2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO DI-*n*-BUTYL PHTHALATE IN THE UNITED STATES

Di-*n*-butyl phthalate is a colorless to faint yellow oily liquid that is not found naturally in the environment. It has a slightly ester smell and a strong, bitter taste. It has moderately low solubility in water, but is quite soluble in organic solvents such as alcohol, ether, benzene, and acetone. Di-*n*-butyl phthalate is used in plastics to make them more flexible, and is found in a number of consumer products, including home furnishings, paints, clothing, and cosmetic products. More than 8,500 tons (17 million pounds) of di-*n*-butyl phthalate was produced in the United States in 1994 by a number of companies in various locations.

Di-*n*-butyl phthalate is released to the environment during its production and use, with the vast majority being released to underground injection wells. Di-*n*-butyl phthalate is not expected to volatilize significantly from water to the atmosphere. In soils, migration to groundwater occurs, but is thought to be limited to sites with low organic content. The half-life of di-*n*-butyl phthalate vapor in air is calculated to be 14 daylight hours; in water and soils, >50% of di-*n*-butyl phthalate is degraded within 1–28 days.

The general population may be exposed to di-*n*-butyl phthalate from the air, water, and some foods. Air is probably the main source of di-*n*-butyl phthalate exposure for the general population, but some exposure may come from dairy products, fish, and seafood. Occupational exposures can occur through skin contact and by inhalation of vapors and dust. It is not known if exposure of children to di-*n*-butyl phthalate differs from that of adults. Di-*n*-butyl phthalate is present in some home furnishings, paints, vinyl flooring and floor wax; however, it is not known if children are more likely than adults to be exposed by increased contact with or proximity to these items. Children may also intentionally or unintentionally ingest soil, which may contain low levels of di-*n*-butyl phthalate.

The level of di-*n*-butyl phthalate exposure for the general population is expected to be in the low ppb range; in Canada, the estimated daily intake is 1.9–5.0 µg/kg body weight. Occupational exposure via inhalation has been estimated to be 143 µg/kg body weight/workday for workers employed in phthalate manufacturing.

Populations residing near hazardous waste disposal sites or municipal landfills may be subject to higher than average levels of di-*n*-butyl phthalate in ambient air or drinking water. No correlation of di-*n*-butyl phthalate fallout rates with specific sources or transport routes was found in a monitoring study in Sweden. However, di-*n*-butyl phthalate has been detected in leachate and groundwater near landfills and in groundwater near rapid infiltration beds where secondary sewage effluent was disposed of. Di-*n*-butyl phthalate has been identified in at least 471 of the 1,585 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL). However, the number of sites evaluated for di-*n*-butyl phthalate is not known.

2.2 SUMMARY OF HEALTH EFFECTS

The primary effects seen in animals following exposure to di-*n*-butyl phthalate are developmental and reproductive alterations. No data are available for developmental or reproductive effects in humans. Animal studies have shown that the development of the male reproductive system, especially the seminiferous epithelium of the testes, may be disrupted by *in utero* exposure to high doses of di-*n*-butyl phthalate during the critical period for reproductive development. Other developmental effects may also occur following *in utero* or perinatal exposure, and include increases in postimplantation losses, decreases in the number of live fetuses per litter, decreases in fetal and pup body weights, and increases in incidences of external, skeletal, and internal malformations. Reproductive effects are also seen in adult animals exposed to di-*n*-butyl phthalate. Fertility is reduced in male and female animals, and is related to testicular atrophy and seminiferous tubule damage in males; the mechanism in females is not known. Reproductive alterations may also extend to the offspring of exposed animals, and may include reduced fecundity and decreased sperm production. Minor liver, hematological, and renal effects, as well as changes in body weight, have also been observed in exposed rats.

Species differences in susceptibility to testicular damage have been noted. More severe testicular damage was seen in rats and guinea pigs than in mice and hamsters at the same dose level. This is thought to be due, at least in part, to differing levels of β-glucuronidase activity that may result in different levels of the free primary metabolite, mono-*n*-butyl phthalate, in the testes (see Section 3.5 Mechanisms of Action).

Developmental Effects. No human data are available for developmental effects of di-*n*-butyl phthalate. Animal studies have shown that acute- and intermediate-duration oral exposure to di-*n*-butyl phthalate causes a number of developmental effects, including increases in postimplantation losses, decreases in the number of live fetuses per litter, decreases in fetal/pup body weights, increases in

incidences of external, skeletal, and internal malformations, and altered reproductive development in the offspring. The lowest levels at which these effects were seen were varied widely. Decreases in the number of live pups/litter were seen following doses as low as 80 mg/kg/day in rats and 1,950 mg/kg/day in mice. Decreases in ano-genital distance, increases in undescended testes, and increases in abortions were seen at 500 mg/kg/day in rats, and increases in the incidence of external and skeletal malformations were seen at 750 mg/kg/day in rats. As discussed in Section 2.3, increased incidence of retained nipples and areolas (an anti-androgenic effect) in male rat pups exposed *in utero* is the basis for the acute-duration minimal risk level (MRL) for oral exposure. The lowest dose level resulting in disruption of androgen-regulated reproductive development in rats was 100 mg/kg/day. This is well above the levels expected to be encountered by the general population or at a well-regulated workplace.

Reproductive Effects. No human data are available for reproductive effects of di-*n*-butyl phthalate. Animal studies have shown that di-*n*-butyl phthalate affects fertility in both males and females. Decreases in fertility indices, reduced pregnancy rates, and shortened length of gestation have been seen in rodents exposed to di-*n*-butyl phthalate before or during gestation. Testicular atrophy has been observed in male rats, mice, and guinea pigs, but not hamsters, acutely exposed to di-*n*-butyl phthalate; however, rats are much more sensitive to the testicular effects than other animals examined (see Section 3.5 Mechanisms of Action).

Hepatic Effects. Mild liver effects have been seen in rats and mice orally exposed to di-*n*-butyl phthalate for acute or intermediate durations. These effects were increased liver weight, increased microsomal enzyme activity, inhibition of mitochondrial respiration, liver necrosis, and peroxisome proliferation. The lowest dose level at which effects were seen was 348 mg/kg/day.

Hematological Effects. Hematological effects have been observed in rats and mice exposed orally to high dose levels of di-*n*-butyl phthalate. These included anemia, decreased hematocrit, hemoglobin, and red blood cell levels.

Renal Effects. Renal effects of di-*n*-butyl phthalate were limited to decreased kidney weight in mice and increased kidney weight in rats exposed to high dose levels.

2.3 MINIMAL RISK LEVELS FOR DI-*n*-BUTYL PHTHALATE.

Inhalation MRLs

Information on the toxicity of inhaled di-*n*-butyl phthalate is sparse. Hypertension and hyperbilirubinemia were reported in workers exposed to 1.7–66 mg/m^3 di-*n*-butyl phthalate. Because the workers were exposed to other plasticizers, these effects cannot be definitively attributed to di-*n*-butyl phthalate exposure. Animal inhalation data are limited to a study that examined organ weight changes and hematological and serum chemistry parameters in rats exposed to di-*n*-butyl phthalate. Although organ weight (lung and brain) effects were observed, the toxicological significance of the alterations cannot be determined without histopathological examination of these tissues. In absence of reliable data, acute-, intermediate-, or chronic-duration inhalation MRLs were not derived.

Oral MRLs

- An MRL of 0.5 mg/kg/day has been derived for acute-duration oral exposure (14 days or less) to di-*n*-butyl phthalate.

The acute-duration oral MRL was based on a no-observed-adverse-effect level (NOAEL) of 50 mg/kg/day for developmental effects in the offspring of rats exposed to di-*n*-butyl phthalate on gestational days 12–21 and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). In this study, groups of 20 pregnant Sprague-Dawley rats (except 11 in the 500 mg/kg/day group) were treated with 0, 0.5, 5, 50, 100, or 500 mg/kg/day di-*n*-butyl phthalate by gavage in corn oil on gestational days 12–21. No developmental effects or clinical signs of toxicity were seen in pups exposed to 50 mg/kg/day or less *in utero*. The only treatment-related effect seen in the 100 mg/kg/day group was retained areolas and nipples in males (normally seen only in females) on postpartum day 14. This effect was dose-dependent, being more prominent at 500 mg/kg/day. Permanence of retained areolas and nipples was not assessed. Other statistically significant effects, seen only in males at 500 mg/kg/day level, were decreased ano-genital distance (12% decrease) and ano-genital distance/body weight at birth; smaller epididymides, dorsolateral prostate, and levator ani-bulbocavernosus muscle at sexual maturity; and decreased testes weight. Malformations of the male reproductive tract included absent or malformed epididymis, absent or malformed vas deferens, hypospadia, and unilaterally absent seminal vesicle. Histopathological lesions of the testis seen were seminiferous tubule degeneration, focal interstitial hyperplasia, and interstitial cell adenoma. In males, no significant changes were seen in age at preputial separation, or body, kidney, liver, adrenal, ventral

prostate, vas deferens, seminal vesicle, or other organ weights (other than those listed above). In female pups, no significant differences from controls were seen in age of onset of vaginal opening, body, liver, kidney, adrenal, ovary, or uterus weight, or gross morphology of the reproductive organs at sexual maturity.

Studies that have examined the acute toxicity of orally administered di-*n*-butyl phthalate have primarily focused on reproductive and developmental end points. Testicular atrophy, decreased testes weight, and decreased number of spermatocytes have been observed in rats, mice, and guinea pigs exposed to doses of 1,000 mg/kg/day and higher; a NOAEL of 500 mg/kg/day was identified. The developmental effects consisted of increases in post-implantation losses, decreases in fetal body weight, increases in external, skeletal, and internal malformations, and androgen-regulated developmental alterations (reduced ano-genital distance, increased number of retained nipples, decreased androgen-dependent tissue weights, delayed preputial separation). The smallest lowest-observed-adverse-effect level (LOAEL) for developmental toxicity was identified in a study in which increases in the incidence of retained areolas and nipples were observed in the offspring of rats exposed orally by gavage to $100 mg/kg/day di-*n*-butyl phthalate on gestational days 12–21. The NOAEL for this effect is 50 mg/kg/day. Although the systemic toxicity of di-*n*-butyl phthalate has not been adequately assessed following acute oral exposure, the results of intermediate-duration studies suggest that developmental toxicity would occur at similar or lower LOAELs than hepatic effects (the most sensitive systemic effect).

An intermediate-duration oral MRL was not derived for di-*n*-butyl phthalate. Systemic, reproductive, and developmental effects have been observed in animals. The liver appears to be the most sensitive systemic target in rats and mice exposed to di-*n*-butyl phthalate in the diet for 13 weeks. The hepatic effects consisted of cytoplasmic alterations suggestive of glycogen depletion, peroxisomal enzyme induction, decreased lipid deposition in the liver, decreased serum triglyceride and cholesterol levels, and inhibition of mitochondrial respiration. The reproductive effects consisted of testicular atrophy (including decreases in testes weight and degeneration of seminiferous tubule germinal epithelium) with decreases in spermatogenesis. Reproductive effects have been observed at 250 mg/kg/day and higher. Serious developmental effects have been observed in intermediate-duration studies. Decreases in fetal/pup survival, decreases in pup body weight, and impaired reproductive development in the male offspring (testicular degeneration and atrophy) have been observed. The lowest LOAEL for developmental toxicity is 80 mg/kg/day; decreases in fetal survival were observed at this dose.

The available intermediate-duration data suggest that developmental toxicity is the most sensitive toxic end point and should be used to derive an intermediate-duration MRL. The lowest LOAEL identified for

developmental toxicity is 80 mg/kg/day for decreases in the average number of pups per litter in rats exposed to dietary di-*n*-butyl phthalate in a continuous breeding study; a NOAEL was not identified. The 80 mg/kg/day is considered a serious LOAEL and is not appropriate for MRL derivation. Thus, an intermediate oral MRL was not derived for di-*n*-butyl phthalate.

No chronic-duration oral studies for humans or animals were identified; thus, a chronic oral MRL was not derived.

A chronic MRL for DNB was not derived. There were no adequate chronic-duration oral studies identified for humans or animals. EPA verified an RfD based on a study by Smith (1953). In this study, 10 rats were fed diets containing 0.01-1.25 % dibutyl phthalate. Half of the high dose group died within the first week of exposure. ATSDR did not have confidence in this study to derive an MRL due to the lack of detail and apparent conflict in the reported results. EPA also had low confidence in the study; the RfD received a low rating.