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Center for the Evaluation of Risks to Human Reproduction—The First Five Years

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The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) was established by the NTP and the National Institute of Environmental Health Sciences (NIEHS) in 1998 to address the impact of chemical exposures on human reproductive and developmental health and to serve as an environmental and reproductive health resource for government agencies and the general public. The purpose of this report is to provide an overview of the Center activities and a summary of NTP conclusions on chemicals evaluated during this time period. CERHR evaluations involve the critical review of reproductive, developmental, and other relevant toxicity data by independent panels of scientists. The products of these evaluations are expert panel reports. The public has opportunities to provide oral comments at the panel meeting and written comments on draft and final expert panel reports. The NTP evaluates these comments, the conclusions of the expert panel, and any new data not available at the time of the panel meeting, and prepares an NTP brief that describes in plain language the NTP's conclusions on the reproductive and developmental hazard from specified chemical exposures. The NTP brief, expert panel report, and public comments comprise the NTP monograph on the chemical. Monographs are sent to federal regulatory agencies, the NTP Executive Committee, and the NTP Board of Scientific Counselors, and are publicly available. Over the last five years, CERHR conducted expert panel evaluations on 14 chemicals. At this time, 13 panel reports have been published and 12 NTP-CERHR monographs have been issued. Additionally, CERHR conducted a 2-day workshop on the role of thyroid hormones in reproductive and developmental health. *Birth Defects Res B* 74:1–8, 2005. Published 2005 Wiley-Liss, Inc.

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INTRODUCTION

The National Toxicology Program Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) was established by the National Toxicology Program and the National Institute of Environmental Health Sciences (NIEHS) in 1998 in response to concerns from scientists, health professionals, and the public regarding the effects of chemical exposures on reproductive health and child development. Some of the reasons for these concerns in the US are: an infertility rate of 5–10% among couples who wish to have children (Dunson et al., 2004); unsuccessful completion of 35–50% of pregnancies, often before the mother realizes she is pregnant (Wilcox et al., 1988; Baird et al., 2003); birth defects in 3–5% of newborns (National Research Council, 2001a); and a reported but unconfirmed drop in human sperm levels (Mosher, 1985; Carlsen et al., 1992; Olsen et al., 1995; Swan et al., 1998). It is not known what proportion of these effects might be the result of environmental exposures.

The mission of the NTP-CERHR is two-fold: 1) To provide scientifically-based, uniform evaluations of the potential for adverse effects on human reproduction and development caused by naturally-occurring and synthetic chemicals to which humans may be exposed. These evaluations are accomplished through rigorous evaluations of the scientific literature by independent panels of scientific experts and are available to the public, federal agencies, and to the scientific community as expert panel reports. 2) To provide information or guidance to information of public interest concerning human reproductive and developmental health. This second element is accomplished through information provided on the CERHR website and through direct communication with the public. Center operations are conducted by NTP staff

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and the CERHR contractor, Sciences International, Inc. Direction is provided by the NTP-CERHR core committee. This committee consists of representatives of NTP government agencies and is currently comprised of members from NIEHS, U.S. Environmental Protection Agency (EPA), U.S. Consumer Product Safety Commission, National Institute of Occupational Safety and Health, Centers for Disease Control and Prevention (CDC) (National Center for Birth Defects and Developmental Disabilities), and the U.S. Food and Drug Administration (FDA). Duties of the core committee include: 1) reviewing chemicals nominated and recommending chemicals for expert panel evaluation, 2) reviewing nominations to the expert registry and proposing expert panelists, and 3) reviewing NTP briefs. The core committee meets quarterly with the director of CERHR, Dr. Michael Shelby of NTP/NIEHS, and principal reproductive toxicologist, Dr. Anthony Scialli of Sciences International, and the CERHR staff. The NTP Board of Scientific Counselors and the NTP Executive Committee provide oversight of and guidance for the priorities, directions, and adequacy of the Center.

EVALUATION PROCESS

An outline of the CERHR chemical evaluation process is presented in Figure 1. Chemical nominations are received by CERHR from private individuals, industry, public interest groups, or government agencies. Four main criteria are used by the core committee in reviewing a nominated chemical, chemical mixture, or class of chemicals: 1) production volume; 2) human exposure (e.g., occupational, environmental, or consumer products); 3) extent of data on reproductive or developmental toxicity; and 4) public concern. The core committee first reviews a preliminary dossier on the nominated chemical, addressing these four criteria. If the chemical is selected for further review, a full dossier, providing a comprehensive summary of available scientific information on developmental and reproductive reports, is prepared. If a chemical is selected by the core committee, it is recommended to the Associate Director of NTP at NIEHS for an expert panel evaluation. If approved, a Federal Register Notice announces the intent of CERHR to evaluate the chemical, and requests

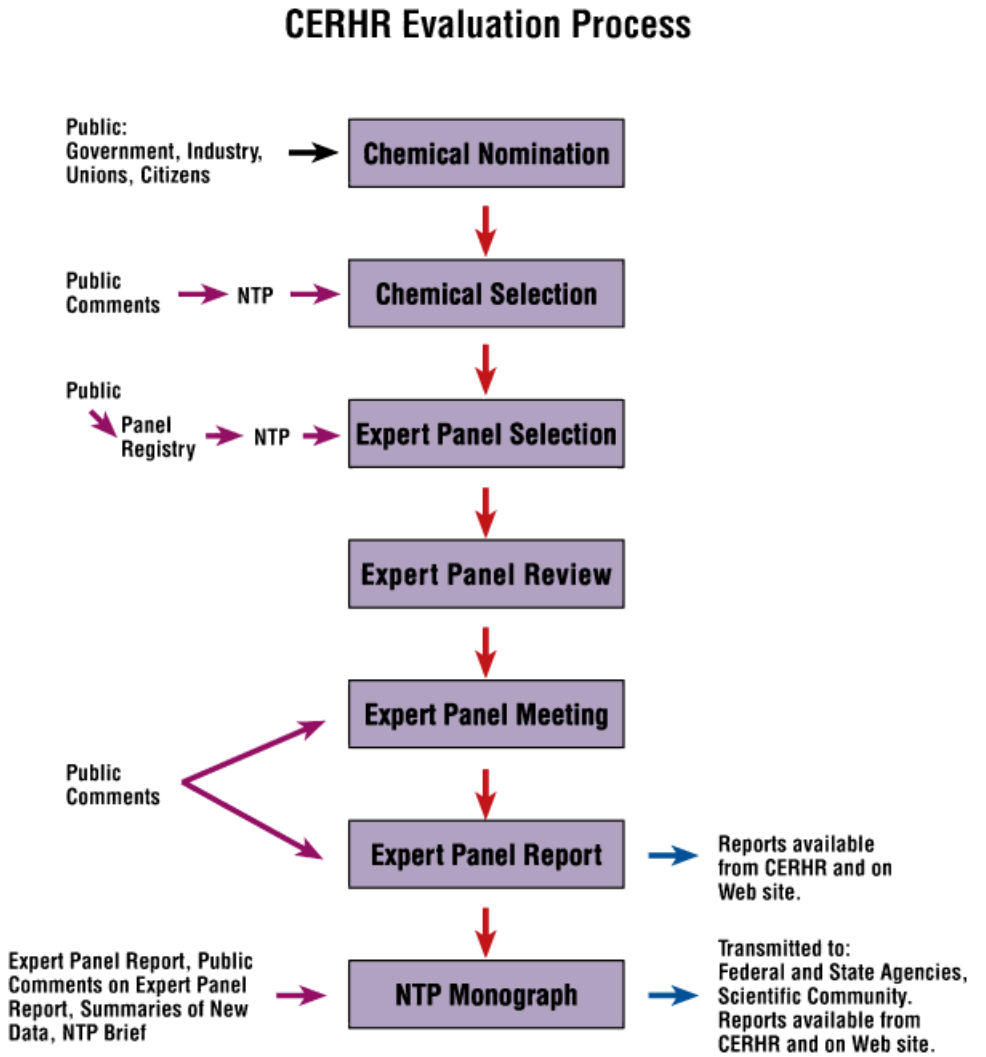

Fig. 1. . The CERHR chemical evaluation process.

comment, data and candidates to serve on a CERHR expert panel. The list of expert panel candidates is developed by CERHR from the CERHR expert registry, core committee recommendations, and public recommendations. Scientists who serve on the panel can be from academia, federal or state government agencies, industry, or private companies. However, panelists must not have a conflict of interest for the chemical being evaluated.

Guidelines (NTP-CERHR, 2001) for NTP-CERHR expert panel members aid the panel in its review and provide uniformity in the expert panel reports. These guidelines were modeled after guidelines from several sources: the Institute for Environmental Health Research (Moore et al., 1995), the International Agency for Research on Cancer (IARC, 2004), and the National Research Council (National Research Council, 2001b).

Each NTP-CERHR expert panel report includes five sections: 1) chemistry, usage, and exposure; 2) general toxicology; 3) developmental toxicology; 4) reproductive toxicology; and 5) summaries, conclusions, and critical data needs. The body of CERHR expert panel reports (sections 1–4) and section summaries are drafted prior to the expert panel meeting by the expert panel with the aid of the NTP contractor, Sciences International, Inc. Publications key to development of conclusions on reproductive and developmental toxicity are identified in utility statements and are brought forward into the section summaries. Although abstracts or review articles may be cited within the body of the report, only research or testing reports with original data are considered by the panel in reaching conclusions on reproductive and developmental toxicity. The availability of the draft panel report is announced in a Federal Register Notice and on the NTP list server and public comments are solicited. A notice of availability and the draft report are posted on the CERHR website. The draft report can also be obtained directly from CERHR. At a public expert panel meeting, public comments on the draft report can be presented and section summaries from this report are reviewed and approved by the panel. Section 5 of the report, which contains the section summaries, conclusions, and critical data needs, is discussed and completed by the expert panel. Section 5 of the report discusses the sufficiency of the data evaluated for determining human reproductive and developmental hazard. Critical data needs are outlined. Final panel conclusions are a consensus of the panel and are expressed as a degree of concern for reproductive or developmental effects under specific exposure conditions or for a specific population. The degree of concern can range from ''negligible concern'' to ''serious concern.'' Degree of concern is a qualitative judgment of the panel and is a consensus of the panel. Conclusions are based on having sufficient, relevant data addressing reproductive and/or developmental studies in experimental animals and/or in humans. Expert panel conclusions are based on known or estimated levels of human exposure and address two main issues: 1) The potential for adverse effects on reproduction or child development as a result of exposures prior to conception, in utero, or during childhood; and 2) The potential for adverse effects on adult reproduction as the result of exposures during adulthood. The final expert panel report is then made available for public comment. All publications used in these reports are on file and available to the public.

Taking into account the expert panel report and conclusions, public comments, and any relevant data published after the panel meeting, the CERHR director and NTP staff draft an NTP brief. This short report, written in plain language, provides a summary of use, human exposure, the scientific evidence presented by the expert panel any new evidence not available to the panel, and conclusion about a chemical's potential to affect human reproduction or development. The brief also contains the NTP's overall conclusions concerning the human reproductive and developmental health hazard for the chemical. The final expert panel report, public comments on that report, and the NTP brief make up the NTP monograph. Monographs are distributed to the NTP executive committee, NTP board of scientific counselors, and appropriate federal agencies, and are available to the public through the CERHR website or by request to the CERHR office.

NTP-CERHR CONCLUSIONS ON CHEMICALS EVALUATED

Over the last five years, CERHR has convened seven expert panels to evaluate 14 chemicals, resulting in 14 expert panel reports. Panel members reviewed existing literature in their areas of expertise and provided summary evaluations for the reports. This effort involved a review of reports covering areas of human exposure, general toxicity, developmental toxicity, and reproductive toxicity. NTP solicited and reviewed public comments on all 14 of these final reports and published NTP monographs and briefs on twelve of these reports. Of the remaining two chemicals, the Di-(2-ethylhexyl)-phthalate (DEHP) Brief is in draft form, pending the inclusion of NTP reproductive toxicity data, and the Acrylamide Brief is undergoing internal review.

In reaching conclusions in the NTP Briefs, human exposure data released subsequent to the expert panel meetings were available for butyl benzyl phthalate (BBP), di-n-butyl phthalate (DBP), DEHP, di-isononyl phthalate (DINP), and di-isodecyl phthalate (DIDP); exposure estimates were not available for di-n-octyl phthalate (DnOP) and di-n-hexyl phthalate (DnHP). These exposure estimates were based on analytical data obtained on phthalate monoester metabolites from spot urine samples in the general population collected and analyzed by the CDC (Blount et al., 2000; Kohn et al., 2000; CDC, 2003). NTP-CERHR exposure estimates and hazard data from the expert panel reports were compared to new data for these five phthalates in a publication by McKee et al. (2003). NTP conclusions on two phthalates, DBP and DINP, and fluoxetine are discussed below as examples. NTP conclusions for human reproductive and developmental toxicity for all chemicals evaluated are presented in Table 1. In this table, it is noted whether the NTP conclusions concur with those of the expert panel. NTP conclusions for acrylamide and DEHP have not been finalized, so the expert panel conclusions are presented for those chemicals.

Di-(n-)butylphthalate (DBP)

Phthalates are commercially important chemicals used primarily as plasticizers to add flexibility to plastics. DBP is used as a plasticizer in cellulose plastics, although DBP

Table 1
Expert Panel Evaluations and NTP Conclusions

Chemical Phthalates	Use	NTP conclusions human reproduction	NTP conclusions human development
Butyl benzyl phthalate (BBP)	Primarily used in the production of vinyl tiles. Also used in food conveyor belts, artificial leather, automotive trim, and traffic cones.	**Negligible concern** for adverse reproductive effects in exposed men; data are insufficient to reach conclusions for exposed women. (concurs with expert panel.)	**Minimal concern** for developmental effects in fetuses and children.
Di-n-butyl phthalate (DBP)	Used as a component of latex adhesives. Used in cosmetics and other personal care products, as a plasticizer in cellulose plastics, and as a solvent for dyes.	**Negligible concern** for reproductive toxicity in exposed adults. (Concurs with expert panel.)	**Minimal concern** for developmental effects on the male reproductive tract when pregnant women are exposed to levels of 2-10 μg/kg bw/day. (Concurs with expert panel.) Some concern when pregnant women are exposed to higher levels.
Di(2-ethylhexyl) phthalate (DEHP)	Used in polyvinyl chloride medical devices such as blood bags and IV tubing. Used in a wide variety of products, including flooring, vehicle upholstery, raincoats, toys, and food packaging. DEHP is not used in toys intended for mouthing, such as nipples or teething rings.	**Minimal concern** for reproductive toxicity in exposed adults. (Concurs with expert panel.) (Expert panel conclusions are presented. NTP conclusions have not yet been determined.)	**Concern** for developmental effects on the reproductive tract of male infants and/or toddlers exposed to DEHP at levels several fold higher than the general population. **Serious concern** that certain medical treatments of critically ill male infants may result in DEHP exposures adversely affecting male reproductive tract development. (Expert panel conclusions are presented. NTP conclusions have not yet been determined.)
Di-n-hexyl phthalate (DHP)	A component of industrially important phthalates such as di-isohexyl phthalate(up to 25%) and C6-10 phthalate (up to 1%). DHP may occur in a variety of commercial products including dip-molded products such as tool handles or dishwasher baskets, flooring, vinyl gloves, flea collars, and conveyer belts used in food processing.	**Insufficient** hazard and/or exposure data (Concurs with expert panel.)	**Insufficient** hazard and/or exposure data. (Concurs with expert panel.)
Di-isodecyl phthalate (DIDP)	Used in a wide variety of products, including covering on wires and cables, artificial leather, toys, carpet backing, and pool liners. Has only limited use in food packaging and handling.	**Negligible concern** for adverse reproductive effects in exposed adults. (Concurs with expert panel.)	**Minimal concern** for developmental effects in fetuses and children. (Concurs with expert panel.)
Di-isononyl phthalate (DINP)	Used in a wide variety of products, including garden hoses, pool liners, flooring tiles, tarps, and toys. Has limited use in food packaging.	**Minimal concern** for adverse effects to human reproduction. (Concurs with expert panel.)	**Minimal concern** for developmental effects in fetuses. (Concurs with expert panel.) **Minimal concern** for developmental effects in children.
Di-n-octyl phthalate (DnOP)	No commercial uses. Makes up approximately 20% of the industrially important C6-10 phthalate mixture used in the manufacture of commercial products.	**Negligible concern** for effects on adult reproductive systems. (Concurs with expert panel.)	**Insufficient** hazard and/or exposure data. (Concurs with expert panel.)
Methanol	Used in chemical syntheses and as an industrial solvent. In a variety of consumer products such as paints, antifreeze, cleaning solutions, and adhesives. Produced as a by-product of fermentation, sewage treatment, and paper	**Negligible concern** for adverse male reproductive effects when exposed to methanol levels that result in a low blood methanol level (<10 mg/L blood). (Concurs with expert panel.) **Insufficient evidence** to assess the effects	**Concern** for adverse developmental effects in fetuses if pregnant women are exposed to methanol at levels that result in high blood methanol concentrations. (Concurs with expert panel.) **Minimal concern** for adverse developmental effects when humans are exposed to

	production. Used as a racing car fuel with potential for expanded use as a vehicle fuel.	of methanol on female reproduction. (Concurs with expert panel.)	methanol levels that result in low blood methanol concentrations (<10 mg/L blood.) (Concurs with expert panel.)
1-Bromopropane	Used as a solvent for fats, waxes, and resins, and as an intermediate in the synthesis of pharmaceuticals, insecticides, flavors, and fragrances. Used as a vehicle in spray adhesives and as a cold bath degreaser.	**Serious concern** for reproductive effects at the upper end of the human occupational exposure range (18–381 ppm.) (Concurs with expert panel.) **Minimal concern** for reproductive effects when humans are exposed at the lower end of the human occupational exposure range (0.04–0.63 ppm.) (Concurs with expert panel.)	**Serious concern** for developmental effects at the upper end of the human occupation exposure range (18–381 ppm). (Concurs with expert panel.) **Minimal concern** for developmental effects when humans are exposed at the lower end of the human occupational exposure range (0.04–0.63 ppm) (Concurs with expert panel).
2-Bromopropane	Used as an intermediate in the synthesis of pharmaceuticals, dyes and other organic chemicals. In Asia, 2-BP was also used as a replacement for chlorofluorocarbons and 1,1,1 trichloroethane and as a solvent/cleaner for micro-electronics. In the US, 2-BP is a contaminant (<0.1%) of 1-bromopropane.	**Some concern** for adverse reproductive effects when people are exposed to concentrations of 2-bromopropane at the high end of the occupational exposure range. (Concurs with expert panel.) **Minimal concern** for adverse reproductive effects when people are exposed to 2-bromopropane at the lower end of the occupational exposure range. (Concurs with expert panel.)	**Insufficient evidence** to assess the developmental effects of 2-bromopropane exposure. (Concurs with expert panel.)
Ethylene Glycol	Used as a chemical intermediate in the production of polyester compounds. Also found in automotive anti-freeze, industrial coolants, hydraulic, and deicer fluids.	**Negligible concern** of adverse reproductive effects from ethylene glycol, (Concurs with expert panel.)	**Negligible concern** of adverse developmental effects from ethylene glycol at exposures below 125 mg/kg bw. (Concurs with expert panel.)
Propylene Glycol	Used as a chemical intermediate in the production of unsaturated polyester resins. Used in liquid detergents, deicing fluids, antifreeze/engine coolant, paints and coatings. Used in foods, cosmetics, tobacco products, and pharmaceuticals.	**Negligible concern** for adverse reproductive effects from propylene glycol exposures in humans. (Concurs with expert panel.)	**Negligible concern** for adverse developmental effects from propylene glycol exposure in humans. (Concurs with expert panel.)
Fluoxetine Prozac®; Sarafem™	A widely prescribed pharmaceutical, used in the treatment of depression. Recently approved for use in 7–17 year-olds. Fluoxetine is also being prescribed to treat premenstrual dysphoric disorder, potentially increasing the number of exposures for women of childbearing age.	**Minimal concern** for reproductive toxicity, specifically orgasmic dysfunction in both sexes, at fluoxetine dose levels encountered in therapy (20–80 mg/day) because of the reversibility of this effect. (Expert panel conclusions are presented. NTP conclusions have not yet been determined.)	**Some concern** for shortened gestational length and poor adaptation occurring in neonates of women exposed during pregnancy to fluoxetine dose levels encountered in therapy (20–80 mg/day). **Insufficient evidence** to assess effects on pregnancy loss and fetal growth, on infant exposure through breast milk, or on children on fluoxetine therapy. (Expert panel conclusions are presented. NTP conclusions have not yet been determined.)
Acrylamide	Acrylamide is used in the production of polyacrylamide, which is used in water treatment, pulp and paper production, mineral processing, and scientific research; and in the synthesis of dyes, adhesives, contact lenses, soil conditioners, cosmetics and skin creams, food packaging materials, permanent press fabrics. Acrylamide has recently been found to be produced in some starchy foods cooked at high temperatures.	**Negligible concern** for adverse reproductive and developmental effects in the general population. **Minimal concern** for acrylamide-induced heritable effects in the general population. Some concern for adverse reproductive and developmental effects, including heritable effects, for exposures in occupational settings. (Expert panel conclusions are presented. NTP conclusions have not yet been determined.)	**Negligible concern** for adverse reproductive and developmental effects in the general population. **Minimal concern** for acrylamide-induced heritable effects in the general population. Some concern for adverse reproductive and developmental effects, including heritable effects, for exposures in occupational settings. (Expert panel conclusions are presented. NTP conclusions have not yet been determined.)

is not used in polyvinyl chloride plastics. DBP is also used in personal care products and is a component of latex adhesives, and is a solvent for dyes. Two important sources of exposure of the general population are 1) processed and packaged foods and 2) cosmetics. The expert panel relied on four authoritative sources (International Program on Chemical Safety; UK Ministry of Agriculture, Fisheries, and Food; Health Canada; and the U.S. Agency of Toxic Substances and Disease Registry) in developing an exposure estimate of less than 10 μg of DBP/kg of body weight/day (Kavlock et al., 2002). In a study published after the expert panel meeting, monoester metabolites of some phthalates were measured from human spot urine samples collected for the National Health and Nutrition Examination Survey (NHANES) conducted by the CDC (Blount et al., 2000). More than 75% of the people surveyed had evidence of exposure to DBP. From these data, Kohn et al. (2000) and David (2000) estimated exposure levels for DBP. For more than 95% of the people with evidence of DBP exposure, exposure estimates were consistent with the expert panel's estimate of less than 10 μg of DBP/kg of body weight/day (Kavlock et al., 2002). There were sufficient data from experimental animal studies to conclude that exposure to DBP at high doses induces clear evidence of adverse effects. Rodents in prenatal and early postnatal stages of development are more sensitive to reproductive effects of DBP than are adult animals with the developing male reproductive system being particularly sensitive. NTP conclusions concurred with the expert panel conclusions of ''minimal concern'' for potential effects on human development, including effects on the developing male reproductive tract. However, the NTP also noted that some women of reproductive age (20–40 years) were exposed to DBP levels greater than 30 μg/kg of body weight/day, with a maximum of 100 μg/kg of body weight/day. These findings raised the NTP level of concern to ''some concern'' for potential effects on human development for this higher exposed population. NTP concurred with the expert panel conclusion of ''negligible concern'' for effects on the reproductive systems of exposed adults.

Di-isononylphthalate (DINP)

DINP is used as a plasticizer in a broad range of consumer products such as garden hoses, pool liners, flooring tiles, construction materials, tarps, and toys. DINP consists of branched, C-9 isomers and is the primary plasticizer used in polyvinyl chloride plastic materials. However, DINP is not used in medical devices and has limited use in food packaging. Exposure can occur through inhalation, ingestion, or dermal contact. Exposure values obtained from calculations of Kohn et al. (2000) and David (2000) estimated that 95% of the general study population was exposed to less than 1.7 μg/kg of body weight/day with a maximum exposure of 22 μg/kg of body weight/day. These values were in agreement with the expert panel's exposure estimate of 3–30 μg/kg of body weight/day. As detailed in the expert panel report, studies in pregnant rats have shown that exposure to high doses of DINP can affect development of the kidneys and skeletal system of the fetus and result in reduced birth weights. There was sufficient scientific evidence to conclude the DINP might adversely affect development of the human fetus if the levels of exposure were sufficiently high. However, because human exposure levels are 1,000–10,000-fold lower than the than the doses in the animal studies that produced adverse developmental effects, NTP concurred with the panel's conclusions of ''minimal concern'' for adverse developmental outcomes resulting from exposure of pregnant women and ''minimal concern'' for adverse effects on the reproductive system of exposed adults. Because soft toys made of DINP-containing plastics can be mouthed by young children, there was public concern for exposure of infants, toddlers, and children to DINP. Because of this concern, the Consumer Products Safety Commission convened a Chronic Hazard Advisory Panel (CHAP) to evaluate whether DINP in consumer products is a chronic health hazard, especially to children mouthing DINP-containing toys. The results of this panel were published (Consumer Products Safety Commission, 2001) after the CERHR phthalates expert panel reports were completed. The CHAP estimated a children's exposure range of 70–280 μg/kg of body weight/day, very similar to values presented in the CERHR Expert Panel Report. These exposure levels are approximately 1,000-fold lower than exposure levels in rats that resulted in developmental effects. Therefore, the NTP concurred with the expert panel conclusion that there was ''low concern'' for potential developmental and reproductive health effects in children who might be exposed to DINP through the mouthing of toys or other DINP-containing objects.

Fluoxetine

Fluoxetine (Prozac®; Sarafem™) is the first pharmaceutical evaluated by CERHR. It is a widely used psychotropic drug and is one of a family of selective serotonin reuptake inhibitors (SSRIs). In adults, fluoxetine is indicated for the treatment of major depressive disorder, obsessive compulsive disorder, bulimia nervosa, and panic disorder. In 2003, the FDA approved the use of fluoxetine for children 7–17 years old for the treatment of major depression and obsessive compulsive disorder (FDA, 2003). Furthermore, the drug is routinely prescribed to adults during their reproductive years and also given to women to treat premenstrual dysphoric disorder (under the trade name Sarafem™). Based upon changes in the pattern of usage of this prescription drug, CERHR determined that an expert panel evaluation would provide timely information to the public and identify data needs critical to ascertaining reproductive and developmental health effects. This evaluation differed from the 12 previous chemical evaluations conducted by CERHR in the amount and type of data available on humans. In previous expert evaluations on a chemical exposure, information on human exposure and toxicological effects were obtained through limited information from environmental, dietary, occupational or accidental exposures to the chemical. Because fluoxetine is a prescribed drug, more information on human exposure and studies on humans were available.

NTP agreed with the conclusions of the expert panel. There was sufficient evidence for minimal concern for reproductive toxicity, specifically orgasmic dysfunction, in both sexes, and some concern for shortened gestational length and poor adaptation occurring in neonates

of women exposed to fluoxetine during pregnancy. NTP also concurred with the expert panel that there were 1) insufficient data to draw conclusions on how breast milk or therapeutic exposures to fluoxetine might affect development, and 2) insufficient data to draw conclusions on an association between fluoxetine therapy in pregnant women and pregnancy loss. Critical data needs identified by the expert panel are described in detail in section 5.0 of the panel's report and include the need for long-term follow-up neurobehavioral studies on children whose mothers received fluoxetine during pregnancy and/or breastfeeding. The NTP brief on fluoxetine is in the process of internal review and will be published in the Fluoxetine Monograph this year.

NTP-CERHR WORKSHOP

An NTP-CERHR workshop, Thyroid Toxicants: Assessing Reproductive Health Effects, was held in April 28–29, 2004 in Alexandria, VA. The purpose of this workshop was to examine and discuss chemical-induced thyroid dysfunction in experimental animals and the relevance of reproductive and developmental effects observed for prediction of adverse effects in humans. Attendees included representatives from government, industry, universities, and testing laboratories. In preparation for this meeting, a background document addressing similarities and differences in thyroid gland development, and the pharmacokinetics and pharmacodynamics of thyroid-active agents in rodents and humans, and addressing the impact of thyroid hormones on prenatal and postnatal development was written by CERHR (Choksi et al., 2003).

The following conclusions were the result of discussions at this workshop.

- In order to predict human health outcomes, a comparison between rodents and humans of the magnitude of thyroid dysfunction resulting in adverse effect is needed.
- Current chemical testing methods do not adequately screen for thyroid perturbations that may affect reproduction and development of offspring.
- It was proposed that an assessment of thyroid status (T3/T4, TSH, thyroid gland histopathology, and weight) be included in animal reproductive toxicity testing protocols.

A workshop report (Jahnke et al., 2004) provides a detailed account of the discussions at this workshop leading to these conclusions.

IMPACT OF EXPERT PANEL REPORTS

The most notable impact of CERHR reports has been from the expert panel evaluation of DEHP, a high production volume chemical. DEHP is used as a plasticizer in a wide variety of consumer products such as vehicle upholstery, raincoats, food packaging and toys. DEHP is found in polyvinyl chloride medical devices such as blood bags and intravenous tubing. The final CERHR expert panel report on DEHP was released for public comment in October 2000. The panel had minimal concern that ambient exposures adversely affect adult human reproduction. The expert panel expressed concern that ambient oral DEHP exposures of pregnant or lactating women may adversely affect the development of their offspring. The panel also expressed concern for exposures in infants/toddlers. The panel expressed serious concern that parenteral exposure to DEHP from medical devices used in the intensive care of infants/children may adversely affect male reproductive tract development. Following release of the expert panel report on DEHP, the FDA issued a warning to minimize exposure to polyvinyl chloride medical devices containing DEHP while performing certain procedures on male infants, pregnant women who are carrying male fetuses, and peripubertal males (FDA, 2002). The California EPA's Office of Environmental Health Hazard Assessment listed DEHP a chemical that could cause reproductive harm (CalEPA, 2004), and the Japanese Ministry of Health, Labor, and Welfare advised hospitals to use alternatives to medical devices containing DEHP (Japan Chemical Week, 2002). Health Canada released an exposure and toxicity assessment on DEHP in medical devices (Health Canada, 2002). This report also referenced the findings of the CERHR DEHP report. Together, these reports have subsequently provided sufficient scientific consensus to increase awareness and promote changes in the type of plastic medical devices used in hospitals on infants, especially those under intensive care.

DINP, a plasticizer present in some plastic toys and flooring tiles, is another phthalate that has been in the news. Because phthalates can leach out of plastic materials, there was public concern about the hazard of exposures in toddlers from the mouthing of plastic toys. To address these concerns, the Consumer Products Safety Commission convened a Chronic Hazard Advisory Panel and used the CERHR expert panel report in drafting their conclusions (Consumer Products Safety Commission, 2001).

The EPA has referenced the CERHR evaluation of 1-bromopropane (also called n-propyl bromide) in its proposed rule for the use of 1-bromopropane as an acceptable substitute for ozone-depleting substances in a limited number of specific applications (EPA, 2003).

And finally, the California EPA recognizes the CERHR expert panel reports as works of an authoritative body for identification of chemicals causing reproductive toxicity (CalEPA, 2003).

CURRENT AND FUTURE CERHR ACTIVITIES

In the course of the last five years, the NTP-CERHR has met its goals of evaluating 2–3 chemicals per year. Consistency in the evaluation and the report process has been aided by the development of guidelines for the expert panel. A monograph series was initiated by NTP-CERHR in order to provide a single source for the expert panel report, public comments on that report, and the NTP brief, which describes in plain language NTP's conclusions. The NTP-CERHR website was developed to provide information on CERHR activities, reports, and monographs; provide exposure information to the public; provide informative links to other reproductive websites; and provide contact information for chemical nominations and queries on human reproductive health.

Recently CERHR requested data, expert panel candidates, and public comments on the following chemicals

under consideration for expert panel evaluation: 1) amphetamines, e.g., Adderall®, d-amphetamine, methamphetamine and methylphenidate, e.g., Ritalin®; 2) genistein and soy formula; and 3) magnesium sulfate (HHS, 2004). At this writing, an expert panel has been selected and is in the process of evaluating data on amphetamines and methylphenidate. An expert panel meeting on these chemicals is planned for January 10–12, 2005.

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