Phenothiazine
[92-84-2]

Review of Toxicological Literature

Prepared for

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EXECUTIVE SUMMARY

Nomination of phenothiazine [92-84-2] to the ICCEC is based on high production volumes and limited toxicological information. Phenothiazine is manufactured by Zeneca Inc. and ICI Americas in the United States. Production and import volumes were not available.

As a drug, phenothiazine is used primarily as a veterinary medication to control horn fly and face fly larvae, and to remove certain internal parasites in ruminants and horses. Phenothiazine has also been used to control insects that breed in manure and to control mites in beehives; as a polymerization inhibitor for acrylic acid, chloroprene, and neoprene; and as an antioxidant for epichlorohydrin elastomers, organic ester lubricating oils, ethylene oxide polymers, tetrahydrofuran polymers, heat transfer fluids, synthetic oils, and functional fluids. Several phenothiazine-derivative psychopharmacological agents (e.g., chlorpromazine, promethazin) have been marketed extensively in the U.S. since the early 1950s.

The ecological magnification (EM) index and biodegradability index (BI) for phenothiazine in various aquatic organisms range from 37-356 and 0.6-9.5, respectively. In an experimental aquatic ecosystem, phenothiazine was largely biodegraded in water and did not bioaccumulate.

A total of 87228 workers in the U.S. are occupationally exposed to phenothiazine. This number, however, does not include agricultural workers, workers in abattoirs, or veterinarians. Although against FDA regulations, the general population may be exposed to phenothiazine via ingestion of milk collected from treated animals. The interim tolerance for phenothiazine in meat, fat, and meat by-products of cattle is 2 ppm. NIOSH and ACGIH have recommended a workroom air limit (8-hour TWA) for phenothiazine of 5 mg/m^3 (0.02 mmol/m^3) with a skin warning. OSHA has not promulgated a PEL.

In a human study to evaluate the efficacy of phenothiazine as a urinary antiseptic, oral administration of up to 42900 mg (215 mmol) did not result in adverse dermal reactions. However, oral administration of phenothiazine (750 mg [3.6 mmol]) did sensitize 2 volunteers to a subsequent sunlamp exposure. Skin irritation and discoloration of the hair and fingernails have been reported in workers exposed to phenothiazine. Oral administration of 425 mg/kg phenothiazine (2.13 mmol/kg) for 5 days to a child was lethal. Overdose and accidental exposure to phenothiazine have caused hemolytic anemia, toxic hepatitis, skin photosensitization, and intense pruritus, but not central nervous system depression.

Due to its low water solubility, the rate of absorption of phenothiazine from the gastrointestinal tract is dependent on particle size; the micronized form is absorbed rapidly. Phenothiazine is also absorbed through the skin. In large therapeutic doses, phenothiazine is absorbed into the bloodstream and distributed throughout the tissues and also crosses the blood-brain barrier. Transplacental transfer of phenothiazine to the fetus is limited during

the early stages of gestation, but phenothiazine passes more freely during later stages. In mammals, phenothiazine is excreted in the urine mainly in the conjugated form as phenothiazine-*N*-glucuronide and leucophenothiazone sulfate. It may take several days or even weeks for near total elimination to occur. The urinary half-life of orally administered phenothiazine ranges from 12 to 18 hours in the horse, 11 to 17 hours in sheep, and is approximately 11 hours in humans.

Phenothiazine is moderately toxic in mammals (oral LD_{50} 500 to 5000 mg/kg; 2-20 mmol/kg). Acute dermal exposure to phenothiazine caused skin irritation in guinea pigs and rabbits in some studies but not others, while ocular irritation in rabbits was not reported. No adverse effects were observed in rats exposed by inhalation to 200 mg/L (200000 mg/m^3; 24500 ppm) phenothiazine for 1 hour. Short-term dermal exposure to phenothiazine caused damage to skin in rabbits, while short-term oral administration to rats, hamsters, rabbits, and dogs caused damage to spleen, liver, kidneys, and/or bone marrow. Phenothiazine significantly enhanced liver regeneration in rats given a partial hepatectomy and a diet containing phenothiazine for 7 days starting 3 days after surgery. Two of 4 chicks fed phenothiazine in the diet for 30 weeks died before the tenth week.

In an *in vitro* study, phenothiazine caused a significant decrease in the number of myotubes in *Drosophila* embryonic cells. *In vivo*, phenothiazine caused an increase in resorptions in pregnant rats treated in the diet for 22 days. However, phenothiazine administered by gavage to pregnant albino mice and pregnant albino rats during gestation days 6-15 was neither fetotoxic nor teratogenic. In hens, there was no significant reduction in egg production when phenothiazine was administered in the diet for 30 weeks.

The incidence of lung tumors was not increased in A/J mice administered phenothiazine i.p. for 4 days (50 mg/kg/day in corn oil; 0.25 mmol/kg/day) and observed for 16 weeks. Neither was the tumor incidence increased in major tissues (not specified) of C57BL/6 H C3H/Anf and C57BL/6 H AKR hybrid strain mice administered phenothiazine orally from 7 days of age until 18 months of age. Phenothiazine (0.1 mg/kg; 0.5 μmol/kg) was administered by gavage at age 7-28 ays, and then in the diet (0.20 ppm; 1 μmol/kg feed) from age 29 days to 18 months. Fischer rats fed phenothiazine for 20 weeks and terminated 40 weeks later did not exhibit any bladder tumors. However, when co-administered with *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT), phenothiazine significantly enhanced the incidence of carcinoma of the bladder as compared to rats fed FANFT alone.

Phenothiazine decreased the incidence of intestinal and urinary bladder tumors in rats by about 60% when it was administered in the diet with bracken fern for 1 year. In mice bearing Ehrlich tumors, phenothiazine administered i.p. for 10 days decreased tumor weight by 73% after 30 days. In a similar study, however, i.p. injection of phenothiazine for 7 or 10 days to mice bearing Ehrlich tumors had no anticarcinogenic activity.

Phenothiazine was found to be negative for mutagenicity in *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation, but positive in mouse lymphoma cells in the absence of metabolic activation. *In vitro*, phenothiazine enhanced the induction

of DNA damage in human colon adenocarcinoma cells by methotrexate and fluorodeoxyuridine. Also, phenothiazine was found to exhibit antigenotoxic activity, as demonstrated by its ability to reduce, in the presence of metabolic activation, the mutagenic activity of benzo[a]pyrene in *S. typhimurium* reverse mutation assays and the number of adducts induced by aflatoxin B1 in calf thymus DNA.

There was no difference in the incidence of toxicosis in lambs administered phenothiazine anthelmintic powder in combination with the insecticide Ciovap® and lambs administered Ciovap® alone, and phenothiazine did not potentiate the toxic effects of the organophosphorus insecticides malathion, coumaphos, trichlorfon, ronnel (fenchlorphos), crotoxyphos/dichlorvos, crotoxyphos, or crufomate in steer and calves. Clinical and pathological signs of toxicity did not differ between rats administered a single dose of a 5:1 mixture containing phenothiazine and Sevin® by gavage and rats administered a single dose of Sevin® alone.

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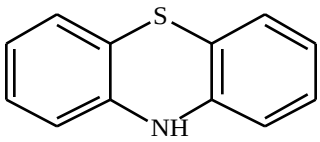
1.0 BASIS FOR NOMINATION

The nomination of phenothiazine [92-84-2] to the ICCEC is based on high production volumes and limited toxicological information.

2.0 IDENTIFICATION AND CLASSIFICATION

Phenothiazine
[92-84-2]



2.1 Chemical Identification

Phenothiazine ($C_{12}H_9NS$, mol. wt. = 199.28) is also called:

10*H*-Phenothiazine (9CI)	Lethelmin
Afi-Tiazin	Nemazene
Agrazine	Nemazine
Antriverm	Nexarbol
Biverm	Orimon
Contaverm	Padophene
Dibenzoparathiazine	Penthazine
Dibenzothiazine	Phenegic
Dibenzo-1,4-thiazine	Phenosan
Dibenzo-*p*-thiazine	Phenoverm
Early Bird Wormer	Phenovis
ENT 38	Phenoxur
Feeno	Phenthiazine
Fenoverm	Phenzeen
Fentiazin	Reconox
Helmetina	Souframine

Thiodiphenylamine	Wurm-Thional
Vermitin	XL-50

2.2 Physical-Chemical Properties

Property	Information	Reference
Color	Grayish-green to greenish-yellow	Ludwig (1994)
Physical State	Rhombic leaflets or diamond-shaped plates	Budavari (1996)
Melting Point, °C	185.1; Sublimes at 130° at 1 mm Hg	Budavari (1996)
Boiling Point, °C, at 760 mm Hg	371	Budavari (1996)
Odor	Slight odor	HSDB (1996)
Solubility:		
Water	Practically insoluble in water	Budavari (1996)
Organic Solvents	Freely soluble in benzene; Soluble in ethyl ether and hot acetic acid; Slightly soluble in ethyl alcohol; Practically insoluble in carbon tetrachloride	Budavari (1996)

Although phenothiazine oxidizes fairly easily when exposed to air and is a combustible solid, it is not a high fire risk. If phenothiazine is involved in a fire or comes in contact with acid or acid fumes, it produces highly toxic fumes of sulfur and nitrogen oxides.

2.3 Purity and Commercial Availability

The product sold by one of the suppliers, Zeneca Inc., is at least 99.6% pure and sold in flake and powder grades in 250 lb drums and 50 lb bags (Strum, 1997). Zeneca Inc. markets the phenothiazine-containing insecticides (fly-control grade) BarFly□ and LSP□ for beef cattle (SRI Int., 1997b). The names of FDA-approved veterinary drugs are identified in **Section 5.0**.

3.0 COMMERCIAL PRODUCTION PROCESS

Phenothiazine is produced by fusing diphenylamine with sulfur. Using iodine as a catalyst improves yields (Budavari, 1996).

4.0 PRODUCTION AND IMPORT VOLUMES

Phenothiazine is manufactured by Zeneca Inc. and ICI Americas in the United States (Strum, 1997; SRI Int., 1996, 1997a,b). Production and import volumes were not available from USITC.

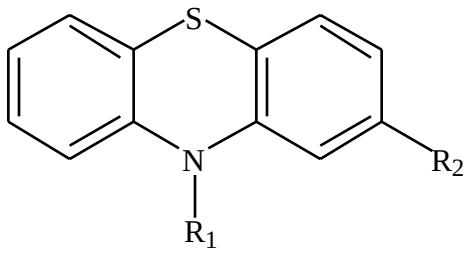
5.0 USES

Phenothiazine was introduced in 1925 as one of the earliest organic insecticides (Farm Chemicals Handbook, 1984; cited by HSDB, 1996). Its anthelmintic activity was first reported in 1938, and it was used extensively in sheep, cattle, goats, horses, and chickens until the 1960s, when broad-spectrum drugs were introduced. Its toxicity precludes its use in dogs, cats, and humans (Roberson, 1988). It was at one time (presumably briefly) also used in humans as an anthelmintic and a urinary antiseptic (Gosselin et al., 1984; cited by HSDB, 1996) with a normal oral dose of 1 to 2 g per day (5-10 mmol/day) (ACGIH, 1986).

As a drug, phenothiazine is used primarily as a veterinary medication (in a salt or mineral supplement) to control horn fly and face fly larvae, and to remove certain internal parasites in ruminants and horses (Farm Chemicals Handbook, 1984, 1986; cited by HSDB, 1996; Roberson, 1988). Phenothiazine is rarely used in swine because of its limited efficacy in these animals (Roberson, 1988). Phenothiazine is a component of the following FDA-approved animal drugs: Wormal tablets and granules; Diquel tablets; Tranvet chewable tablets; Parvex Plus; Baymix crumbles and 11.2% feed mix; Negabot/Combot paste; Dyrex T.F. 200-500-1000; Purina 6 Day

Worm-Kill feed and concentrate; Combotel/Negabot Plus paste; Equigel; and Equigard/Verdisol (FDA, 1996). Phenothiazine has also been used to control insects that breed in manure (Booth and McDonald, 1982; cited by HSDB, 1996) and to control mites in beehives (Fernandez-Muño et al., 1995).

Several phenothiazine-derivative psychopharmacological agents have been marketed in the United States since the early 1950s. In 1995, the Physicians' Desk Reference (PDR, 1995) included 7 of the 29 "phenothiazines" listed in the 12th edition of The Merck Index (Budavari, 1996). These phenothiazine derivatives differ by the substituents in the 2- (R_1) and 10-position (R_2) of the phenothiazine ring system:



The oldest derivative is chlorpromazine, where $R_1 = (CH)_3N(CH_3)_2$ and R_2 = Cl. The hydrochloride salt is marketed as the antipsychotic agent Thorazine□ (Sternbach and Horst, 1982). Between 1962 and 1993, the U.S. production volume of phenothiazine-derivative tranquilizers quadrupled from 78.7 million pounds to 323.9 million pounds (SRI Int., 1997c). Other phenothiazine-based pharmaceuticals include the antihistamine, sedative, and antiemetic compound promethazein (where $R_1 = -CH_2CH(CH_3)N(CH_3)_2$ and R_2 = H) hydrochloride (Houlihan and Bennett, 1981; Budavari, 1996). The 12th edition of the Merck Index lists several of the classes of other drugs containing the phenothiazine ring system (Budavari, 1996).

Several dyes appear to be phenothiazine derivatives (e.g., methylene blue, methylene azure, azures A-C, and thionine) (HSDB, 1996), however, these dyes are apparently not manufactured from phenothiazine (Budavari, 1996). Diester synthetic lubricating oils (widely used for jet engines, hydraulic fluids, air compressors, etc.) are often stabilized with an antioxidant such as 0.5% phenothiazine (Booser, 1981).

Phenothiazine is used in concentrations of 0.01 to 0.5 wt.% as an antioxidant for polyethers (tetrahydrofuran [THF] polymers and ethylene oxide polymers) to prevent thermal degradation during processing or use (Braun and DeLong, 1982; Dreyfuss and Dreyfuss, 1982). Phenothiazine is also the antioxidant of choice to be used in combination with acid acceptor stabilizers in the compounding systems of synthetic polyether elastomers to enhance the aging resistance of the vulcanizate (Vandenberg, 1979). In addition, phenothiazine is one of the stabilizers that has been used to prevent bulk polymerization of chloroprene monomers (Johnson, 1979).

6.0 ENVIRONMENTAL FATE

The ecological magnification (EM) index and biodegradability index (BI) for phenothiazine in algae (*Oedogonium cardiacum*), daphnia (*Daphnia magna*), mosquitoes (*Culex pipiens quinquefasciatus*), snails (*Physa* sp.), and fish (*Gambusia affinis*) were 261, 201, 85, 37, and 356 (EM); and 9.4, 1.4, 3.3, 9.5, and 0.6 (BI), respectively (Coats et al., 1976). The EM index and the BI reflect the degree of bioconcentration and ease of biodegradation of a chemical and were measured in the organisms in an experimental 2-L aquatic ecosystem into which an unspecified amount of phenothiazine was added.

Coats et al. (1976) also investigated the fate of phenothiazine excreted by mice into an experimental terrestrial-aquatic ecosystem. Female Swiss white mice were administered a single dose of 2 mg/kg phenothiazine (0.01 mmol/kg) in olive oil, and were suspended over the

ecosystem in a cage. By day 33 of the experiment, phenothiazine had been largely biodegraded in the water. Detected metabolites included phenothiazine sulfone (15%), phenothiazine sulfoxide (29%), 2 unknown compounds (19%), and 1 unknown compound of polar in nature (33%). None of the organisms in the experimental ecosystem had detectable levels of phenothiazine.

7.0 HUMAN EXPOSURE

7.1 Occupational Exposure

Information from the National Occupational Exposure Survey (NOES) (NIOSH, 1984) on the number of U.S workers exposed to phenothiazine is presented in **Table 1** by occupation and in **Table 2** by industry.

Table 1. NIOSH National Occupational Exposure Survey (NOES)[a]: By Occupation

Industry	Number of Plants	Number of Employees	Number of Female Employees
Administrative Support Occupations, N.E.C.	52	52	0
Aircraft Engine Mechanics	243	2425	243
Assemblers	423	9373	1360
Automobile Mechanics	63	5672	0
Camera, Watch, and Musical Instrument Repairers	3	23	0
Carpenters	32	253	0
Cementing and Gluing Machine Operators	34	171	171
Chemical Engineers	3	64	3
Chemical Technicians	3	129	6
Chemists, Except Biochemists	36	38	0
Construction Laborers	204	409	0
Construction Trades, N.E.C.	254	3816	254
Crushing and Grinding Machine Operators	58	1170	0
Electricians	3	3	0
Engineering Technicians, N.E.C.	113	1533	3
Extruding and Forming Machine Operators	238	857	24
Fabricating Machine Operators, N.E.C.	82	247	247
Folding Machine Operators	59	710	651

Industry	Number of Plants	Number of Employees	Number of Female Employees
Forging Machine Operators	57	57	0
Freight, Stock, and Material Movers, Hand, N.E.C.	21	4489	0
Furniture and Wood Finishers	17	51	0
Grinding, Abrading, Buffing, and Polishing Machine Operators	26	156	0
Hand Molders and Shapers, Except Jewelers	26	156	0
Hand Packers and Packagers	52	103	52
Heavy Equipment Mechanics	435	468	0
Industrial Truck and Tractor Equipment Operators	345	777	0
Insulation Workers	3	40	0
Janitors and Cleaners	569	7409	1748
Laborers, Except Construction	191	1234	0
Machine Feeders and Offbearers	58	58	0
Machine Operators, not specified	247	4773	18
Machinists	360	799	0
Mechanical Controls and Valve Repairers	79	2515	0
Milling and Planing Machine Operators	160	1923	0
Millwrights	24	121	0
Misc. Material Moving Equipment Operators	26	78	0
Miscellaneous Machine Operators, N.E.C.	364	2872	0
Miscellaneous Printing Machine Operators	341	442	0
Miscellaneous Textile Machine Operators	132	4322	435
Miscellaneous Woodworking Machine Operators	57	51	0
Mixing and Blending Machine Operators	714	3045	283
Molding and Casting Machine Operators	280	2737	370
Not Specified Mechanics and Repairers	626	10245	0
Operating Engineers	129	129	129
Packaging and Filling Machine Operators	154	442	0
Painting and Paint Spraying Machine Operators	94	319	0
Personnel, Training, and Labor Relations Specialists	25	50	0
Plumbers, Pipefitters, and Steamfitters	82	1974	0
Printing Machine Operators	35	35	0
Production Inspectors, Checkers, and Examiners	112	437	92
Production Samplers and Weighers	34	68	0
Roasting and Baking Machine Operators, Food	58	117	0
Shoe Machine Operators	33	1614	165
Shoe Repairers	22	262	87

Industry	Number of Plants	Number of Employees	Number of Female Employees
Slicing and Cutting Machine Operators	194	2313	2245
Specified Mechanics and Repairers, N.E.C.	3	72	0
Stock and Inventory Clerks	61	70	0
Stock Handlers and Baggers	129	773	0
Supervisors, Production Occupations	687	1043	0
Technicians, N.E.C.	62	205	36
Textile Cutting Machine Operators	34	171	0
Tool and Die Makers	33	66	0
Traffic, Shipping, and Receiving Clerks	54	249	54
Upholsterers	3	58	0
Vehicle Washers and Equipment Cleaners	34	34	0
Weighers, Measurers, and Checkers	52	103	0
Welders and Cutters	173	405	116
Wood Lathe, Routing, and Planing Machine Operators	353	353	0
TOTAL		87228	8792

Abbreviations: NEC = not elsewhere classified
[a] NIOSH (1984)

Table 2. NIOSH National Occupational Exposure Survey (NOES)[a]: By Industry

Industry	Number of Plants	Number of Employees	Number of Female Employees
Auto Repair, Services, and Garages	511	1532	0
Business Services	7	7	0
Chemicals and Allied Products	151	2166	164
Communication	5	42	10
Electric and Electronic Equipment	85	992	244
Electric, Gas, and Sanitary Services	289	17716	116
Fabricated Metal Products	76	4562	428
Food and Kindred Products	341	5508	0
Furniture and Fixtures	255	1643	260
General Building Contractors	168	287	129
Health Services	62	215	38
Heavy Construction Contractors	402	402	0
Leather and Leather Products	55	2139	252
Machinery, Except Electrical	187	3897	1329

Industry	Number of Plants	Number of Employees	Number of Female Employees
Paper and Allied Products	447	9675	18
Printing and Publishing	256	512	0
Rubber and Misc. Plastics Products	566	11458	3098
Special Trade Contractors	483	4346	254
Textile Mill Products	48	1062	171
Transportation by Air	621	11500	1953
Transportation Equipment	48	6504	156
Wholesale Trade-Durable Goods	410	1882	170
TOTAL		88047	8790

[a] NIOSH (1984)

No information was available in the NOES survey on exposure of agricultural and livestock workers, workers in abattoirs (slaughterhouses), and veterinarians. In an unattributed statement, ACGIH (1986) stated that workers pulverizing and packaging phenothiazine dust developed symptoms on exposure to 15 to 48 mg/m^3.

7.2 Non-Occupational Exposure

Humans have been treated with phenothiazine at oral doses of 1 to 2 g per day as a urinary antiseptic (ACGIH, 1986). The likelihood of accumulation in humans of phenothiazine from food is small. Milk from animals administered phenothiazine may contain phenothiazine as well as phenothiazine metabolites. Roberson (1988) reported that although such milk has a pink discoloration that lasts 2-3 days following treatment of lactating animals, the milk is not harmful to drink. However, the FDA requires that lactating animals not be treated with phenothiazine (21 CFR 505). The interim tolerance for phenothiazine in meat, fat, and meat by-products of cattle is 2 ppm (40 CFR 180, Subpart C). Strict limits apply to phenothiazine-containing polymers that may be in contact with food during processing or packaging. Human drugs that are metabolized to phenothiazine could comprise a potential exposure source. No information was

found as to whether phenothiazine is a metabolite of any phenothiazine antihistamines, tranquilizers, or other drugs containing the phenothiazine ring system unsubstituted at position 10.

8.0 REGULATORY STATUS

NIOSH and ACGIH have recommended a workroom air limit (8-hour TWA) for phenothiazine of 5 mg/m^3 (0.2 mmol/m^3) with a skin notation, indicating dermal exposure may contribute to toxicity; but OSHA has not promulgated a permissible exposure limit (Ludwig, 1994; ACGIH, 1986; 29 CFR 1910.1000). Regulations are listed on the following page.

REGULATIONS

	Regulation	Effect of Regulation/Other Comments
EPA	40 CFR 180. Tolerances and Exemption. [1972]	Subpart C, Specific Tolerances, states that the interim tolerance for phenothiazine in meat, fat, and meat by-products of cattle is 2 ppm.
	40 CFR 455. Pesticide Chemicals. [1978]	Phenothiazine is listed as an active ingredient in organic pesticides.
	40 CFR 716. Health and Safety Data Reporting	Phenothiazine is covered under section 4(a) of the Toxic Substances Control Act (TSCA). Health and safety information must be submitted to the EPA.

	Regulation	Effect of Regulation/Other Comments
F D A	21 CFR 175. Indirect Food Additives: Adhesives and Components of Coatings.	§175.105 (Adhesives) regulates phenothiazine use in adhesives that are used in packaging, transporting, or holding food. Phenothiazine may only be used as a polymerization-control agent.
	21 CFR 176. Indirect Food Additives: Paper and Paperboard Components.	§176.170 (Components of Paper and Paperboard in Contact with Aqueous and Fatty Foods) regulates the use of phenothiazine as a component of uncoated or coated paper and paperboard that is intended for use in producing, manufacturing, packaging, processing, preparing, treating, packing, transporting, or holding aqueous and fatty foods. Phenothiazine may only be used as an antioxidant in dry resin size.
	21 CFR 177. Indirect Food Additives: Polymers.	§177.2600 (Rubber Articles Intended for Repeated Use) mandates that the amount of phenothiazine in rubber products intended for repeated use may not exceed 5% by weight.
	21 CFR 505. Interpretive Statements Re: Warnings on Animal Drugs for Over-the-Counter Sale.	§505.20 (Recommended Animal Drug Warning and Caution Statements; Anthelmintics: Phenothiazine) warns that lactating dairy animals should not be treated with phenothiazine. It also cautions that a veterinarian should be consulted before using phenothiazine in severely debilitated animals and that some animals are occasionally sensitive to phenothiazine.

	Regulation	Effect of Regulation/Other Comments
FDA	21 CFR 520. Oral Dosage Form New Animal Drugs.	§520.500 (Coumaphos Crumbles) mandates that coumaphos crumbles, used as a top dressing on daily feed ration of cattle for control of gastrointestinal roundworms, should not be used in conjunction with feeds containing phenothiazine.
	21 CFR 520. Oral Dosage Form New Animal Drugs. §520.1802c (Piperazine-Carbon Disulfide Complex with Phenothiazine Suspension).	Piperazine-carbon disulfide complex with phenothiazine suspension is used in horses and ponies for removing various parasites. Each fluid ounce contains 5 g piperazine-carbon disulfide complex and 0.83 g phenothiazine.
	21 CFR 520. Oral Dosage Form New Animal Drugs.	§520.2520g (Trichlorfon, Phenothiazine, and Piperazine Dihydrochloride Powder) regulates use and labeling of water dispersible powder. Trichlorfon, phenothiazine, and piperazine dihydrochloride powder is to be used for horses for removal of various parasites. Dose should be 18.2 mg trichlorfon, 12.5 mg phenothiazine, and 40.0 mg piperazine base per pound body weight. This drug should not be used in horses intended for use as food.

9.0 TOXICOLOGICAL DATA

Summary: In a human study to evaluate the efficacy of phenothiazine as a urinary antiseptic, oral administration of up to 42900 mg (215 mmol) did not result in adverse dermal reactions. However, oral administration of phenothiazine (750 mg [3.6 mmol]) did sensitize 2 volunteers to a subsequent sunlamp exposure. Skin irritation and discoloration of the hair and fingernails have been reported in workers exposed to phenothiazine. Oral administration of 425 mg/kg phenothiazine (2.13 mmol/kg) for 5 days to a child was lethal. Overdose and accidental exposure to phenothiazine have caused hemolytic anemia, toxic hepatitis, skin photosensitization, and intense pruritus, but not central nervous system depression.

Due to its low water solubility, the rate of absorption of phenothiazine from the gastrointestinal tract is dependent on particle size; the micronized is absorbed rapidly. Phenothiazine is also absorbed through the skin. In large therapeutic doses, phenothiazine is absorbed into the bloodstream and distributed throughout the tissues and also crosses the blood-brain barrier. Transplacental transfer of phenothiazine to the fetus is limited during the early stages of gestation (species not specified), but phenothiazine passes more freely during later stages. In mammals, phenothiazine is excreted in the urine mainly in the conjugated form as phenothiazine-*N*-glucuronide and leucophenothiazone sulfate. It may take several days or even weeks for near total elimination to occur. The urinary half-life of orally administered phenothiazine ranges from 12 to 18 hours in the horse, 11 to 17 hours in sheep, and is approximately 11 hours in humans.

Phenothiazine is moderately toxic in mammals (oral LD_{50} 500 to 5000 mg/kg; 2-20 mmol/kg). Acute dermal exposure to phenothiazine caused skin irritation in guinea pigs and rabbits in some studies but not others, while ocular irritation in rabbits was not reported. No adverse effects were observed in rats exposed by inhalation to 200 mg/L (200000 mg/m^3; 24500 ppm) phenothiazine for 1 hour. Short-term dermal exposure to phenothiazine caused damage to skin in rabbits, while short-term oral administration to rats, hamsters, rabbits, and dogs caused damage to spleen, liver, kidneys, and/or bone marrow. Phenothiazine significantly enhanced liver regeneration in rats given a partial hepatectomy and a diet containing phenothiazine for 7 days starting 3 days after surgery. Two of four chicks fed phenothiazine in the diet for 30 weeks died before the tenth week.

In an *in vitro* reproductive/teratological study, phenothiazine caused a significant decrease in the number of myotubes in *Drosophila* embryonic cells. *In vivo*, phenothiazine caused an increase in resorptions in pregnant rats treated in the diet for 22 days. However, phenothiazine administered by gavage to pregnant albino mice and pregnant albino rats during gestation days 6-15 was neither fetotoxic nor teratogenic. In hens, there was no significant reduction in egg production when phenothiazine was administered in the diet for 29 weeks.

The incidence of lung tumors was not increased in A/J mice administered phenothiazine i.p. for 4 days (50 mg/kg/day in corn oil; 0.25 mmol/kg/day) and observed for 16 weeks. Neither was the tumor incidence increased in major tissues (not specified) of C57BL/6 H C3H/Anf and C57BL/6 H AKR hybrid strain mice administered phenothiazine orally from 7 days of age until 18 months of age. Phenothiazine (0.1 mg/kg; 0.5 µmol/kg) was administered by gavage from age 7-28 days, and then in the diet (0.20 ppm; 1 µmol/kg feed) at age 29 days to 18 months. Fischer rats fed phenothiazine for 20 weeks and terminated 40 weeks later did not exhibit any bladder tumors. However, when co-administered with *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT), phenothiazine significantly enhanced the incidence of carcinoma of the bladder as compared to rats fed FANFT alone.

Phenothiazine decreased the incidence of intestinal and urinary bladder tumors in rats by about 60% when it was administered in the diet with bracken fern for 1 year. In mice bearing Ehrlich tumors, phenothiazine administered i.p. for 10 days decreased tumor weight by 73% after 30 days. In a similar study, however, i.p. injection of phenothiazine for 7 or 10 days to mice bearing Ehrlich tumors had no anticarcinogenic activity.

Phenothiazine was found to be negative for mutagenicity in *Salmonella typhimurium* and *Escherichia coli* with or without metabolic activation but positive in mouse lymphoma cells in the absence of metabolic activation only. *In vitro*, phenothiazine enhanced the induction of DNA damage in human colon adenocarcinoma cells by methotrexate and fluorodeoxyuridine. Also, phenothiazine was found to exhibit antigenotoxic activity, as demonstrated by its ability to reduce, in the presence of metabolic activation, the mutagenic activity of benzo[a]pyrene in *S. typhimurium* reverse mutation assays and the number of adducts induced by aflatoxin B1 in calf thymus DNA.

There was no difference in the incidence of toxicosis in lambs administered phenothiazine anthelmintic powder in combination with the insecticide Ciovap® and lambs administered Ciovap® alone and phenothiazine did not potentiate the toxic effects of the organophosphorus insecticides malathion, coumaphos, trichlorfon, ronnel (fenchlorphos), crotoxyphos/dichlorvos, crotoxyphos, or crufomate in Hereford and Angus steer and heifer calves. Clinical and pathological signs of toxicity did not differ between rats administered a single dose of a 5:1 mixture containing phenothiazine and Sevin® by gavage and rats administered a single dose of Sevin® alone.

9.1 Human Data

9.1.1 Experimental Exposure

In a study that investigated the efficacy of phenothiazine as a urinary antiseptic, 92 patients were orally administered 3120-42900 mg (16-215 mmol) of the compound (duration of exposure not specified) (DeEds et al., 1939; cited by DeEds et al., 1940). No adverse dermal reactions were observed. In another study, oral administration of phenothiazine (3 doses of 250 mg [1.2 mmol]) to 2 volunteers followed 12 hours later by exposure to a sunlamp caused photosensitization (DeEds et al., 1940).

9.1.2 Occupational Exposure

Following field testing of phenothiazine in orchards for control of codling moths, workers complained of intense itching, irritation, and reddening of skin (reviewed by DeEds et al., 1940). In some cases, the reactions were severe enough to require hospitalization.

Workers handling phenothiazine developed keratitis, but it was not clear if this effect was due to mechanical irritation from phenothiazine crystals or to reaction to hydrogen sulfide released during its manufacture (Grant, 1974; cited by HSDB, 1996).

Workers who were involved in the pulverizing and packaging of phenothiazine, and who were exposed to 15-48 mg/m^3 (0.075-0.24 mmol/m^3) phenothiazine, developed pinkish-red colored hair, brown fingernails, and skin irritation (ACGIH, 1986). Discoloration of the hair and fingernails deepened with increasing exposure and was due to the dyeing effect of phenothiazine. Workers who initially had skin irritation developed tolerance within 1 to 4 weeks of exposure to phenothiazine. All symptoms disappeared with cessation of exposure.

9.1.3 Therapeutic Overdose and Accidental Exposure

As mentioned in Section 5.0, phenothiazine was used at one time in humans as an anthelmintic and a urinary antiseptic (Gosselin et al., 1984; cited by HSDB, 1996). Oral administration of 425 mg/kg phenothiazine (2.13 mmol/kg) for 5 days to a child (age and sex not given) was lethal (Lancet, 1942; cited by RTECS, 1996).

Overdose and accidental exposure to phenothiazine have caused hemolytic anemia, toxic hepatitis, skin photosensitization, and intense pruritus, but not central nervous system depression (doses not given) (Gosselin et al., 1984; cited by HSDB, 1996).

Oral consumption of average or large doses of phenothiazine (doses not given) have caused abdominal cramps, tachycardia, gastrointestinal and dermal irritation, and kidney damage, as well as allergic contact dermatitis without exposure to light (ACGIH, 1986).

There were also no adverse dermal reactions following application of phenothiazine (dose not given) mixed with hydrous wool fat (lanolin), or 2% phenothiazine in alcohol to forearms of volunteers (DeEds et al., 1940).

9.2 General Toxicology

9.2.1 Chemical Disposition, Metabolism, and Toxicokinetics

9.2.1.1 Absorption

Due to its low solubility, the rate of absorption of phenothiazine from the gastrointestinal tract is dependent on particle size; the microionized form of the drug is absorbed rapidly (ILO, 1983; cited by HSDB, 1996). Phenothiazine is also absorbed through the skin (Lewis, 1993).

9.2.1.2 Distribution

In large therapeutic doses, phenothiazine is absorbed into the bloodstream and distributed throughout the tissues, also crossing the blood-brain barrier (species not specified) (Mitchell, 1982).

In rats (strain not specified) administered a dose of 11 mg phenothiazine/kg/day (0.055 mmol/kg/day) by gavage for 3 days, phenothiazine distributed mainly to kidneys, heart, and liver (West Chem. Products, 1970a). In male Harlan-Wistar rats administered a single dose of phenothiazine (11 mg/kg; 0.055 mmol/kg) by gavage, the highest concentrations of phenothiazine were found in fat, liver, and kidneys after 48 hours (West Chem. Products, 1982). In male albino rats administered a single dose or 5 daily doses of 1.5 mg/kg (0.0075 mmol/kg) phenothiazine, the compound was distributed mainly to liver and kidneys (ICI Americas Inc., 1982). Three days after administration of the single dose and 10 days after administration of multiple doses, liver and kidneys of the rats contained < 0.05 ppm phenothiazine.

In female Charolais-Holstein calves, 24 hours after drenching with phenothiazine (220 mg/kg body weight; 1 mmol/kg), most of the compound was distributed into stomach, intestines, and liver (Bureau of Veterinary Medicine, 1972). Very little (< 0.001%) of the dose was found in blood, muscle, and fat. In a related study, 24 hours after oral administration of 10000 mg/kg phenothiazine (50 mmol/kg) to Charolais calves, most of the dose was excreted, with only ~ 1.3% retained by mainly the liver and kidneys (Guyton et al., 1976). In steers orally administered 0.0025 or 2.5 mg/lb/day (0.004 or 4 µmol/kg/day) for 10 days, or a single dose of 0.29 mg/lb (0.7 µmol/kg) or 0.5 mg/kg (2 µmol/kg), the liver contained the highest residue of phenothiazine (ICI Americas Inc., 1977a; 1980a; 1983).

Transplacental transfer of phenothiazine to the fetus is limited during the early stages of gestation (species not specified), but phenothiazine passes more freely during later stages (Dencker and Danielsson, 1987).

9.2.1.3 Metabolism

In mammals, phenothiazine is excreted in the urine mainly in conjugated forms as phenothiazine-*N*-glucuronide and leucophenothiazone sulfate (Mitchell, 1982). See **Figure 1** and **Table 3** for identification of phenothiazine metabolites.

9.2.1.4 Excretion

Phenothiazine is excreted by mammals mainly in urine and feces. It may take several days or even weeks for near total elimination to occur (Mitchell, 1982). See **Table 4** for details on excretion of phenothiazine.

Several studies have shown that colored phenothiazine derivatives are secreted in the milk of cows, goats, and sheep. In sheep, although the entire milk yield is colored following administration of phenothiazine, the amount of phenothiazine derivatives in milk accounts for

only 0.2% of the dose (reviewed by Mitchell, 1982).

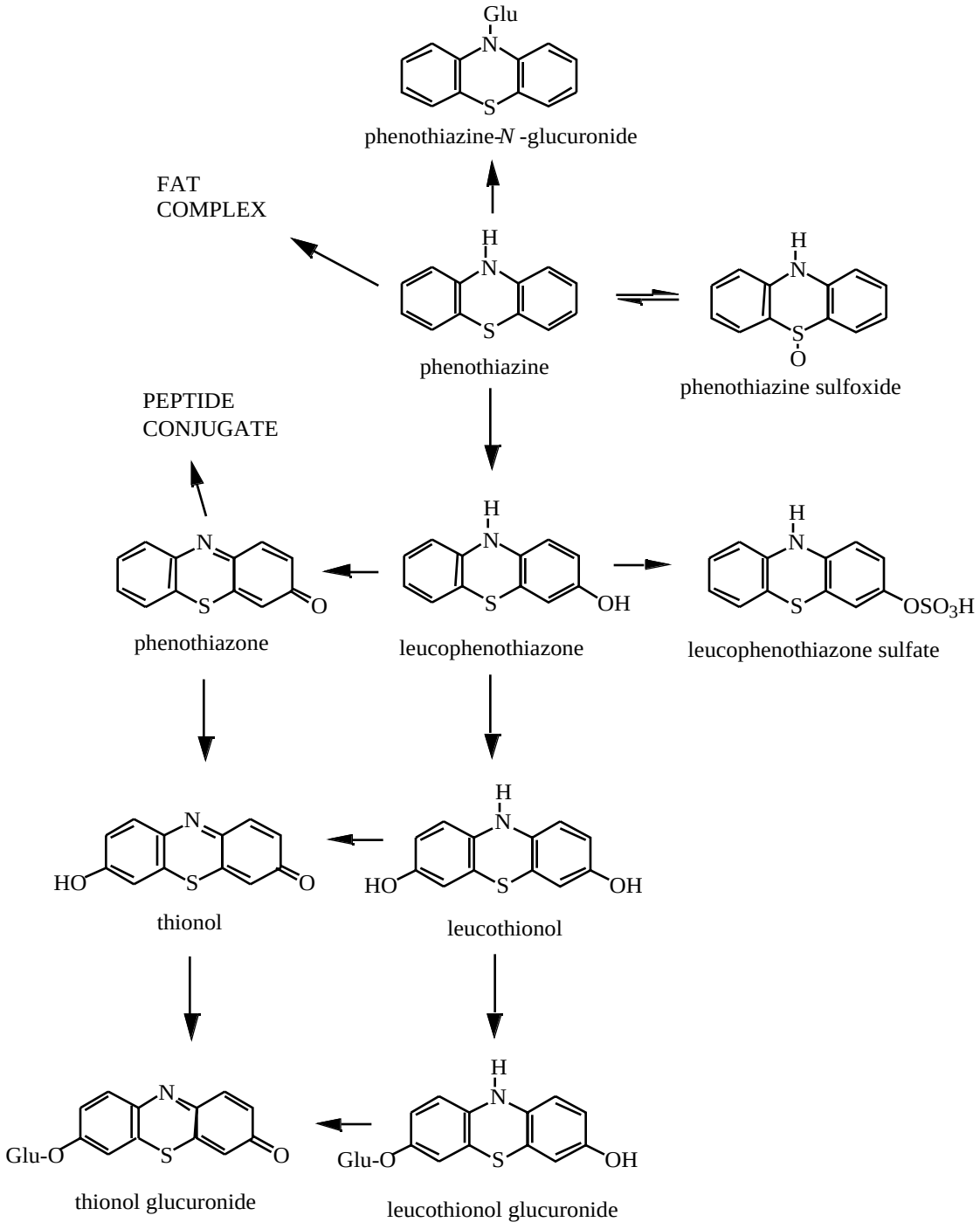

Glu
N
S
phenothiazine-*N* -glucuronide
FAT
COMPLEX
H
N
S
phenothiazine
O
phenothiazine sulfoxide
PEPTIDE
CONJUGATE
phenothiazone
leucophenothiazone
OH
OSO_3H
leucophenothiazone sulfate
HO
thionol
leucothionol
Glu-O
thionol glucuronide
leucothionol glucuronide

Table 3. Phenothiazine Metabolites

Figure 1. Mammalian Metabolism of Phenothiazine (Adapted from Mitchell, 1982)

Metabolite Name	System or Species	Experimental Details	Enzymes	Comments	Reference
3-Hydroxy-phenothiazine	dog (strain n.p.)	n.p.	n.p.	n.p.	Goodwin (1976; cited by HSDB, 1996)
Leucophenothiazone sulfate	mouse (male), rat, hamster (Syrian golden), and gerbil (sex otherwise n.p.)	Phenothiazine (150 mg/kg body weight; 0.75 mmol/kg) was administered via gavage, as a suspension in corn oil. Urine was collected for 24 hours.	n.p.	Leucophenothiazone sulfate accounted for 64.6, 58.1, 11.7, and 55.6% of the administered phenothiazine dose in the 24-hour urine of mice, rats, hamsters, and gerbils, respectively.	Mitchell (1980)
Leucothionol	rabbit and dog (strains and sex n.p.)	Rabbits received 3 g (15 mmol) phenothiazine by gavage; dogs received 1.5 or 1.75 g (7.5 or 8.8 mmol) phenothiazine in gelatin capsules. Bile was obtained from rabbits and dogs 6 hours after dosing.	n.p.	Leucothionol was detected in rabbit and dog bile, but it was not quantitated.	DeEds and Thomas (1941)
	human (male)	Urine was obtained from an orchard worker who had a dermal reaction associated with spraying of phenothiazine.	n.p.	Leucothionol was detected in urine, but was not quantitated.	DeEds et al. (1940)
	human (sex n.p.)	Bile was collected from a patient being treated with phenothiazine for a urinary tract infection.	n.p.	Leucothionol was detected in bile, but was not quantitated.	DeEds and Thomas (1941)
Phenothiazine	n.p.	Phenothiazine was administered orally. The dose was not specified.	n.a.	Approximately 30-50% of the administered dose passed through the alimentary tract unchanged.	Clarke et al. (1981; cited by HSDB, 1996)
	mouse (female Swiss white)	Phenothiazine (2 mg/kg; 0.01 mmol/kg) was administered orally in olive oil.	n.p.	Approximately 14% of the administered dose was excreted unchanged in urine and feces at 72 hours.	Coats et al. (1976)
	mouse (male), rat, hamster (Syrian golden), and gerbil (sex otherwise n.p.)	Phenothiazine (150 mg/kg body weight; 0.75 mmol/kg) was administered via gavage, as a suspension in corn oil. Urine was collected for 24 hours.	n.p.	Only a small portion of the administered dose was excreted unchanged (urinary phenothiazine accounted for 0.8, 0.2, 0.5, and 0.6% of the administered dose in mice, rats, hamsters, and gerbils, respectively).	Mitchell (1980)

Abbreviations: n.p. = not provided; s.c. = subcutaneous

Table 3. Phenothiazine Metabolites (continued)

Metabolite Name	System or Species	Experimental Details	Enzymes	Comments	Reference
	rabbit and dog (strains n.p.)	Rabbits received 3 g (15 mmol) phenothiazine by gavage; dogs received 1.5 or 1.75 g (7.5 or 8.8 mmol) phenothiazine in gelatin capsules. Bile was obtained from rabbits and dogs 6 hours after dosing.	n.p.	Phenothiazine was detected in rabbit and dog bile, but it was not quantitated.	DeEds and Thomas (1941)
	cattle (female Charolais-Holstein calves)	Calves were drenched with 220 mg phenothiazine/kg body weight (1 mmol/kg) and were killed 24 hours later.	n.p.	Unchanged phenothiazine accounted for ~ 70% of the administered dose in liver and muscle, 100% in fat and tripe, and ~ 30% in kidneys.	Bureau of Veterinary Medicine (1972, 1973)
	human (sex n.p.)	Bile was collected from a patient being treated with phenothiazine for a urinary tract infection.	n.p.	Phenothiazine was detected in bile, but was not quantitated.	DeEds and Thomas (1941)
Phenothiazine-*N*-glucuronide	mouse (male), rat, hamster (Syrian golden), and gerbil (sex otherwise n.p.)	Phenothiazine (150 mg/kg body weight; 0.75 mmol/kg) was administered via gavage, as a suspension in corn oil. Urine was collected for 24 hours.	n.p.	Phenothiazine-*N*-glucuronide accounted for 29.0, 17.4, 85.3, and 28.5% of the administered phenothiazine dose in the 24-hour urine of mice, rats, hamsters, and gerbils, respectively.	Mitchell (1980)
Phenothiazine-5-oxide	cattle (female Charolais-Holstein calves)	Calves were drenched with 220 mg phenothiazine/kg body weight (1 mmol/kg) and were killed 24 hours later.	n.p.	Phenothiazine-5-oxide accounted for 16% of the administered dose in liver, ~ 30% in muscle, ~ 20% in kidneys, and ~90% in blood. It was not detected in fat or tripe.	Bureau of Veterinary Medicine (1972, 1973)
Phenothiazine sulfate	cattle (lactating Holstein-Friesian dairy cows)	Cows were given 100,000 mg phenothiazine (500 mmol/kg; route n.p.) and urine was collected during first 48 hours after dosing.	n.p.	The potassium salt of the ethereal sulfate of 3-hydroxyphenothiazine was detected in urine, but it was not quantitated.	Ellison et al. (1957)
	n.p.	n.p.	n.p.	Metabolism of phenothiazine occurred in the gut.	Mackison (1981; cited by HSDB, 1996)
Phenothiazine sulfone	mouse (female Swiss white)	Phenothiazine (2 mg/kg; 0.01 mmol/kg) was administered orally in olive oil.	n.p.	Phenothiazine sulfone accounted for 4.7% of the administered dose in urine and feces at 72 hours.	Coats et al. (1976)
Phenothiazine sulfoxide	enzymes of the proglottids (proglottids contain the reproductive organs) of the cestode *Moniezia expansa*, and cytosol of intestinal epithelial cells of the nematode *Ascaris suum*	n.p.	see "System or Species" column.	Enzymes in these systems also metabolized phenothiazine sulfoxides to thioethers under anaerobic conditions.	Dough (1979; cited by HSDB, 1996)

Abbreviations: n.p. = not provided; s.c. = subcutaneous

Table 3. Phenothiazine Metabolites (continued)

Metabolite Name	System or Species	Experimental Details	Enzymes	Comments	Reference
	guinea pig (adult and neonate Dunkin-Hartley)	Phenothiazine (150 mg/kg; 0.70 mmol/kg) was administered orally or s.c.	n.p.	In orally dosed adults, phenothiazine sulfoxide accounted for 1.8% of the dose in urine; trace amts. were detected in feces. In neonates and adults treated s.c., phenothiazine sulfoxide accounted for 4.0-12.5 and 6.5% of the dose, respectively, in urine; none was detected in feces.	Mitchell and Waring (1979)
	mouse (female Swiss white)	Phenothiazine (2 mg/kg; 0.01 mmol/kg) was administered orally in olive oil.	n.p.	Phenothiazine sulfoxide was the primary metabolite detected in urine and feces, accounting for 42-44% of the administered dose at 72 hours.	Coats et al. (1976)
	mouse (male), rat, hamster (Syrian golden), and gerbil (sex otherwise n.p.)	Phenothiazine (150 mg/kg body weight; 0.75 mmol/kg) was administered via gavage, as a suspension in corn oil. Urine was collected for 24 hours.	n.p.	Phenothiazine sulfoxide accounted for 1.2, 0.4, 0.8, and 0.5% of the administered phenothiazine dose in the 24-hour urine of mice, rats, hamsters, and gerbils, respectively.	Mitchell (1980)
Phenothiazine sulfoxide (concluded)	rat (male albino)	Phenothiazine (1.5 mg/kg body weight; 0.0075 mmol/kg) was administered via gavage, in corn oil, either once or as 5 daily doses.	n.p.	Phenothiazine sulfoxide accounted for 30% (single dose) or 38% (multiple doses) of the administered phenothiazine dose in livers of rats 4 hours after treatment.	ICI Americas (1982)
Phenothiazone	mouse (male), rat, hamster (Syrian golden), and gerbil (sex otherwise n.p.)	Phenothiazine (150 mg/kg body weight; 0.75 mmol/kg) was administered via gavage, as a suspension in corn oil. Urine was collected for 24 hours.	n.p.	Phenothiazone accounted for 3.8, 1.5, 0.4, and 1.2% of the administered phenothiazine dose in the 24-hour urine of mice, rats, hamsters, and gerbils, respectively.	Mitchell (1980)
	mouse (female Swiss white)	Phenothiazine (2 mg/kg; 0.01 mmol/kg) was administered orally in olive oil.	n.p.	Phenothiazone accounted for ~ 2.7% of the administered dose in urine and feces at 72 hours.	Coats et al. (1976)
	cattle (female Charolais-Holstein calves)	Calves were drenched with 220 mg phenothiazine/kg body weight (1 mmol/kg) and were killed 24 hours later.	n.p.	Phenothiazone accounted for < 10% of the administered dose in liver and for ~ 15% of the administered dose in kidneys. Phenothiazone was not detected in muscle, fat, tripe, or blood.	Bureau of Veterinary Medicine (1972, 1973)
Thionol	mouse (male), rat, hamster (Syrian golden), and gerbil (sex otherwise n.p.)	Phenothiazine (150 mg/kg body weight; 0.75 mmol/kg) was administered via gavage, as a suspension in corn oil. Urine was collected for 24 hours.	n.p.	Thionol accounted for 4.2, 4.7, 1.3, and 1.7% of the administered phenothiazine dose in the 24-hour urine of mice, rats, hamsters, and gerbils, respectively.	Mitchell (1980)

Abbreviations: n.p. = not provided; s.c. = subcutaneous

Table 3. Phenothiazine Metabolites (continued)

Metabolite Name	System or Species	Experimental Details	Enzymes	Comments	Reference
	rabbit and dog (strains not specified)	Rabbits received 3 g (15 mmol) phenothiazine by gavage; dogs received 1.5 or 1.75 g (7.5 or 8.8 mmol) phenothiazine in gelatin capsules. Bile was obtained from rabbits and dogs 6 hours after dosing.	n.p.	Thionol was detected in rabbit and dog bile, but it was not quantitated.	DeEds and Thomas (1941)
	human (male)	Urine was obtained from an orchard worker who had a dermal reaction associated with spraying of phenothiazine.	n.p.	Thionol was detected in urine, but was not quantitated.	DeEds et al. (1940)
	human (sex n.p.)	Bile was collected from a patient being treated with phenothiazine for a urinary tract infection.	n.p.	Thionol was detected in bile, but was not quantitated.	DeEds and Thomas (1941)
Thionol glucuronide	mouse (male), rat, hamster (Syrian golden), and gerbil (sex otherwise n.p.)	Phenothiazine (150 mg/kg body weight; 0.75 mmol/kg) was administered via gavage, as a suspension in corn oil. Urine was collected for 24 hours.	n.p.	Thionol glucuronide accounted for 4.5, 17.7, 0, and 11.9% of the administered phenothiazine dose in the 24-hour urine of mice, rats, hamsters, and gerbils, respectively.	Mitchell (1980)

Abbreviations: n.p. = not provided; s.c. = subcutaneous

Table 4. Excretion of Phenothiazine

Route	Species (Strain)	Dose[a] mg/kg (mmol/kg)[b]	Time	% Excreted in Urine	% Excreted in Feces	Reference
oral	cattle (crossbred Angus/Hereford steers)	0.001 (5×10^{-6}) for 10 days	n.p.	50%	40%	ICI Americas Inc. (1977a)
	cattle (steers; strain n.p.)	1.1 (0.0057) for 10 days	n.p.	47-57%	36-41%	ICI Americas Inc. (1983)
	cattle (steers; strain n.p.)	0.13 (0.0007)	72 hr.	48.9%	27.0%	ICI Americas Inc. (1983)
	cattle (crossbred Angus/Hereford steer)	0.5 (0.003)	72 hr.	48.9%	27%	ICI Americas Inc. (1980a)
	cattle (male Friesian calves)	200 mg (1.0)	24 hr.	~ 40%	n.p.	Waring and Mitchell (1985)
	cattle (female Charolais-Holstein calves)	220 (1.1)	6-24 hr.	~ 50%	~ 50%	Bureau Veterinary Medicine (1972)
	cattle (cow; strain n.p.)	220 (1.1)	24 hr.	24.8%	n.p.	Mitchell (1982)
	cattle (Holstein-Friesian, Aberdeen Angus, Milking Shorthorn, or Jersey cows)	100000 mg (bolus or microionized) (0.5)	n.p.	19% (bolus and microionized)	54-67% (bolus) 19-26% (microionized)	Richardson and Todd (1958)
	gerbil	150 (0.75)	24 hr.	30%	n.p.	Mitchell (1980)
	guinea pig (adult Dunkin-Hartley)	150 (0.75)	24 hr.	3.7%	7.0%	Mitchell and Waring (1979)
	hamster (Syrian golden)	150 (0.75)	24 hr.	44%	n.p.	Mitchell (1980)
	horse (strain n.p.)	55-130 (0.28-0.65)	24 hr.	9-12%	n.p.	Mitchell (1982)
	human	6 (0.03)	24 hr.	25.4%	n.p.	Mitchell (1982)
	mouse (strain n.p.)	150 (0.75)	24 hr.	44%	n.p.	Mitchell (1980)
	rabbit (strain n.p.)	1500 (7.5)	24 hr.	25%	n.p.	Mitchell (1982)
	rat (male albino)	1.5 (0.0075)	30 days	54-58%	36-41%	ICI Americas (1982)
	rat (male albino)	1.5 (0.0075) for 5 days	3 days	61-67%	28-36%	ICI Americas (1982)
	rat (strain n.p.)	150 (0.75)	24 hr.	18%	n.p.	Mitchell (1980)
	rat (male Harlan-Wistar)	11 (0.055)	48 hr.	40%	n.p.	West Chem. Products (1970b, 1982)
	rat (male and female albino)	n.p. (rats were fed liver from a dosed steer)	48 hr.	5%	85%	ICI Americas (1979)
	sheep (strain n.p.)	220-840 (1.1-4.2)	24 hr.	10-20%	n.p.	Mitchell (1982)
s.c.	guinea pig (adult and neonate Dunkin-Hartley)	150 (0.75)	24 hr.	3%, adults; 3-13%, neonates	0%	Mitchell and Waring (1979)

[a] single dose except when noted
[b] except when noted

Table 4. Excretion of Phenothiazine

Abbreviations: n.p. = not provided; s.c. = subcutaneous

9.2.1.5 Pharmacokinetics

The urinary half life ($t_{1/2}$) of orally administered phenothiazine ranges from 12 to 18 hours in the horse, 11 to 17 hours in sheep, and is approximately 11 hours in humans. In horses, sheep, and humans, the largest amount of phenothiazine is excreted within the first 24 hours after dosing, with the fastest rate of excretion occurring during the first 9 hours (Mitchell, 1982).

9.2.2 Acute Exposure

The LD_{50} data for phenothiazine are presented in **Table 5** and **Table 6**; other acute exposure data are presented in **Table 7.**

Table 5. Acute Toxicity Values for Phenothiazine

Route	Species (strain)	LD_{50} mg/kg (mmol/kg)	Reference
i.p.	mouse (strain n.p.)	400-800 (2-4)	Eastman Kodak (1987)
	rat (strain n.p.)	1600-3200 (8-16)	Eastman Kodak (1987)
i.v.	mouse (strain n.p.)	178 (0.894)	U.S. Army (year not given; cited by RTECS, 1996)
oral	mouse (strain n.p.)	1600-3200 (8-16)	Eastman Kodak (1987)
	mouse (strain n.p.)	5000 (25)	Develop. Neurosci. (1980; cited by RTECS, 1996)
	rabbit (strain n.p.)	4000 (20)	Marhold (1986; cited by RTECS, 1996)
	rat (Sprague-Dawley)	1330 (6.67)	ICI Americas Inc. (1977c)
	rat (Wistar)	3000 (15)	Union Carbide (1971)
	cattle (strain n.p.)	500 (2.51)	Marhold (1986; cited by RTECS, 1996)

Abbreviations: i.p. = intraperitoneal; i.v. = intravenous; n.p. = not provided

Table 6. Acute Toxicity Values for Phenothiazine in Combination with Other Treatments

Route	Species (strain)	LD_{50}	Reference
oral	rat (Wistar)	933 mg/kg (5:1 phenothiazine-Sevin® mixture)	Union Carbide (1971)

Table 7. Acute Toxicity of Phenothiazine

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
9.2.2.1 Dermal Exposure						
guinea pig (strain and age n.p.)	n.p.	phenothiazine, purity n.p.	n.p. Skin was occluded	24 hr.; observation duration n.p.	Skin irritation was not observed.	DuPont (1947)
guinea pig (strain and age n.p.)	exposed: 3 (sex n.p.) controls: n.p.	phenothiazine, ~ 100% pure	250-1000 mg/kg (1.2-5 mmol/kg) It was not specified if skin was occluded	24 hr.; 2 wk.	Slight to moderate irritation was observed.	Eastman Kodak (1987)
guinea pig (strain and age n.p.)	exposed: 1 (sex n.p.) controls: 1 (sex n.p.)	phenothiazine, purity n.p.	5000 mg/kg (25 mmol/kg) Guinea pigs were exposed to sunlight 1 hour/day for 9 days after treatment with phenothiazine	n.p.	There were no signs of photosensitivity.	DuPont (1987)
rabbit (strain and age n.p.)	exposed: 1 (sex n.p.) controls: 0	phenothiazine, purity n.p., in a 3- to 6-wk-old ethanol solution	1% solution of phenothiazine in 95% ethanol (3-6 week old decomposing solution) Skin was occluded	24 hr.; immediately after treatment	Severe skin irritation developed.	Dow Chemical (1937)
rabbit (20-wk-old New Zealand white)	exposed: 2 rabbits/dose/ purity (sex n.p.) controls: 0	phenothiazine, 95 or 99.8% pure	3900, 6000, or 9400 mg/kg (20, 30, or 50 mmol/kg) applied to intact or abraded skin; it was not specified if skin was occluded	24 hr.; 2 wk.	No skin irritation was observed.	ICI Americas Inc. (1977f,g)
rabbit (8-wk-old New Zealand white)	exposed: 6 rabbits/purity (sex n.p.) controls: 0	phenothiazine, 95 or 99.8% pure	500 mg (2.5 mmol) applied to intact or abraded skin; it was not specified if skin was occluded	n.p.	No skin irritation was observed.	
9.2.2.2 Ocular Exposure						
rabbit (20-wk-old New Zealand white)	exposed: 6 rabbits/ purity (sex n.p.) controls: 0	phenothiazine, 95 or 99.8% pure	100 mg (0.5 mmol) instilled into 1 eye/rabbit; unwashed	72 hr. (exposure and observation)	Eye irritation was not observed.	ICI Americas Inc. (1977h,i)

Abbreviations: F = female; i.p. = intraperitoneally; M = male; n.p. = not provided

Table 7. Acute Toxicity of Phenothiazine (continued)

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
9.2.2.3 Inhalation Exposure						
rat (albino; age n.p.)	exposed: 10 M controls: 0	phenothiazine, 95 or 99.8% pure	200 mg/L (200000 mg/m^3; 24540 ppm)	1 hr.; 2 wk.	No adverse clinical or pathological effects were observed.	ICI Americas Inc. (1977j,k)
9.2.2.4 Oral Exposure						
mouse and rat (strains and ages n.p.)	exposed: 5 mice; 5 rats (sex n.p.) controls: n.p.	phenothiazine, ~ 100% pure	200-3200 mg/kg bw (1-16 mmol/kg bw) by gavage as a 10% suspension in 2% sodium cellulose sulfate in water	single dose; 2 wk.	Weakness was observed in mice and rats. Death occurred in mice within 8 days of dosing (number of deaths not reported). None of the rats died.	Eastman Kodak (1987)
rat (strain and age n.p.)	exposed: 1 rat for each of 3 lowest doses; 5 rats for each of 3 highest doses (sex n.p.) controls: 0	phenothiazine, purity n.p.	600, 1000, 2000, 3000, 4000, or 5000 mg/kg (3-25 mmol/kg) by gavage	single dose; 2 wk.	4/5 rats given 4000 mg/kg (20 mmol/kg) and 5/5 rats given 5000 mg/kg (25 mmol/kg) died. All other rats survived.	Dow Chemical (1944)
rat (strain and age n.p.)	n.p.	phenothiazine, 99%, containing oriental licorice, diisopropyl naphthalene or alkyl naphthalene sodium sulfonate, and $Na_2B_4O_7$	n.p.	single dose; observation duration n.p.	Toxicities of several doses were described as being "very low."	Dow Chemical (1945)
rat (Wistar; age n.p.)	exposed: 5 F per dose controls: 0	phenothiazine, purity n.p.	1600, 3200, 6400, or 12,800 mg/kg (8, 16, 32, or 64 mmol/kg) in corn oil by gavage	single dose; 2 wk.	All rats in the 2 highest dose groups died. 3/5 rats at 3200 mg/kg (16 mmol/kg) died. None of the low-dose rats died. Clinical signs of toxicity included sluggish, rapid breathing 2 min after dosing, and prostration at 2 hr. Congestion throughout the lungs and abdominal viscera was observed.	Union Carbide (1971)
rat (Sprague-Dawley; 40- to 50-day-old)	exposed: 1 M, 1 F per dose controls: 0	phenothiazine, 95% pure	2000, 3170, 5024, 7964, or 12623 mg/kg (10-63 mmol/kg) in cottonseed oil by gavage	single dose; observation duration n.p.	All rats died within 28 hours and showed evidence of having diarrhea.	ICI Americas Inc. (1977c)

Abbreviations: F = female; i.p. = intraperitoneally; M = male; n.p. = not provided

Table 7. Acute Toxicity of Phenothiazine (continued)

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
rat (Sprague-Dawley; 40- to 50-day-old)	exposed: 1 M, 1 F per dose controls: 0	phenothiazine, 95% pure	500, 793, 1257, 1992, or 3157 mg/kg (2.5-16 mmol/kg) in cottonseed oil by gavage	single dose; observation duration n.p.	Diarrhea, weakness, lethargy, and unconsciousness were observed in rats given 500 mg/kg (2.5 mmol/kg). 1 M administered 793 mg/kg (4.0 mmol/kg), 1 F administered 1257 mg/kg (6.3 mmol/kg), and all rats administered 1992 and 3157 mg/kg (10 and 16 mmol/kg) died within 3 days.	
rat (Sprague-Dawley; 40- to 50-day-old)	exposed: 5 rats/sex/dose (exception, 1 M for 855 mg/kg) controls: 0	phenothiazine, 95% pure	600, 755, 855, 951, 1197, or 1508 mg/kg (3-8 mmol/kg) in cottonseed oil by gavage	single dose; observation duration n.p.	1 rat from the 600-, 755-, and 951-mg/kg (3-, 4-, and 5-mmol/kg) groups died. Multiple deaths occurred at higher doses.	ICI Americas Inc. (1977c)
rat (Sprague-Dawley; 120 day-old)	exposed: 1 M, 1 F per dose controls: 0	phenothiazine, 99.8% pure	A. 951, 1197, 1508, 2000, or 2518 mg/kg (5-13 mmol/kg) in dioctyl sodium sulfosuccinate-methocal solution by gavage B. 1600, 2536, 4020, 6371, or 10098 mg/kg (8-50 mmol/kg) in dioctyl sodium sulfosuccinate-methocal solution by gavage	single dose; 1 wk (treatment A) or 2 wk (treatment B).	No adverse effects were observed at any dose.	ICI Americas Inc. (1977d)
guinea pig (strain and age n.p.)	n.p.	phenothiazine, purity n.p.	3000 mg/kg (15 mmol/kg) by gavage	single dose; observation duration n.p.	No adverse effects were observed.	Dow Chemical (1937)
guinea pig (strain and age n.p.)	exposed: 1 (sex n.p.) controls: n.p.	phenothiazine, purity n.p.	7500 mg/kg (38 mmol/kg) as a suspension in peanut oil	single dose; observation duration n.p.	Death occurred 10 days after dosing. Diarrhea, yellow-stained fur, polyuria, labored breathing, emaciation, and sunken eyes were observed before death.	DuPont (1987)
guinea pig (strain and age n.p.)	n.p.	phenothiazine, purity n.p.	1500, 5000, 7500, or 11000 mg/kg (7.5-55 mmol/kg) as a suspension in guar gum	single dose; observation duration n.p.	Nervousness or exhaustion and temporary weight loss were observed. There were no pathological changes.	
cattle and pig (strains and ages n.p.)	n.p.	phenothiazine, purity n.p.	n.p.	n.p.	Skin of cattle and pigs became photosensitized.	Grant (1974; cited by HSDB, 1996)

Abbreviations: F = female; i.p. = intraperitoneally; M = male; n.p. = not provided

Table 7. Acute Toxicity of Phenothiazine (continued)

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
9.2.2.5 Intradermal Injection						
n.p.	n.p.	phenothiazine, ~ 100% pure	30 mg (0.15 mmol)	single dose; 1 wk.	The dose caused erythema which progressed to necrosis and finally to eschar formation at 1 week.	Eastman Kodak (1987)
9.2.2.6 Intraperitoneal Injection						
mouse and rat (strains and ages n.p.)	exposed: 5 mice; 5 rats (sex n.p.) controls: n.p.	phenothiazine, ~ 100% pure	200-3200 mg/kg bw (1-16 mmol/kg bw) i.p. as a 10% suspension in 2% sodium cellulose sulfate in water	single dose; duration of observation period n.p.	Weakness was observed in mice and rats. Rats also had rough coats. Deaths occurred within 1-2 days.	Eastman Kodak (1987)
9.2.2.7 Unspecified Route						
horse (strain and age n.p.)	n.p.	phenothiazine, purity n.p.	n.p.	n.p.	Signs of toxicity include anorexia, dullness, weakness of hind legs, staggering, hemolysis of red blood cells leading to anemia, jaundice, and hemoglobinuria, weak rapid pulse, dyspnea, colic, and prostration.	Clarke et al. (1981; cited by HSDB, 1996)
pig (strain and age n.p.)	n.p.	phenothiazine, purity n.p.	n.p.	n.p.	Signs of toxicity include marked uncoordination with evidence of other nervous abnormalities. In later stages, posterior paralysis, prostration, and coma may occur. Corneal opacity may also occur and may cause temporary blindness; pigs usually recover within a few days. Few deaths occurred.	

Abbreviations: F = female; i.p. = intraperitoneally; M = male; n.p. = not provided

9.2.2.1 Dermal Exposure

Skin irritation was not observed in guinea pigs (strain not provided) that received an unspecified dose on skin for 24 hours (DuPont, 1947). Slight to moderate skin irritation was observed in guinea pigs (strain not provided) treated with 250-1000 mg/kg (1.2-5 mmol/kg) phenothiazine for 24 hours (Eastman Kodak, 1987). The guinea pigs were observed for 2 weeks.

The skin of a guinea pig (strain not provided) administered 5000 mg/kg (25 mmol/kg) phenothiazine and exposed to sunlight 1 hour/day for 9 days after treatment showed no signs of photosensitivity (DuPont, 1987).

Severe skin irritation was observed in a rabbit (strain not provided) that had a 3- to 6-week old decomposing solution of 1% phenothiazine in 95% ethanol applied for 24 hours (Dow Chemical, 1937).

Skin irritation was not observed in New Zealand rabbits treated with 500-9400 mg/kg (2.51-50 mmol/kg) phenothiazine for 24 hours (ICI Americas, 1977f,g).

9.2.2.2 Ocular Exposure

No ocular irritation was observed in New Zealand white rabbits that had 100 mg (0.5 mmol) phenothiazine instilled into 1 eye for 72 hours (ICI Americas Inc., 1977h,i).

9.2.2.3 Inhalation Exposure

Adverse clinical or pathological effects were not detected in albino rats exposed to 200 mg/L (200,000 mg/m^3; 24,500 ppm) phenothiazine for 1 hour and observed for 2 weeks (ICI Americas Inc., 1977j,k).

9.2.2.4 Oral Exposure

Severe toxicity leading to death occurred within 8 days in mice (strain not provided) administered a single dose of 200-3200 mg/kg (1-16 mmol/kg) phenothiazine, while slight toxicity was observed in rats (strain not provided) over the same dose range (Eastman Kodak, 1987).

Severe toxicity leading to death occurred in rats (strain not provided) administered a single dose of 4000 or 5000 mg/kg (20 or 25 mmol/kg) phenothiazine (Dow Chemical, 1944). Administration of lower doses of phenothiazine (600-3000 mg/kg; 3-15 mmol/kg) was not lethal.

Administration of a single dose of phenothiazine containing trace (< 1%) amounts of oriental licorice, diisopropyl naphthalene or alkyl naphthalene sodium sulfonate, and $Na_2B_4O_7$ to rats (strain not provided) was only slightly toxic (Dow Chemical, 1945). The actual dose administered was not specified.

Severe toxicity leading to death occurred in Wistar rats administered a single dose of 3200-12800 mg/kg (16-64 mmol/kg) phenothiazine (Union Carbide, 1971), and in weanling Sprague Dawley rats administered a single dose of 500-1508 mg/kg (2.5-7.6 mmol/kg) phenothiazine (purity, 95%) in cottonseed oil by gavage (ICI Americas Inc., 1977c). However, mortality was not induced in young adult Sprague Dawley rats administered a single dose of 951-10098 mg/kg (4.8-51 mmol/kg) phenothiazine (purity, 99.8%) in dioctyl sodium sulfosuccinate-methocal solution by gavage (ICI Americas Inc., 1977d).

No adverse effects were observed in guinea pigs (strain not provided) administered a single dose of 3000 mg/kg (15 mmol/kg) phenothiazine by gavage (Dow Chemical, 1937). Slight toxicity was observed in guinea pigs (strain not provided) administered a single dose of 1500-11000 mg/kg (7-50 mmol/kg) phenothiazine (DuPont, 1987). Severe toxicity leading to death occurred in a guinea pig (strain not provided) administered a single dose of 7500 mg/kg (40 mmol/kg) phenothiazine (DuPont, 1987).

The skin of cattle and pigs (strain not provided) became photosensitized following oral administration of an unspecified dose (Grant, 1974; cited by HSDB, 1996).

9.2.2.5 Intradermal Injection

Severe skin irritation was observed in animals (species not provided) that received a single intradermal injection of 30 mg (0.15 mmol) phenothiazine (Eastman Kodak, 1987). The dose caused erythema which progressed to necrosis and finally to eschar formation at 1 week.

9.2.2.6 Intraperitoneal Injection

Death occurred within 1 to 2 days in mice and rats (strains not provided) administered 200-3200 mg/kg (1-16 mmol/kg) phenothiazine i.p. (Eastman Kodak, 1987). Weakness was observed in mice and rats, and rats exhibited rough coats.

9.2.2.7 Unspecified Route

Severe toxicity was observed in horses and pigs following administration of phenothiazine (route, dose, and animal strain were not provided) (Clarke et al., 1981; cited by HSDB, 1996). In horses, the signs of toxicity included anorexia, dullness, weakness of hind legs, staggering, hemolysis of red blood cells leading to anemia, jaundice, and hemoglobinuria, weak rapid pulse, dyspnea, colic, and prostration. In pigs, the signs of toxicity included marked incoordination with evidence of other nervous abnormalities. In later stages, posterior paralysis, prostration, and coma may occur. Corneal opacity may also occur and may cause temporary blindness; pigs usually recover within a few days. Few deaths occurred.

9.2.3 Short-Term and Subchronic Exposure

The studies described in this section are presented in **Table 8**.

9.2.3.1 Dermal Exposure

Occluded abdominal skin of rabbits exhibited moderate irritation with multiple applications of a 1% solution of phenothiazine in 95% ethanol (8 applications over 10 days; 9 applications over 15 days; or 22 applications over 34 days) (Dow Chemical, 1937). The same treatment on ears caused no irritation.

9.2.3.2 Oral Exposure

Significantly greater liver regeneration was observed in male Holtzman rats given a partial hepatectomy and a diet containing 0.075% phenothiazine (750 ppm; 3.8 mmol/kg feed) for 7 days starting 3 days after surgery, than in rats given only a partial hepatectomy without phenothiazine treatment (Gershbein, 1973). In the same study treatment of male Charles River rats, without partial hepatectomy, with phenothiazine (0.075% in diet; 750 ppm; 3.8 mmol/kg feed) for 10 days, caused an increase in liver weight at the end of the exposure period.

In rats and rabbits (strains and ages not specified), repeated oral administration of 500-2000 mg/kg (2.5-10 mmol/kg) (rats) or 1000-5000 mg/kg (5-25 mmol/kg) (rabbits) phenothiazine (duration of exposure not provided) caused liver and spleen damage, and slight hyperplasia of bone marrow. Kidney damage was also observed in animals administered the higher doses (Dow Chemical, 1944). The livers and kidneys of rabbits (strain and age not provided) administered 100-2000 mg/kg (0.5-10 mmol/kg) phenothiazine showed dose-dependent signs of toxicity, including swelling with the lower doses and severe damage with the higher doses (Dow Chemical, 1937).

Table 8. Short-Term and Subchronic Toxicity of Phenothiazine

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
9.2.3.1 Dermal Exposure						
rabbit (strain and age n.p.)	exposed: 1 rabbit/ treatment controls: 0	phenothiazine, purity n.p.	1% solution of phenothiazine in 95% ethanol	8 applications over 10 days; 9 applications over 15 days; or 22 applications over 34 days applied to ears and abdominal skin; abdominal skin was occluded	Abdominal skin became moderately irritated. There was no adverse reaction in ear skin. The rabbit administered 8 applications over 10 days died ~ 3 wk after end of treatment.	Dow Chemical (1937)
9.2.3.2 Oral Exposure						
dog (eagle, young adult)	exposed: 3 M, 3 F per dose controls: 3 M, 3 F	phenothiazine, purity n.p.	50, 200, 500, or 2000 ppm in diet (0.25, 1, 2.5, or 10 mmol/kg feed)	13 weeks; all dogs were killed at end of treatment period	All high-dose dogs had dark colored spleens; spleen weight was elevated in 2/3 high-dose females. High dose dogs also exhibited marked congestion and hematopoiesis of the spleen; deposition of hemosiderin in spleen, liver, kidneys, and bone marrow; and hyperplasia of bone marrow. Dogs administered the 500 ppm diet also exhibited some of these symptoms, but to a lesser degree.	ICI Americas Inc. (1974a,b)
dog (beagle, young adult)	exposed: 4 M and 4 F per dose per grade controls: 4 M, 4 F	phenothiazine, pharmaceutical and technical grade [purity n.p.]	2000 ppm in diet (10 mmol/kg feed)	13 wk; all dogs were killed at end of treatment period	All dogs had dark colored spleens; spleen weight was elevated in some. All dogs exhibited marked congestion and hematopoiesis of the spleen; deposition of hemosiderin in spleen, liver, kidneys, and bone marrow; and hyperplasia of bone marrow.	
guinea pig (strain and age n.p.)	n.p.	phenothiazine, purity n.p.	200 mg/animal/day (1 mmol/animal/day)	1 wk; duration of observation period n.p.	No adverse effects were observed.	DuPont (1947)

Abbreviations: F = female; M = male; n.p. = not provided

Table 8. Short-Term and Subchronic Toxicity of Phenothiazine (continued)

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
guinea pig (strain and age n.p.)	exposed: n.p. controls were used, but number n.p.	phenothiazine, purity n.p.	5000 mg/kg/day (25 mmol/kg/day)	10 days; duration of observation period n.p.	Phenothiazine-treated guinea pigs were paler and had slower weight gain than controls.	DuPont (1987)
rabbit (strain and age n.p.)	exposed: 1 rabbit/ treatment controls: 0	phenothiazine, purity n.p.	4 doses of 2000 mg/kg (10 mmol/kg) over 7 days; 4 doses of 1000 mg/kg (5 mmol/kg) over 6 days; 11 doses of 500 mg/kg (2.5 mmol/kg) over 25 days; 15 doses of 250 mg/kg (1.2 mmol/kg) over 38 days; 17 doses of 100 mg/kg (0.5 mmol/kg) over 19 days followed by 13 doses of 500 mg/kg (2.5 mmol/kg) over 19 days; or 19 doses of 100 mg/kg (0.5 mmol/kg) over 25 days	7-38 days [see Dose]; rabbits were killed several days after cessation of treatment	Dose-dependent toxicity (swelling progressing to severe damage) was observed in liver and kidneys.	Dow Chemical (1937)
rabbit (strain and age n.p.)	exposed: 1-3 rabbits/dose controls: 1 rabbit (sex n.p.)	phenothiazine, purity n.p.	100, 1000, 2000, or 5000 mg/kg (0.5, 5, 10, or 25 mmol/kg)	up to 20 doses were administered (see Results/Comments; duration of exposure n.p.)	Nineteen doses of 100 mg/kg (0.5 mmol/kg) caused no adverse effects. Twenty doses of 1000 mg/kg (5 mmol/kg) caused slight liver and spleen damage and hyperplasia of bone marrow. Fourteen and 20 doses of 2000 mg/kg (10 mmol/kg) caused marked liver and spleen damage and hyperplasia of bone marrow. Four and 10 doses of 5000 mg/kg (25 mmol/kg) caused marked liver and spleen damage and congestion of kidneys (bone marrow not examined). 1/3 rabbits given 1000 mg/kg (5 mmol/kg) died; 1/2 given 2000 mg/kg (10 mmol/kg) died; 2/3 given 5000 mg/kg died (25 mmol/kg).	Dow Chemical (1944)

Abbreviations: F = female; M = male; n.p. = not provided

Table 8. Short-Term and Subchronic Toxicity of Phenothiazine (continued)

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
rat (strain and age n.p.)	exposed: 1-2 rats/dose controls: 2 rats (sex n.p.)	phenothiazine, purity n.p.	100, 500, 1000, or 2000 mg/kg (0.5, 2.5, 5, or 10 mmol/kg)	up to 19 doses were administered (see Results/Comments; duration of exposure n.p.)	Nineteen doses of 100 mg/kg (0.5 mmol/kg) caused no adverse effects. Nineteen doses of 500 mg/kg (2.5 mmol/kg) caused slight spleen damage, slight to marked liver damage, and slight hyperplasia of bone marrow. Five doses of 1000 mg/kg (5 mmol/kg) caused marked liver damage, slight spleen and kidney damage, and slight hyperplasia of bone marrow. Five doses of 2000 mg/kg (10 mmol/kg) caused marked liver and kidney damage, and slight hyperplasia of bone marrow. 1/2 rats given 1000 mg/kg (5 mmol/kg) and 1/2 rats given 2000 mg/kg (10 mmol/kg) died.	
rat (Holtzman; age n.p.)	exposed: 8 M controls: 14 M	phenothiazine, purity n.p.	0.075% in diet (3.8 mmol/kg feed), beginning 3 days after partial hepatectomy (controls also received partial hepatectomy)	7 days; rats were killed on the 10th post-operative day	There was a significantly higher amount of liver regeneration in phenothiazine-treated Holtzman rats given a partial hepatectomy than in controls given a partial hepatectomy. In Charles River rats (not given a partial hepatectomy), phenothiazine caused a significant increase in liver weight.	Gershbein (1973)
rat (Charles River; age n.p.)	exposed: 11 M controls: 11 M	phenothiazine, purity n.p.	0.075% in diet (3.8 mmol/kg feed) [no partial hepatectomy]	10 days; rats were killed at the end of treatment period		
sheep (strain and age n.p.)	n.p.	phenothiazine, purity n.p.	12.5 mg/kg/day (0.0627 mmol/kg/day) orally	20 or 35 days; duration of observation period n.p.	Administration of phenothiazine increased the total content of volatile fatty acids in the rumen by increasing the acetic acid level. No other details were given.	Sirotkina and Grotsenko (1971)

Abbreviations: F = female; M = male; n.p. = not provided

Table 8. Short-Term and Subchronic Toxicity of Phenothiazine (continued)

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
steer and heifer calf (Hereford and Angus breeds; 6- to 8-mo-old)	exposed: 7 (sex n.p.) controls: 0	phenothiazine, 95% pure	Six calves were given a single high dose of phenothiazine (60 g; 300 mmol) in feed, followed by a lower dose (2 g/day; 10 mmol/day) in feed for 30 days; 1 calf was given only the 60-g high dose.	30 days; length of observation period n.p.	No adverse effects were observed.	Schlinke and Palmer (1973)

Abbreviations: F = female; M = male; n.p. = not provided

No adverse effects were observed in guinea pigs (strain and age not provided) administered 200 mg/kg/day phenothiazine (1 mmol/kg/day) for 1 week (duration of observation not provided) (DuPont, 1947). Only slight toxicity (paleness and slower weight gain) was observed in guinea pigs (strain and age not provided) administered 5000 mg/kg/day (25 mmol/kg/day) for 10 days (DuPont, 1987).

Signs of toxicity were observed in spleen, liver, kidneys, and bone marrow of young adult beagle dogs administered 500 or 2000 ppm (2.5 or 10.0 mmol/kg feed) phenothiazine in diet for 13 weeks (ICI Americas, 1974a,b). The high-dose dogs exhibited dark colored spleens, marked congestion and hematopoiesis of the spleen, deposition of hemosiderin in spleen, liver, kidneys, and bone marrow; and hyperplasia of bone marrow. Dogs administered the 500 ppm diet exhibited some of these symptoms, but to a lesser degree. No toxic signs were seen at 50 or 200 ppm (0.25, 1.0 mmol/kg feed).

Oral administration of 12.5 mg/kg/day (0.063 mmol/kg/day) phenothiazine to sheep (strain and age not provided) for 20 or 35 days increased the total content of volatile fatty acids in the rumen by increasing the acetic acid level (Sirotkina and Grotsenko, 1971). No other experimental details were given.

No adverse effects were observed in 6- to 8-month-old Hereford and Angus steer and heifer calves administered a single high dose of phenothiazine (60 g; 300 mmol) in feed, followed by a lower dose (2 g/day; 10 mmol/day) in feed for 30 days (Schlinke and Palmer, 1973).

9.2.4 Chronic Exposure

Studies described in this section are presented in **Table 9**.

In four New Hampshire chicks fed phenothiazine in the diet for 30 weeks (weeks 0-4, 1400 mg/kg feed [7 mmol/kg]; weeks 5-29, 2300 mg/kg feed [11 mmol/kg]), weight gain was significantly depressed during weeks 0-7, but returned to control levels during weeks 8-29 (Ross

and Sherman, 1960). Two of the chicks died; one on day 12, and one on day 68 of the experiment.

9.3 Reproductive and Teratological Effects

The studies described in this section are presented in **Table 10**.

Table 9. Chronic Toxicity of Phenothiazine

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Exposure/ Observation Period	Results/Comments	Reference
chick (New Hampshire; 9-day-old)	exposed: 4 (sex n.p.) controls: 4 (sex n.p.)	phenothiazine, purity n.p.	wk 0-4, 1400 mg/kg feed (7 mmol/kg); wk 5-29, 2300 mg/kg feed (11 mmol/kg)	30 wk.	Weight gain was significantly depressed during wk 0-7, but returned to control levels during wk 8-29. 2/4 chicks died during the experiment.	Ross and Sherman (1960)

Abbreviations: n.p. = not provided

Table 10. Reproductive and Teratological Effects of Phenothiazine

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Duration of Exposure	Results/Comments	Reference
9.3.1 In Vitro						
Drosophila embryonic cells (Oregon R, Canton S_{109}, and Canton S)	n.a.	phenothiazine, purity n.p.	0.01 mM	24 hr	The dose caused a significant decrease in the number of myotubes.	Bournias-Vardiabasis et al. (1983)
9.3.2 In Vivo						
mouse (pregnant albino, age n.p.)	exposed: 20-25 F per dose controls: 20 F	phenothiazine, purity n.p.	30, 100, or 300 mg/kg/day (0.15, 0.5, or 1.5 mmol/kg/day) by gavage	Dams were dosed during gestation days 6-15 and killed on gestation day 17	No clinical signs of maternal toxicity were observed in dams and there was no statistically significant fetotoxicity or teratogenicity in their offspring.	ICI Americas Inc. (1977m)
rat (pregnant albino, age n.p.)	exposed: 18-21 F per dose controls: 21 F	phenothiazine, purity n.p.	15, 50, or 150 mg/kg/day (0.075, 0.2, or 0.75 mmol/kg) by gavage	Dams were dosed during gestation days 6-15	No clinical signs of maternal toxicity were observed in dams and there was there was no statistically significant fetotoxicity or teratogenicity in their offspring.	ICI Americas Inc. (1977l)
rat (Walter Reed-Carworth Farms strain, age n.p.)	exposed: 10 F controls: 126 F	phenothiazine, purity n.p.	250 mg/day (1.2 mmol/day) in diet	Administered for 22 days after positive mating; dams were killed at the end of the treatment period	In litters from dams treated with phenothiazine, 70% had 1 or more resorptions (vs. 40.8% of control litters) and 15.7% of all recognizable implantations had terminated in resorptions (vs. 10.6% in control litters). No signs of toxicity were observed in dams.	Telford et al. (1962)

hen (New Hampshire; 48-week old)	exposed: 4 F controls: 4 F	phenothiazine, purity n.p.	wk. 0-4, 1400 mg/kg feed (7 mmol/kg); wk. 5-29, 2300 mg/kg feed (11 mmol/kg)	29 wk	There was no significant reduction in egg production. The only consistent abnormality in eggs from phenothiazine-treated hens was a dark and mottled appearance of egg yolks.	Ross and Sherman (1960)

Abbreviations: F = females; n.a. = not applicable; n.p. = not provided

9.3.1 *In Vitro*

There was a significant decrease in the number of myotubes in Oregon R, Canton S_{109}, and Canton S *Drosophila* embryonic cells incubated in a 10 µM phenothiazine solution for 24 hours (Bournias-Vardiabasis et al., 1983).

9.3.2 *In Vivo*

Phenothiazine administered by gavage to pregnant albino mice and pregnant albino rats during gestation days 6-15 was neither fetotoxic nor teratogenic (ICI Americas Inc., 1977l,m). Pregnant mice received 30, 100, or 300 mg/kg/day (0.15, 0.50, or 1.50 mmol/kg/day) phenothiazine; pregnant rats received 15, 50, or 150 mg/kg/day (0.075, 0.20, or 0.750 mmol/kg/day) phenothiazine.

Phenothiazine caused an increase in resorptions in female Walter Reed-Carworth Farms strain rats treated with 250 mg/day (1.20 mmol/day) in the diet for 22 days after insemination (Telford et al., 1962).

There was no significant reduction in egg production in four New Hampshire hens administered phenothiazine in the diet for 30 weeks beginning at 48 weeks of age (weeks 0-4, 1400 mg/kg feed [7 mmol/kg]; weeks 5-29, 2300 mg/kg feed [11 mmol/kg]) (Ross and Sherman, 1960). The only consistent abnormality in eggs from phenothiazine-treated hens was a dark and mottled appearance of egg yolks.

9.4 Carcinogenicity

Studies described in this section are presented in **Table 11**.

The incidence of lung tumors was not increased in male A/J mice administered phenothiazine i.p. (50 mg/kg/day in corn oil; 0.25 mmol/kg/day) for 4 days, beginning at 6 weeks of age (Yamamoto et al., 1971). Rats were observed for 16 weeks following exposure.

There was no increase in tumor incidence in major tissues (not specified) of male and female C57BL/6 H C3H/Anf and C57BL/6 H AKR hybrid strain mice administered phenothiazine orally from 7 days of age until 18 months of age. Phenothiazine (0.1 mg/kg; 0.5 µmol/kg) was administered by gavage at age 7-28 days, and then in the diet (0.20 ppm; 1 µmol/kg feed) from age 29 days to 18 months (Innes et al., 1969). In a review of this study, McGregor et al. (1994) argue that phenothiazine would have probably tested positive for carcinogenicity if a more sensitive

Table 11. Carcinogenicity of Phenothiazine

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Duration of Exposure/ Observation Period	Results/Comments	Reference
mouse (A/J; 6-wk-old)	exposed: 14 M (phenothiazine alone) controls: 26 M (phenothiazine + urethan); 10 M (urethan alone); 9 M (untreated)	phenothiazine, purity n.p.	50 mg/kg/day (0.25 mmol/kg) i.p. in corn oil	4 days; 16 wk.	The incidence of lung tumors in rats treated with phenothiazine alone (4/14; 29%) was not significantly different from the incidence of lung tumors in untreated controls (1/9; 11%).	Yamamoto et al. (1971)
mouse (C57BL/6 H C3H/Anf and C57BL/6 H AKR hybrid strain; 7-day old)	exposed: 18 mice/sex/ strain controls: 18 mice/sex/ strain (untreated); 18 mice/sex/ strain (gelatin controls)	phenothiazine, purity n.p.	0.1 mg/kg (0.5 :mol/kg) in gelatin by gavage (age 7-28 days) 0.20 ppm in diet (1 :mol/ kg feed) (age 29 days-18 mo)	lifetime exposure (18 mo)	There was no increase in tumor incidence in major tissues (not specified) of phenothiazine-treated mice.	Innes et al. (1969)
rat (Fischer; age n.p.)	exposed: 49 F (FANFT + phenothiazine); 16 F (phenothiazine alone) controls: 15 F (basal diet alone); 47 F (FANFT alone)	phenothiazine and FANFT, purities n.p.	phenothiazine, 0.2% in diet; FANFT, 0.188% in diet (total amount ingested: phenothiazine, 3.0 g/rat; FANFT, 2.9 g/rat)	20 wk; rats were killed at the end of 40 wk.	No increase in bladder tumors in phenothiazine treated rats (0/16) compard to untreated control (0/15); administration of FANFT + phenothiazine significantly increased the incidence of carcinoma of the bladder (27/49 [55%] rats vs 8/47 [17%] for FANFT alone.	Wang and Hayashida (1984)

Abbreviations: F = female; FANFT = *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide; M = male; n.p. = not provided

current protocol, such as the one designed by the U.S. National Toxicology Program (NTP), had been used.

Female Fischer rats administered phenothiazine in feed (0.2%) for 20 weeks and killed after 40 weeks did not exhibit carcinoma of the bladder (Wang and Hayashida, 1984). However, co-administered of phenothiazine in the diet with *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]formamide (FANFT) at 0.188% resulted in a significantly increased incidence of bladder carcinomas compared to rats fed FANFT or phenothiazine alone.

9.5 Anti-Carcinogenicity

Studies described in this section are presented in **Table 12**.

9.5.1 Oral Exposure

Phenothiazine, when administered at a dose of 2 mg/g diet (10 :mol/g diet) with bracken fern for 1 year, decreased the incidence of intestinal and urinary bladder tumors in weanling albino rats by about 60% (Pamukcu et al., 1971). Bracken fern is associated with cancers of the intestine and urinary bladder in many different mammalian species (IARC, 1987).

9.5.2 Intraperitoneal Injection

In mice (strain and age not specified) bearing Ehrlich tumors, i.p. injections of 0.03 mg phenothiazine/day (0.1 µmol/day) for 10 days led to a 73% decrease in tumor weight after 30 days (Showa Denko, 1981). In another study, however, i.p. injection of 10 mg phenothiazine/day (50 µmol/day) for 7 or 10 days to mice bearing Ehrlich tumors had no anticarcinogenic activity (Motohashi, 1983; cited by Motohashi et al., 1991).

9.6 Genotoxicity

Studies described in this section are presented in **Tables 13 and 14**.

9.6.1 Prokaryotic Mutation Assays

Phenothiazine did not induce photo-activated gene mutations in the excision repair deficient *Salmonella typhimurium* strain TA2637 (Jose, 1979). Using a modified pre-incubation method, bacteria were exposed to 10-200 µg/mL (50-1000 µM) phenothiazine for 30 minutes in the absence of S9 followed by near-UV radiation exposure between 320 and 400 nm for 0-7 minutes.

Table 12. Anti-Carcinogenic Activity of Phenothiazine

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Duration of Exposure/ Observation Period	Results/Comments	Reference
9.5.1 Oral Exposure						
rat (albino; 35-day old)	1) 13 M, 20 F (bracken fern alone) 2) 20 M, 25 F (phenothiazine and bracken fern) [phenothiazine alone for 115 days] 3) 14 M, 12 F (untreated)	phenothiazine, purity n.p.	2 mg/g phenothiazine in diet (0.01 mmol/g diet); bracken fern was ground and mixed with diet	1 yr; during the first 15 days of the study, groups 1 and 3 received basal diet, and group 2 received basal diet containing phenothiazine. Beginning on the 16th day, groups 1 and 2 received bracken fern and bracken fern-phenothiazine in the diet, respectively, for the remainder of the study.	All rats received s.c. injections of 2 mg thiamine hydrochloride in 0.2 mL 0.9% NaCl solution once/week during the study to maximize the incidence of intestinal and urinary bladder neoplasms. Phenothiazine significantly decreased the incidence of intestinal and urinary bladder neoplasms (intestinal tumors, 19/21 rats fed bracken fern alone vs. 11/28 rats fed bracken fern-phenothiazine; bladder tumors, 19/21 rats fed bracken fern alone vs. 10/28 rats fed bracken fern-phenothiazine). No tumors were detected in liver, heart, brain, or stomach of rats from any group.	Pamukcu et al. (1971)
9.5.2 Intraperitoneal Injection						
mouse (male; strain and age n.p.) bearing Ehrlich tumors	n.p.	phenothiazine, purity n.p.	0.03 mg/day (0.0001 mmol/day)	10 days; duration of observation period n.p.	Tumor weight was decreased by 73% after 30 days.	Showa Denko (1981)
mouse (strain and age n.p.) bearing Ehrlich tumors	exposed: 4 (sex n.p.) controls: n.p.	phenothiazine, purity n.p.	10 mg/day (0.05 mmol/day)	7 or 10 days; duration of observation period n.p.	Phenothiazine did not have anticarcinogenic activity.	Motohashi, (1983; cited by Motohashi et al., 1991)

Abbreviations: F = female; M = male; n.p. = not provided; s.c. = subcutaneous

Table 13. Genotoxicity of Phenothiazine

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Doses Used	Endpoint Response	Comments	Reference
9.6.1 Prokaryotic Mutation Assays							
Salmonella typhimurium strain TA2637 (excision-repair deficient)	photo-activated *his* gene mutations	-	phenothiazine and derivatives, n.p.	10-200 µg/mL (0.05-1 mM) phenothiazine for 30 min followed by near-UV radiation between 320 and 400 nm for 0-7 min	negative	Phenothiazine was not mutagenic when exposed to UV or in the dark. The derivatives that had a chlorine substituent (chlorophenothiazine, chlorpromazine, compazine, and perphenazine) were photo-activated mutagens.	Jose (1979)
S. typhimurium strains TA100, TA98, TA1535, TA1537, and TA1538	*his* reverse gene mutations	-/+	phenothiazine, n.p.	5 to 500 µg/plate (0.03 to 2.51 µmol/plate) via the plate incorporation method and 1 to 20 µg/mL (5 to 100 µM) via the liquid suspension method	negative/negative		ICI Americas, Inc. (1980b)
S. typhimurium strain TA98	*his* reverse gene mutations	+	phenothiazine and derivatives, n.p.	doses up to 30 nmol/plate (full range not provided)	negative		Kittle et al. (1981)
S. typhimurium strains TA100, TA98, TA97, TA1535, and TA1537	*his* reverse gene mutations	-/+ rat or hamster	phenothiazine, n.p.	100, 333, 1000, 3333, and 10,000 µg/plate (0.5 to 50.2 µmol/plate) via the pre-incubation method	negative/negative	Precipitate was present in all cultures above 333 µg/plate (1.67 µmol/plate).	Mortelmans et al. (1986; cited by HSDB, 1996)
S. typhimurium strains TA100, TA98, TA1535, and TA1537	*his* reverse gene mutations	-/+	phenothiazine, n.p.	9.8 to 156.3 µg/plate (0.049 to 0.784 µmol/plate) via the plate incorporation method	negative/negative	In a toxicity test, toxicity was observed from 312.5 to 5000 µg/plate (1.568 to 25.09 µmol/plate)	Dow Corning (1988)
Escherichia coli strain WP2	*trp* reverse gene mutations	-/+	phenothiazine, n.p.	9.8 to 156.3 µg/plate (0.049 to 0.784 µmol/plate) via the plate incorporation method	negative/negative	In a toxicity test, toxicity was observed from 312.5 to 5000 µg/plate (1.568 to 25.09 µmol/plate).	
9.6.2 In Vitro Mammalian Mutagenicity Assays							

Abbreviations: NA = not applicable; n.g. = doses not given; n.p. = purity not provided

Table 13. Genotoxicity of Phenothiazine (continued)

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Doses Used	Endpoint Response	Comments	Reference
L5178Y TK +/- mouse lymphoma cells	*tk* gene mutations	-/+	phenothiazine, n.p.	20 to 113 µg/mL (100 to 567 µM) -S9 for 4 h and 15 to 92 µg/mL (75 to 462 µM) +S9 for 4 h	positive/negative	Four of the nonactivated cultures exhibited mutant frequencies greater than twice the mean mutant frequency of the solvent controls.	Procter and Gamble (1987)
9.6.3 In Vivo Human Chromosomal Damage							
11 hospitalized schizophrenic patients	chromosomal aberrations in peripheral blood leukocytes	NA	phenothiazine and other tranquilizers, n.p.	Continuous therapy with various phenothiazine drugs (actual doses not provided)	positive	Fifty cells were scored per patient. Single chromatid and chromosome breaks and chromosome-type rearrangements were increased compared to the control groups.	Gilmour at al. (1971)
9.6.4 Enhancement of DNA Damage							
Human colon adenocarcinoma cells	Enhanced DNA damage (DNA fragmentation assessed electrophoretically)	-	phenothiazine, n.p.	[^{3}H]thymidine for 24 h followed by 10 µM methotrexate or 1 mM 5-fluorodeoxyuridine for 60 min followed by 10, 25, or 50 µM phenothiazine for 24 hr	positive	Following the final exposure, cells were lysed, the DNA extracted and separated by electrophoresis on agarose gels, and the radioactivity of 1 mm gel slices counted on a scintillation counter. Higher concentrations of phenothiazine resulted in more DNA fragmentation after incubation with antineoplastic drugs.	Lönn and Lönn (1988)
L5178Y TK +/- mouse lymphoma cells	*tk* gene mutations	-/+	phenothiazine, n.p.	20 to 113 µg/mL (100 to 567 µM) -S9 for 4 hr and 15 to 92 µg/mL (75 to 462 µM) +S9 for 4 hr	positive/negative	Four of the nonactivated cultures exhibited mutant frequencies greater than twice the mean mutant frequency of the solvent controls.	Procter and Gamble (1987)

Abbreviations: NA = not applicable; n.g. = doses not given; n.p. = purity not provided

Table 14. Antigenotoxicity of Phenothiazine

Test System	Biological Endpoint	S9 Metabolic Activation	Chemical Form, Purity	Doses Used	Endpoint Response	Comments	Reference
9.6.5.1 Prokaryotic Antimutagenicity							
S. typhimurium strain TA98	inhibition of *his* reverse gene mutations	+	phenothiazine, n.p.	0.06 µmol/plate plus 6.0 nmol benzo[a]pyrene/plate, 0.94 nmol 6-methyl-benzo[a]pyrene/plate, or 2.9 nmol 10-methyl-benzo[a]pyrene/plate	positive	Phenothiazine reduced the number of revertants per plate by 41% for BaP, 9% for 6-MeBaP, and 55% for 10-MeBaP.	Calle et al. (1978)
S. typhimurium strain TA98	inhibition of *his* reverse gene mutations	+	phenothiazine, n.p.	0.003 to 0.3 µmol/plate plus 6 nmol/plate BaP	positive	Phenothiazine inhibited the mutagenicity of BaP in a concentration dependent manner from 40 to 75%.	Sullivan et al. (1980; cited by HSDB, 1996)
S. typhimurium strain TA98	inhibition of *his* reverse gene mutations	+	phenothiazine and derivatives, n.p.	doses expressed as ratios of 0.25 to 50 nmol derivative/nmol BaP	positive	None of the phenothiazine derivatives were mutagenic at concentrations up to 0.03 µmol/plate. Phenothiazine, 2-chlorophenothiazine, 10-phenylphenothiazine, and perphenazine significantly inhibited the mutagenicity of BaP at all concentrations.	Kittle et al. (1981)
S. typhimurium strain TA98	inhibition of *his* reverse gene mutations	+	phenothiazine, n.p.	0.082 and 0.41 µmol/plate plus 8.2 nmol benzo[a]pyrene/plate	positive	The number of revertants per plate were 133±21 at 0.082 µmol/plate and 181±13 at 0.41 µmol/plate compared to 539±54 for BaP alone.	Calle and Sullivan (1982)
S. typhimurium strain TA98	inhibition of *his* reverse gene mutations	+	phenothiazine, n.p.	200 to 150,000 µmol/plate plus 6-methyl-benzo[a]pyrene (2,800 µmol/plate) or 6-hydroxymethyl-benzo[a]pyrene (1,300 µmol/plate)	negative	A slight though statistically insignificant inhibition of BaP mutagenicity was observed at higher doses of phenothiazine. The plate incorporation method was used with rat liver S9 activation.	Bayless et al. (1986)
9.6.5.2 Inhibition of DNA Adduct Formation							
calf thymus DNA	inhibition of aflatoxin B_1 - induced DNA adducts	+	phenothiazine, n.p.	100 and 500 µM plus 2 µM [^{3}H]aflatoxin B_1 for 60 min at 37^{o}C	positive	Following exposure, the DNA was extracted, precipitated, washed three times, and the radioactivity counted. 100 and 500 FM gave reductions of 22 and 7.6 % of the BaP control, respectively.	Bhattacharya et al. (1984)

Abbreviations: BaP = benzo[a]pyrene; NA = not applicable; n.g. = doses not given; n.p. = purity not provided

Phenothiazine was also not mutagenic when the exposure was performed in the dark. Of the 10 phenothiazine derivatives tested, only those that had a chlorine substituent (chlorophenothiazine, chlorpromazine, compazine, and perphenazine) were photo-activated mutagens.

ICI Americas, Inc. (1980b) also reported that phenothiazine did not induce *his* gene mutations in *S. typhimurium.* Strains TA98, TA100, TA1535, TA1537, and TA1538 were exposed to doses ranging from 5 to 500 µg/plate (0.03 to 2.51 µmol/plate) using the plate incorporation method, or to doses ranging from 1 to 20 µg/mL (5 to 100 µM) using the liquid suspension method in either the presence or absence of rat liver metabolic activation.

Kittle et al. (1981) found that phenothiazine and 10 of its derivatives did not induce *his* gene mutations in *S. typhimurium.* Strain TA98 was exposed at concentrations up to 30 nmol/plate (full dose range not provided) using the plate incorporation method in the presence of rat liver metabolic activation.

As reported by Mortelmans et al. (1986), phenothiazine did not induce *his* gene mutations in *S. typhimurium.* Strains TA100, TA98, TA97, TA1535, and TA1537 were exposed to doses ranging from 100 to 10,000 µg/plate (0.5 to 50.2 µmol/plate) using the pre-incubation method in either the presence or absence of 10% rat or hamster liver metabolic activation. Precipitates were present in all cultures above the 333 µg/plate (1.67 µmol/plate) dose.

Likewise, Dow Corning (1988) reported that phenothiazine did not induce *his* gene mutations in *S. typhimurium* or *Escherichia coli.* Salmonella strains TA98, TA100, TA1535, and TA1537 and *E. coli* strain WP2 were exposed to doses ranging from 9.8 to 156.3 µg/plate (0.049 to 0.784 µmol/plate) using the plate incorporation method in both the presence or absence of rat liver metabolic activation. In a toxicity test, toxicity was observed at doses from 312.5 to 5000 µg/plate (1.568 to 25.09 µmol/plate).

9.6.2 *In Vitro* Mammalian Mutagenicity Assays

Procter and Gamble (1987) found that phenothiazine induced gene mutations in L5178Y TK+/- mouse lymphoma cells in the absence of but not in the presence of metabolic activation. Cells were exposed for 4 hours to doses ranging from 20 to 113 µg/mL (100 to 567 µM) in the absence of, and from 15 to 92 µg/mL (75 to 462 µM) in the presence of rat liver S9.

9.6.3 *In Vivo* Human Chromosomal Damage

Humans exposed to strong tranquilizers such as the phenothiazines exhibited chromosomal aberrations in their peripheral blood leukocytes (Gilmour et al., 1971). Blood samples were drawn from 11 hospitalized schizophrenic patients under continuous therapy with various phenothiazine drugs (actual doses were not provided). Fifty cells were scored per patient. The number of single chromatid and chromosome breaks and chromosome-type rearrangements were increased in these subjects as compared to the control groups. The study is, however, of limited value since the observed aberrations could also have been caused by other factors associated with long-term psychiatric illness.

9.6.4 Enhancement of DNA Damage

Lönn and Lönn (1988) reported that phenothiazine reduced the ability of cells to repair DNA damage induced by two antineoplastic agents. Human colon adenocarcinoma cells were preincubated for 24 hours at 37°C with [^{3}H]thymidine followed by exposure to either 10 µM methotrexate or 1 mM 5-fluorodeoxyuridine for 60 minutes followed by incubation with 10, 25, or 50 µM phenothiazine for an additional 24 hours. Following the final exposure, cells were lysed, the DNA extracted, and separated on agarose gels by electrophoresis. The radioactivity was counted in 1 mm gel slices on a scintillation counter. Higher concentrations of phenothiazine induced more DNA fragmentation after incubation with methotrexate and 5-fluorodeoxyuridine.

9.6.5 Anti-Genotoxicity

9.6.5.1 Prokaryotic Antimutagenicity

Phenothiazine inhibited the mutagenicity of several benzo[*a*]pyrene (BaP)-related compounds in *S. typhimurium* (Calle et al., 1978). Strain TA98 was exposed to phenothiazine at 0.06 µmol/plate plus either 6.0 nmol BaP/plate, 0.94 nmol 6-methyl-BaP/plate, or 2.9 nmol 10-methyl-BaP/plate in the presence of rat liver S9. Phenothiazine reduced the number of revertants per plate by 41% after exposure to BaP, 9% after 6-MeBaP, and 55% after 10-MeBaP.

Sullivan et al. (1980; cited by HSDB, 1996) also reported that phenothiazine at concentrations of 0.003 to 0.3 µmol/plate inhibited the mutagenicity of 6 nmol/plate BaP in a concentration dependent manner from 40 to 75%, respectively. *S. typhimurium* strain TA98 was exposed using the plate incorporation method in the presence of rat liver S9 activation.

As further reported by Kittle et al. (1981), phenothiazine and its various derivatives inhibited *his* gene mutations in *S. typhimurium* exposed to BaP. Strain TA98 was exposed (doses expressed as ratios of 0.25 to 50 nmol derivative/nmol BaP) using the plate incorporation method in the presence of rat liver metabolic activation. None of the phenothiazine derivatives were mutagenic at concentrations up to 0.03 µmol/plate. Phenothiazine, 2-chlorophenothiazine, 10-phenylphenothiazine, and perphenazine significantly inhibited the mutagenicity of BaP at all concentrations.

Calle and Sullivan (1982) later reported that phenothiazine at both 0.082 and 0.41 µmol/plate in the presence of rat liver S9 strongly inhibited (greater than 25%) the mutagenicity of 8.2 nmol BaP/plate in *S. typhimurium* strain TA98.

However, in a study by Bayless et al. (1986), phenothiazine exhibited (at high doses only) a slight but statistically insignificant inhibition of the mutagenicity of both 6-methyl-BaP and 6-hydroxymethyl-BaP in *S. typhimurium.* Strain TA98 was exposed to 6-methyl-BaP (2800

µmol/plate) or 6-hydroxymethyl-BaP (1300 µmol/plate) and phenothiazine (doses ranging from 200 to 150,000 µmol/plate) using the plate incorporation method in the presence of rat liver S9.

9.6.5.2 Inhibition of DNA Adduct Formation

Bhattacharya et al. (1984) reported that co-exposure to phenothiazine significantly inhibited the formation of aflatoxin B_1 adducts in calf thymus DNA. A reaction mixture containing the DNA was incubated at 37°C with 2 M [^{3}H]aflatoxin B_1 plus 100 or 500 µM phenothiazine for 60 minutes in the presence of rat liver S9. Following exposure, the DNA was extracted, precipitated, washed three times, and the radioactivity counted. Doses of 100 and 500 µM gave reductions in radioactivity of 22 and 7.6 % of the BaP control, respectively.

9.7 Immunotoxicity

No data were found.

9.8 Toxic Effects of Phenothiazine in Combination with Insecticide Treatments

The studies described in this section are presented in **Table 15**.

Table 15. Toxic Effects of Phenothiazine in Combination with Insecticide Treatments

Species, Strain, Age	Number of Animals	Chemical Form, Purity	Dose	Duration of Exposure/ Observation Period	Results/Comments	Reference
9.8.1 Organophosphorus Insecticides						
lamb (mixed breed; 6-mo old)	1) 4 F (phenothiazine anthelmintic powder + Ciovap®) 2) 5 F (Ciovap® alone) 3) 4 F (phenothiazine anthelmintic powder alone) 4) 5 F (untreated)	phenothiazine anthelmintic powder (54% phenothiazine as active ingredient) and 0.25% dichlorvos-crotoxyphos emulsion (Ciovap®; 2.3% dichlorvos, 10% crotoxyphos)	Lambs in groups 1 and 3 received 1 g phenothiazine anthelmintic powder (3 mmol) in diet for 3 consecutive days. On the third day, lambs in groups 1 and 2 were sprayed with 1 gal. (3784 mL) Ciovap®	3 days; 21 days after cessation of treatment	None of the phenothiazine or untreated controls displayed signs of toxicosis. There was no difference in the incidence of toxicosis between lambs in group 1 (phenothiazine + Ciovap®) and lambs in group 2 (Ciovap® alone).	Mohammad and St. Omer (1985)
steer and heifer calf (Hereford and Angus breeds; 6- to 8-mo-old)	exposed: 2-3 calves per group (sex n.p.) controls: 1 calf per group (insecticide alone; sex n.p.); 1-3 calves per group (phenothiazine alone; sex n.p.)	phenothiazine, 95% pure	Calves were given a single high dose of phenothiazine (60 g; 300 mmol) in feed, followed by a lower dose (2 g/day; 10 mmol/day) in feed for 30 days. On day 28, calves were sprayed with either malathion, coumaphos, trichlorfon, ronnel, crotoxyphos/dichlorvos, crotoxyphos, or crufomate	30 days; observation duration n.p.	Only 1 calf exhibited signs of toxicity. The animal had been given ronnel and phenothiazine and showed signs of ataxia and paralysis. It was noted that these signs could have been caused by a parasitic infection.	Schlinke and Palmer (1973)
9.8.2 Sevin® (Carbaryl; 1-Napthyl N-methylcarbamate)						
rat (Wistar; age n.p.)	exposed: 5 F per dose controls: 10 F (Sevin® alone; 200 or 400 mg/kg)	5:1 phenothiazine-sevin® mixture, purities n.p.	500, 1000, or 2000 mg/kg in corn oil by gavage (phenothiazine dose, 417, 833, or 1670 mg/kg [2.09, 4.18, or 8.38 mmol/kg])	single dose; 2 wk.	Clinical and pathological signs of toxicity did not differ between rats treated with the phenothiazine-Sevin® mixture and rats treated with Sevin® alone.	Union Carbide (1971)

Abbreviations: F = female; n.p. = not provided

9.8.1 Organophosphorus Insecticides

There was no difference in the incidence of toxicosis in lambs administered phenothiazine anthelmintic powder (54% phenothiazine as active ingredient) in combination with Ciovap® (Ciovap® contains 2.3% dichlorvos, 10% crotoxyphos) and lambs administered Ciovap® alone (Mohammad and St. Omer, 1985). The lambs in the first group were given 1 g (3 mmol) phenothiazine anthelmintic in the diet for 3 consecutive days, and on the third day, they were sprayed with 1 gal. (3784 mL) Ciovap®. All lambs were observed for 21 days after cessation of treatment.

Phenothiazine did not potentiate the toxic effects of the organophosphorus insecticides malathion, coumaphos, trichlorfon, ronnel (fenchlorphos), crotoxyphos/dichlorvos, crotoxyphos, or crufomate in 6- to 8-month-old Hereford and Angus steer and heifer calves (Schlinke and Palmer, 1973). The calves were given a single high dose of phenothiazine (60 g; 300 mmol) in feed, followed by a lower dose (2 g/day; 10 mmol/day) in feed for 30 days. On day 28, calves were sprayed with one of the listed insecticides.

9.8.2 Sevin® (Carbaryl; 1-Napthyl *N*-methylcarbamate)

Clinical and pathological signs of toxicity did not differ between female Wistar rats administered a single dose of a 5:1 mixture containing phenothiazine and Sevin® (500, 1000, or 2000 mg/kg; phenothiazine dose, 417, 833, or 1670 mg/kg [2.09, 4.18, or 8.38 mmol/kg]) in corn oil by gavage and female Wistar rats administered a single dose of Sevin® alone (200 or 400 mg/kg) (Union Carbide, 1971). All rats were observed for 2 weeks.

10.0 STRUCTURE-ACTIVITY RELATIONSHIPS

Structure-activity relationships among phenothiazine and phenothiazine derivatives such as methylene blue and psychotropic drugs classified as phenothiazines were not investigated.

11.0 ONLINE DATABASES AND SECONDARY REFERENCES

11.1 Online Databases

Chemical Information System Files

SANSS (Structure and Nomenclature Search System)
TSCAPP (Toxic Substances Control Act Plant and Production)
TSCATS (Toxic Substances Control Act Test Submissions)
DIALOG Files
359 Chemical Economics Handbook (cited in Section 12 as SRI Int. 1997)
302 Kirk-Othmer Encyclopedia of Chemical Technology Fulltext
161 NIOSHTIC (Occupational Safety and Health)

Internet Databases
Code of Federal Regulations full text. 1996 versions of various titles via GPO Gate, a gateway by the Libraries of the University of California to the GPO Access service of the Government Printing Office, Washington, DC. Internet URL http://www.gpo.ucop.edu/

National Library of Medicine Databases
EMIC and EMICBACK (Environmental Mutagen Information Center)

STN International Files
BIOSIS (Biological Abstracts)
CANCERLIT
CSNB (Chemical Safety News Base)
EMBASE (Excerpta Medica)
HSDB (Hazardous Substances Data Bank)
IPA (International Pharmaceutical Abstracts)
MEDLINE (Index Medicus)
RTECS (Registry of Toxic Effects of Chemical Substances)
TOXLINE
TOXLIT

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB

International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicology Research Projects	CRISP
NIOSHTIC7	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

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