoisomerase activities. Normal cell functions associated with these enzymatic activities could potentially be impaired in animals through ingestion of soybean products.*"

Crisp Data Base National Institute of Health, H Wei reports, "*Genistein one of the major soybean isoflavones has been shown to inhibit tyrosine protein kinase growth, DNA topoisomerase II, and ribosomal S6 kinases, and induce differentiation of several malignant cell lines.*"

2002, "EXCLI Journal" JG Hengstler et al report, "*Dietary topoisomerase II-poisons: contributions of soy products to infant leukemia? Recently, some alarming studies have been published, suggesting that maternal exposure to low doses of dietary topoisomerase II-poisons, including bioflavonoids such as genistein….may contribute to the development of infant leukemia: approximately 80% of infants with acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL0 have chromosome translocations involving the MLL (mixed lineage leukemia) gene. Due to the periods of rapid cell turnover it is likely that fetal tissues or tissues of children are more susceptible to some environmental or dietary genotoxic agents. Recently, some studies suggested a causal relationship between infant leukemia induced in utero and maternal exposure to dietary bioflaonoids- that besides many other effects, especially those as endocrine disruptors also act as topoisomeras II-poisons (Ross, 2000, Strick et al, 2000, Alexander et al, 2001, McDonald et al 2001, Abe, 1999). However, the consequences of exposure to bioflavonoids (soybeans and soy products), may differ between adults and transplacentally exposed embryos. Due to rapid cell proliferation the aspect of topoisomerase II inhibition by bioflavonoids may be much more critical for embryos than for adults. In this review, we report about the mechanisms of action of topoisomerase II-poisons, carcinogenic effects of the latter and discuss some recent studies suggesting that dietary exposure to topoisomerase II poisons may have a causative role in infant leukemia. If healthy cells survive exposure to topoisomerase II-poisons DNA double strands may lead to chromosomal aberrations…..some recent studies provide evidence that transplacental exposure of embryos to isoflavones may contribute to infant leukemia. In addition, the incidence of infant leukemia is almost 2-fold higher in several Asian cities, for example Hong Kong or Osaka, than in Western countries. This difference might be explained by the high food intake of bioflavonoids in may regions of Asia, especially by consumption of soybeans and soybean products, (Strick et al, 2000). ….soy products and other foods containing high levels of topoisomerase II-poisons should not be consumed during pregnancy.*"

1996, "Cancer Causes and Control," JA Ross reports, "*A report from the Children's Cancer Group- ….Nearly 80 percent of infant leukemias present an abnormality involving the MLL gene at 11q23……agents which are known to inhibit DNA topoisomerase II often manifest the same MLL abnormalities. It has been*

hypothesized that de novo infant leukemias may occur as a result of maternal exposure to agents in diet and medications that inhibit DNA topoisomerase II. However, within the AML (acute myeloid leukemias) stratum, there was a statistically significant positive association (P tend= 0.04) with increasing consumption of DNA topoisomerase II-inhibitor containing foods…..…. Results of this preliminary studying combination with molecular data, should be used in future investigations of childhood leukemia to justify the incorporation of a detailed dietary history."

1998, "International Journal of Cancer," JA Ross reports, "*….nearly 75% of infant leukemias demonstrate a specific abnormality involving a gene, MLL, on chromosome 11q23. Molecular studies suggest strongly that these leukemias occur in utero. ……maternal exposure during pregnancy to environmental agents that inhibit DNA topo 2 may be associated with the development of leukemia in infants. DNA topo 2 inhibitors have been found in…..soy…..as well as in certain pesticides, solvents, and medications….there was an approximately 10-fold higher risk of infant AML (acute myeloid leukemias) with increasing maternal consumption of DNA topo 2 inhibitor-containing foods."*

2008, "Journal of Agricultural and Food Chemistry" W Wang et al report, "*Identification and characterizations of topoisomerase II inhibitory peptides from soy protein hydrolysates……..In conclusion, three peptides (FEITPEKNPQ, IETWNPNNKP, AND VFDGEL) released from in vitro gastrointestinal enzyme digestion of soy proteins inhibited human topoisomerase II activity through binding to the active site of the CTD domain."*

2000, "PNAS," Julie A. Ross, Department of Pediatrics, University of Minnesota Cancer Center, reports, "*The observation of a higher risk in infant females is particularly notable given the overall higher risk of leukemia in male children under the age of 15 as compared with female children. The majority of infant cases (including about 80% of infants with ALL (acute lymphocytic leukemia) and 65% of infants with AML (acute myeloid leukemia) have rearrangements involving the MLL gene on chromosome band 11q23 in their leukemia cells. ….there is strong molecular evidence that these Mll abnormalities occur in utero. ….DNA topoisomerase II inhibition is postulated to be directly related to the MLL abnormalities observed in the secondary AML's. ….we hypothesized that maternal exposure to DNA topoisomerase II inhibitors during pregnancy could be associated with an increased risk of infant leukemia. Natural and synthetic DNA topoisomerase II inhibitors include the flavonoids……..genistein(soy). Our preliminary epidemiologic study suggested that increased maternal consumption during pregnancy of foods that contain dietary topoisomerase II inhibitors is positively associated with infant AML ……..(i) dietary constituents that inhibit DNA topoisomerase II can have a direct effect on the MLL gene, and (ii) these compounds can cross the placenta and reach the fetus. Strick and colleagues demonstrate that several of the bioflavonoids available in the diet can induce cleavage of the MLL gene in human myeloid and lymphoid progenitor cells and in cell lines. These findings provide evidence that dietary flavonoids may be directly involved in causing genetic damage……a fetus, who has periods of rapid cell turnover, may be more susceptible than an adult to the effect of dietary DNA topoisomerase II inhibitors. For infant leukemia, it is unclear when the fetus might be most vulnerable. We have learned from the therapy-related leukemias that frequent (weekly) exposure to DNA topoisomerase II inhibitor(s)…… may increase*

risk. Strick et al's study provides another important piece of the puzzle that supports the hypothesis that maternal exposure to dietary DNA topoisomerase II inhibitors may be associated with an increased risk of infant leukemia. Because cell cycling is a dynamic process, it should be remembered that what might be beneficial at one point in time could be harmful at another."

2000, "PNSA," R Strick et al report, "*Chromosomal translocations involving the MLL gene occur in about 80% of infant leukemia. In the search for possible agents inducing infant leukemia, we identified bioflavonoids,…..that cause site-specific DNA cleavage in the MLL breakpoint cluster region in vivo…..results suggest that maternal ingestion of bioflavonoids may induce MLL breaks and potentially translocations in utero leading to infant and early childhood leukemia."*

The EPA confirms, "*Genistein, one of the major soybean isoflavones, has been shown to inhibit tyrosine protein kinase, DNA topoisomerase II, and ribosomal S6 kinase…..*" (All that is shown to be most damaging to fetal, infant, and child health.)

SOY STIMULATION OF THE P13 KINASE/Akt, CAUSATION OF LEUKEMIA-

2002 "Journal of Neuroendocrinology," T Ivanova et al report, "*Rapid stimulation of the P13-kinase/Akt signaling pathway in developing midbrain neurons by estrogen. Our study clearly indicates that estrogen can rapidly stimulate the P13-kinast/Akt signaling cascade……."*

2005, journal of "Leukemia," VL Grandage et al report, "*….P13-kiinase signaling pathway plays a key role in the regulation of cell survival and proliferation. We show that the P13kinase/Akt pathway is constitutively active in primary acute myeloid leukemia (AML) cells. Inhibitors of P12-kinase and Akt may be useful in the treatment of AML."*

SOY DAMAGE TO INTERLEUKINS- are a group of cytokines also proven to be disturbed by soy isoflavones. The function of the immune system depends in a large part on interleukins and interleukin dysfunction is a cause of autoimmune diseases that can lead to the cause or promotion of many diseases including cancers.

Soy isoflavones are proven to disturb normal interleukin levels involving: IL-2, IL-3, IL-4, IL-6, IL-8, and IL-1beta that can cause inflammation, deficient immune responses, encourage numerous disorders, and potentially cause and/or promote life-threatening diseases.

INTERLEUKIN-6, (IL-6) IN THE CAUSE OF LEUKEMIA: Il-6 is involved in inflammation and the development of plasma cell tumors. There are several reports concluding the involvement of excessive interleukin-6 production in the cause and stimulation of leukemia.

2008, "Journal of Parenteral and Enteral Nutrition," A Gawecka et al report, *"Immunologic Properties Differ in Preterm Infants Fed Olive Oil vs Soy-Based Lipid Emulsions During Parenteral Nutrition….Interleukin (IL) -6 production was significantly higher in the soybean oil (SO) group. Conclusions; SO-based lipid emulsions may promote an excess of IL-6 production, especially in the T cell-dependent way of the peripheral blood mononuclear cells activation……"*

1999, "Planta Medica" P Diel et al report, "*Many compounds of plant origin with the ability to bind to the estrogen receptor have been identified…..there is evidence that the consumption of some of these phytoestrogens …..may act as endocrine disrupters. For this reason there is need to characterize the estrogenic potency of these substances…..widespread terms for the investigation of non-classical estrogenic effects have been established. An example for such an effect is the modulation of the expression of interleukin-6, a cytokine that appears to be key molecule in the osteoporotic process by estrogens."*

2002, book, "Phytoestrogens and Health," GS Gilani and JJB Anderson report, "*Estrogens are known to modulate the immune response and enhance cytokine production. Feeding high isoflavone soy had been shown to increase IL-6 production……negative effect of soy is the suggestion that isoflavones may cause a rare form of childhood leukemia and brain atrophy 'in old age.'"*

2006, "Toxicology," JV Meeuwen et al report, *"…iv vivo epithelial (tumor) cells surrounded by connective tissue communicate via a feed back-loop where fibroblasts excrete estradiol (E2), which will promote estrogen depended tumor cells, which in exchange start excreting factors E2, interleukin-6 (IL-6), IL-6 soluble receptor (IL-6sR) stimulating CYP19 gene transcription in fibroblasts."*

Soy isoflavones are well known to mimic estradiol actions.

1991, "Leukemia and Lymphoma," T Hahn et al report, "*Involvement of Interleukin-6 in the Autocrine Stimulation of Chronic Lymphocytic Leukemia B Cells by Tumor Necrosis Factor."*

1996, "The Journal of Immunology," E Giraudo et al report, "*IL-6 is an in-vitro and in-vivo autocrine growth factor for middle T antigen-transformed endothelial cells- Since IL-6 is a pleiotrophic cytokine that also regulates endothelia cell functions related to angiogenesis, we studied the relevance of IL-6 in tumorigenicity of polyomavirus (PmT)-endothelial cells. We conclude that IL-6 is involved in the progression of vascular tumors induced by PmT……...including Kaposi's sarcoma"*

2008, Division of Hematology-Oncology, UCLA, SA Miles et al report, "*The AIDS Kaposi Sarcoma (AIDS-KS) cell lines secreted large amount of immunoreactive and biologically active IL-6. These results show that both IL-6 and IL-6-R are produced by AIDS-KS cells and that IL-6 is required for optimal AIDS-KS cell proliferation and they suggest that IL-6 is an autocrine growth factor for AIDS-KS cells."*

1999, "Japanese Foundation for Cancer Research," Etsuro Ogata reports, "*Parathyroid hormone-related protein (PTHrP) as a potential target of therapy for cancer-associated morbidity- In clinical studies, Group B patients (with elevated plasma PTHrP….tended to exhibit higher plasma levels of tumor necrosis factor IL-5, and IL-8, and had significantly higher levels of IL-6. The levels of tumor necrosis factor-a and IL-6 correlated with those of PTHrP."*

Interleukin-6 is reported to cause multiple myeloma, a type of cancer formed by malignant plasma cells. Soy causes significant increase in IL-6.

2009, American Cancer Society reports, *"Detailed Guide: Multiple Myeloma- Researchers have found that patients with plasma cell tumors have important abnormalities in other bone marrow cells and that these abnormalities may also cause excess plasma cell growth. Excess IL-6 production by these cells appears to be an important factor in development of plasma cell tumors."*

2005, "European Journal of Immunology," T Hirano et al report, *"High levels of interleukin 6 (IL-6/B cell stimulatory factor-2) were detected in synovial fluids from the joints of patients with active rheumatoid arthritis (RA). The cells found in freshly isolated synovial fluid constitutively expressed IL6 mRNA. ……IL6 can function as B cell growth differentiation factor as well as hepocyte-stimulating factor."*

2008, "The Journal of Trauma, Injury, Infection and Critical Care," JL Sperry et al report, "*IL-6 serum levels were statistically higher in males, relative to females. This higher level of IL-6 expression in males remained statistically significant over time even after controlling for differences in age…..conclusions: Persistently elevated IL-6 levels in males are associated with higher rate of multiple organ failure…Persistent IL-6 expression is responsible for the gender-based differential outcomes……"*

Incidence rates of all leukemias are higher among males, and the increasing cause of IL-6 may be a very good explanation as to why. Soy isoflavones increase IL-6 levels.

PREECLAMPSIA- caused by excessive maternal IL-6 as caused by soy isoflavones-

2008, "American Journal of Pathology," CJ Lockwood et al report, *"Preeclampsia, a common pregnancy disorder associated with an increase in systemic inflammation, is the leading cause of maternal and fetal morbidity and morality throughout the world. It is associated with shallow extravillous trophoblast invasion of the decidua, leading to uteroplacental blood flow that is inadequate for developing fetal-placental unit. In preeclamptic women, interleukin-6 (IL-6) levels in plasma, but not placenta, are elevated, prompting evaluation of excess, circulating IL-6. The current study found significantly higher immunohistochemical staining for IL-6 in decidual cells from preeclamptic versus preterm, gestational age-matched control placentas…..excess circulating IL-6 levels that can promote both endothelial cell dysfunction (and subsequent vascular dysfunction) and an excess of decidual macrophages implicated in shallow extravillous trophoblast invasion of the decidua. Maternal-fetal interactions create a mild systemic inflammatory state exemplified by activation of both vascular endothelium and leukocytes that is most apparent in the third trimester of uncomplicated human pregnancies. Preeclampsia is……the leading cause of maternal and fetal morbidity and mortality. Numerous reports indicate that the plasma of preeclamptic patients contains elevated levels of interleukin-6 (IL-6), a multifunctional cytokine that regulates hematopoiesis as well as acute phase reaction and modulates both pro-and anti-inflammatory events. That IL-6 also interferes with endothelial cell function suggests that preeclampsia-associated elevated plasma IL-6 levels contribute to the systemic endothelial activation and vascular damage that culminates in the maternal syndrome."*

2002, "Metabolism," DJ Jenkins et al report, "*Effects of high-and low-isoflavone soy foods on inflammatory biomarkers and proinflammatory cytokines in middle-aged men and women- Women showed significantly higher interleukin-6 (IL-6) values after the high-isoflavone soy diet (P=.013) compared to control values. For women, the difference between the high-and low-isoflavone IL-6 values was significant using the unadjusted data (P =.048) but not after adjustment."*

CORNEAL DAMAGE-

2005, "Cornea," T Suzuki and DA Sullivan report, *"Researchers have proposed that the secretion of proinflammatory cytokines and matrix metalloproteinases (MMPs) by corneal epithelial cells contributes to the development of ocular surface inflammation in dry eye syndromes. Results- Our results demonstrate that 17beta –estradiol (soy-mimic) upregulates the expression of proinflammatory cytokine and MMP genes in human corneal epithelial cells. Estrogen administration increased the levels of IL-1beta, IL-6, GM-CSF mRNAs, as well as MMP 2, 7, and 9 mRNAs compared with those of placebo-treated controls. This estrogen effect was found after 6 and/or 24 hours of hormone treatment. CONCLUSIONS: Our findings show that 17beta-estradiol increases the expression of inflammatory genes in human corneal epithelial cells."*

Interleukin-1, IL-1a, IL-1b are pro-inflammatory cytokines and are factors that could induce fever, control lymphocytes, increase the number of bone marrow cells, and cause degeneration of bone joints. Soy isoflavones mimic estradiol and estradiol is proven to disrupt IL-1b levels potentiating a variety of developmental disorders.

INTERLEUKIN-4, IL-4:

Increasing IL-4 production as caused by soy isoflavones is involved in the causation of lymphocytic leukemia and other diseases/disorders.

Lymphocytic leukemia is caused by uncontrollable growth of B- or T-lymphocytes as caused by soy isoflavones. Disrupting the normal functions of IL-4 reveals biological effects, including the stimulation of activated B-cells and T-cell proliferation, (as a proven cause of lymphocytic leukemia), and the differentiation of CD4+ T-cells into Th2 cells as an increasing cause of immune deficiency diseases, including allergic diseases.

2006, "Journal of Nutritional Science and Vitaminology," T Sakai et al report, "*Genistein enhances antigen-specific cytokine production in female DO11.10 transgenic mice. Genistein is a phytoestrogen contained at high levels in soy products and has been shown to regulate immunoresponse. Oral administration of 20 mg/kg genistein increased IFN-gamma and IL-4 production from DO11.10+ T cells……"*

Aberrant IFN-gamma expression is also associated with a number of autoinflammatory and autoimmune diseases.

2006, "Endocrine Disrupters," M. Chalubinski and ML Kowalski report, *"Endocrine disrupters- potential modulators of the immune system and allergic response- Endocrine-disrupting effect is obtained by mimicking the action of the steroid hormones and has been associated with several reproductive disorders as well as cancerogenesis…in humans. Endocrine disruptor can also influence synthesis of cytokines, immunoglobulins and cell mediators as well as immune cell activation and survival. Modulation by EDs of interleukin-4 production, Th1/Th2 balance and lgE production suggest their potential effect on allergic immune responses."*

INTERLEUKIN 3, IL-3:

Increasing Il-3 as caused by soy isoflavones is involved in the causation of myeloid leukemia.

1999, "Protein Engineering," DA Vallera et al report, "*The IL-3 receptor was expressed on a high frequency of myeloid leukemia cells and also on hematopoietic and vascular cells. Il-3 was toxic when administered to mice at doses as low as 0.1ug/day."*

1997, "Nutrition and Cancer," W Wang et al report, "*Daidzein and genistein are two prominent soy isoflavones……The secretion of cytokine interleukins-2 and -3 from concanavalin A-activated lymphocytes was significantly increased again by daidzein…."*

1998, "British Journal of haematology," A Dolzhanskly et al report, "*Complementary and antagonistic effects of IL-3 in the early development of human megakaryocytes in culture- The effects of IL-3 on the early steps in the growth and development of megakaryocytes (MK) in culture has been studied…..IL-3 plays an important role in early MK development but inhibits further maturation after endoreduplicaton begins. Thus, prolonged contact with IL-3 results in the appearance of cells that do not mature normally."*

1989, "Blood" FH Uckun et al report, "*The purpose of this study was to analyze the expression of functional interleukin-3 (IL-3) receptors on leukemic B-cell precursors (BCPs)……IL-3 stimulated the proliferation activity of leukemic BCPs in a dose-dependent fashion……low receptor occupancy is sufficient for growth stimulation of leukemic BCPs by rIL-3."*

2004, "Leukemia" U Testa et al report, "*Recent studies indicate that abnormalities of the interleukin-3 receptor (IL-3R) are frequently observed in acute myeloid leukemias and may contribute to the proliferation advantage of leukemic blasts. Furthermore, there is evidence that the IL-3Ra is a marker of leukemic stem cells….."*

INTERLEUKIN 2, IL-2:

1991, "Med- Hypotheses" RS Smith reports, "*Excessive production of Interleukin-2 (IL-2) and IL-2 receptors (IL-2R) ….is hypothesized as the cause of schizophrenia. It is based on: IL-2 given to human volunteers can cause all the symptoms of schizophrenia…."*

2005, "Toxicological Sciences," V Selvaraj et al report, "*We have shown that IL-2 and IL2Ra mRNA are significantly increased by 17-B estradiol and genistein."*

JOINT DISEASE-

2003, "Journal of Oral and Maxilllofacial Surgery," K Yun, et al report, "*The expression and concentration of IL-1B, IL-6, and IL-8 were increased with increasing concentration of 17-B estradiol. These findings suggest that estrogen has the potential to cause temporomandibular joint disease with induction of the proinflammatory cytokines, IL-1B, IL-6 and IL-8."*

ARTHRITIS-

1998, "Journal of Experimental Medicine," A Tonino et al report, "*Interleukin 6 Is Required for the Development of Collagen-induced Arthritis."*

Soy isoflavones are reported to increase IL-6 levels.

SOY CAUSATION OF ALLERGIES:

Soy is an allergen. Reactions to allergens including: coughing, sneezing, runny nose, hives, diarrhea, sleep disturbances, bedwetting, sinus and ear infections, crankiness, joint pain, chronic fatigue, gastrointestinal woes, swallowing difficulties, asthma attacks, and possibly fatal anaphylactic shock.

Soy infant formula can be an allergen. Infant milk formulas often contain soy increasing the possibly that the suspected lactose allergy is instead allergy to soy.

2005, "Immunology," J Park et al report, "*Phyto-oestrogens are polyphenolic non-steroidal plant compounds with oestrogen-like biological activity. Phyto-oestrogens*

have many biological effects inducing oestrogen agonistic-antagonist properties. In this study we investigated whether….daidzein and equol affect production of interleukin(Il-4) a pro-inflammatory cytokine closely associated with allergic immune response…..daidzein and equol significantly enhanced Il-4 production from both CD4+ T cells and EL4 cells in a dose-dependent manner…..daidzein and equol also enhanced IL-4 gene promoter activity in EL4 cells…..In addition…daidzein and equol increased AP-1 DNA binding activities……These results suggest that phyto-oestrogens and some of their metabolites may increase allergic responses via the enhancement of IL-4 production in T-cells."

Most importantly, many studies conclude that soybean food and/or beverages can trigger lactose and peanut allergic reactions.

"New England Journal of Medicine" 2003 study by G. Lack et al reports, *"The prevalence of peanut allergy appears to have increased in recent years. Peanut allergy was independently associated with intake of soy milk or soy formula. The association with soy protein could arise from cross-sensitization through common epitopes. Confirmation of these risk factors in future studies could lead to new strategies to prevent sensitization in infants who are at risk for subsequent peanut allergy."*

Journal of Clinical Gastroenterology," JD Gryboski et al reports, "*Immunoglobulin deficiency in gastrointestinal allergies- Combined (gastroingestinal allergy) sensitivities were milk and soy…. Such a high incidence of immunoglobulin abnormalities has not been previously reported in children with allergic gastroenteritis."*

"Archives Francaises de Pediatrie," J.J. Baudon et al repot, "*….administer soybean proteins with caution in patients with cow's milk intolerance."*

Seizures, abdominal pain, and allergies are also commonly reported as related to neurological disorders. Allergic reactions can directly influence brain function in children and have profound effects on behavior.

2009, "Men's Health" magazine article by Jim Thornton reports, "*American Medical Association surveyed over 800 adults, ages 20 to 34 who were fed either soy-based or cow's-milk formulas during their infancy. …..the group raised on soy formula regularly used more asthma and allergy medications in adulthood…..could it represent a subtle impairment of immune function"*

SOY CAUSATION OF ASTHMA-

2004, U.S. Dept of HHS- CRISP Data Base, TL Guo reports, "Genistein Exacerbation of Asthma in Mice- *Genistein, a soy isoflavone, has been suggested to mediate its biological function mainly as an endocrine disruptor……there are concerns about the long-term effects of this compound on human health, especially that of infants and young children. The recent epidemiological finding indicate that there is an increase in the use of asthma or allergy drugs in young adults who have been fed soy formula during infancy as compared to those who have been fed cow milk formula. One important mechanism for development of asthma is that allergens repeatedly stimulate T helper (Th) 2-polarized T-cell immunity in local airway tissue. Our studies have provided evidence that the developing immune system, especially the function of T cells, was altered following oral exposure to genistein at physiologically relevant concentrations in experimental animals. It is hypothesized that developmental exposure to genistein modulates the chromatin structure of Th2 cytokine genes (e.g.,Il-4 and Il-13)*

and, thus lead s to an increase in the hypersensitivity responses to respiratory allergen……Results of this investigation will provide a rational basis for understanding the health implications associated with the consumption of this compound. By identifying possible cytokines that are important at increasing risks, by looking at vulnerable periods in life, and by identifying (estrogenic_ environmental factors which through different mechanisms may be driving the immunological processes (amongst others) that lead to asthma, we will gain better insight with which to make informed decisions…..”

According to the results and conclusions of a large collection of published studies, irreversible adverse health effects caused to fetus and infants exposed to soy isoflavone plant-estrogens and antinutrients include: endocrine disruption, enzyme inhibition, essential mineral deficiencies, heavy metal contamination, plant-toxins, damage to developmental neural; pathways, amino acids, and transmitters, lack of important developmental sulfer-amino acids, as well as developmental cholesterol, cause oxidative damage, along with adverse health effects due to excessive sugars and corn syrup added.

Crisp Data Base, National Institute of Health reports under the title, “*Genistein Exacerbation of Asthma in Mice: that genistein, a soy isoflavone has been suggested to mediate its biological function mainly as an endocrine disruptor. There are concerns about the long-term effects of this compound on human health, especially that of infants and you children. There is an increase in the use of asthma or allergy drugs in young adults who have been fed soy formula during infancy. Our studies have provide evidence that the developing immune system, especially the function of T-cells (involving thyroid function) was altered following oral exposure to genistein at physiologically relevant concentrations in experimental animals.”*

Soy phytotoxicity is more recently discovered as transgenerational with potential damaging health effects accumulating with each generation.

SOY’S MULTIPLE ANTI-NUTRIENTS- DAMAGE HEALTH:

TRYPSIN (enzyme) INHIBITORS- Produced in the pancreas, trypsin is an essential enzyme necessary to digest protein**.** Soy inhibits trypsin enzymes therefore debilitating the body’s ability to digest proteins and cause intestinal obstructions. The boiling of soybeans may reduce, but not eliminate trypsin inhibitors. Particularly hard to digest, soy isolate protein powders as commonly used for soy-based infant formulas contain soybean inhibitors that block the action of trypsin enzymes and other enzymes necessary for protein digestion and absorption. Soy inhibition causes chronic deficiencies in amino acid uptake required to facilitate the production of protein for development and repair of cells and tissues and commonly causes: nausea, vomiting, bloating gastrointestinal pain, constipation, and other adverse effects. Cystic fibrosis is caused by a deficiency in transport of trypsin and other digestive enzymes. Inhibition of trypsin, such as caused by soy, is a known growth suppressor. Inhibition of trypsin is reported to cause extensive damage to the pancreas with greatest risks during fragile developmental time-frames.

1997, “Journal of Nutritional Science and Vitaminology” Y. Miyagi et al report, “*The results suggest that soybean products (after heating) retain 2.5-12.5% trypsin*

inhibitor activity of the whole soybean and that humans are consuming some active trypsin inhibitors in their daily lives."

When soy lecithin supplements were given throughout perinatal development the soy reduced activity in the cerebral cortex and according to "Brain Resource Bulletin," J.M. Bell et al report, "*….altered synaptic characteristics in a manner consistent with disturbances in the neural function."*

Soybean inhibition of important enzymes is reported to also cause enlargement and enhancement of pathological conditions of the pancreas. Blocking trypsin enzymes may inhibit growth by stimulating secretory activity of the pancreas with capabilities in the long term to cause pancreatic cell adenoma, a benign condition with potential to become malignant.

1986, "Advances in Experimental Medicine and Biology," MR Gumbmann et al report, "*The effects on the pancreas of chronic dietary exposure to defatted soy flour and soy protein isolate have been studied in 2 year feeding trials in rats. Emphasis was placed on detecting changes that might accompany low levels of dietary trypsin inhibitor (TI) as might be found in edible grade soy products…….The major pathological findings in the pancreas were nodular hyperplasia(NH) consisting of foci of hyperplastic acinar cells often grossly visible by 6 months, and the benign neoplastic lesion , acinar adenoma (AA)which developed more slowly. The incidence of both NH and AA was positively related to the TI content of the diet."*

FDA Federal Register, 1999, reports, "*Trypsin Inhibitors: Potential Effects on Pancreatic Function…..deleterious effects in the pancreas….responsible for hyperplasia and formation of nodules-seen in animal studies. Further, Leiner (author of published study, 1 of 4 listed) demonstrated that infusion of high levels of isolated trypsin inhibitor in humans can evoke this mechanism…."*

Based upon a variety of circumstances, the amount of trypsin inhibitors found in soybeans can vary as much as 5-fold, depending upon preparation of soybeans. Trypsin inhibitors can cause severe gastric distress and weight reduction that is repeatedly reported as caused by soy-based infant formulas. Soy is also reported to increase brain weight.

Inhibition of trypsin as caused by soy can lead to deficiencies in the absorption of essential vitamins and minerals necessary for body and brain development. Soybean causation of anti-trypsin activity as well as phytic acid content, forces inconsistencies in factory-added vitamins and minerals to soy food and beverages, which may result in too little or too much in the body systems of developing fetus, infants and children.

Besides the cause of growth inhibition, digestive distress, and many health problems, neurotoxicity as caused by soy plant-estrogens and thyroid disease, is compounded by the soy abundance of antinutrients of which each and all contribute to damaging brain functions. The majority of soy products marketed in the U.S.A. are manufactured from unfermented soybeans. Unfermented soybeans contain much larger quantities of plant- toxins than the fermented Asian soybeans resulting in higher levels of antinutrients that severely interfere with soy protein digestion, essential mineral absorption, and oxygenation of cells. Body growth and development, vital organ functions, and brain development are all reportedly at risk from soybean estrogenic endocrine disruption, and from the multitude of soybean antinutrients.

Soy plant-estrogens and soybean antinutrients actively interrupt and damage a number of brain cell functions. Studies also report that phytoestrogens have been shown to inhibit the oxidation of cells, which is implicated in a host of damaging effects to developing body and brain.

Autistic individuals experience greater numbers of abdominal disorders, seizures, and physiological disorders, of which can be caused by soy plant-estrogens and antinutrients.

Soy plant-estrogens and soy anti-nutrients are proven to vary significantly among soybean crops. Exposure to developing fetus, infants and children to soybean antinutrients are not entirely deactivated after processing or during ordinary cooking, resulting in an extensive list of ill-effects.

1995, National Center for Agricultural Utilization Research, "Journal of Nutrition" RL Anderson, WJ Wolf report, "*Compositional changes in trypsin inhibitors, phytic acid, saponins and isoflavones related to soybean processing: Soybeans are high in protein but also contain a number of minor constituents traditionally considered to be antinutritional factors. These included trypsin inhibitors, phytic acid, saponins and isoflavones. Soybean processing changes the content of these…..in various ways."*

Manufacturers of soy-based infant formulas, as all marketed soy products are not required to include content labeling for levels of active plant-estrogens and antinutrients, and no maximum levels for these overwhelming prenatal and postnatal developmental health hazards are determined.

It is also true that: adults, adolescents, children, infants, and fetus anatomically digest, metabolize, and eliminate soy plant-estrogen and antinutrients differently, proving that the damaging effects caused by active soy plant-estrogens and multiple antinutrients are unpredictable for all people.

PHYTIC ACID- binds and prevents essential mineral absorption. Phytates are present in plant foods, with greatest quantities found in soybeans and prevents the uptake of a large variety of necessary essential minerals most urgently important especially during brain and body development and to assure normal biological functions. The high levels of soy's phytic acid can block calcium, magnesium, iron, zinc, and other most important minerals that are essential for fetal and infant physiological and neurological development. Soy's phytic acid content causes high risk for essential mineral deficiencies.

Unlike any other marketed food, the soybean has a higher phytate (phytic acid) content than any other grain or legume studied, and industry attempts to eliminate phytic acid is impossible. While attempting to lower phytate levels through heat or chemical processing, sacrificing soybean nutrients is an end result.

1994, "Acta Paediatrica Supplement" B. Lonnerdal reports, "*The presence of phytic acid in soy formula presents a problem with regard to mineral and trace element bioavailability."*

Alarmingly, phytic acid (trypsin inhibitors, and soy-plant estrogen) soybean content among individual soybean plants and therefore soy products largely varies.

1997, "Plant Foods for Human Nutrition" T. Mebrahtu et al reports, "*A total of 17 vegetable-type soybean genotypes were planted in four-row plots arranged in a randomized complete block design……Each genotype was harvested at 4 developmental stages and evaluated for phytate content. Highly significant differences for phytate*

content were observed among the stages of harvest and genotypes……The significant differences observed for phytate content among genotypes indicated that genetic variation exists among the tested genotypes."

Rather than absorbed as nutrients, proteins and essential minerals bind to phytates and are consequently lost in waste elimination. Phytic acid blocks absorption and utilization of essential minerals while lowering bioavailability of: zinc, calcium, magnesium, copper, and iron, (and more) that are all critically important for normal pre- and postnatal body, bone, brain development and function.

Because of industry-known phytate problem, soy formulas can be dangerously over-supplemented with minerals, while studies report that supplementation can be insufficiently absorbed, and that supplementation may be in excess. Deficient as well as excessive essential mineral content can result in damaging individual health consequences particularly during fetal, infant, and child development..

The FDA, Federal Register 64 FR 57699 October 26, 1999, reveals, "*Comments raised concerns about the potential deleterious effect of soy protein and its phytate content on mineral status. Phytate, the salt of phytic acid or inositol hexaphoshate, is a natural plant constituent containing six negatively charged phosphate groups that can form strong complexes with divalent actions upon calcium, magnesium, iron, zinc, and copper. Concerns relative to soy have concentrated mainly on iron and zinc. One comment cited a study in which a soy protein-based purified diet induced iron deficiency in monkeys…..and two studies in humans. A comment raised concerns about the effect of soy protein on zinc status based on studies of absorption of zinc from soy infant formula ..…produce mild zinc deficiency. One comment provided additional information on the mechanism of phytate interference with zinc homeostasis. Phytate can remove zinc from the duodenum that is mainly derived from pancreatic secretions……expressing concern that high consumption of soy protein might exacerbate marginal zinc deficiency which is difficult to diagnose. Agency (FDA) recognizes that adequacy of iron and zinc status in largely plant-based diets is a legitimate concern. FDA finds that the evidence of potential adverse effects of soy protein on iron and zinc status is equivocal. Zinc absorption is more impaired with zinc deficiency, in contrast to the effect of low iron status, which enhances iron absorption."*

Soybean phytic acid greatly inhibit essential minerals that in test animals cause enlarged organs, particularly the pancreas and thyroid gland, and increased fatty acids in the liver among countless other health-risk factors. Phytic acid inhibition of essential minerals is detrimental to development, and especially deficiency of zinc, the brain mineral, is known as critically necessary for optimal brain and nervous system development and function.

2008, Department of Nutrition, Davis CA, B. Loonerdal reports, "*…some aspects of soy formula composition need further consideration. Protein level of soy formula is usually higher than that of milk-based formulae, partially because of differences in protein digestibility and partly because of differences in amino acid composition. The presence of phytic acid is soy formula presents a problem with regard to mineral and trace element bioavailability. Finally the high levels of manganese in soy formula present a potential problem in that manganese absorption and retention are high during infancy."*

LECTINS- are another soybean anti-nutrient that not only deteriorate the soybean protein quality, but interfere and block the absorption of important nutrients such as proteins that are crucial during child development. Lectin is nature's plant toxicity, a defense against the attack of pests and insects, and can be harmful to humans. The risks of acute toxicity from lectins are low but the prolonged exposure to low levels of lectins can be harmful to human health particularly that of fetus and infants exposed.

Lectins can influence and aggravate inflammatory disorders and intensify effects of autoimmune disorders. Lectins are not degraded by stomach acid, impair the release of digestive enzymes, and cause resistance to digestion.

Lectins can reduce natural killer cell activity that is one of the body's most important defenses against viruses and other invaders.

Lectins can stimulate polyamine overproduction also having negative effects. Excess polyamine production as caused by lectins may be the result of an effort to repair the damage to intestinal microvilli, as well as increase size of intestines, liver, and pancreas. Lectins initiate allergic reactions and have influences on bodily tissues. Depending upon gut microvilli lectins gain access into the blood and lymph system allowing lectins to enter into systemic circulation.

Lectins in the gut are more potent since the gut is more heavily glycosylated, or has more sugar receptors. Immature cells of infants and children are more glycosylated and therefore more susceptible to lectin attachment.

Individual genetic inheritance and antibodies can determine to what degree lectins can cause harm.

Soybean lectins exert amino acids involved in metal binding, dangerous for developing fetus and infants. Processing and cooking soybeans lessens but does not eliminate lectin content.

"Journal of Nutrition" reports, "*Rats fed the soy protein isolate-based diet absorbed significantly less iron than did control rats fed the casein-based diet. Our results suggest that a portion of the reduction in iron absorption in rats fed SPI may be due to lectins.*"

Iron is an essential mineral detrimental to fetal and infant body and brain development.

FDA Federal Register 1992, "*Plants are known to produce naturally a number of toxicants and anti-nutritional factors such as protease inhibitors hemolytic agents and neurotoxins which often serve the plant as natural defense compounds against pests or pathogens. Many legumes (including soybeans) contain relatively high levels of lectins (toxic in varying degrees, to gut, brain, etc) and cyanogenic glycosides (plant toxin releases cyanide)….that if not destroyed by cooking can cause severe nausea, vomiting and diarrhea. Levels of cyanogenic glycosides in some legumes can lead to death or chronic neurological disease…is these foods are eaten uncooked.*"

Journal, Biology of Neonate reports that cyanogenic agents as found in soybeans cause, "*Lower birth weights, reduced brain weights, and poor development.*"

Lectins and cyanogenic toxic compounds are present in soybean protein products in small quantities usually tolerated, metabolized, and eliminated from the adult body, while there remains no evidence of prenatal or postnatal tolerance. Fetal and infant soybean toxicity is not FDA investigated. Lectins and cyanogenic glycosides are proven to cause stomach pain, allergies, aggravate inflammatory and digestive disorders, cause

damage to the: brain, digestive system, joints, skin, and are reportedly involved in the causation of autoimmune diseases such as implicated in the onset of type 1diabetes.

HEMAGGLUTININS- can be added to the long list of soybean antinutrients. Unfermented soybeans as utilized in soy-based formulas and most soy products marketed in this country contain hemagglutinins, a clot promoting antinutrient that causes red blood cells to clump together. Hemagglutinins decrease the ability of red blood cells to properly absorb and distribute oxygen throughout the body. This deprivation of oxygen to cells as caused by soy antinutrients can contribute to oxygen deprivation that is extremely damaging to all cells and especially damaging during brain cell development.

It is well known in scientific literature that a number of soy antinutrients individually and together suppress growth, and cause a cascading of adverse health effects that leads to a variety of developmental disorders.

CYANOGENIC-glycosides release low levels of cyanide poison. Cyanide is well-known as poisonous to animals (livestock) and humans. Cyanogenic glycosides or cyanide levels in plants can vary depending upon season, soil, and environmental variations. Soybeans naturally contain varying levels of cyanogenic properties.

Study reported in, "Plant Physiology" concludes, "*In soybean, endogenous cyanide (levels) increased within 3 hours, increased again 6 hours after exposure (to pesticides) and continued to increase throughout the experimental period."*

Cyanide is rapidly distributed to all organs and tissues via the blood. Cyanide can accumulate in body cells, and found within 30 minutes after ingesting large doses in the stomach, brain, liver, kidneys and urine. Cyanide is usually rapidly detoxified in the efficient functioning adult body, however detoxification of cyanide in developing fetus when maternally exposed, or in infants exposed to soy-based infant formulas, or children exposed to soy foods is not FDA investigated. The public water supply often contains very low levels of cyanide, and when mixed with soy-based infant formula results in additional cyanide toxicity.

1983, "Journal of Agriculture, Food Chemistry," David H. Honig et al report, "*Determination of cyanide in soybean and soybean products,- These studies indicate that cyanogenic compounds are present in soybean protein products in very small amounts….In addition to hydrolytic or enzymatic release of cyanide from plant materials, overheating of the sample during a cyanide determination can also lead to cyanide formation (Rosenthaler, 1932)…..cyanide is rapidly converted to thiocyanate or other compounds which must also be accounted for to determine the actual amount ingested (Pettigrew and Fell, 1973). Small amounts of cyanide may act as a brake on cellular oxidative processes; however, consumption of foods containing large amounts of cyanogenic glycosides has resulted in death or has been associated with chronic neurological effects, (Montgomery 1980)."*

The vast majority of marketed soybeans are routinely awash with pesticides, and in fact the large majority of harvested soybeans are also Genetically Engineered (GE) with Roundup Ready gene implants……that are never found to be safe for human particularly infant consumption….to be discussed in detail later in this report.

SAPONINS- are another potential toxic anti-nutrient found in soybeans that are poorly absorbed in humans. Soy saponins damage the mucosal lining of the intestine that contributes to gastrointestinal disorders and abdominal pain. Another well-known toxic effect of saponins is when plant compounds such as soybeans are given in high dosages it

breaks-up red blood cells by disrupting their membranes, or having a hemolytic effect. Hemolytic effect is an excessive premature breakdown or destruction of red blood cells in the bloodstream that can result in abnormally low red blood cells or hemoglobin causing anemia and other damaging effects. Hemoglobin is the iron containing component of red blood cells that delivers oxygen to tissues throughout the body. Hemoglobin transports oxygen from the lungs to the rest of the body where it releases oxygen for cellular use. Saponins can damage oxygen transport to important areas of the body and brain particularly damaging during fetal and infant development.

2007, "Journal of Agriculture and Food Chemistry" reports, "*Soybean-induced enteritis (inflammation of small intestine) in Atlantic salmon is induced by soya saponins alone or by soya saponins in combination with other factors…..*"

Even "The Robert Abady Dog Food Co. LTD." warns, "*Soybeans and beet pulp are ingredients that are commonly used in dog feeds. Both contain saponins; substances that may be hazardous to your dog's health.*"

There is no FDA regulation to test soy products for soybean antinutrient contents, that fetus, infants, and children are consuming, of which antinutrients are capable of causing significant developmental adverse health effects.

NITRATES- are toxic components found in varying levels in plants such as soybeans, and can greatly increase during high temperature-drying processing. Plant nitrate levels rise most often during cooler temperatures, cloudy days or drought, also where heavy use of nitrate fertilizers are used. In regards to nitrate consumption, the lower the body weight the greater the chance is for toxicity. Acidic conditions of the stomach can encourage higher nitrate levels. Newborns often have higher acidic levels.

FDA CFSAN Database October 2006, reports, "*It is recognized that soy protein isolates constitute a currently minor source of nitrite as far a human exposure is concerned. The Select Committee ….concludes, It is essential that specifications for food grade soy protein isolates be established including provisions for acceptable levels of lysinoalanine, nitrite and nitrosamines.*"

FDA Federal Register 1999 reports, "*No data were submitted to document the current le*vels of nitrites or nitrosamines in soy protein isolates. *GRAS status of soy protein food ingredients, (soy-based formula is without GRAS status), ….did not include a thorough evaluation of the safety of potentially harmful components, e.g. lysinoalanine, nitrites, and nitrosamines, trypsin inhibitors, phytate, and isoflavones.*"

Health Action Network Society claim, "*Nitrates, potent carcinogens are formed during (soy) spray-drying, and toxic lysinoalanine is formed during alkaline processing.*"

1985, Institute of Food Technologists, DC Havery, T Fazio report, "*human exposure to nitrosamines from foods- The U.S. Food and Drug Administration's activities in cooperating with industry to reduce carcinogenic nitrosamine levels in various area, (bacon, beer, malt, nonfat dry milk, soy protein foods and rubber nipples for infants) are reviewed, and trends observed in nitrosamine levels over the years are described. This review acknowledges the need for continued cooperative effects between universities, food manufacturers and producers, and the U.S. government.*"

Dr. Richard Brouse, Certified nutritional Advisor reports, "*Studies have shown decreased levels of food nutrients and increased levels of nitrates in chemically fertilized crops……In particular with soybeans, a powerful and deadly weed spray called Round Up is usually used.*"

Majority of soybeans are genetically modified with inserted Round Up Ready gene….no one is certain about the ill-effects caused by eating RR genes, so that soybean plants can survive heavy weed spraying with Round Up.

FURAN- It is reported that currently the FDA is examining health concerns related to levels of the toxin furan found in soy protein isolate (infant formula), hydrolyzed soy protein, and other foods.

2004, Environment News Service reports, "*The FDA has announced that it will embark on a thorough scientific assessment of the health significance of very low levels of furan- a chemical produced though the heating process….. FDA is soliciting information on the best available and most-up-to-date science on furan including human exposure, why furan forms in certain foods, and effect on furan on humans at the low levels found in food. The presence of furan is a potential concern because based ona animal tests, furan is tested in the Department of Health and Human Services Report on Carcinogens and is considered possibly carcinogenic to humans by the International Agency for Research on Cancer. Some animal data suggests that high levels of furan exposure might have a carcinogenic effect in humans, but its true effects in humans, especially at very low levels, (and to fetus and infants exposed) are not known……FDA scientists has revealed that very low levels of furan are found in a wider range of foods than previously suspected. FDA will decide on the appropriate next steps, which may include……potential strategies to reduce furan levels, and toxicology studies to address mechanisms of toxicity and dose response."*

Endocrine disrupting soy plant-estrogens along with multitude of soy antinutrients separately and especially in combination are documented as multiple contributing factors to dangerous health effects: low birth weight, (causing a host of damaging effects), hyperactivity, physio- and neuro-toxicity- leading to the cause of irreversible learning disabilities, attention deficit disorders, behavioral and emotional disorders, etc, blocks the absorption of important vitamins and essential minerals, increases insulin levels- related to infant/childhood diabetes and related diseases, suppresses the immune system- increasing a variety health risks and diseases related to autoimmune diseases, encourages hypertension and heart disease, increases risk of childhood obesity and related diseases, causation of epileptic seizures, and causation of gastrointestinal distress.

CORN SYRUP and SUGAR- Soybeans are horribly bitter and therefore soy products commonly contain outrageous levels of sugars *and* corn syrup, often more than what is found in a can of soda pop. Ingredient labels on soy products, and focusing on soy-based infant formulas confirm contents as nearly 50% corn syrup (sometimes more), with additional sugar added. Read the soy label sweetener ingredients for yourself.

For the long-term, and several times each day, infants are dangerously fed high levels of soy-based plant-estrogen infant formulas containing highest levels of sugars and corn syrup. Sugars and corn syrup added to soy-based infant formulas and soy food products at such extreme volumes are proven to be anatomically and neurologically health damaging especially to developing fetus, infants, and children.

High-fructose corn syrup has undergone enzymatic processing to convert glucose into fructose. Fructose and sucrose are recognized by endocrinologists particularly Dr. Robert Lustig as the "true poison" of which are found in increasing levels throughout soy products. Infant formulas are commonly overdosed with sugar and corn syrup sweeteners while dangerously consumed in high volumes by infants that encourages

future desperation for more sugars known to cause neurological disorders, obesity, diabetes type II, and in fact multiple diseases. The label stating "corn syrup solid" is industry disguise for fructose, glucose, dextrose, or sucrose. Fructose and sucrose being the most health-damaging, as are all sugars.

1987, "Anesthesiology" WL Lanier et al report, "*The effects of dextrose (glucose) infusion and head position on neurologic outcome after complete cerebral ischemia in primates……Dextrose infusion resulted in significantly greater cerebral injury at 96 hours postischemia when comparing both neurologic and histopathology scores. Specifically, dextrose administration resulted in the greatest injury to the insular cortex, thalamus, Purkinje cells, and substantia nigra. These infusions produced increases in blood glucose……and increases in brain glucose……"*

Certainly there are hundreds of studies confirming sugar's toxic effects. No infant/child disorder or (irreversible) disease can be excluded from the extensive list of adverse health risks that endocrine disrupting soy phytoestrogens, soy anti-nutrients, soy sugars, soy corn syrup are extensively capable of causing.

ADIPONECTIN DAMAGE- is a protein hormone produced and secreted exclusively by adipocytes (fat cells) that regulates the metabolism of lipids and glucose. Adiponectin modulates a number of metabolic processes, including fatty acid catabolism, glucose regulation, influences the body's response to insulin, and also has anti-inflammatory effects on the cells lining the walls of blood vessels. Adiponectin exerts some of its weight reduction effects via the brain.

2006, "Wei Sheng Yan Jin," SW Chen et al report, "*Effects of soy isoflavone on gene expression of adiponectin in insulin-resistance rats induced by high-fat and high-sugar diet- Conclusion:……soy isoflavone may decrease adipose deposition, increase serum adiponectin level……..".*

2008, "Menopause," C Charles, et al report, "*Results:….a small but significant increase in serum adiponectin levels in the isoflavone group compared with the placebo group."*

2005, "Current Diabetes Reports," S Maxaki-Tovi et al report, "*Adiponectin and human pregnancy- …adiponectin, a modulator of insulin resistance, is subject to investigation during gestation. Furthermore, conditions associated with increased insulin resistance, such as gestational diabetes and preeclampsia, may be influenced by this hormone. Adiponectin, a key modulator of insulin action and glucose metabolism, both known to regulate fetal growth, is a plausible candidate for regulation of intrauterine fetal development."*

2008, "AJP- Lung Cellular Molecular Physiology," SE Wert reports, "*…serum levels of adiponectin appear to increase in autoimmune diseases and/or chronic inflammatory conditions that are unrelated to obesity, such as rheumatoid arthritis, systemic lupus erythrematosis, type 1 diabetes, and Crohn's disease. In these diseases, increased serum levels of adiponectin are correlated with increased serum levels of IL-6, CRP, TNF-a, and leptin. Serum levels of adiponectin are also increased in patients with chronic heart failure, end stage renal disease, and anorexia nervosa, all diseases associated with cachoeira, or body wasting. Likewise, long-term caloric restriction in adult mice increases circulating adiponectin and insulin sensitivity. In a Japanese study….serum levels of adiponectin were elevated in both groups and were correlated with increased serum TNF-a and IL-6 levels as well as with severity of lung disease*

2006, "Endocrine," H Raff, and ED Bruder report, "*Adiponectin and Resistin in the Neonatal Rat- We also conclude that adiponenctin is increased during hypoxia in response to decrease in the sensitivity to insulin. Increases in adiponectin are thought to increase insulin sensitivity. The findings of growth retardation and increased adiponectin in this study, and insulin resistance in previous experiments….are similar to a variety of other pathophysiological states including prenatal growth restriction, and anorexia or bulimia nervosa. This initial study will hopefully lead to a more complete evaluation of the control of adiponectin release……"*

SOY AND DIABETES CONNECTIONS- Dr. William Sears reports, "*……..corn syrup should be avoided……this artificial sweetener is anything but healthy. Too much HFCS (high fructose corn syrup) can lead to serious health problems. New research suggests that overconsumption of HFCS can lead to type II diabetes and heart disease. It can increase the blood level of triglycerides…..and contribute to cardiovascular disease…..overconsumption is a real risk. What you feed your children when they are young will effect their eating habits….and their health….for the rest of their life. Artificial sweeteners in infant formulas can only increase the intensity of the sweet tooth that babies are already born with. In selecting a formula….stick to those that contain lactose, not fructose……"*

2006, "Diabetes" D Liu et al report, "*Genistein acutely stimulates insulin secretion in pancreatic beta-cells through a cAMP-dependent protein kinase pathway- Here, we present evidence that genistein increases rapid glucose-stimulated insulin secretion (GSIS) in both insulin-secreting cell lines (INS-1 and MIN6) and mouse pancreatic islets. Genistein elicited significant effects at a concentration as low as 10 nmol/l with a maximal effect at5 micromol/l. consistent with its effect on GSIS, genistein increases intracellular cAMP and activates protein kinase A (PKA) in both cell lines and islets……The induced cAMP by genistein, at physiological concentrations, may result primarily from enhanced adenylate cyclase activity……the insulinotropic effect of genistein is primarily mediated through PKA. These findings demonstrated that genistein directly acts on pancreatic beta-cells, leading to activation of the cAMP/PKA signaling cascade to exert an insulinotropic effect, thereby providing a novel role of soy isoflavones in the regulations of insulin secretion."*

2003, Diabetes Research and Clinical Practice in China reports, "*Analyses showed soy milk formula consumption at 4-12 months of age was associated with a twofold higher risk of type 1 diabetes."*

The American Academy of Pediatrics (AAP) also reports, "*Results of studies in animal models using a diabetes-prone rat suggested an increased frequency of diabetes when ingesting a soybean meal diet."*

2008 "Nature", L. Wen et al report, "*Type 1 diabetes is a debilitating autoimmune disease that results from T-cell–mediated destruction of insulin producing B- cells."*

Soy plant estrogens are known to damage T-cells that damage insulin producing B-cells.

Connecticut Center for Health reports, "C*orn syrup and other refined foods may be partly responsible for the huge increase in type 2 diabetes in the U.S. People are getting more and more of their carbs in the form of processed grains and sugars- most of all, in corn syrup. It is hard to ignore the fact that 20G% of our carbohydrates are*

coming from corn syrup…..Many studies have linked a high intake of refined carbs….with a high 'glycemic index' to the development of diabetes."

It is reported that refined carbohydrates lead to Alzheimer's disease and that prolonged and excessive insulin and insulin-like growth factor signaling is reported to increase brain cell damage.

Published study by Fort et al, as reported in the 2006 NTP CERHR report: "Soy Formula" states, *"The feeding histories of the diabetic children were compared to those of a control group consisting of 194 non-diabetic siblings and an additional 95 non-diabetic friend living in the same area. Almost twice as many diabetic children had been fed soy formulas compared to controls. The authors postulated that diabetic infants might have a higher incidence of gastrointestinal alterations…."*

2006, NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) reports, *"There is a significant association between adult overweight and having been fed a soy formula as an infant. Gastrointestinal effects- infants with soy protein induced intestinal villous atrophy (wasting away of intestinal villi, causing the lack of absorption of nutrients and water). Soy consumption was an independent risk factor for peanut allergy. Preterm infants on soy formula gained less weight….had lower serum phosphorus and higher serum alkaline phosphatase. Bone mineral density and plasma zinc higher in breast-fed than soy formula-fed infants at 4 months of age. From birth to 4.5 months of age immunoglobulins were lower in low-protein soy group than other groups. Soy formula-fed infants had more episodes of infection than breast-fed children."*

1986, "Journal of the American College of Nutrition," P Fort et al reports "(there are) *Twice as many diabetic children received soy containing formula in infancy as compared to control children. The incidence of positive thyroid antibodies as two and one half times higher in (soy) formula-fed diabetic children than in breast-fed ones."*

SOY DAMAGE TO ESSENTIAL MINERALS:

Balanced trace elements or essential minerals are important for all people, while most important for proper transmission of nerve impulses between brain cells for optimal prenatal and postnatal brain function development. A deficiency of essential nutrients can modify genetic expression.

Breast milk (from non-soy product consuming mothers) is the best source for balanced mineral levels that are most important for the developing immune system, nervous system, vital organs, blood-sugar levels, and best infant health.

According to studies, concentrations of essential elements in soy infant formulas can vary considerably. Essential mineral whether deficient or in excess are recognized as causing health problems especially during fetal, infant, and child development.

Soybean phytic acid and other soy antinutrients have negative effects on essential mineral contents: metabolism, and absorption thus risking essential mineral deficiencies. Essential mineral supplementation of soy formulas does not always result in higher bioavailability compared to non-supplemented formulas, while on the other hand supplementation might result in excessive mineral levels. Amounts of soybean phytic acid and antinutrients that severely block essential mineral absorption can largely vary depending upon soil, fertilizer, processing, fortifications, storage containers, and preparation. Even in low concentrations phytic acid and antinutrients are proven to

inhibit essential mineral levels resulting in damaging health effects to the most vulnerable fetus, infants, and children.

The book, "Handbook of Developmental Cognitive Neuroscience" reports, "*Many minerals are considered essential for brain development but deficiencies in these nutrients will lead to abnormal brain function mostly through alternating neuronal electrical function.*"

Deficient mineral/vitamin content or excessive mineral/vitamin content of soy-based infant formulas are proven to cause cellular neuronal dysfunction, particularly during fetal and infant brain development.

ZINC Deficiency- Zinc is a nutrient required for RNA synthesis. Zinc is well recognized as especially important for pathological cerebral cortex development and function. Zinc plays an important role in the transmission of nerve impulses between brain cells. Adequate levels of zinc (and many essential minerals) are sorely compromised due to soybean phytic acid and antinutrient contents, as contained in soy-based formulas. Added zinc supplementation, when in excess interferes with copper absorption, along other damaging effects.

Bioavailable zinc is reportedly involved in over 300 enzymatic activities, involving the brain, nervous system, immune system, production of white blood cells, pancreatic release of insulin, production of sperm, fetal development, and protection from heavy metal poisoning. Zinc deficiency during pregnancy and lactation has been shown to be related to many congenital abnormalities of the nervous system in offspring.

Childhood or infant deficiencies in zinc have been associated with lower learning abilities, lethargy, mental retardation, growth inhibition, skin and hair abnormalities, compromised function of the immune system, diarrhea, and multiple other problems.

Zinc containing neurons have evolved into a complex and elaborate associational network that interconnects most of the cerebral cortex and limbic structures. Studies report that zinc deficiency may contribute to brain cell death as seen in dementia.

Department of Nutrition, Davis University, "*Results suggest that the low bioavailability of zinc from soy formula is a function of its phytate concentration and can be overcome by removal of phytate.*"

Most manufacturers of soy products in this country do not remove phytates, and it is repeatedly proven that phytates can not be entirely removed from soy products, or from soy-based formulas. The addition of zinc does not always remedy this soy problem. It is reported that to provide equivalent amounts of available zinc the total zinc content of soy-based formula would need to be at least 20% higher than milk formulas.

Federal Register 64 FDA 57699 October 1999, FDA discuss, "*Increased intake of soy protein could lead to zinc deficiency.*"

A 1982 study published in "Biological Psychiatry" reports, "*Insufficient levels of zinc have been associated with lowered learning ability, apathy, lethargy, and mental retardation.*"

1987 "Archives of Pediatrics & Adolescent Medicine" G. Chan et al report, "*We studies 40 healthy term infants who received a soy-based formula. Ten exclusively breast-fed infants served as controls…..at 4 months of age, the breast-fed group had a higher plasma zinc level than both (soy) formula-fed groups at 2 and 4 months of age, and had higher bone mineral content and bone density.*"

Sept. 2008 "Journal of Nutrition" confirms, *"Levels of phytic acid approaching 2% caused very poor growth of rats……..and zinc absorption could not be assessed. It appears that a calcium depression of zinc absorption can occur in the presence of a high level of phytic acid. The percentage of zinc absorption was consistently less from the soy protein diets than from casein (protein found in milk) diets at each level of calcium."*

Zinc deficiency is reported to potentially cause increased absorption of aluminum, a dangerous heavy metal known to be neuro-toxic.

"Journal of Nutrition" B. Momcilovic et al report, "*The lower availability of the total zinc in the soy protein-based formula could be attributed to the formation of highly insoluble zinc-calcium phytate complexes…..it is necessary that sufficient zinc be added to soy-based formula so that the total zinc content is at least 20% more than the total amount of zinc in milk-based formula."*

Soy also inhibits a zinc-containing enzyme known as carbonic anhydrase which helps transport gases across the intestinal wall, resulting in abdominal discomfort and excessive flatulence. Soy is highly capable of causing varying levels of gastrointestinal disorders and abdominal distress.

Researchers testing infant formula found that soy causes negative zinc balance in every infant to whom it was given, even when diets were supplemented with zinc. Zinc is poorly absorbed from soy formula as evidence by reduced growth rate in soy fed infants. Zinc is of crucial importance during brain development.

2008, "Food Chemistry" A Ikem et al report, "*….estimated daily intakes of elements were determined….Some (infant formula) brands had low nutritional contents when compared with recommended dietary allowances and dietary reference intakes for use in North America. Only brands ….(4 from UK, and 3 from US out of 17 infant formula brands) 13, 16, and 17 met the dietary reference intakes for zinc."*

FLUORIDE- Concentrations of fluoride found in soy-based formulas can also contribute to zinc deficiency. Fluoride content is reported to vary significantly between batches. When mixed with fluoridated water, zinc deficiency is increased even more than that caused by soy-based formulas. Average fluoride content of dairy milk is 0.030ppm, while soy milk contains as much as 0.491ppm. Excessive fluoride exposure to children is reported to cause abnormalities: gastrointestinal, cardiovascular, and neurological.

Department of Biological Sciences in Brazil, *"Some brands of bottled water usually marketed for infants and used to dilute infant formulas may increase fluoride concentrations beyond recommended levels…..."*

IODINE DEFICIENCY- Soy is overwhelmingly documented as a goitrogen confirming that soy-estrogens damage the thyroid. Soy reduces thyroid functions by blocking the thyroid enzyme peroxidase. Deficient thyroid peroxidase can cause iodine deficiency that is responsible for irreversible abnormal brain development and physical defects such as growth impairment, or possibly lead to increased risk of infant mortality. Soy causation of deficient iodine during pregnancy may cause fetal death.

CALCIUM OVERDOSE- Calcium is a most abundant essential metal essential for living organisms particularly in cell physiology where movement of the calcium ion is a signal for many cellular processes. In brain cells, calcium selective ion channels are important for synaptic transmission through the release of neurotransmitters and specialized junctions of which neurons signal to other neurons, muscles, or glands. Each time brain cells fire, more calcium enters the cell.

Studies report that estrogens including soy plant-estrogens increase calcium that damages brain cell signaling. Symptoms caused by excess calcium can affect every major organ in the body. Hypercalcemia can cause: nausea, headache, rapid heart rate, heart dysfunction, kidney damage, stiff and swollen joints, mental confusion, slurred speech, personality changes, lethargy, coma, and death.

2007, "Journal of Biomedical Science," U. Ying et al report, "*Both genistein and daidzein at 50 uM, increased the intracellular calcium level (Ca2+) significantly….*"

The thyroid gland produces calcitonin hormone that regulates the amount of calcium in the blood, the soy estrogenic and antinutrient components cause thyroid damage (hypothyroidism) that disrupts calcitonin production, proving multiple ways that another soy plant-estrogens cause irregularities in calcium circulation, of which normal balance is crucial during body and brain development. These estrogenic alterations causing calcium homeostasis as also caused by soy plant-estrogens is expected to be neurotoxic.

Ca2+ and cAMP signaling are important second messengers that regulate multiple cellular processes important in many biological processes and intracellular signal transduction, such as transferring the effects of hormones. There is highly coordinated interplay between Ca2+ and cAMP signaling that are abnormally manipulated by soy plant-estrogens.

1999 "Biochemistry Pharmacology" YH Gao et al report, *"The present study demonstrated that genistein has a potent inhibitory effect on osteoclast-like cell formation in mouse marrow culture. The inhibitory action of genistein may be involved in cyclic AMP (cAMP) signaling."*

Dr. R. Brouse, a nutritional advisor reports- "*Some negative reports about soy say that soy powders are Very Acidic and cause bone loss because it causes calcium to be drawn from the bones!!!! Therefore, adequate calcium must be added to cause the powder to be neutral again…..Many (soy) protein powder manufacturers do not add any or enough calcium."*

1993, "Neuroreport," C. Batini et al report, "*Excessive intracellular calcium in neurons is thought to underlie the pathophysiology of several neurodegenerative diseases. …..calbindin containing neurons can regulate their Ca2+ buffering capacity…."*

2002, European Journal Histochemistry, N. Tolosa de Talamoni et al report, "*…..the results suggest that Ca2+ homeostasis in the retina is well regulated, probably to avoid excessive accumulation of Ca2+ which often leads to neurodegeneration."*

Genistein and daidzein are proven to cause excessive intracellular calcium in neurons, causing excessive cholecystokinin (neuroendocrine peptide), as well as overexpression of calbindin of which each and all reportedly lead to a variety of damaging health effects including neurotoxicity.

CALBINDIN D28k: is a rapid endogenous calcium-buffering protein that is a neuroprotective calcium–binding protein by preventing cellular toxic calcium levels that may otherwise lead to neurodegeneration. Studies report that at least four types of Ca2+ signals are affected by calbindin deficiency or calbindin overexposure. Calbindin has a distinct distribution in the brain and sensory system and is abundant in specific neuronal cell types. Calcium toxicity remains a central focus of ischemic brain injury, while calbindin proteins can buffer excessive intracellular calcium and maintain calcium

homeostasis. Calbindin affects a variety of neuronal signaling processes, and it is known that overexpression of calbindin-D28k can promote neuronal injury.

Soy plant-estrogens, particularly genistein is found to cause overexpression or an overdose of calbindin D28k that contributes to the cause of deleterious neurological and motor effects to include visual disconnection.

2004, Toxicological Sciences, FDA, Division of Neurotoxicology, A. Scallet et al report, "*The adult rat brain develops through an interplay of neuronal proliferation and programmed cell death. Endocrine disrupters (EDs) may also alter brain development by mimicry or modulation of endogenous hormone systems. Two EDs that have recently been studied in protocols involving lifespan exposures are the phytoestrogen genistein and the weakly estrogenic compound para-nonylphenol used in production of surfactants and plastics. Both genistein and nonylphenol were found to increase the volume of calbindin D28k-sexually dimorphic nucleus in male rats."*

2004, "Hippocampus," T. C. Dumas et al report, *"Overexpression of Calbindin D28k in dentate gyrus granule cells alters mossy fiber presynaptic function and impairs hippocampal-dependent memory- Calcium is a key signaling ion for induction of synaptic plasticity processes that are believed to influence cognition. We used herpes simplex amplicons to overexpress calbindin D28k selectively in dentate gyrus granule cells. Calbindin D28k overexpression increased mossy fiber excitatory postsynaptic potentials and reduced paired-pulse facilitation…..reduced long-term potentiation, caused a frequency –dependent inhibition of post titanic potentiation and impaired spatial navigation. Thus, increasing calibindin D28k levels selectively in the dentate gyrus disrupts mossy fiber presynaptic function and impairs spatial cognition. The results demonstrate the power of gene delivery in the study of neural substrates of learning and memory and suggest that mossy fiber synaptic plasticity is critical for long-term spatial memory."*

Mossy fiber axon terminals of the hippocampal dentate gyrus granule cells are reportedly involved in the cause of seizures, epilepsy, and multiple brain damaging effects as caused by overexpression of calbindin D28k of which soy plant-estrogens are stated as capable of causing calbindin overexpression, particularly damaging during fetal and infant brain development.

2001, "Biochemistry and Biophysical Research Communications," WS Choi et al report, "*Overexpression of calbindin-D28k induces neurite outgrowth in dopaminergic neuronal cells via activation of p38 MAPK- Overexpression of calbindin-D28K in MN9D cells resulted in significant increases in the number of neuritis, the length of primary neuritis, and the total extent of neuritis. This robust neurite outgrowth occurred without cessation of cell division…..this morphological differentiation was accompanied by increased expression of such markers of maturation as the synaptosomal protein SNAP-25. During calbindin D28k-evoked neurite outgrowth in MN9D cells, phosphorylation of p38mitogen-activated protein kinase (MAPK) dramatically increased…..These data support an idea that calbindin-D28k and its associated p38 signaling pathway play a role in dopaminergic neuronal differentiation."*

Cell line MN9D is a fusion of embryonic ventral mesencephalic and neuroblastoma cells, extensively used as a model of dopamine neurons because it expresses tyrosine hydroxylase and synthesizes and releases dopamine. SNAP-25 is a membrane bound protein contributing to the formation of the exocytotic fusion complex

in neurons. Subsequent studies have suggested that at least some of the SNAP-25 gene mutations predispose humans to ADHD. MAPK are specific protein kinases that respond to extracellular stimuli and regulate various cellular activities, such as gene expression, mitosis, differentiation, and cell survival or cell death.

1998 "Neuroscience" GJ Klapstein et al report, "C*ytoplasmic calcium-binding proteins, (calbindin-D28K) are thought to shield neurons against damage induced by excessive Ca2+ elevations. ….. ….a mobile cellular Ca2+ buffer (calbindin) could just as well promote neuronal injury by facilitating the rapid dispersion of Ca2+ throughout the cytoplasm. Our findings provide direct experimental evidence against a neuroprotective role for calbindin-D28k."*

2008, "Proceedings of the National Academy of Sciences," R. Morgan and I. Soltesz report, "*Nonrandom connectivity of the epileptic dentate gyrus predicts a major role for neuronal hubs in seizures- Our findings demonstrate the functional relevance of nonrandom microcircuits in epileptic brain networks and they provide a mechanism that could explain the role of granule cells with hilar basal dendrites in contributing to hyperexcitability in the pathological dentate gyrus."*

2004, "Journal of Neurophysiology" V. Santhakumar et al report, "*Mossy cell loss and mossy fiber sprouting are two characteristic consequences of repeated seizure and head trauma. (is it) the loss of mossy cells or the sprouting of mossy fibers that leads to dentate hyperexcitability…… …even weak mossy fiber sprouting resulted in the spread of seizure-like activity to the adjacent model hippocampal laminae……the spatially restricted, lamellar distribution of the sprouted mossy fiber contacts reported in in-vivo studies was an important factor in sustaining seizure-like activity in the network…… These results indicate the crucial role of mossy fiber sprouting even in situation where there is only relatively weak mossy fiber sprouting……"*

2001, "Neuroscience", E. Aronica et al report, "*Excitotoxicity, which is mediated by the excessive activation of glutamate receptors has been implicated in the pathogenesis of amyotrophic lateral sclerosis (ALS). With respect to specific neuronal populations, metabotropic glutamate receptors (mGluRs) GlR2/3 and mGluR5 appeared to be most frequently expressed in calbindin-containing and calretinin-containing cells respectively. In particular, metabotropic glutamate receptor expression was increased in reactive glial cells in both gray and white matter of ALS spinal cord. Upregulation of mGluRs in reactive astrocytes may represent a critical mechanism for modulation of glial function and changes in glial-neuronal communication in the course of neurodegenerative diseases."*

2003, "Journal of Neuroscience" J. Barski et al report, "*Calbindin in Cerebellar Purkinje Cells Is a Critical Determinant of the Precision of Motor Coordination- Long-term depression (LTD)of Purkinje cell-parallel fiber synaptic transmission is a critical determinant of normal cerebellar function. Impairment of LTD through……disruption of the metabotropic glutamate receptor IP3-calcium signaling cascade in mutant mice results in severe deficits of both synaptic transmission and cerebellar motor control. Our results reveal a unique role of Purkinje cell calbindin in a specific form of motor control and suggest that rapid calcium buffering may directly control behaviorally relevant neuronal signal integration. Furthermore, overexpression or deletion of calbindin in hippocampal neurons resulted in the selective modification of posttetanic potentiation presumably by changing the global Ca2+ concentration increase in presynaptic*

terminals necessary for mediating potentiation of neurotransmitter release on a second to minute time scale…..a wide range of cellular actions involving rapid Ca2+ signaling may contribute to the behavioural deficits. Animals with reduced Purkinje cell activity are severely impaired in short-term but much less so in long-term adaptability of eye movements. It needs to be stressed that rapid Ca2+ signaling …in association with action potential firing, is a general property of all central neurons. Therefore, the impact of our results may extend far beyond Purkinje cell and cerebellar function, indicating a widespread role of rapid Ca2+ signaling in neuron computation."

2008, Department of Pharmacological and Physiological Sciences, P.S. Chard et al, *"Regulation of excitatory transmission at hippocampal synapses by calbindin D28k-….this protein has a profound effect on synaptic plasticity. In particular, we show that that overexpression of calbindin D28k suppresses posttetanic potentiations."*

Tetanic potentiations consist of a high-regency sequence of individual stimulations of a neuron and long-lasting improvement in communications between two neurons that cause an increase in transmitter release, or post-tetanic potentiation, a presynaptic event caused by calcium influx, resulting in an important neurochemical foundation for learning and memory.

Overexpression of Calbindin D28k as caused by plant-estrogens, suppress these important neuronal connections and actions.

2000, "Journal of Neurobiology" D. Brager et al, report, "*Developmental sex differences in calbindin-D28k….immunoreactivity in the neonatal rat hypothalamus. The sex differences observed in calcium binding proteins (calbindin D28k) parallel our previously observed sex differences in excitatory Y-aminobutyric acid and glutamate early in development and may be related to mechanisms of sexual differentiation of the brain."*

Calbindin is highly expressed in the Purkinje cells (GABAergic neurons) of the cerebellar cortex. Study results show that calbindin immunoreativity caused by excitatory glutamate encourages neurotoxicity by altering calcium homeostasis.

2005, "Progress in Brain Research" JE Slemmer et al report, "*Because they (Purkinje cells PCs) represent the only output cell of the cerebellar cortex, they play a vital role in the normal function of the cerebellum. Interestingly, PCs are highly susceptible to a variety of pathological conditions that may involve glutamate-mediated 'excitotoxicity', a term coined to describe an excessive release of glutamate and a subsequent over-activation of excitatory amino acid (NMDA, AMPA, and Kainite) receptors. Purkinje cells possess various calcium-binding proteins such as calbindin-D28k and parvalbumin, and glutamate transporters, in order to prevent glutamate from exerting deleterious effects. Bergmann glia are gaining recognition as key players in the clearance of extracellular* glutamate….."

1997, "Proceedings of the National Academy of Sciences USA," D. Reddy et al report, "*Transfection and overexpression of the calcium binding protein calbindin-D28k results in a stimulatory effect on insulin synthesis in a rat B cell line (RIN 1046-38)-Calbindin D28k is present in the highest concentrations in the mammalian kidney, brain and pancreas. Various functions have been proposed for calbindin based on its calcium-binding properties……protection of neurons against excitatory calcium toxicity, and action as a mobile calcium buffer restricting evoked calcium signals in nerve synapses and hair cells. Calbindin-D28k is also present in pancreatic B cells, but its function in*

these cells is not known. In cells transfected with calbindin, there was a marked increase in the expression of insulin mRNA. Besides an increase in insulin mRNA, calbindin overexpression was also associated with an increase in insulin content and release. These studies provide the first direct evidence (to our knowledge) for a role for calbindin in B cell function."

2005, "The Federation of American Societies for Experimental Biology," JH Kim et al report, "*Overexpression of calbindin-D28k in hippocampal progenitor cells increases neuronal differentiation- Excitatory stimuli are known to be a potent regulator for induction of neuronal differentiation. Calbindin- D28k buffers intracellular Ca2+ and modifies synaptic functions in neurons. ……we demonstrated that calbindin-D28k at physiologically relevant level promoted neuronal differentiation and neurite outgrowth. Increase of neuronal differentiation by calbindin- D28k overexpression was concurrent with the expression of basic helix-loop-helix transcriptional factors (bHLH) transcriptional factors…..…… KN-62, a highly specific CaMKII inhibitor, blocked the up-regulation of proneural bHLH genes, p-CaMKII and pSer(336)NeuroD. Calbindin-D28k appeared to facilitate neuronal differentiation of both fetal and adult hippocampal progenitor cells. Together, these findings establish the novel calbindin-regulated function of CaMKII and NeuroD in control of neuronal differentiation and neurite outgrowth."*

CaMKII plays a critical role in preserving memories throughout life, NeuroD is a helix-loop-helix (important in development or cell activity) transcription factor expressed in certain parts of the brain, in the beta pancreatic cells and the enteroendocrine cells. It is involved in the differentiation of nervous system and development of pancreas….and controls the transcription of a variety of genes. Soy plant-estrogens cause overexpression of calbindin resulting in a host of damaging neurotoxic effects.

2007, "Journal of Neurotrauma" M. Folkerts et al report, "*Traumatic brain injury can dramatically increase levels of intracellular calcium (Ca2+). One consequence of increased Ca2+ would be altered activity and function of calcium-regulated proteins, including calcium-calmodulin-dependent protein kinase II (CaMKII) which is autophosphorylated…..These results demonstrate that traumatic brain injury alters the autophosphorylation state of CaMKII, an important neuronal regulator of critical cell functions, including enzyme activities, cell structure, gene expression, and neuronal plasticity, and provide a molecular mechanism that is likely to contribute to cell injury and impaired plasticity after traumatic brain injury."*

There are countless ways that soy plant-estrogens as well as soy antinutrients encourage neurotoxicity that is most damaging to fetus, infants and fetus exposed.

IRON Deficiency- Soybean phytic acid is reported to encourage iron deficiency, another important essential mineral critical to neurological development.

1994, "Journal of Nutrition" NS Shaw et al report, "*We conclude that a vegetarian diet that is rich in soybean products and restricted in animal foods is limited in bioavailable iron and is not adequate for maintaining iron balance in men and women."*

Iron forms hemoglobin which carries oxygen through the blood to rapidly growing cells and tissues throughout the body and brain that is especially crucial during pre- and postnatal body and brain development. Iron is required for enzymes that regulate central nervous system cell division, dopamine synthesis, myelination, and

oxidative metabolism. The effects of iron deficiency on the growing brain are well documented. Too little dietary iron could result in anemia, weakness, muscle fatigue, abnormal gastrointestinal, motility, irritability, and listlessness. Iron is essential for proper mental development, and the reduction of cognitive ability due to iron insufficiency can not be reversed when iron levels are normalized again.

Bio-Medicine reports, *"A study published in Archives of Pediatrics and Adolescent Medicine- Findings showed that the lower the levels of iron the worse are the learning, memory and thinking functions."*

1995, "Journal of Nutrition" NS Shaw et al report, *"A vegetarian diet rich in soybean products compromises iron status in young students. …50% prevalence of iron deficiency and 30% prevalence of anemia among young adult female vegetarians who consumed soy frequently."*

1981, "American Journal of Clinical Nutrition," JD Cook et al report, "*The soy products tested in this study have a pronounced inhibitory effect on the absorption of nonheme iron."*

1982, "American Journal of Clinical Nutrition," L Hallberg and L Rossander report, "*…half of the meat protein was substituted with various soy protein products. The reduction of the meat content……reduced the percentage nonheme iron absorption by 25%....The addition of defatted soy flour reduced the percentage (of iron) absorption further. A removal of phytates from soy flour did not increase the nonheme iron absorption. The total amount of iron absorbed, including the heme iron, is much lower when the content of meat was reduced by half in the soy-meat hamburgers."*

However, excessive iron supplementation (ferrous sulfate) with the objective of preventing iron deficiency from soy-based infant formulas is also reported to pose potential risks also involving the causation of neuronal damage. Iron supplementation can reduce the absorption of zinc and other essential minerals.

2008, Medscape Medical News, News Author, M. Kerr reports, "*Neurodevelopmental Delays Associated With Iron-Fortified Formulas for Healthy Infants- Dr. Lozoff told Medscape Pediatrics- The randomized trial design suggests a causal relation between the 12mg/L iron-fortified formula and poorer developmental outcome at 10 years. The results raise the possibility that long-term development is adversely affected in iron-sufficient infants who receive formula fortified with iron at the level commonly used in the United States. Dr. Georgieff said, Most of us in the iron field would be comfortable with formulas having less iron in them, more in the range of 4 to 7mg/L, and that there may be potential toxicity in certain groups consuming high-iron formula."*

COPPER Deficiency- can have serious consequences for the health of fetus, infants, and children. Copper is another vital trace element that plays a key role in a whole series of biological growth and development processes supporting: normal brain functions, cardiovascular system (transporting iron to protect cells from oxidation destruction) immune system function, respiratory system, and strong bones. Copper influences blood pressure regulation, blood coagulation, cholesterol metabolism, and glucose metabolism. Copper deficiency for an extended period of time can interrupt or damage the proper function of these anatomical systems.

It has been known since the late 1920's that copper is essential for good health, and overwhelmingly confirmed in 1962 when Menkes disease proved to largely be a

result of abnormal intestinal copper absorption with secondary deficiency in copper-dependent enzymes. Symptoms of Menkes disease include: sparse and coarse hair, developmental delay, weakened muscle tone and bones, calcium deposits in the occipital bone at the base of the skull, seizures, failure to thrive, deterioration of the nervous system, mental retardation, extensive neurodegeneration in brain gray matter, twisted brain arteries. The same soy phytic acid cause of deficiencies in essential minerals, is a cause of significantly lower copper bioavailability.

1999, "American Journal of Clinical Nutrition" B. Lonnerdal et al report,…..*Soy formulas….also contain phytate which may negatively affect trace element absorption. Plasma copper was significantly lower in monkeys fed low-phytate soy formula from 2 to 4 months. Several studies in animals and human subjects showed a negative effect of phytate on zinc absorption. This method of reduction the phytate content of soy formula is relatively costly, however, and has not yet been applied on a commercial scale. A low phytate soy-protein isolate has recently become available and may be used for infant formula if advantages to its use can be documented. Increasing the amount of an element in a diet may reduce the efficiency of absorption of the element, this usually occurs only when there is a large increase in the original concentration. No negative effect of the higher copper concentration was found on plasma zinc concentrations….. iron status may have been lower in the infants fed the regular soy formula…..Phytate had been found to have an inhibitory effect on manganese absorption….. although this effect is not as pronounced as the effect on zinc absorption. Improved zinc nutritive during infancy with concomitant maintenance of adequate copper status appears to be worthwhile and achievable goal that may have positive effects on growth, morbidity, and development."*

Lowering phytic acid from the normally high phytic acid content in soy foods and beverages including soy-based formulas is not FDA inspected, and is expensive for industry and therefore unlikely. On the other hand, industry may pour excessive minerals into soy formulas.

2003, "Journal of Pediatric Gastroenterology & Nutrition," M Araya et al report, "*Copper deficiency and excess have been recognized as potential health problems for infants, and children worldwide. Clinical manifestations of copper deficiency and excess are well characterized…..*"

Copper excess is known to cause liver damage in infants, and besides the adverse health effects previously mentioned, copper deficiency can be a cause of anemia. Anemia is a deficiency of hemoglobin that causes deficiency in oxygen from the lungs to the tissues, causing hypoxia or the lack of oxygen in bodily tissues and organs. All human cells depend on oxygen for survival and varying degrees of anemia can have a wide range of clinical consequences. Hypoxia is in fact also considered the cause of brain/behavioral disorders, to include autism. Eventually copper deficiency may lead to chronic anemia resulting in behavioral disturbances as a direct result of impaired neurological development in infants, and reduced scholastic performance in children of school age.

Along with other well balanced essential minerals, copper can ensure the good health of the central nervous system and in particular brain tissue. Copper is crucial in the formation and preservation of myelin, a protective layer surrounding neurons. Copper-dependent enzymes are needed for the synthesis of neural transmitters enabling communications between neurons.

There are most important interactions between copper and essential minerals. When taken frequently, iron and/or zinc supplements can encourage copper deficiency.

At least 20 different enzymes depend upon copper to function properly and the importance of copper for normal fetal and infant development is well known. Maternal copper deficiency is reported to affect the normal course of pregnancy that can encourage complications during pregnancy. During gestation the fetal copper reserves are stored in the liver and brain. A host of data relating to animals report that even a slight copper deficiency during pregnancy can result in congenital malformations and low birth weight.

1998, "American Journal of Clinical Nutrition' B. Lonnerdal report, *"Zinc and copper can interact, high concentrations of one element can inhibit the absorption of the other. Interactions between iron and cooper may be of more concern in pediatric nutrition. High iron fortification has negative effects on copper metabolism."*

Human milk ratio = 1:1, formulas are up to 20:1 or higher. The excessive mineral addition to soy formulas, (due to known lower essential mineral levels as caused by phytates), can greatly damage the bioavailability of the other essential minerals.

THIAMIN (B1) Deficiency- Parents must be sure that thiamin is added to soy infant formula. Early symptoms of thiamin deficiency include vomiting, lethargy, irritability, abdominal distension, diarrhea, respiratory symptoms, developmental delay, failure to thrive, infection, fever.

Department of Imaging, Medical Center of Israel reports, "*Study group including six infants aged 2-10 months with encephalopathy (disease of the brain) had been fed with solely soy-based formula devoid of thiamine from birth."*

Clinician awareness of any thiamine deficiency is important for early recognition and prevention of irreversible brain damage.

SELENIUM- is another essential trace mineral essential for cellular function. Selenium, if in excess is reported to cause: gastrointestinal disorders, hair loss, fatigue, irritability, and neurological damage.

A study reference from The Ohio State University, Department of Human Nutrition reports, "*Soy products typically contain a significant amount of selenium and soy phytoestrogens may also influence selenium status."*

Journal of "Teratology" reports, "*We previously showed that selenium caused morphological abnormalities in specific sites in cultured rat embryos….."*

PHOSPHORUS- naturally regulated levels of phosphorus compounds are most important during body, bone, and brain development, but as with the majority of important developmental minerals, can be unnaturally manipulated by soy.

Book, "Phosphate in Pediatric Health and Disease" by Uri Alon et al, reports, **"***High phosphorus content of soy formulas is a response to the finding that nearly 20% of phosphorus available in soy formula is bound to phytates in soy protein and consequently lost in stool. This mineral loss may partially account for earlier reports of neonatal rickets in infants predominately fed soy formula."*

1981, Journal, "Pediatrics" concludes, "*Phosphorus absorption was diminished with the feeding of soy formula, which resulted in relative hypophosphatemia. Extended use of such a formulation needs to be monitored for potential adverse effects on skeletal mineralization."*

"Toxicological Sciences" reports, "A high phosphate diet caused an increase in serum inorganic phosphate (Pi) accompanied by a decrease in calcium and a decrease in

body weight coupled with decreased relative weight of cerebellum. In conclusion, the results indicate that high dietary Pi can perturb normal brain growth….in developing mice."

MAGNESIUM DEFICIENCY- 1993, "Journal of Nutrition," M. Govers et al report, "*Recently we showed that soybean protein compared with casein stimulates the fecal excretion of endogenous magnesium. We conclude that the stimulatory effect of soybean protein on endogenous magnesium excretion is due to a soybean protein-specific damage of colonic epithelial cells, which results in a compensatory epithelial cell hyperproliferation."*

MANGANESE Toxicity: Manganese is an essential trace mineral that is toxic in higher levels, posing the largest threat to infants.

2008, Soy Online Service reports, "*The soybean plant has the ability to absorb manganese from the soil and concentrate it to an extent that soy-based infant formulas can contain as much as 200 times the level of manganese found in natural breast milk. In babies excess manganese that cannot be metabolized is stored in body organs. Around 80% of the excess manganese in the diet is stored in the brain and in close proximity to the dopamine-bearing neurons responsible in part for adolescent neurological development. The implications are that the one in eight infants raised on soy formula during the first 6 months of life may be at risk of brain and behavioural disorders that do not become evidence until adolescence."*

2005, Kaayla Daniel PhD reports in her book, "The Whole Soy Story: Manganese is an essential trace mineral, but high levels are neurotoxic to newborns. Infant fed soy infant formula ingest as much as 80 times more manganese per day than those who are breast fed…...neonates exposed to high levels of manganese present in soy formula are at increased risk for neurodevelopmental abnormalities, including an impaired ability to make the neurotransmitter dopamine and damage to the substantia nigra, caudate, putamen and globus pallidus area of the brain. These findings suggest that soy infant formula is a likely contributor to the epidemic of ADD/ADHD and other cognitive and behavioral disorders."

Newborns can readily absorb excessive manganese delivered from soy-based products because of their underdeveloped organs. By eight months of age, an infant fed soy-based formula is reported to ingest 1.1mg of manganese per day above the metabolic need, and manganese is 75 to 80 times higher than concentrations found in breast milk. Overload of manganese mutates into heavy metal exposure capable of causing neurotoxic exposure. Manganese toxicity also has effects on lowering dopamine levels, becoming double-damaging in the cause of behavior disorders.

2004, "Journal of the American College of Nutrition," KA Cockell et al reports, "*Manganese content of soy or rice beverages is high in comparison to infant formulas. Well-meaning but inadequately informed parents may perceive plant-based beverages such as soy or rice beverages as an alternative to infant formula. Manganese is an essential mineral nutrient found at high levels in plants such as soy and rice. Excessive manganese exposure increases the risk of adverse neurological effects. Soy beverages had the highest levels of manganese (16.5+/-8.6micro g/g dry wt, mean +/-s.d.) followed by Rice beverages (9.9+-1.7)……soy-based infant formulas (2.4+/-0.7micro g/g dry wt and milk-based infant formulas (0.70 +/-0.35 micro g/g dry wt). Soy and rice beverage exceeded the range derived from ULs and typical energy intakes of 1-3 year olds. …no*

Tolerable Upper Intake Level (UL) for manganese is available for infants under one year of age. Soy beverage and rice beverage should not be fed to infants because they are nutritionally inadequate and contain manganese levels which may present an increased risk of adverse neurological effects if used as a sole source of nutrition."

2006, "Birth Defects Research Part A, Clinical and Molecular Teratology," FM Crinella reports, "*Manganese (Mn) can cause a neurotoxic syndrome due to its interactions with monoamine systems, especially dopamine. Perturbations of the dopamine system are known to underlie a number of neurobehavioral problems, including attention deficit hyperactivity disorder. Mn homeostasis develops slowly and the infant is therefore vulnerable to excess dietary Mn. Mn in soy-based infant formula can contain up to 80 times the Mn concentrations of breast milk. We hypothesized that ingestion of soy formula in infancy could influence overabsorption of Mn and neurobehavioral consequences. Weekly behavior observations (of rhesus monkeys) indicated that the soy groups were generally more active, changing their form of ongoing activity more often during 30 second sampling periods. The soy groups performed less well on measures of impulse control. The soy monkeys tended to play les, but cling more. Chase play was particularly affected, and the average duration of play behavior was lower. We tentatively conclude that, during infancy, the ingestion of high levels of manganese as found in soy-based infant formula is associated with a variety of behavioral deficits."*

2004, "Mothering Magazine," Kaayla Daniel writes, "*Although trace amounts of manganese are vital to the development of the brain toxic levels accrued from ingestion of soy formula during infancy have been found in children suffering from attention-deficit disorders, dyslexia, and other learning problems."*

Department of Oncology and Medicine, "*Manganese is an essential trace nutrient that is potentially toxic at high levels of exposure. Manganese plays an important role in a number of physiologic processes in mammals. Excessive manganese exposure may lead to adverse neurodevelopmental outcomes due to the disruption of thyroid homeostasis. Manganese may directly or indirectly affect thyroid function by injuring the thyroid gland or dysregulating dopaminergic modulation of thyroid hormone synthesis."*

1998 "Biological Trace Element Research," M. Krachler et al report, *"A preformula supplemented with manganese had a 10 times higher manganese concentration than preformulas without supplementation."*

2008 "Neuroscience" S.A. McDougall et al report, "*Postnatal manganese exposure alters dopamine transporter function…..Results showed that postnatal manganese exposure caused persistent declines in dopamine transporter protein expression and dopamine uptake in the striatum and nucleus accumbens as well as long-term reductions in striatal dopamine efflux. Manganese-exposed rats did exhibit substantially more amphetamine-induced stereotypy than vehicle controls. Interestingly, acquisition of a fixed ratio task was impaired in manganese-exposed rats suggesting a deficit in procedural learning. In summary these results indicate that postnatal manganese exposure causes persistent declines in various indices of presynaptic dopaminergic functioning. Manganese-induced alterations in striatal functioning may have long-term impact on associative and nonassociative behavior."*

1994, "Acta Paediatrica Supplement," B. Lonnerdal reports, "*Finally, the high levels of manganese in soy formula present a potential problem in that manganese absorption and retention are high during infancy."*

The FDA simply states essential mineral requirements for infant formulas, but the FDA does not investigate absolute essential mineral contents found in soy infant formulas or any infant formulas.

2002, "Food Chemistry" A Ikem et al, *"Some (soy and milk-based infant formula) brands had low nutritional (essential metal) contents when compared with the recommended dietary allowances and dietary intakes for use in North America."*

SOY CAUSES HEAVY METAL CONTAMINATION: Heavy metals are toxic and especially poisonous during body and brain development. Heavy metal toxicity accumulates in the bloodstream and subsequently becomes trapped in various parts of the body and accumulates in the brain. Brain tissue is reported to have an attraction for heavy metals, while interfering with natural brain chemistry eventually causing brain damaging effects. Heavy metals are readily available from pollution, smoking, pesticides, toxins, etc. as well as soybean plants.

Estrogenic soy isoflavones, soy cause of thyroid disease, soy antinutrients damaging the bioavailabilty of essential minerals, and soy exposure and entrapment of heavy metals, each and all contribute to the soy cause of anatomical and neurological toxicity particularly during fetal, infant, and child development.

Daily, the human body is assaulted by unavoidable chemicals, while the consumption of soybeans increases an accumulating exposure to heavy metal toxicity. Heavy metals plug the biological spaces that are supposed to be filled by necessary essential minerals. Increasing heavy metal levels contaminate the body while causing a host of toxic health effects in the blood, bone, intestines, vital organs, brain, with greatest damaging effects occurring during fetal and infant development.

Healthy adults are able to bind (chelate) heavy metal atoms and remove unwanted metals from the body through normal elimination. However, metabolism and excretion of excessive toxic metals is difficult, and potentially impossible for the developing fetus and infants due to their immature liver, kidneys, intestines, and entire digestive system. Fetus, infants, and children will have higher levels of heavy metals in their blood than their parents. Dose dependent, soybeans are capable of increasing and accumulating heavy metal toxicity as a health threat to the entire developmental physiology of fetus and infants exposed.

In children, chelation therapy treatments may be applied in attempt to mop up the heavy metal toxicity deposited by soy-based formulas, beverages, and foods. Soy-based infant formulas contribute to heavy metal toxicity that is stated to contribute to the cause of learning disabilities and behavioral disorders such as Attention Deficit Disorders, Attention Deficit-Hyperactivity Disorder, and brain disorders such as autism. Autism and other brain disorders are results of heavy metal contamination.

The FDA does not actively test soy infant formulas for heavy metal contents that can largely fluctuate among soy plants, soy manufacturing, and individual abilities to rid the body of contaminants.

A study by Division of Natural Sciences, State University of New York, reports, *"The results suggest that soy-based powder infant formulas generally had higher element*

(metal) levels than milk based powder formulations……and the US EPA standard for thallium (a highly toxic chemical) was violated in some infant formula brands."

ALUMINUM Contamination: Aluminum is present in soy formulas because mineral salts must be added in attempt to lessen the depletion of essential minerals as caused by soy antinutrient-phytic acid. Packaging is also a concern while soy is often acid washed in aluminum tanks, leaching high levels of aluminum into the final product. Soybean aluminum contamination is in fact reportedly excessive. Aluminum content of soy-based formulas is said to be at least 10 times greater than milk formulas. Aluminum is seldom measurable in breast milk, but can be in the higher range while also depending upon maternal consumption of soy products. Health risks caused by aluminum toxicity is repeatedly documented as most damaging to the brain, and the most vulnerable of aluminum contamination, accumulation, and toxicity are the fetus, infants, and children.

Soy isoflavones are known to contain high concentrations of aluminum which according to the, Division of Nephrology, UCS School of Medicine "….*aluminum causes hyper- parathyroidism causing damaging kidney effects that plays a major role in the genesis of nervous system dysfunction. Excess parathyroid hormone mediates its deleterious effect by causing elevation in cytosolic (acutely regulated) calcium of brain cells."*

American Academy of Pediatrics (AAP), journal of "Pediatrics," Vol 101, January 1998, reports, *"In 1996 the AAP issued a statement on aluminum toxicity in infants and children and discussed the relative high content of aluminum in soy-based formulas. Although the aluminum content of human milk is 4 to 65ng/mL, that of soy protein-based formula is 600 to 1300 ng/mL. Aluminum…..has no known biological function in humans. The toxicity of aluminum is traced to increased deposition in bone and in the central nervous system, particularly in the presence of reduced renal (kidney) function……aluminum competes with calcium for absorption, increased amounts of dietary aluminum from isolated soy protein-based formula may contribute to the reduced skeletal mineralization….."*

2008, "Pediatrics" official journal of the AAP, J Bhatia et al report, "*Although the aluminum content of human milk is 4 to 65ng/mL, that of soy protein-based formula is 600 to 1300ng/mL. Mineral salts used in formula production are the source of the aluminum. Aluminum….has no known biological function in humans. The toxicity of aluminum is traced to increased deposition in bone and in the central nervous system…..Because aluminum competes with calcium for absorption, increased amounts of dietary aluminum from isolated soy protein-based formula may contribute to the reduced skeletal mineralization (osteopenia) observed in preterm infants and infants with intrauterine growth retardation."*

Aluminum levels largely increases again during soy infant formula and soy product manufacturing and packaging.

1999, "Journal of Pediatric Gastroenterology and Nutrition," J Fernandez-Lorenzo et al report, *"Aluminum toxicity is well documented and contamination of milk formulas has been implicated as the source of accumulation in bone and brain tissues. Aluminum concentrations in infant formulas differed markedly among manufacturers…..and could be reduced by more than 70% at the manufacturing stage by using low aluminum components. The results of the present study support the*

recommendations for infant formula manufacturers to strive to reduce aluminum concentration in their products."

1988, "Journal of the American College of Nutrition" W. Koo et al reports, *"…the kidney is the dominant organ for aluminum excretion. However, even with normal renal function, (in adults) only 30-60% of an aluminum load….is excreted in the urine, resulting in tissue accumulation of aluminum. The risk for aluminum toxicity is greatest in infants with chronic renal insufficiency….. and preterm infants with low aluminum binding capacity. The rapid growth of the infant would theoretically potentiate aluminum toxicity in all infants, although the critical level of aluminum loading causing bond disorders is not known. To minimize tissue burden, aluminum content of infant nutrients should be……less than 50 micrograms/L."*

Aluminum is distributed through the blood to the bone, liver, testes, kidneys and brain. Chronic exposure to aluminum has been associated with various neurological syndromes. Respiratory system is another target of aluminum contamination, increasing lung weight and risk of pneumonia.

Medical Unit, in UK reports, "*We conclude that infants may be at risk from aluminum toxicity when consuming formula containing > 300 micrograms…."*

Neuroscience Research Group concludes, "*Aluminum is known to pass the placenta and blood brain barrier and has been suggested to produce deleterious effects on fetal brain. Findings suggest that in-utero exposure to aluminum may significantly affect neurobehavioural development of newborn."*

Reported in 2008, Medscape Medical News: *"Study Highlights- Soy formula composition meets U.S. FDA and AAP guidelines- Aluminum is higher in soy formula vs. human milk (600 - 1300ng/mL vs 4 - 65 ng/mL)."*

Contaminating the infant body with increasing aluminum levels causes a drastic reduction in essential metal absorption that is critical for neurological development. Accumulation of aluminum can cause calcium and phosphorus deficiency that is critical for bone development. Elevation in aluminum levels can disrupt the central nervous system, cause abnormal kidney function, bone disorders, and gastrointestinal tract pain.

As reported in, "*Special Topics in Endocrinology and Metabolism- Aluminum absorption is enhanced in the presence of elevated circulating parathyroid hormone (PTH)…..and elevated PTH leads to the deposition of aluminum in brain and bone. PTH is likely involved in the pathogenesis of toxicities in those organs."*

2001, "Journal of Nutrition," K. Cox and M. Dunn report, "*Aluminum toxicity alters the regulation of calbindin-D28k protein and mRNA expression in chick intestine- Previous studies have shown that aluminum inhibits vitamin D-dependent calcium absorption. These results show that in chicks fed a low calcium diet, aluminum intake decreases transcription and/or stability of intestinal calbindin mRNA, and that aluminum may inhibit the expression of vitamin D-dependent genes."*

2008, "Journal of Parenteral and Enteral Nutrition," RL Poole et al, report, "*Aluminum toxicity can cause serious central nervous system and bone toxicities. Premature neonates requiring high doses of calcium and phosphate to mineralize their bones, children with impaired renal function, and children on parenteral nutrition therapy for prolonged duration are at the highest risk. Effective July 2004, the FDA mandated labeling requirements for aluminum content in all PN solution components. Manufacturers must identify, develop, and adopt new methods to reduce the aluminum*

contamination in their products. Health care professionals should calculate aluminum loads in patients……..”

To date, the FDA disregards labeling requirements for the high aluminum contents as found in soy products, and soy-based infant formulas.

CADMIUM TOXICITY- Cadmium is a transition metal proven to be toxic even in low concentrations, and in overabundance is known to cause confusion, aggression, and damaging health effects. Single or combined deficiencies in zinc, copper, iron, protein, and/or calcium markedly exacerbate the toxic effects of cadmium. Many investigators have shown that the nutrient composition of the diet can markedly influence the severity of toxic. manifestations that occur after a few days, or weeks of feeding high levels of cadmium.

“Journal of Association of Official Analytical Chemists” report- *“Soy-based formula contained 8-15 times more cadmium than did milk-based formulas.”*

Journal, “Toxicology” R. Ohtanl-Kaneko et al, report, “*Suppressive effects of cadmium on neurons and affected proteins in cultured developing cortical cells- Administration of cadmium suppressed dendritic as well as synaptic development…..low-dose cadmium distorts brain development…..We identified three proteins with different expression after cadmium treatment; dihydropyrimidinase-related protein 2, 14-3-3-epsillon and calmodulin. Though the number of identified proteins was small, these proteins are known to be involved in neuronal development.”*

1997, “Environmental Health Perspectives,” M. R. Fox et al report, “*Different tissue concentration patterns of cadmium and essential minerals were obtained with low purified control diets, one based on casein-gelatin and the other on soy isolate…….The data show that relatively small dietary changes can markedly affect tissue levels of cadmium, and that a low intake of zinc may increase the risk to dietary cadmium exposure. The complexity of the nutrient interrelationships and their effects on cadmium require further study. …problems of cadmium toxicity in man are not due to high levels of cadmium intake, but rather to very long-term cadmium accretion in the kidney until levels that can cause kidney damage occur.”*

THALLIUM- is a natural occurring highly toxic metal ubiquitously found in nature in low concentrations, with highest levels accumulating in plants. Thallium is manufactured in pesticides, semiconductors, glass, electronics, mercury lamps, fireworks, imitation gems, iron and zinc refineries, contaminating soil and water. Main hazards of chronic thallium poisoning accumulate in the liver, brain, kidney, skeletal muscles.

2008, “Environmental Toxicology and Chemistry,” S Radic et al report, “*The metal thallium accumulates in bean plants, were it increases harmful oxygen radicals (a process called oxidative stress) that break DNA strands. It is important to understand because many crops accumulate the metal, which can affect plant growth can be passed on to human consumers. Concentrations in the environment are increasing because of human activities. Human exposure occurs mainly through eating plants grown in thallium-contaminated soils. Very low levels can be lethal to people. In this study bean plants were exposed to thallium concentrations (some environmentally relevant) using short-term water exposures. The extent of oxidative stress and resulting DNA damage were evaluated…..”*

2007, “Chemosphere” P Madejon et al report, “*In general, trace element (thallium) content was unremarkable in all plant parts, despite the concentrations present*

in soil. Thallium was the only element whose concentration in both plant species was above normal for plants. The data presented here show that thallium content of plants growing in semi-arid conditions can be significantly influenced by precipitation. In dry years, plant thallium may be significantly reduced."

2002, "Food Chemistry," A Ikem et al report, "*Levels of 26 elements in infant (soy and milk-based) formula from USA,…….the presence of toxic elements (heavy metals) in powdered and liquid infant milk may create significant health problems for infants. The results suggest that soy-based powder infant formulas generally had higher element levels than milk-based powder formulations.……...and the US EPA standard for thallium were violated in some infant formula brands"*

LEAD TOXICITY- Lead another toxic metal capable of physiological build-up, known to cause aggression and hyperactivity, is also found in soy isoflavones as confessed personally by Novasoy, marketers of soy formulas, "The lead content of our Novasoy is below detection limits." with no guarantee. Food Chemical Codex 'request' specifications are to test for "excessive levels" of (lead), copper, arsenic, cadmium, antimony, lead, mercury, bismuth, tin, silver, or molybdenum.....again with no guarantee that tests will be performed, or that levels are below specifications.

Heavy metal tests for soy products or soy-based infant formulas are not FDA regulated. The FDA confirms, "*Lead is a toxic substance of no known nutritional benefit to humans. It has been recognized as a health hazard for centuries. There is no known acceptable or normal body burden level. High levels can harm the nervous system, kidneys, liver, reproductive, cardiovascular, immune and gastrointestinal systems. Lead may cause learning and behavioral disorder in children."*

Journal- "*Association of Official Analytical Chemists"* concludes, "*Lead levels exceeding about 10-15 ng/g were attributed to contamination from either the can used to store (infant) formula or formula ingredients. Even lead-free cans contain about 1.7ng/g of lead."*

Lead also opposes calcium, iron, and zinc, as proven to cause cognitive and behavior effects in children.

COMPLEXING AGENTS- or chelating agents (process to bind concentrations of toxic metals for removal or flushing from body tissue) are being explored as treatments for neurological diseases, while soy is proven to encourage the accumulation of these metals.

Increasing amounts of lead also depend upon pesticide used, leaving questions about Roundup Ready (RR) soybeans. Not only is the RR gene incorporated directly into soybeans, but soybean fields can be sprayed and over-sprayed by Roundup to kill surrounding weeds and pests, contaminating but not killing genetically engineered soybeans.

Rather than avoid consumption of soy-isoflavones, the controversial treatment for autism, is chelation therapy, a painful attempt to detoxify high levels of toxic metals: aluminum, cadmium, copper, manganese, lead, arsenic, (pesticides/herbicides) from the child's body. Multiple toxic metals well known to cause brain disorders are found in soy plant-estrogens. It would be very difficult to explain how else infants and children could be diagnosed with a bloodstream overflowing with levels of multiple heavy metals.

To magnify the severity of health effects caused by soy plant-estrogen endocrine disruptors, and antinutrients, soy's multiple metal contents are a compounding effect

proven as capable of causing a variety of direct and indirect irreversible prenatal and postnatal neurological disorders, to include autism.

There are no FDA regulations to test soybean products for contaminating levels of active plant-estrogens, antinutrients, or heavy metals prior to fetal, infant, and child exposure, as proven to cause a host of significant developmental disorders or diseases.

OXIDATIVE STRESS- is an imbalance between the production of reactive oxygen and a biological system's ability to readily detoxify the reactive intermediates or easily repair the resulting damage. The effects of oxidative stress depend upon the size of these changes, and the cell being able to overcome small perturbations and regain its original state. The major portion of long-term effects is inflicted by damage on DNA. Several of soybean; antinutrients, toxins, and heavy metal contents, reportedly cause cellular oxygen deprivation that adults may be able to overcome, while exposed fetus, infants and children may not.

A child's blood sugar can drop about 20 minutes after eating sugar, which again leads to a lack of oxygen. Oxygen is essential for proper body and brain development. Clearly the amount of excessive sugar and sweeteners found in soy infant formula is capable of causing a host of health problems with heightened damage to neurological development.

In addition to soy's high sugar content causing oxygen deficiency, a 2004 journal study by the Department of Environmental Molecular Medicine, "Biochemistry" reports, "*These findings suggest that oxidative DNA damage by (soy) isoflavones metabolites plays a role in tumor initiation and that cell proliferation by isoflavones via estrogen receptors, estrogen response element binding induces tumor promotion and/or progression resulting in cancer of estrogen-sensitive organs.*"

2002, "Acta Biochimical Polonica," J Kobiela et al report, "*Selectivity of oxidative stress targeting in estrogen-induced experimental nephrocarcinogenesis-Specificity of targeting of the oxidative stress towards lipid and protein fractions in a model of estrogen-induced Syrian hamster nephrocarcinogenesis was evaluated. The amount of proteins modified by oxidative stress was significantly elevated as early as one month after the initial implantations of estradiol to the experimental versus the control group. ….oxidative stress target was determined by the analysis of protein oxidation in subcellular fractions of kidney cells. The endoplasmic reticulum membranes were the fraction most affected by the oxidative stress.*"

Soy plant-estrogens are a proven estradiol mimic.

2007, Pat Levitt director of the Vanderbilt Kennedy Center for Research on Human Development, as reported by Jill Neimark, "*…..the activity of the (MET) gene is affected by what is known as oxidative stress-the kind of damage one sees with excessive exposure to toxins.*"

The MET gene is identified in the cause of autism as previously reported.

Oxidative cellular damage has been associated with a wide range of pathological conditions: multiple sclerosis, carcinogenesis, stroke, autoimmune disease, inflammation, and more. Added to the soy cause of low birth weight, and countless other fetal and infant adverse health effects, hypoxia or shortage of oxygen is reported to also cause a wide range of teratogenesis effects: digestive system diseases, abdominal distress, seizures, neurodegenerative disorders, and cerebral palsy.

SOY ENCOURAGES CEREBRAL PALSY: Cerebral Palsy is brain injury that may be caused by proinflammatory cytokines. Premature birth is another stated cause. Children with cerebral palsy are also prone to stomach difficulties. Soy isoflavones are proven to encourage specific interleukin/cytokine proinflammatory conditions, gastrointestinal distress, and low birth weight a condition of premature birth.

Soy-caused adverse effects that may encourage the risk of CP includes: immune deficiency, fetal exposure to soy endocrine disruptors, maternal/fetal hypothyroidism and exposure to hypothyroid medications, premature birth weight, oxidative stress, and countless other potential soy-caused adverse effects.

2002, "Journal of Obstetrics and Gynecology," LA Patrick and GN Smith report, "*Objective: To review the etiology of impaired fetal neurodevelopment, in particular the relationship between…… cytokines and cerebral palsy…..maternal/fetal proinflammatory cytokine release….is damaging to the developing fetal nervous system. Elevated cytokine concentrations may interfere with glial cell development and proliferation in the late second trimester of pregnancy ….is most vulnerable. Clearly some relationship exists between …cytokines and the development of cerebral palsy."*

Between 40 to 50% of all children who develop cerebral palsy are born prematurely. In addition, the risk of a baby having CP increases when birth weight decreases. Low-birth-weight, premature infants are more likely than full-term, normal-weight babies to be diagnosed with developmental disorders and neurotoxicity. It is estimated that 70-80% of children with CP experienced a disruption in the normal developmental areas of the brain during fetal growth. As a proven endocrine disruptor soy plant-estrogens and soy antinutrients disrupt physiological and neurological development..

Soy isoflavones reportedly contribute to damaging muscle development and growth.

1999, "Journal of Nutrition," S Ji et al reports, "*Soybean isoflavones, genistein and genistin, inhibit rat myoblast proliferation, fusion and myotube protein synthesis-Genistein strongly inhibited in vitro myoblast proliferation and fusion in a dose-dependent manner with effective genistein concentration as low as 1 micromol/L. Genistein or genistin inhibited protein accretion in myotubes. Decreased protein accretion is largely a result of inhibition on cellular (myofibrillar) protein synthesis rate. Results suggest that if sufficient circulating concentrations are reached in tissues of animals consuming soy products, genistein/genistin can potentially affect normal muscle growth and development."*

2005, "Journal of Medicinal Food," KL Jones et al report, "*This study was performed to observe the effects of the soy isoflavones genistein, daidzein and glycitein on cell cultures of rat skeletal muscles. Genistein reacted most similarly to estradiol …. A combinations of phytoestrogens resulted in significant inhibition of cell proliferation, but not to the extent observed with genistein alone. In addition, at higher total combined concentrations, daidzein and glycitein may be able to out compete genistein for receptor sites. These results suggest that soy isoflavones in the diet may potentially modulate normal (muscle) growth and development in humans and animals that ingest soy-based products."*

SOY CAUSATION OF WORSENING HEART DISEASE-

2006, "Journal of Clinical Investigation," BL Stauffer et al report, "*Soy diet worsens heart disease in mice- ……in a transgenic mouse model of hypertrophic cardiomyopathy……On a soy diet, males with a mutation in the alpha-myosin heavy chain gene progress to dilation and heart failure.*"

2006, "Journal of Clinical Investigation," C.J. Hatcher et al, "*Taking a bite out of hypertrophic cardiomyopathy (HCM): soy diet and disease. ….Stauffer et al have explored the influence of a soy diet on cardiac growth and function in mouse model of HCM. They report that mice fed a soy diet exhibited significantly worse HCM than mice fed a soy-free (milk protein) diet.*"

1982, "Medical Hypotheses," S. Seely reports, "*When phytoestrogens are consumed directly in plants like soya beans, they appear to be correlated with cerebrovascular disease.*"

SOY CAUSATION OF CANCERS AND/OR METASTASIS: Soy is a known estrogenic endocrine disruptor, and estrogenic endocrine disruptors are well known to increase the risk of cancer and cancer metastasis. Exposures to soy estrogenic endocrine disruptors during fetal and/or infant/child developmental timeframes especially increase the risk of cancers.

2000, "Phytoestrogens and Health," GS Gilani, JJB Anderson report, "*The animal data…..clearly show the carcinogenic potential of genistein.*"

2005- "Cancer Resources" I Baik et al report, "*Association of fetal hormone levels with stem cell potential: evidence for early life roots of human cancer- Intrauterine and perinatal factors have been linked to risk of childhood leukemia, testicular cancer, and breast cancer in the offspring. The pool of stem cells in target tissue has been suggested as a critical factor linking early life exposures to cancer. These findings indicate that levels of growth factors and hormones are strongly associated with stem cell potential in human umbilical cord blood and point to a potential mechanism that may mediate the relationship between in utero exposure to hormones and cancer risk in the offspring.*"

Certified Nutritional Advisor Dr. Richard Brouse reports, "*It is true that 'overcooked' soy does contain 'carcinogenic' compounds When soy is extruded through high temperature, high pressure steam nozzles to form what is called 'textured vegetable protein- TVP….this form of pressing renders the soy 'meat substitute' carcinogenic or cancer causing. Whole soybeans are high in plant fat. If soybeans are roasted to eat as soy nuts, the heat alters the fat and makes it a trans-fatty acid which causes both cancer and heart disease. If a person consumes more than 2 grams of (soy) protein per pound of body weight daily and does not consume adequate carbohydrates with it, this could cause kidney damage.*"

"Biochemistry," Japan, School of Medicine, journal reports, "*Genistein and daidzein induce cell proliferation and metabolites cause oxidative DNA damage in relation to isoflavone-induced cancer of estrogen-sensitive organs…..DNA damage by isoflavone metabolites plays a role in tumor initiation and that cell proliferation by isoflavones induces tumor promotions and/or progression resulting in cancer of estrogen-sensitive organs.*"

The National Center for Toxicological Research confirms, "*Studies of soy isoflavones (having estrogenic effects), in experimental animals suggest possible adverse*

effects that includes enhancement of reproductive organ cancer, modulation of endocrine function, and anti-thyroid effects."

Published in Cancer Research by University of Illinois, "*Soy diets containing varying amounts of genistein stimulate grow of estrogen-dependent tumors in a dose-dependent manner."*

LYMPHOMA- is cancer in the cells of the lymph glands involving the immune system. It is reported that some subsets of lymphocytes are sensitive to estrogens.

2002, "International Journal of Toxicology," Office of Preventive Oncology, National Cancer Institute reports, "*Genotoxicity and carcinogenicity studies of soy isoflavones- Mouse lympohoma cell mutagenesis experiemtns conducted with and without metabolic activation revealed statistically significant increases in mutation frequesty at PTI G-2535 (an investigational soy isoflavone drug product) concentrations > or = 0.8 and 12 microg/ml respecitively; such increases were dose related and increases in the frequency of both small and large colonies were observed. The apparent risk/benefit of isoflavone ingestion may ultimately depend on the dose and developmental timeing of exposure."*

As far back as 1956 it has been reported by Paul Toch et al, "*Lymphoid Tumor Incidence in Mice Treated with Estrogen….. "An even greater increase in lymphoid tumors resulted when estrogen was administered to either intact or castrated animals."*

Soy is an active plant-estrogen.

BREAST CANCER-

2004, "Biochemistry," M Murata et al report, "***Genistein and daidzein induce cell proliferation and their metabolites cause oxidative DNA damage in relation to isoflavone-induced cancer of estrogen-sensitive organs.*** *Recent studies indicated that genistein and/or daidzein induced cancer of reproductive organs in rodents such as the uterus and vulva…..we examined the ability of genistein, daidzein and their metabolites….to cause DNA damage and cell proliferation. An E-screen assay revealed that genistein and daidzein enhance proliferation of estrogen-sensitive breast cancer MCF-7 cells…..These findings suggest that oxidative DNA damage by isoflavone metabolites plays a role in tumor initiation and that cell proliferation by isoflavones via estrogen receptors/ estrogen response element binding induces tumor promotion and/or progression, resulting in cancer of estrogen-sensitive organs."*

Health Action Network Society reports, "*In 1996, researchers found that women consuming soy protein isolate had an increased incidence of epithelial hyperplasia, a condition that preceded malignancies. Additionally genistein was found to stimulate breast cells to enter the breast cancer cycle. Soy products may increase breast cancer in pregnant women. …people also have much higher rates of cancer of the esophagus, stomach, liver, pancreas and thyroid particularly as soy causes these same types of cancer in laboratory rats."*

2008, Journal of Environmental Science and Health. Part C, Environmental Carcinogenesis & Ecotoxicology Reviews," RS Tomar and R Shiao report, *"Early life and adult exposure to isoflavones and breast cancer risk- Isoflavones are structurally similar to estrogens and may act as estrogen agonists or antagonists by finding to estrogen receptors. ….dietary intakes of (soy) isoflavones are increasing in children and*

adolescents in North America. Estrogens are a know component of numerous hormone related cancers including breast cancer. Isoflavones are weak estrogens and their effects depends upon the dose, time of exposure, and species involved."

1994, "Food Chemistry and Toxicology" IE Bosselaers et al report, "*Differential effects of milk protein…It is concluded that casein, its pepsin hydrolysis products and BSA may protect mammalian cells against certain genotoxic compounds, whereas other milk proteins, such as whey protein, beta-lactoglobulin and soy protein, do not have this protective action."*

2006, "Carcinogenesis," YH Ju et al report, "Effects of dietary daidzein ….on the growth on estrogen-dependent human breast cancer (MCF-7) tumors in ovariectomized athymic mice- Dietary daidzein had a slight but significant stimulatory effects on MCF-7 tumor growth in mice."

2008, "Inflammopharmacology," Y Zhang et al report, "*Studies in our laboratory showed that genistein, the major soy isoflavone, could stimulate osteoblastic functions as well as human breast caner cell growth. As increasing the purity of genistein is known to increase its ability to induce human breast cancer cell growth…..."*

2007, "Molecular Nutrition & Food Research," KA Power and LU Thompson report, "*…..recent studies raise concern over the safety of soy and its isoflavones, particularly genistein for postmenopausal breast cancer, due to their potential stimulatory effects on human breast tissue and on the growth of existing tumors in rodents.*

2008, "Endocrine-Related Cancer," R Dip et al report, "*…..phytoestrogens, achievable through soy-rich diets, stimulate the proliferation of estrogen-sensitive tumor cells. Soy phytoestrogens induce a genomic fingerprint that is indistinguishable from the transcriptional effects of the endogenous hormone 17B-estradiol. Highly congruent responses were also observed by comparing the physiologic estradiol with daidzein, coumestrol…..each representing distinct phytoestrogen structures. Therefore, phytoestrogens appear to mitigate estrogenic signaling in the presence of both ER subtypes but, in late-stage cancer cells lacking ERB, these phytochemicals contribute to a tumor-promoting transcriptional signature."*

2008, "Inflammopharmacology," WG Helferich et al report, "*Genistein is an isoflavone with estrogenic activity that is present in a variety of soy products as a constituent of complex mixtures of bioactive compounds, whose matrix profiles play an important role in determining the overall estrogenic bioactivity of genistein. We review data on how the profile of soy bioactive compounds can modulate genistein-stimulated estrogen-dependent tumor growth. Our research has focused on the effects of dietary genistein on the growth of estrogen dependent mammary tumors both in vitro and in vivo. Genistein enhances the proliferation of estrogen-dependent human breast cancer tumor growth. The extent of soy processing modulates the effects of dietary genistein in vivo as soy protein isolate, a highly purified and widely used source of protein that is processed to contain low, medium, and high amounts of isoflavones, stimulate the growth of the E-dependent mammary tumors in a dose dependent manner……dietary genistein was able to negate the inhibitory effect of tamoxifen on estrogen-stimulated tumor growth. In summary, genistein can act as an estrogen agonist resulting in proliferation of estrogen-dependent human breast cancer tumors in vivo and its activity can be modulated by the presence of other bioactive components in complex soy foods. ….dietary genistein can*

negate the inhibitory effect of tamoxifen on estrogen-stimulated growth of MCF-7 cell tumors……"

2007, "Nutrition and Cancer," DA Tonetti et al, "*More concerning is the concurrent consumption of soy isoflavones with tamoxifen (TAM) for prevention or treatment of breast cancer. Interestingly, coadministration of TAM with either daidzein or genistein produced tumors of greater size than with Tam alone. These findings suggest that simultaneous consumption of isoflavone supplements with TAM may not be safe."*

2008, "Carcinogenesis," YH Ju et al report, "*Genistein a soy isoflavone stimulates growth of estrogen-dependent human tumor cells……Antiestrogens and aromatase inhibitors are frontline therapies for estrogen-dependent breast cancer. We have demonstrated that dietary genistein can negate the inhibitory effect of tamoxifen. In conclusion dietary genistein increased the growth of MCF-7Ca tumors implanted in ovariectomized mice and could also negate the inhibitory effect of letrozole on MCF-7 Ca tumor growth. ….Genistein can revers4e the inhibitory effect of letrozole and on tumor growth and adversely impact breast cancer therapy."*

2002, "Human Reproduction," S. Whitehead et al report, "*….phytoestrogen genistein ….is found in substantial amounts in soy products. Genistein however stimulates the growth of breast cancer cells lines…..biological estrogenic effects of genistein have been observed in vivo and studies in vitro have demonstrated that it can stimulate transcriptional activity of both a and B estrogen receptors….An alternative target for the action of genistein is on steroidogenic enzymes, and in this respect genistein has been shown to inhibit the reduction of estrone to more active estradiol by inhibiting 17B-hydroxysteroid dehydrogenase (play an important role in the regulation of intracellular levels of biologically active sex steroid hormone in various human tissues).*

Acute and chronic effects of genistein….Genistein is also a potent inhibitor of tyrosine kinase activity…."

2002, "Toxicological Sciences," L You et al report, "*Modulation of mammary gland development in prepubertal male rats exposed to genistein and methoxychlor- The estrogenic isoflavone genistein is a common dietary component that has been shown to affect reproductive development……The objective of the present study was to examine interactions of genistein and the hormonally active pesticide methoxychlor on mammary glad development in juvenile rats. Rats were fed these diets starting on gestation day 1 and continuing through pregnancy and lactation until postnatal day 22…..genistein enhanced the ductile branching. The 2 compounds in combination promoted the development of alveolar-lobular structure, an effect not observed with either compound alone. Increased immunostraining for insulin-like growth factor-1 receptor estrogen receptor alpha, and progesterone receptor in the genistein + methoxychlor group suggested that local factors involved in regulating mammary growth may have played a role in propagating the endocrine effects of these 2 compounds. These results indicated that ….juvenile male rather than juvenile female rats may be more sensitive to certain endocrine-active compounds and that high levels of phytoestrogens have the potential to alter the toxicological behaviors of other hormone mimics."*

2005, Government Reports Announcements & Index (GRA&I), Issue 14, Fred Hutchinson Cancer Research Center, C Atkinson reports, "*Equol-Producing Bacteria and Estrogen Metabolism- Intestinal bacteria are involved in estrogen metabolism. Thus,*

inter-individual differences in intestinal bacterial populations may contribute to variation breast cancer risk via effects on estrogen metabolism. One-third to one-half of the population harbors the yet-to-be-identified bacteria that metabolize daidzein, a soy isoflavone to equol. Our objective was to determine whether fecal bacterial metabolism of estrogens differs according to equol-producer phenotype. Fecal bacteria from equol-producers were more likely than non-producers to convert 2-hydroxyestrogen to 2-hydroxyestradiol. Furthermore, equol producers, compared to non-producers converted significantly more estrone to estradiol, an…….These finding suggest differences may exist between equol-producers and non-producers in bacterial estrogen metabolism. ….the conversion of estrogen to estradiol could present potentially …...detrimental ….pathways in terms of breast cancer risk."

That soy isoflavone equol producers are also more likely to convert estrone to the more powerful estradiol resulting in greatest potential for a highly potent combination of estrogenic toxicity is alarming.

2004, "Cancer Epidemiology Biomarkers & Prevention," PB Grace et al report, "*……seven phytoestrogens (daidzein, genistein, glycitein, O-desmethylangolensin, equol, enterodiol, and enterolactone) were measured in 114 spot urines and 97 available serum samples from women who later developed breast cancer. …...mean serum levels of phytoestrogens were up to 600 times greater than postmenopausal estradiol levels. Phytoestrogen concentrations in spot urine correlated strongly with that in serum……There were significant relationships between both urinary and serum concentrations of isoflavones across increasing tertiles of dietary intakes. Exposure to all isoflavones was associated with increased breast cancer risk, significantly so for equol and daidzein. These estimates of risk are similar to those established for estrogens and androgens in postmenopausal breast cancer……"*

Georgetown University reports, "*Human and animal data indicate that a high maternal estrogen exposure during pregnancy increases breast cancer among daughters. Some phytoestrogens such as genistein which is a major component in soy-based foods have estrogenic effects on the reproductive system, breast and brain. Findings indicate the maternal exposure to physiological doses of genistein mimics the effects of estradiol (*a highly potent endogenous estrogen)*, on the mammary gland and reproductive systems in the offspring. Our results suggest that genistein acts as an estrogen in utero and may increase incidence of mammary tumors if given through a pregnant mother."*

A published study from England confirms, "*Exposure to all isoflavones was associated with increased breast cancer risk."*

"Cancer And Developmental Exposure To Endocrine Disruptors" "*Prenatal exposure to natural and synthetic estrogens is associated with increases in breast and vaginal tumors in humans as well as uterine tumors in animals. New findings suggest that causes of endocrine-related cancers or susceptibility to cancer may be a result of developmental exposures rather than exposures existing at or near the time of tumor detection."*

UTERINE CANCER-

CRISP Data Base NIH (no author stated) reports, "*Perinatal Estrogen, Oxidative Damages & Uterine Lesions- ….exposure of the uterus to synthetic and natural estrogens during the perinatal period might alter the uterine genome during development, which, in*

turn, ay predispose an individual to the development of adverse effects, including cancer."

2003, CRISP Data Base NIH, "…..how exposure of the uterus to synthetic and natural estrogens during the perinatal period might alter the uterine genome during development, which, in turn, may predispose an individual to the development of adverse effects including cancer."

2002, "Phytoestrogens and Health," GS Gilani and JJB Anderson report, "*…..concern still exists regarding other (soy) estrogen-like mechanisms of uterine carcinogenesis. Prenatal and neonatal exposure to synthetic estrogens such as DES has been associated with several reproductive abnormalities, including uterine carcinoma. A recent study demonstrated that one daily subcutaneous injection of genistein for 5 days at a dose of 50mg kg body-day to neonatal mice generated uterine adenocarcinomas 18 months postadministration…… comparable to that produced by an equipotent dose of DES. Data compiled from 20 studies evaluating soy isoflavone effects on uterine weights……. indicate significant differences in uterine weight vs controls. These studies highlight the importance of timing of exposure in determining uterine responses and also the need for endometrial assessment in phytoestrogen studies."*

On May 31, 2001 the National Institute of Health issued a Press Release reporting, "*Infant mice given genistein developed cancer of the uterus later in life.\ scientists at the NIEHS reported today. In the study published in the June issue of Cancer Research, the scientists treated female mice for five days after births with genistein a substance in soy that is similar to the female hormone, estrogen. 'The data suggest that genistein is carcinogenic if exposure occurs during critical periods in a young animal's development,' lead author Retha Newbold of NIEHS said. In the study newborn mouse pups were injected with an amount of genistein within the range similar to what a newborn human infant might receive in soy-based infant formula. The finding is similar to work Newbold did with DES exposure in unborn mice. Christopher Portier, Ph.D NTP associate director said, "These data clearly suggest that more research is needed."*

Retha Newbold et al, Cancer Resources 2001:Jun 1;61(11), " (*In female mice) At 18 months the incidence of uterine adenocarcinoma was 35% for genistein, and 31% for DES. These data suggest that genistein is carcinogenic if exposure occurs during critical periods of differentiation. The use of soy-based infant formulas…..should be closely examined."*

PROSTATE CANCER-

A study published by the, National Center for Toxicological Research, FDA, 2002, Sept 25; 777(1-2):249-60, titled "*Estrogen receptor expression in the prostate of rats treated with dietary genistein (soy). "Genistein, a naturally occurring bioflavonoid primarily found in soybeans, interacts with estrogen receptors alpha and ER beta with preferential affinity for ER beta. This is one mechanism whereby genistein may affect growth and development and potentially alter susceptibility to carcinogenesis. Given the growing body of knowledge on the significance of ER beta in the prostate, the evidence…. by genistein may have implications for reproductive toxicity and carcinogenesis that warrants further investigation."*

BLADDER CANCER-

2002, "Cancer Epidemiology Biomarkers & Prevention," CL Sun et al report, "*Dietary Soy and Increased Risk of Bladder Cancer- High intake of soy food was statistically significantly related to an elevated risk of bladder cancer. Relative to the lowest quartile of energy-adjusted total soy intake (<36.9g/1000 Kcal), the highest quartile of total soy intake (>or equal to 92.5g/1000 Kcal) was associated with a 2.3-fold increase in bladde3r cancer risk(95% confidence interval=1.1-5.1)……Similar results were obtained for intakes of soy protein and soy isoflavones. The soy food-bladder cancer risk association did not differ significantly between men and women and was not explained by other dietary factors. The soy-cancer relationship became stronger when the analysis was restricted to subjects with longer (>or equal to 3 years) duration of follow-up."*

2003, "American Journal of Clinical Nutrition," Walter Willett reports, "*…several intervention studies using high doses of soy estrogens have shown changes in breast nipple fluid that would predict higher rates of breast cancer."*

2005, "Toxicological Sciences," A Nishikawa et al report, "*….thyroid tumorigenesis in rats treated with excess soybean and iodine-deficient diets- Thus co-exposure to excess soybean and iodine deficiency results in synergistic promotion of DHPN (2-hydroxypropyl nitrosamine)-initiated thyroid tumorgenesis in rats, of which mechanisms appear to primarily involve effects on serum hormone levels."*

2008, "World Journal of Gastroenterology" L. D. Wang et al report, "*Phytoestrogen genistein…can directly inhibit the contractile activity of isolated gallbladder muscle both at rest and in response to stimulation. The mechanisms responsible for the inhibitory effects (are) probably due mainly to inhibition of tyrosine kinase, Ca(2+) influx though potential-dependent calcium channels, and Ca(2+) release from sarcoplasmic reticulum, but were not related to the estrogen receptors."*

STOMACH CANCER-

1992, "Beijing Institute for Cancer Research," (no author stated), "*The experimental results showed that the extract of the sour corn-soybean cakes containing carcinogenic and mutagenic subjects could have some casual relationship with the incidence of stomach cancer."*

COLON CANCER AND GASTROINTESTINAL DAMAGE-

2007, "Food and Chemical Toxicology" KT Daly et al report, "*The purpose of this study was to investigate the effects of dietary soy isoflavones on early stage colon cancer in various ages of female rats. Young (1 month), mature (11 month) and old (22 month) female Fisher 344 rats were fed either the control diet or a diet containing 0.4% soy isoflavone isolate for…..15 weeks. The concentration of isoflavones in the diet was 2g/kg diet, composed of 1.2g/kg genistein, 0.7g/kg daidzein, and 0.1g/kg other isoflavone including …..genistein, daidzein and glycitein. Five of the 21 rats fed the soy supplement died before the end of the experiment while all animals on the control diet survive to term. The density of normal crypts lining the colonic mucosa was reduced in rats fed the soy compared to control diet, indicating gastrointestinal damage. Uterine weights, serum estradiol and serum isoflavone levels were increased in……. the soy-supplemented diets compared to age-matched controls, suggesting an increasing estrogenic response with age to isoflavone supplementation."*

2007, "Journal of Endocrinology," R Xiao et al report, "*We examined effects of dietary soy protein isolate (SPI) or genistein (GEN; soy isoflavone) during pregnancy on development of colon cancer in male progeny Sprague-Dawley rats. Maternal-only SPI increased the percentage of animals bearing multiple colon tumors…..Serum insulin and leptin concentrations were decreased by lifetime SPI……Results indicate an effect of dietary protein type during pregnancy on colon tumor multiplicity and colon tissue gene expression……"*

LIVER CANCER/DAMGE- 2005, "Toxicology Research Division" A Hierlihy et al report, "*Effects Of Diets Containing High Soy Protein And Isoflavones On Gene Expression In Female Rat Livers- Phytoestrogens have been implicated both as agonists and antiagonists of estrogen dependent cancers. These naturally occurring compounds have been shown to have estrogenic properties. The major human dietary source of isoflavones is obtained from soy foods. ……..possible concerns exist in their (phytoestrogen) actions as endocrine disrupters. Particularly in populations where exposure is high such as in infants consuming soy-based milk formulas. Data comparing the effects of control vs high isoflavone diets on female liver from day 28 show greater than 2-fold increases in gene expression in several metallothione genes. Temporal expression of estrogen-responsive receptors was observed. Furthermore, downregulation of several genes involved in fatty acid metabolism may have serious consequences. Investigation into the changes in gene expression at day 70 and day 240 are ongoing"*

PANCREATIC CANCER- Food Safety Research Unit, USDA-ARS, report, "*Feeding soy concentrate to weaning rats over a one-week period produced a dose-related increase in pancreatic weight."*

1979- Pubmed, NIH medical study site reports, "*Carcinogenic effects…..in male Wistar rats; promotion of pancreatic cancer by a raw soya flour diet- The group fed raw soya flour developed hyperplastic and adenomatous pancreatic nodules and pancreatic adenocarcinomata. We conclude that a diet of raw soya four augments the carcinogenicity of pancreatic carcinogens in the rat."*

Studies confirm that the soybean inhibition of trypsin interrupts the endocrine system, such as the cholecystokinin (CCK) hormone system and through this action soybeans abnormally increase CCK hormone levels.

1997, "Toxicology and Applied Pharmacology" JD Obourn et al report, "*Evidence that A8947 enhances pancreas growth via a trypsin inhibitor mechanism. ….suggesting a mechanism of action similar to that of raw soy protein, in which trypsin inhibition in vivo results in increased CCK levels followed by pancreatic acinar cell hypertrophy and proliferation." (*As stated in detail on page 121).

1984, "AJP- Gastrointestinal and Liver Physiology," PS Oates and RG Morgan report, "*Short-term effects of feeding raw soya four on pancreatic cell turnover in the rat…..Feeding RSF (raw soya flour) for 2 days resulted in significant increase in pancreatic weight and RNA content……Histological studies of the pancreas during the first week showed cell damage and tissue necrosis, possibly due to exposure to high levels of cholecystokinin released by RSF."*

1995, "British Journal of Nutrition," Grorge Grant et al report, "*However, long-term exposure to a soya-bean- or cowpea-based diet induced an extensive increase in the relative and absolute weights of the pancreas and caused an increase in the incidence of*

macroscopic pancreatic nodules and possibly pancreatic neoplasia. Long-term consumption of the cowpea-, kidney-bean-, lupin-seed- or soya-bean-based diets by rats resulted in a significant increase in the relative weight of the caecum and colon."

1991, "Food Chemistry Toxicology," BA Myers et al report, "*All groups of azaserine-initiated rats had large numbers of atypical acinar cell foci per cm3 of pancreas. Of these, the group fed 3.7% STIC, (Soya bean trypsin inhibitor concentrate) had pancreatic foci that occupied a significantly greater percentage volume of pancreas than did groups fed 20% corn oil or control diets, which contained 5% corn oil and no added trypsin inhibitor."*

1987, "Cancer Research" BD Roebuck et al report, "*Effects of Dietary Fats and Soybean Protein on Azaserine-induced Pancreatic Carcinogenesis and Plasma Cholecystokinin in the Rat. Both dietary unsaturated fat and raw soybean products are known to enhance pancreatic carcinogenesis when fed during the postinitiation phase. A comparison of these two dietary components was made to evaluate the relative potency of each ingredient for enhancing pancreatic carcinogenesis and to determine if this enhancement was correlated with an increase in plasma chyolecystokinin (CCK). Both the 20% corn oil diet and raw soy protein isolate diet enhanced pancreatic carcinogenesis. The effects of the raw soy protein isolate on the growth of the carcinogen-induced lesions were significantly greater than the effects of the 20% corn oil diet. Plasma CCK values were….. significantly elevated in rats fed the raw soy protein isolate."*

Studies report that increased CCK can also aggravate pancreatitis and worsen the prognosis of pancreatitis by stimulating the injured pancreas, resulting in the vicious circle via endogenous CCK release.

2004, "Biochemical Pharmacology" P Melin et al report, "*The isoflavone genistein stimulates the wild-type and delF508-cystic fibrosis transmembrane conductance regulator (CFTR) channel activity…By contrast, the response of G1349D- and G551D-CFTR to genistein is dramatically altered…..genistein stimulates G551D-CFTR without any inhibition at high concentrations. We conclude from these results that…..because both mutations alter specifically the mechanism of CFTR channel activation by genistein, we believe that the signature sequences of CFTR act as molecular switches that upon interaction with genistein turn on and off the channel."*

KIDNEY DISEASE/CANCER-

2001, Reproductive Toxicology," KB Delclos et al report, "*Genistein is a naturally occurring isoflavone that interacts with estrogen receptors and multiple other molecular targets. Human exposure to genistein is predominantly through consumption of soy products, including soy-based infant formula and dietary supplements. Both sexes showed an increase the incidence and/or severity of renal tubal mineralizations at doses of 250 ppm and above. Dietary genistein thus produced effects in multiple estrogen-sensitive tissues in males and females that are generally consistent with its estrogenic activity. These effects occurred within exposure ranges achievable in humans."*

2009, Hugo Gene Nomenclature Committee, (HGNC) reports, "*The protoncogene kinase activity MET product is the hepatocyte growth factor receptor and encodes tyrosine-kinase activity. Various mutations in the MET gene are associated with papillary renal carcinoma."*

SOY CAUSATION OF ADDITONAL DAMAGE TO HEALTH:

BONE DISEASE-

Study in "Toxicology" reports- "*Results demonstrated that developmental and adult exposures of rats to endocrine active chemicals at the concentrations tested had varied degrees of myelotoxicity (destruction of bone marrow) with Genistein being the most potent."*

GASTROINTESTINAL DISTRESS-

AAP also reports, "*Severe gastrointestinal reactions to soy protein formula have been described for >30 years…..Severe enterocolitis (inflammation of both small and large intestine) has also been well described in infants receiving soy protein-based formulas. Eosinophilic proctocolitis, (inflammation of rectum and colon …also has been reported in infants receiving soy protein-based formula."*

"Journal of Pediatric Gastroenterology & Nutrition" reporting on abdominal discomfort in infants, "*Little is known about the type and amount of gas produced by the infant's colonic microflora ….. CH 4 (malodorous methane gas) was produced in greater amounts by infants fed soy formula than infants on other diets. Production of CH 3 SH (methanethiol) was conspicuously low by feces of breast-fed infants, and production of H2S (hydrogen sulfide) was high by soy formula-fed infants."*

CH 4 methane is a component of natural gas, methanethiol at high concentrations is toxic, H2S hydrogen sulfide is highly toxic, all proving damaging to the gastrointestinal system as well as the central nervous system particularly during fetal and infant development.

INTESTINAL DAMAGE-

2004, "Journal of Nutrition," An-Chian Chen and Sharon M. Donovan report, *"Genistein at a Concentration Present in Soy Infant Formula Inhibits Caco-2BBe Cell Proliferation by Causing G2/M Cell cycle Arrest- ……U.S. infants are fed soy formulas containing up to 47mg/L of isoflavones thus, these infants' intestines are exposed to a high dose of genistein, a phytoestrogen and tyrosine kinase inhibitor. The low genistein concentration increased intestinal cell proliferation by 28% (in human intestinal cells)…….In contrast the high genistein concentration reduced cell number by 40%, proliferation by 94%, and caspase-3 activity by 50% compared to control. Cell cycle analysis after 48 hour exposure to high genistein reveal 37% of cells in G0/G1 and 35% in G2/M vs 71% in G0/G1 and 17% in G2/M for the control and low genistein groups. Thus, a biphasic effect of genistein was seen with a low dose stimulating intestinal cell proliferation through the estrogen receptor, whereas a high dose of genistein inhibited intestinal cell proliferation and altered cell cycle dynamics. A high dose of genistein (as found in soy formulas containing up to 47mg/L of isoflavones) may potentially compromise intestinal growth."*

LIVER DISEASE-

1987- SoyOnline Service reports the study, *"Dietary estrogens-a probable cause of infertility and liver disease in captive cheetahs,"* by KD Setchell et al- *"At this time, however, reproductive failure and liver disease threaten the future of captive cheetah population. Histopahological evaluation of more than 100 cheetah livers identified venocclusive disease as the main hepatic lesion responsible for liver disease in this species. Analysis of the commercial feline diet by high-performance liquid*

chromatography and gas-liquid chromatography-mass spectrometry revealed large amounts of two phytoestrogens identified as daidzein and genistein. These compounds were found to be derived from a soybean product that was a component of the cheetah diet, and their concentrations both ranged from 18 to 35 micrograms/g diet. We conclude that the relatively high concentrations of phytoestrogns from soybean protein present in the commercial diet fed to captive cheetahs in North American zoos may be one of the major factors in the decline of fertility and in the etiology of liver disease in this species. The survival of the captive cheetah population could depend upon a simple change of diet by excluding exogenous estrogen."

SIDS-

"Sudden Infant Death Syndrome: The Colon Connection" by Drs. Mann and Rossaro report, "*Some sulfate reducing bacteria in the colon produce hydrogen sulfide H2S hydrogen sulfide which is as toxic as hydrogen cyanide. We are putting forth the hypothesis that in some cases of SIDS colonocytic mechanism for detoxifying H2S may not have matured by the age of 3 months, and H2S (increased by soy-based formula and foods) may be absorbed resulting in SIDS."*

SOY POTENTIAL CAUSE OF TUBERCULOSIS-

2004, "Clinical & Experimental Immunology" EM Curran et al report, "*Collectively, these results suggest that dietary soy isoflavones, such as genistein, may impact resistance or susceptibility to infection. Interestingly, an epidemiological study reported that the vegetarian diet of Asian immigrants in the United Kingdom was a risk factor for tuberculosis…..dietary factors, such as the phytoestrogens content were not ruled out."*

2002, BOOK REVIEW: *"Phytoestrogens and Health,"* by GS Gilani and JJB Anderson report, "*The use of phytoestrogen supplements (soy protein isolates) at potentially ….higher doses raises the possibilities of potential harmful effects from excessive consumption. The distinction between healthy intakes and excessive intakes must be determined. The risk of deleterious effects of phytoestrogens when ingested in high quantities remains an area of great concern……Those actively investigating the health effects of isoflavones include the U.S. Federal government…..Although soybeans do contain numerous biologically active constituents including phytic acid, phenolic acids, saponins, oligosaccharides, protease inhibitors, glyceollins, phytosterols, a-linolenic acid……it is the presence of isoflavones that is overwhelmingly responsible for the interest in soy. These physically active compounds have similarities to 17-B estradiol. The classical definition of phytoestrogens is that they are compounds that exert estrogenic effects on the central nervous system, induce estrus, and stimulate growth of the genital tract of female mammals. Therefore, phytoestrogens (phytochemicals have estrogenic properties), can act either as estrogen agonists or as estrogen antagonists….Current knowledge is not sufficient to support dietary recommendations for individual phytoestrogens……Finally, the recommendations regarding the intake of dietary phytoestrogens should be made with caution.*

Coumestrol in human food is found in soybean sprouts, and abundant in alfalfa sprouts, clover sprouts, and mung bean sprouts. Irvine et al found highly variable amounts of phytoestrogens in food products made from cereals, with genistein ranging from 3 to 287 pu/g and daidzein from 2 to 276 pu/g.

In particular, phytoestrogens with relatively high estrogenic potency and known adverse effects should be defined as pharmaceuticals and controlled accordingly.

The phytoestrogen concentrations in soy products depend on plant variety, location, year of harvest, and maturity. Total concentrations and daidzein are very different in soy products, such as alcohol-extracted soy protein concentrate and soy protein isolate (SPI). The range of average total concentrations of isoflavones in different varieties of soybeans is 1-3mg/g, but the concentrations of isoflavones vary widely depending on a number of factors, such as environmental variables affecting growth of the plant, the genetic makeup of the plant, time of harvesting and conditions of processing.

Assuming that consumption of phytoestrogens is always beneficial would be naive because excessive or inappropriate consumption may be harmful. In addition the estrogenic effect of phytoestrogens may be unpredictable. Phytoestrogens have been shown to induce infertility and developmental toxicity in certain animals.

Excessive intake of phytoestrogens could exert detrimental, if not toxic, estrogenic effects. This issue is a cause for serious concern…..

Significant dose-related increases in genistein content were observed in brain, liver, mammary, ovary, prostate, testes, thyroid and uterus. Despite the lower total genistein in offspring serum, the level of genistein in brain (0.2pmo/mg) …..were three-to fivefold higher than that found in adult rats. These findings and the increased sensitivity of developing brain to toxicological effects of chemicals are consistent with the transplacental effects of genistein on mammary glade differentiation and promotion of mammary carcinogenesis and effects on the developing CNS in rats treated in utero. Furthermore, the high concentrations of isoflavones measured in cord plasma and amniotic fluid….demonstrated efficient transfer from the maternal circulation (to infants) in humans.

The many remarkable similarities between genistein metabolism in humans and rats suggests the validity of this interspecies comparison for further assessments of biological activity based on these metabolites. Considerable intersubject variation is found in the absorption, metabolism, and excretion of isoflavones. The FDA-approved health claim is not specific about the isoflavone content in the soy protein….isoflavone supplements are becoming common, and there is increasing evidence to suggest that pure isoflavone supplements may be harmful to some individuals.

Genistein has similar bioavailability when ingested as either aglycone or as the glucoside conjugates present in soy. The extensive conjugation of genistein that occurs in the intestine and liver leads to enterohepatic recirculation, which significantly prolongs the time of elimination and helps maintain serum steady-state levels. Despite the extensive conjugation of circulating genistein, the small remaining fraction of aglycone is sufficient to drive accumulation in lipophilic tissues from repeated dosing to levels consistent with significant occupancy and activation of ER a and B. Such estrogenic activity is presumably responsible for many of genistein's biological activities. There are 12 isoflavone chemical entities that can be present in soy foods, 3 aglycones and 9 glucosides, and the proportions of these differ among the various soy foods. Therefore, there is potential for differences in the bioavailabilites of these various chemical forms, both in terms of the possible influence of structure on cellular transport as discussed earlier, as well as on resistance to bacterial metabolism. In addition to the

differences in the chemical forms of isoflavones in the different foods, other factors such as the physical form and consistency of food, (liquid, solid, or pill) may also potentially influence availability of isoflavones for absorption. In addition because large individual-to-individual differences exist, particular care must be taken with study design……In the last few years, there has been substantial progress in our understanding of the digestion, transport, and metabolism of the isoflavones, and the related areas of bioavailability and pharmacokinetics. For example, contrary to earlier belief, it is now recognized that the hydrolysis of glucosides by bacterial hydrolases is not mandatory for intestinal transport. Although a large number of bacterial and mammalian metabolites have now been identified we have yet to account for all the ingested isoflavones. The amount of isoflavone absorbed, its rate of absorption, and the length of time serum levels remain elevated may all influence the action of the isoflavone……it is also possible that enhanced fermentation (rarely is fermented soy marketed in this country) may result in bacterial metabolism of the aglycone rendering it unavailable for absorption, and less rather than more isoflavone may be absorbed….chemical forms of the isoflavones can be altered as a result of heat treatment or enzyme reactions during fermentation. In the human diet, soybeans constitute the most abundant source of phytoestrogens. There is increasing interest in the possible effects of dietary phytoestrogens on human health because phytoestrogens are suggested to play a role in the development of hormone-dependent diseases. …..it has been suggested that phytoestrogens, similar to any other hormonally active agents in the environment, may act as endocrine disruptors and cause adverse effects in the reproductive system. Clearly, if a compound is an estrogen (i.e. interacts with ER) it may have the potential for beneficial or adverse effects, depending on the target cell or tissue, age and time of exposure, the hormonal milieu, and the dose or concentration in the target tissue. Furthermore, in addition to estrogen-like activity, phytoestrogens exert multiple other biological actions that occur independently of ER……studies indicate that isoflavonoids and coumestans can induce typical estrogen-like effects in may estrogen target organs…..it is likely that effects may occur via both ER subtypes. At a low dose range, isoflavonoids may induce tissue-selective effects……

…..the actions of isoflavones in stimulating the synthesis and secretion of other important osteoclastogenesis-related proteins, including IL-6, OPG, and RANKL, have been largely ignored. Estrogens are known to modulate the immune response and enhance cytokine production. Feeding high isoflavone soy has been shown to increase IL-6 production……. negative effect of soy is the suggestion that isoflavone may cause a rare form of childhood leukemia and brain atrophy ……

The soybean and its products have been considered goitrogenic in humans and animals. Specific concerns have been raised because of reports of goiter and hypothyroidism in infants receiving soy-containing formula. Studies are warranted to confirm whether an inverse association exists between intake of phytoestrogens and thyroid cancer, especially in populations with substantially higher intake levels.

Interestingly, in the ecologic study conducted by Nagata et al, these investigators, reported significant positive correlations between colorectal cancer mortality rates and soy product intake in men and women……. It has now been demonstrated that ER are present in the colon mucosa. Thus it seems reasonable that estrogen or estrogen-like substances may influence colon cancer. People consuming soy products or isoflavone supplements would clearly have sufficient genistein in the colon and blood to elicit an

estrogenic response via the ERB. Lastly, the observation that genistein increased chemically induced colon cancer alerts us to the possibility that phytoestrogens consumed as pure compounds at levels found in food matrices may have adverse consequences.

We conducted a detailed review of (soy food) studies and found that 10 of the 15 studies showed that high intake of fermented soy foods was associated with an increased risk of stomach cancer.

Prenatal and neonatal exposure to synthetic estrogens such as DES has been associated with several reproductive abnormalities, including uterine carcinoma. Recently neonatal exposure to genistein at 50mg/(kg body-d) was associated with a 35% incidence of uterine adenocarcinomas in CD-1 mice at 18mo. comparable to that produced by an equipotent dose of DES. These studies highlight the importance of timing of exposure in determining uterine responses and also the need for endometrial assessment in phytoestrogen studies.

…..experimental studies clearly indicate that isoflavonoids stimulate the growth of estrogen-responsive breast cancer cells, and that this effect is likely to occur via ERa

Phytoestrogens and soy isoflavone in particular, also have critical mechanisms of action occurring independently of the ER, including antioxidation, effects on growth factor-induced signal transduction, and modulation of estradiol metabolism…..nonhormonal actions, and the complex determinants of these actions in vivo, represent important lines of inquiry.

….consensus regarding their (phytoestrogen) application to cancer prevention is lacking, due in part to concern over potential estrogen-like actions in the breast and uterus, and general statements regarding aggregate benefit of risks of phytoestrogen consumption cannot yet be made. Further research is required in the following areas: to define clinical conditions and doses for …..harmful effects; to elucidate tissue-specific phytoestrogen metabolism and receptor status; and to evaluate phytoestrogen inter-actions with estradiol, enzymes of estradiol biosynthesis, antiestrogens, and other dietary components. It is important that these questions be addressed in the process of making dietary recommendations on human phytoestrogen consumption.

Topoisomerases constitute a family of conserved essential enzymes that resolve topological problems during DNA replication transcription and recombination. ….topo II inhibitors are distinguished into catalytic inhibitors or poisons……genistein can be classified as a topo II poison. Because normal topo II activity is essential for chromosomal segregation, the catalytic inhibitors of top II are expected to cause abnormalities in sister chormatid segregation during the mitotic phase of the cell cycle. These abnormalities can result in chromosomal breakage and apoptosis…..the formation of the cleavable complex by topo II poisons (including genistein) can be dissociated from the downstream signals that lead to catastrophic DNA damage and apoptosis. …..sublethal doses of genistein may cause permanent genetic alterations. If these alterations involve key regulatory genes such as transcription factors, oncogenes, or tumor suppressor genes, carcinogenesis may be initiated. …..myeloid leukemia is an example of this delayed adverse effect of topo II poison-induced genetic toxicity. The determination that certain tissues, including the mammary gland, accumulate higher levels of genistein than those found in serum, supports the possibility that genistein may cause delayed adverse effects by producing low levels of DNA damage either by

stabilizing the interactions between DNA and topo II or by promoting abnormal chromosomal segregation.

Deleterious Effects of Genistein Following Exposure During Critical Stages of Development- Genistein, the principal isoflavone in soy, interacts with estrogen receptors and multiple molecular targets. Despite all of the hypothesized beneficial effects of soy genistein, the potential for deleterious effects has not received equal attention. It is well know that the developing fetus and neonate are uniquely sensitive to perturbation with estrogenic chemicals……A recently published epidemiologic study by Strom et al found differences between young adults who were fed soy formula as infants vs those fed cow's milk; problems reported in the soy formula group included increased incidence of multiple births, stillborn deliveries, preterm deliveries, and greater discomfort with menstruation……a recent study by North et al reports that male infants, born to vegetarian mothers consuming high levels of phytoestrogens, have an increased incidence of hypospadias, suggesting that phytoestrogens do indeed play a role in the deleterious effects on the developing reproductive system. Additional evidence for adverse effects of genistein can be seen with experimental studies that show that exposure of pregnant dams to genistein enhanced 12-dimethyl benz(a)anthracene (DMBA)-induced mammary tumors in their female offspring. Furthermore, adverse effects of soy-containing foods and soy components on reproductive processes of experimental animals and human have been reported. ….the effects of genistein on representative estrogen target tissues of outbred CD-1 mice…..were evaluated by treating neonates on day 1-5 of life with genistein dissolved in corn oil as previously described for other estrogenic substances. The doses were administered as subcutaneous injections (0.5, 5.0, and 50mg/kg – d) and compared with DES at 0.001mg/kg- d), which is equal in estrogenicity to the highest dose of genistein (50mg/kg-d)….we showed that th4e maximal circulating serum levels of genistein (conjugated + aglycone) in the high dose group were comparable to those reported from dietary exposures in rats and in human infants consuming soy-based formulas. Alterations observed in the ovary, reproductive tract (oviduct, uterus, cervix, and vagina), and mammary gland after development exposure to relevant levels of genistein were discussed. Genistein, long recognized for its estrogenic activity, has been shown to exhibit a 20-fold higher relative binding affinity for estrogen receptor ERB than ERa….the role of Era and ERB and the extent to which each contributes to the actions and possible toxicity of genistein exposure has only recently come under investigation. …unique to the study of genistein is its well-described tyrosine kinase inhibitory properties. Genistein has also been reported to have genotoxic activity…..mice treated with higher doses of genistein yielded a reduced number of ovulated oocytes….mice exposed to the lowest dose of genistein are apparently ovulating more oocytes, they may possibly exhibit premature depletion of oocytes resulting in early reproductive senescence. In fact, our laboratory has previously shown a similar phenomenon in mice exposed prenatally to low doses of DES….. It is interesting to note that the dose of genistein that induced the highest level of ERa expression in the (ovarian) granulose cells is the same dose that caused the highest number of oocytes following superovulation.

Incidence of selected abnormalities in mice (ages: 6-8 weeks, 4-6 months, and 18 month old) related neonatally with (similar levels of) DES or genistein- uterine hyperplasia, excess vaginal keratinization, uterine squamous metaplasia, uterine

adenocarcinoma progressive proliferative lesion of the oviduct, cystic endometrial hyperplasia. These data suggest that some of the effects of genistein are similar to those of DES, but others such as lack of corpora lutea, may be even more severe with genistein than equal estrogenic doses of DES. Low numbers of corpora lutea suggest that these mice exhibit some level of subfertility. Indeed, high doses (genistein 50mg/(kg-d) such as those reported do contribute to persistent vaginal cornification, lack of cyclicity, and infertility. Abnormalities in the oviduct were seen in both the DES and genistein treatment groups at 18 mo. of age…..progressive proliferative lesion of the oviduct was seen in 100% of the aged genistein-treated mice. AT 6-8 weeks and 4-6 months of age, uterine hyperplasia, and squamous cell metaplasia were typical findings in DES and genistein treated mice but not controls; uterine hyperplasia was higher in genistein-treated mice compared with DES at both ages….At (18 month) age, the incidence of cystic endometrial hyperplasia of the uterus was similar in both DES and genistein treatment groups….genistein caused a significantly increased incidence of cystic endometrial hyperplasia, suggesting that CEH was related to estrogen treatment….unlike the younger ages, the incidence of uterine squamous cell metaplasia of the uterus was higher in the genistein-treated mice than in the DES-treated mice…..64% in genistein group and 38% in DES group but not in control, again suggesting that this lesion was definitely treatment related. Furthermore, other severe pathologies occurred after neonatal exposure to both DES and genistein. Atypical hyperplasia of the uterus….35% of genistein treated mice had cellular alterations that progressed to uterine adenocarcinoma. Some tumors extended through the myometrium to the serosal surface of the uterus. Mitotic figures and nuclear pleomorphism were frequently observed. In comparison, at an equal estrogenic dose of DES (0.001mg/9kg-d), 31% had uterine adenocarcinomas. Similar malignant lesions were not observed in control mice of this strain. These data show the induction of benign and malignant reproductive tract lesions….in mice treated neonatally with genistein. The dose of genistein was within the range to which humans may be exposed in soy infant formulas based on levels reported by Setchell. The association of estrogenicity and carcinogenicity in the neonate is supported by results of other studies comparing metabolites of estradiol……..Newgold et al recently reported that genistein administered by sc injection on PND 1-5 at 50mg/kg produced uterine adenocarcinomas in mice with an incidence similar to that of equally estrogenic dose of DES. This dose resulted in low……..serum levels of genistein (Doerge et al) and clearly demonstrates an adverse estrogenic effect of genistein after developmental exposure.

……the effects of genistein on the development of the mouse mammary gland were examined at 5 and 6 weeks of age after neonatal exposure. Terminal end buds (TEB) are responsive to local and systemic hormones that drive ductal morphogenesis. Mice treated with the lowest dose of genistein (0.5mg/(kg-d) showed similar increase (to controls) in the number of TEB from 5-6 wk but the numbers are higher overall than those of controls at both ages. Strikingly, the genistein 5mg dose group showed a different pattern of mammary gland development with more TEB present at 5wk of age and less at 6wk of age, suggesting an advance in differentiation at this dose. The highest dose of genistein (50mg/(kg-d) showed a number of TEB similar to that of controls, but mammary gland morphology was abnormal with smaller ducts and less ductal branching. These measurements (length of the furthest elongated duct from the lymph node) showed

that the expanding mammary ductal mass increased after exposure to genistein at the 5mg/kg dose at 5wk, and at the 0.5 and 5mg/(kg-d) doses at 6 wk of age. The 50mg/(kg-d) dose at both time points showed a shorter expansion into the fat pad than controls and the amount of mammary gland in the fat was less than all of the other treatment groups. This stunted development was evidence throughout the life of the mice….the lactational function of this hypoplastic mammary gland was not tested due to poor fertility experience by this dosed group. Rats treated neonatally with genistein have been reported to have low progesterone levels. ….Further indication of progesterone's role in this abnormal (mammary gland) morphology is demonstrated in progesterone receptor knockout mice which have severely limited mammary gland development similar to our high-does genistein-treated mice. In addition, a recent report of Hilavkivi-Clark et al showed that lower doses {~0.067-1 mg(kg-d)}given prenatally resulted in high incidences of DMBA-induced mammary cancer. Therefore, the effects of genistein on the mammary gland are complicated because of dose dependency and timing of exposure. Russo and Russo established the rodent mammary gland as a useful tool for testing carcinogenic compounds……..because rodent lesions are similar to those found in humans……

Feeding of genistein to Sprague-Dawley rats from GD 7 throughout PND 50 at doses of 250-1250 pg/g resulted in hyperplasia and hypertrophy of ductal and alveolar mammary glands in male pups evaluated at PND 50.

In the case of the isoflavone genistein, interactions with estrogen receptors does occur at lower concentrations than does interactions with many other molecular targets, although inhibition of thyroid peroxidase by genistein has been clearly demonstrated in rats at low dietary dose levels. The DNA damage reported by Strick et al….results from the inhibition of topoisomerase II….and soy-induced goiter likely results from inhibition of thyroid peroxidase by soy components including isoflavones.

A variety of exposure regimens have been used to evaluate the safety and toxicity of phytoestrogens in developing rodents. These include exposures during pregnancy, the neonatal period, the prepubertal period, or a time period that spans part or all of these developmental stages. In some cases, experimental designs that include developmental exposures to phytoestrogens continue treatment into adulthood……Importantly ….studies have shown that substantial transfer of isoflavones occurs to the fetus and nursing pup from treated dams.

Furthermore, prenatal and early neonatal treatment of human subjects with genistein should be approached with utmost caution because of the toxic and carcinogenic effects of genistein on differentiating reproductive tract tissues.

Effects of developmental exposures to phytoestrogens or phytoestrogen-containing foods observed in female rodents……..include birth weight and litter size decreases, acceleration or delay of puberty…..altered length of estrous cycles, changes in serum sex hormone, altered ovarian, uterine, and vaginal histology, altered mammary gland development, alterations of sexually dimorphic structures in the brain, altered pituitary responsiveness to gonadotropin-releasing hormone, altered fertility, and cancer. The occurrence, magnitude, and direction of these effects have been shown to depend on the timing, and magnitude of the dose administered……

In addition, Thigpen et al and Brown and Setchell pointed out the high levels of isoflavones present in soy-containing diets, and the latter authors reported high serum levels in newborns and adult animals consuming these diets.

Estrogens are known to affect multiple organs outside of the reproductive tract and mammary glands, some of which, such as the central nervous system and pituitary have direct effects on reproductive behavior and function; others such as bone do not. Recent data from a series of short-term studies conducted with genistein suggest that some of the nonreproductive end points may be more sensitive (show effects at lower doses) than the reproductive end points.

Neuroendocrine effects of genistein, zearalenone, coumestrol and flaxseed have been reported.

Summary of effects of dietary genistein on Sprague Dawley (male and or female) rats) in a series of short-term studies …from gestational day 7, dosing (5 or 25 pg/g feed) continued throughout pregnancy and lactation up to PND 77. End point/effect: Increased anti-CD3-mediated splenocyte proliferation, altered spleen T- and B-cell populations, decreased bone marrow subpopulations, decreased thyroid peroxidase activity, mammary gland hypertrophy and hyperplasia, decreased volume of SDN and POA, mineralization of renal tubules, increased hepatic 5a-reductase, mammary gland hyperplasia, vaginal dyssynchrony, epididymis, hypospermia, ovarian degeneration, increased spleen lgM-forming cell response to T-cell-dependent antigen, decreased body weight, increased consumption of salt-flavored solution, inflammation, dorsolateral prostate, decreased ventral prostate weight and secretory material, depletion and retention of elongated spermatids, decreased hepatic cyrochrome P 450 isozymes.

….. studies indicate that phytoestrogens can affect the perinatal organization of the brain and reproductive system and produce lasting effects on reproductive behavior. In addition to effects on reproductive behavior, Flynn et al examined the effects of dietary genistein on other sexually dimorphic behavior in Sprague-Dawley rats. All of these behaviors have been shown to be sexually dimorphic and can be altered by interfering with sex hormones during the time of central nervous system development. …..genistein was able to feminize this behavior in males and hyperfeminize the behavior in females, although the extent to which this effect was induced during the organization of the central nervous system could not be determined from study design used.

….peak bone mass achieved in younger animals is a major determinant of risk for later osteoporosis. Migliaccio et al determined that perinatal treatment of mice with DES induces changes in bone development with effects that last into adulthood. Fukazawa et al also reported that neonatal exposure to DES resulted in shorter bones,…..decreased osteoblast numbers, implying decreased bone formation. …..it is possible that environmental estrogens may affect bone development……Given the high exposure of some infants to soy phytoestrogens, additional targeted studies on potential beneficial and adverse long-term effects of developmental phytoestrogen exposures on bone seem warranted. Changes in B- and T-cell populations and myelotoxicity were also seen in the pups (Sprague-Dawley), but not the dams, and these effects varied according to dose and sex.

……rodent studies indicate that developmental exposure to phytoestrogens or phytoestrogen-containing foods can alter multiple end points in both sexes in multiple organ systems ranging from the reproductive system, for which considerable data have been generated, to the immune system, which is only beginning to be examined. The magnitude and direction of the responses are dependent on the compound, the dose, and the timing of the dose. Many, but not all of the observed effects are consistent with the

conclusion that the interaction of the compounds with estrogen receptors is an important component of the mechanism of action. For developing humans, exposure to phytoestrogens can occur in utero, a time period that is well modeled in rodents. However, the time of highest exposure to phytoestrogens is the postnatal period, a time in which development of multiple systems continues…..

In 1929, Hill and Stuart were the first to report the use of soy formula for infants with allergies to cow's milk protein. Since those early reports, the quality and acceptability of soy formula have improved tremendously. Soy protein isolate (used in commercially available soy formula) has several phytochemicals associated with it, including isoflavones. The soy isoflavones are in the form of glucosides in the soybean and in the isolated soy protein used in infant formula; however, they are found as aglycones, glucuronides, and sulfates in body fluids.

…circulating isoflavone concentrations can become much greater than those of 17-B estradiol. These high blood isoflavone concentrations are of interest because humans do not normally have high circulating concentrations of gonadal steroids until after puberty. Although circulating endogenous estrogens are low until puberty, phytoestrogens can attain very high concentrations early in human and animal development. The true potency in target cells of human infants is very difficult to ascertain, and has never been reported. Even if one were to consider isoflavones as being 1000 times less potent that 17B-estradiol, infants fed soy formula have formidable circulating concentrations of these phytoestrogens. Thus, given the uncertainty about the potency of isoflavones in infants, the high plasma isoflavone concentrations in infants raises the possibility that these isoflavones could exert estrogenic effects.

The other important lifecycle exposure to period for soy is in utero because there is maternal to fetal transport of soy components across the placenta. Fetal exposure to isoflavones is a consequence of the dietary habits of the mother…..genistein and daidzein plus their respective metabolites, O-desmethylangolensin and equol, were determined in maternal plasma, cord plasma and amniotic fluid at the time of deliver. The results showed that isoflavonoids pass from the maternal circulation into the amniotic fluid through the placenta. At delivery, the fetus is exposed to isoflavonoids at concentrations similar to those in the mother's plasma, (range of total isoflavonoids in amniotic fluid: 56-799 vs. 19-744nmol/L in mother's plasma. During pregnancy, however, fetal exposure to isoflavonoids may be much higher than these levels. Given that isoflavones have a circulating half-life of <8 hours and that most others did not eat for at least 2 hours before delivery the fetus is probably exposed to even greater concentrations of isoflavones. Animal data are consistent with these (human fetal) findings. In rats, oral administration of the aglycone form of genistein results in the aglycone form of genistein crossing the placenta and the conjugated for circulating in fetal blood and tissues.

Evidence for developmental toxicity is stronger in animal studies, which have shown that isoflavones can cause changes in estrogen-sensitive tissues. For example, subcutaneous injections of genistein to pregnant rats at doses as low as 0.1mg/kg bw/d during day 15 through 20 of gestations showed that the pups were more susceptible to the development of mammary gland cancer when later exposed to chemical carcinogens.

Dietary exposure of dams to genistein at doses as low as 11mg/kg bw/day from gestation day 7 through weaning, with pups continuing the same diet as the dams until postnatal day 50, resulted in microscopic changes in the mammary gland tissue and

reproductive tissues of pups. In the mammary gland ductal/alveolar hyperplasia and hypertrophy were observed in the female progeny.

The authors concluded that the consumption of soy protein was an estrogenic stimulus to breast tissue on the basis of the findings of increased nipple aspirate fluid (NAF) volume and the presence of hyperplasia of epithelial cells in NAF…..soy produces a very mild estrogenic effect.

Additional histologic changes in female progeny ….included abnormal cellular maturation in the vagina and abnormal antral follicles in the ovaries. In male progeny, delayed spermatogenesis was seen when dams had received doses > or equal to 70mg/kg bw/ day. Both sexes showed development al delays, such as late eye opening, and ear unfolding….Generally, the findings showed that genistein in the range of 60-100 mg/kg bw/day can cause slight developmental delays or accelerations, minor weight changes to reproductive organs, and minor alterations to some sex-related behaviors.

Infants who are fed soy-based infant formula are the subpopulation most heavily exposed to isoflavones from the diet. Setchell examined the isoflavone composition of 5 different brands of commercially available soy-based infant formula. The findings showed that the soy-based formulas contained concentrations of total isoflavones (genistein plus daidzein_ between 32 and 47 pg/mL. This is much greater than the 5-15 ng/mL present in breast milk from mothers consuming a Western diet of the 50-150ng/mL of women who have consumed soy products during lactation. On the basis of this concentrations range in the soy formula, it was calculated that an average 4-month-old infant fed a soy-based formula consumed between 4.5 and 8.0mg/kg bw of total isoflavones daily.

It was determined that the 4-month-old infants consuming soy-based formula had mean plasma concentrations of genistein and daidzein of 684 +443 and 295 + 60ng/mL respectively. These values were significantly greater than the concentration so genistein and daidzein found in the plasma of infants fed cow's milk formula (3.2 +0.7 and 2.1 + 0.3 ng /mL respectively or human breast milk (2.8 + 0.7 and 1.4 +0.1ng/mL respectively. Further, equol, a metabolite of daidzein that is more estrogenic than daidzein itself, was present in the plasma of some infants in the concentration range of 3-5 ng/mL. Equol was observed in this concentration range regardless of which (soy-based) formula the infant was consuming.

The paradox of high isoflavone exposure during infancy was expressed by Setchell who stated 'that phyto-estrogens circulate in soy formula-fed infants at concentrations that are 13,000-22,000 times higher than plasma estradiol concentrations which ranges from 40-80 pg/mL in the newborn. ……dietary isoflavones must have some biological activity in the infant.' The article also points out that the plasma concentrations of isoflavones in infants fed these formulas is an order of magnitude greater than in adults who consume a traditional Japanese diet.

It was observed that women who had been fed soy-based formula had a small increase but statistically significant, in the length of menstrual bleeding period……..also reported greater discomfort during menstruation…..the incidence of cervical cancer was higher in the women fed soy-based formula……

The (one) case was noteworthy because the infant was born with an abnormal thyroid and the soy-based formula exacerbated the infant's condition. Interestingly, a series of animal and in vitro studies have elegantly shown that genistein and daidzein

irreversibly inhibit thyroid peroxidase. This enzyme is required to catalyze the tyrosine iodination necessary to synthesize thyroid hormone. ……inhibition would result in isoflavone decreasing thyroid function (hypothyroidism) by preventing the production of adequate amounts of the hormone.

Many years ago, a series of reports observed an increased incidence of premature thelarche associated with the ingestion of soy-based infant formula. Hypothetically, the early breast development observed in the girls less than 8 years old was due to the estrogenic effect of the isoflavones present in soy-based infant formula. ….the event was unusual in that it was observed only in Puerto Rico and not reported elsewhere…..(nor investigated elsewhere).

The animal data….clearly show the carcinogenic potential of genistein. A recent study demonstrated that on daily subcutaneous injection of genistein for 5 days at a dose of 50mg/kg bw/d to neonatal mice generated uterine adenocarcinoma 18 months post administration. ……..the relevance to humans is not clear.

A major concern arising from the ingestion of isoflavones is the possibility of infertility. …phytoestrogens have been observed to cause infertility in wildlife and laboratory animals.

……nearly 4000 Japanese-American men found an association between high tofu consumption during midlife and decreased cognitive function in later life. High tofu consumption was defined as eating tofu > or equal to 2 times a week.

The health risk assessment of isoflavones is complicated because of many factors. Soy-based foods contain a large number of biologically active substances in addition to isoflavones. Their presence makes the interpretation of the studies difficult because the phenomena observed may be due to the activity of these other substances (phytochemicals/phytotoxins) and not isoflavones. Alternatively, the other substances may increase for decrease isoflavone activity. For example, the presence of certain carbohydrates in soy-based foods can promote the growth of gut bacteria and lead to enhanced daidzein metabolism with greater equol production. The consequence of increased amounts of equol could be greater estrogenic activity…..

Interpretation of these studies is further complicated by the fact that soy-based foods contain several types of isoflavones….and all their precursors, metabolites, and conjugated forms are not equal in terms of there estrogenic properties……comparing the effects of total isoflavones used in different studies is not always appropriate because the putative estrogenicity of the soy food can vary depending on the relative levels and the forms of the isoflavone compounds present.

Genistein has been shown to act as a tyrosine kinase inhibitor, an inhibitor of topoisomerase activity, and an inhibitor of angiogenesis.

Other complications in evaluating studies with soy-based foods or pure substances relate to individual metabolic variation.

(Drs. Gilani and Anderson, *"Phytoestrogens and Health") Conclusions-*

Each of these (human) subgroups possesses a distinct biology; as a result, isoflavones may interact with each subpopulation to generate unique biological outcomes. Generally, the fetus is considered most sensitive subpopulation to toxic substances. The effect of supradietary amounts (of isoflavone supplements) on the health of the fetus is not known. Even at dietary levels, supplement use may pose a problem. This form of consumption may result in peaks of elevated concentrations of isoflavones in

the blood above those created by consuming food containing isoflavones…..the use of isoflavone supplements even at dietary amounts cannot be considered safe (especially to fetus) without further investigation.

Infants constitute another subpopulation very sensitive to toxins…..Even mothers who eat a substantial amount of isoflavones pass…..very small amounts through their breast milk to their infants…..in contrast, infants fed soy-based formula consume larger amounts of isoflavones per kilogram of body weight than any other subpopulations…..

As mentioned in previous sections, reproductive toxicities including infertility have been observed in wildlife, farm and laboratory animals. These animals consumed large amounts of phytoestrogens for prolonged periods of time before these toxicities were observed.

….the use of a supplement….could lead to levels of isoflavones in the blood that exceed a safe concentration. The putative dangers are greater when it is considered how easily a supradietary dose can be achieved. This pharmacologic aspect of supplements is a concern and requires further investigations to establish safe levels of consumption."

GENETICALLY ENGINEERED, ROUND-UP READY SOYBEANS:

In addition to the multitude of evidence proving soy phytoestrogen/antinutrient damaging physiological and neurological health effects as outlined above, and without any adequate safety investigations, at least 91% of soybeans produced in the U.S.A. are further classified as: "Genetically Modified Organism," (GMO) or genetically engineered (GE)..

A large majority of soybeans are GE, or created in a laboratory by transforming the DNA with promise of these super-seeds to increase food production and profits. Legitimately, skeptics denounce GMO foods as "Frankenfoods," an ongoing runaway experiment without official regulators, without adverse health investigations or follow-up, and without regard for human health safety.

FDA describes "G*enetic modifications meaning the alteration of the genotype of a plant. Used in a broad context to mean alteration in composition of food that results from adding, deleting or changing hereditary traits."*

It is the established rule of the FDA that irresponsibly states, "*Producers of GMO foods have an obligation under the act 402(a)(1) to ensure that the foods they offer consumers are safe."*

2008, "Physicians and Scientists for Responsible Application of Science and Technology report, "*alarming facts about genetically engineered foods- top researchers confirm that genetic engineering is inherently unsafe and unpredictable. It may therefore generate unexpected harmful substances in DE food. What foods are genetically engineered? Many common foods are, including……soy….common infant feeds, may contain unexpected harmful substances. And remember, the US, the GE foods are not labeled. Commercial applications of genetically engineering for production of foods cannot be scientifically justified and carries with it unpredictable and potentially serious consequences. It has been scientifically established that unexpected effects can occur from genetic engineering that are hazardous to health and the surroundings. Why GE foods should be banned immediately- Considering that GE organisms are unsafe to eat and that they expose the environment to unpredictable and irreversible risks they should be banned. It is not justified to take any risk at all in using them as there is no need for*

them to feed the world and because they perpetuate unsustainable agriculture that is harmful to health and to the environment."

At the same time the FDA also confirms, "*Virtually all breeding techniques (of GE food substances) have potential to create unexpected pleiotropic (multiple effects resulting from a single genetic change) effects."*

There are studies also reporting that GE crop production create unstable genes causing GE-related problems resulting in GE crops that had gone bad due to genetic rearrangements. GE plants with identical gene sequences might differently rearrange genes.

Monsanto laboratory monopolizes the development of GE soybeans, by further inserting a "Roundup Ready" (RR) gene mutation, allowing plants to survive heavy field RR pesticide fumigation. Soy is transformed into a multiple-damaging endocrine disruptor of which is routinely consumed by infants, children, adolescents, and adults.

Roundup chemical name is Glyphosate that kills plants by interfering with the synthesis of multiple amino acids that blocks protein biosynthesis. GE / RR soybean plant alterations is reported as capable of disrupting genetic programming of the human genome that is particularly alarming for those during very early life stages.

Monsanto 'Chemical' Company, a multi-billion dollar corporation, was also the first to bring rBGH biotech growth hormones in milk products to our kitchen tables.

Monsanto is also responsible for estrogenic endocrine disruptor dioxin, best known as Agent Orange and then refusing to pay Vietnam Vets their rightful settlements.

Monsanto also manufactures aspartame, a toxic sweetener, as well as herbicides, fungicides, pesticides.

From 1930-1977 Monsanto under the trade name Aroclor, was the only manufacturer of toxic pollutants PCB's in the USA, that continue to poison this country.

A win/win for Monsanto; to monopolize GMO RR seed that several million acres across the USA are planted in, (and suing farmers if they save seeds to plant the following year), while largely profiting a second time from the required sale of herbicide/pesticide Roundup to saturate millions of acres of precious soil planted in GMO RR plants. A loose/loose for the environment, water supplies, birds, bees, reptiles, animals, and for all humans: babies, children, and adults.

In the Spring of 1995, although classified as "*dangerous for the environment,"* it was the Environmental Protection Agency, not the FDA or Center for Food Safety that granted approval for edible Roundup Ready soybeans, the same soy pulverized into soy-based infant formulas. The Environmental Protection Agency does not require chemical companies to test their chemicals for immune system damage or neurological harm caused to people, to children, to babies, to fetus.

Coincidence or not……it must be mentioned that information states that Supreme Court Judge, Clarence Thomas was at one time Monsanto's lawyer, U.S. Secretary of Agriculture, Anne Veneman was on Board of Directors of Monsanto's Calgene Corporation, Secretary of Defense, Donald Rumsfeld was on Board of Directors of Monsanto's Searle pharmaceuticals, U.S. Secretary of Health, Tommy Thompson received $50,000 in donation from Monsanto to win Wisconsin governor campaign, and two congressmen receiving the most donations from Monsanto, are Larry Combest Chairman of the House Agricultural Committee and Attorney General……John Ashcroft.

(Note- Deciding whether growth hormone rBGH derived milk should be labeled for public information fell under jurisdiction of FDA official Michael Taylor, who previously worked as lawyer for Monsanto. For decades the food and drug growth hormone rBGH labeling was withheld from the American public).

February 2005, research published by Sophie Richard et al, about Roundup (glyphosate) herbicide, "*Its residues may thus enter the food chain and glyphosate is found as a contaminant in rivers. Some agricultural workers using glyphosate have pregnancy problems. Here we show that glyphosate is toxic to human placental cells within 18 hr concentrations lower than found with agricultural use. We conclude that endocrine and toxic effects of Roundup can be observed in mammals.*"

In comparison to the USA where a whopping 25% of infants are fed soy-based formulas, the majority of countries from around the world restrict soy-fed formulas to a minimum, while warning labels are fairly stated, and in some countries soy-based infant formula is prohibited.

Food Safety Authority in Ireland randomly analyzed three soy-based infant formulas whose manufacturers claimed not to be GM. All 3 were found positive for GM content and positive for Roundup Ready herbicide. In 18 samples of various soy products, 15 tested positive for Roundup Ready herbicide, proving that Roundup Ready soybeans contain unexpected gene fragments and RR residues. Monsanto is also associated with organic and natural food production companies.

March 2008, study published by CH Lee et al, "*The Early Prognostic Factors of glyphosate (Roundup) surfactant intoxication. Conclusion- Glyphosate surfactant poisoning is multiorgan toxicity.*"

A study out of Argentina reports, "*Results suggest that maternal exposure to agrochemicals(Roundup ready glyphosate) during pregnancy induces a variety of functional abnormalities in the specific activity of the enzymes in the studies organs of the pregnant rats and their fetuses.*"

A recent report from University of Washington concludes- "*glyphosate increases incident of multiple myeloma,*" (cancer of plasma cells which are immune system cells that is regarded as incurable).

It has also been discovered that Roundup Resistant soybean seeds are causing an increase in soil contamination called, Fusarium fungus, and increasing elevations of xenoestrogen (manmade estrogenic toxins) accelerating toxic levels soy plant-estrogens.

GERR (Genetically Engineered Roundup Ready) alfalfa fed to livestock, not soybeans fed directly to infants was in the spotlight when FDA Center for Food Safety (CFS) sued the U.S. Department of Agriculture on behalf of farmers who complained that GERR alfalfa seed could contaminate organic alfalfa used for livestock feed. Livestock will do not willingly feed on soybean crops, due to inert knowledge of soy toxicity.

Farmers are actively suing Monsanto due to their GERR soybean seed is contaminating their organic soy fields.

The FDA Center for Food Safety remains mute about overwhelming toxic effects reported as caused by GERR soy plant-estrogens especially to fetus, infants and children.

In 2006, Canadian Food Inspection Agency reported, "*A sensitive method using liquid chromatography with electrospray ionization tandem mass spectrometry….. validated to quantify and confirm 13 pesticides in soy-based infant formula.*"

There are no FDA-CFS pre-marketing or post-marketing regulations or follow-up for GM Roundup Ready soy plant-estrogens. There are no FDA-CFS quality control inspections measuring estrogen, vitamin, or mineral levels in soy-based infant formulas. There are no requirements for soybean testing for Fusarium fungus, GMO content, or Roundup herbicide toxicity of soy foods that are promoted as "healthy," while directly targeting our children. Warning labels on soy products are not FDA approved, and research indicates that the USA is the only country in the world that prohibits the labeling of "*GMO RR- free*" foods and beverages. Labeling will hurt GMO RR corporate profits.

Alliance for Biointegrity, finds that the FDA violates the U.S. Food, Drug and Cosmetic Act by allowing genetically engineered food to saturate the marketplace without first being proven as safe, as well as refusing to enforce labeling information to help to notify the public of Roundup Ready GMO infested foods and beverages.

FDA Deputy Director Janice Oliver, Center for Food Safety and Applied Nutrition states, "*The Food and Drug and Cosmetic Act requires that foods must be properly labeled. While FFDCA does not include a specific provision for warning statements, it does give FDA the authority to require information on the label of a food to prevent the food from being misbranded. Section 403(a)-food is deemed to be misbranded if its labeling is false or misleading. Section 201(n) determines whether labeling or advertising of a food is misleading. FDA could establish requirements of a warning statement if it had evidence that information about the use of a food product was material information needed for consumers. FDA could require a waning statement on the product label based on valid scientific data. We would have to be provided valid scientific information that show for whom soy isoflavones are unsafe, why and how they are unsafe for the target population."*

IN SUMMARY-

These studies presented here are only a drop-in-the-bucket of the thousands of published studies all confirming extreme and outrageous health disorders are caused by soy phytotoxic effects. With substantial scientific evidence as confirmed throughout multiple study results, it can no longer be denied or refuted that dietary soy's large assortment of phytotoxins are in fact proven to cause extensive and irreversible physiological and neurological damaging health effects especially when exposure occurs during the most vulnerable fetus, infant, and child developmental time-frames.

In comparison with other extensively dangerous endocrine disruptors, soy is the only phytotoxin that is increasingly promoted and ingested by humans. Numerous adverse health effects causing pain and suffering for a lifetime, or until death, are reportedly caused by soy phytotoxicity: low birth weight, inadequate growth and bone development, allergies, asthma, gastrointestinal distress, intestinal changes and damage, constipation, diarrhea, disruptions in sleep and appetite, damage to spleen, bone diseases, immunodeficiency disease, infertility and extensive reproductive abnormalities, early puberty for girls, longer and more painful menstrual periods, later puberty for boys, gender abnormalities to both boys and girls, homosexuality, growth abnormalities, toxicity to estrogen sensitive organs, seizures, hypothyroidism (and the cascading diseases thyroid damage causes), diabetes, liver disease, kidney disease, pancreatic disease, heart disease, leukemia, extensive neurological disorders; ADD, ADHD, autism,

seizures, dementia, cerebral palsy, and also the causation and/or stimulation of several cancers.

At this same time of increasing disease, and several children's diseases, exposure to soy phytotoxicity is not questioned, monitored, calculated or forewarned with appropriate WARNING labels.

Continual soy phytotoxic consumption solves the mystery surrounding the increasing number of children within the same family diagnosed with extreme health disorders and diseases such as autism. Autism, as well as other behavioral disorders and diseases as an epidemic in both girls and boys, is more often diagnosed 4 to 1 in boys, can also be explained by the proven greater sensitivity of male gender to soy's estrogenic toxicity as can be expected.

FDA's published rules dictate: *"Safety evaluation of food ingredients must be based on 'reasonable certainty of no harm.'"* In truth, the FDA has NO existing evidence that soy foods/ beverages, such as soy-based infant formulas can be classified with: *"reasonable certainty of no harm,"* especially while overwhelmingly numbers of published studies confirm soy is very phytotoxic and highly capable of causing a long list of severe and fatal diseases.

The FDA also has NO evidence that GMRR soy foods/ beverages, and infant formulas can be categorized within; *"Reasonable certainty of no harm."*

In regards to sorely deficient public WARNING disclosures surrounding the overwhelmingly marketed soy products and soy-based infant formulas, the FDA must stop ignoring their own law: *"Consumer intake of contaminants that may be present in foods under Section 402(a)(1) are adulterated foods, to mean a food that contains any poisonous or deleterious substance which may render it injurious to health."*

Most disturbing is that GMRR soy phytoestrogen/antinutrient protein isolate, textured vegetable soy proteins, soy food fillers, are all extensively included in school lunch programs while heavily promoted behind industry manipulations of good nutrition.

The NIH acknowledges soy phytoestrogens in the category of dangerously "active endocrine disruptors," at the same time the FDA allows ongoing safe/healthy soy product promotions. NIH websites: Toxnet and Pubmed are loaded, in fact overloaded with not 'just' hundreds, but thousands of published studies confirming extreme and outrageous soybean toxicity as critically health damaging, without evidence that fetus, infants and children can normally survive.

Soy isoflavones have been extensively studied with countless studies concluding damaging effects while at this same time the NIEHS a division of the NIH is quietly organizing a SEAD (Study of Estrogen Activity and Development) soy study to investigate whether another study should be organized to investigate the evidence of soy-estrogen damaging effects….. as a multitude of existing published studies have repeatedly concluded.. SEAD will focus on the development of hormonally responsive tissues and levels of phytoestrogens and naturally occurring hormones over the first year after birth. NIEHS researcher Rogan explains, "*We are reasoning that by examining the hormonally responsive anatomy in infants, the effect of an active estrogen in the child's diet would be to prolong those physical findings."*

NIEHS states, "*This cross-sectional (SEAD) pilot study will be undertaken in order to establish methods for a 'future' multi-center study designed to assess the potential effects of soy formula on estrogen activity in infants."*

It is unbelievable that without public acknowledgment, research funded by the NIH, NIEHS includes a series of studies on, "*several endocrine active compounds including genistein to determine the endocrine disrupting effects on reproduction, behavior, and carcinogenesis….over multiple generations.*"

The NIH is reportedly recruiting "***healthy children up to one year of age.***"

While industries are profiting to the tune of several billion dollars from the marketing of soy foods, beverages, and infant formulas there exists no consumption safety profile, while soy is also marketed in the manufacture of: candles, cleaners, composite materials, crayons, diesel additives, fabric conditioner, flooring, hair conditioners, shampoos, hair styling aids, hand cleaners, paint removers, wood adhesives, resins, solvents, polish, pens, tables/furniture, wax and more.

Overflowing with confirming evidence of phytotoxicity, as a matter-of-fact there is absolutely no evidence that any fetus, infant, or child may normally survive soy contamination due to soy's multiple toxic effects as conclusive evidence confirms throughout extensive published studies, as well as NIH confirmation.

With this information, I am most hopeful you will agree that it is past due for the American public to be allowed the "right-to-know" of truthful soy phytotoxic effects to especially protect our most valued treasure……the best health of our children.

I encourage you to please consider, in all righteousness, this request that soy-based formulas be completely WITHDRAWN, or to the least prescribed, with adverse health effects carefully monitored by attending physician.

This is also a request that past due WARNING labels become responsibly posted on all soy products for public notification as well-known to cause developmental health disorders and diseases especially during fetal, infant, and child exposures.

Of all of life's tragedies that harm and kill our children, soy phytotoxic contamination is the most preventable. The American public deserves the right-to-know the truth about the extensive published study evidence concluding soy phyto-toxic contamination of their children, until proven otherwise.

I will greatly appreciate and look forward to your reply.

Respectfully,

Gail Elbek

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