
**The Risk of Chronic Toxicity Associated with Exposure to Diisononyl
Phthalate (DINP) in Children's Products**

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Summary

Dialkyl phthalates are plasticizers that are used in products made from polyvinyl chloride (PVC), including teething rings, rattles, and squeeze toys. Because plasticizers are not covalently bound to the PVC polymer, oral exposure can occur when children place PVC products into their mouths. The principal plasticizer found in children's products was diisononyl phthalate (DINP), which was present in 31 of 35 children's products tested by CPSC that contained phthalates. The DINP content ranged from 15.1 to 54.4 percent by weight.

In lifetime feeding studies in the rat and mouse, DINP exposure was toxic to the liver and other organs and increased the incidence of hepatocellular adenoma and carcinoma. In contrast to certain other phthalates such as di-(2-ethylhexyl) phthalate (DEHP), DINP had little or no effect on reproduction or development. The no observed adverse effect level (NOEL) for histopathological effects in the livers of male rats was 15 mg/kg-d. An acceptable daily intake (ADI) value of 0.15 mg/kg-d (150 µg/kg-d) was derived from the NOEL. The ADI is the dose at which we would not expect humans to experience harmful effects.

The staff measured the migration of DINP from children's products using a laboratory method (impaction) previously used for DEHP. The test product was positioned in a stainless steel beaker and immersed in a saliva simulant at 37 °C. A pneumatic piston impacted the product to approximate the effects of a child's biting or chewing. Using this methodology, DINP migrated from the test samples at rates ranging from 1 to 48 µg/h for a surface area of 11 cm², which is an estimate of the average surface area that can fit in an infant's mouth. Migration rates did not correlate with the DINP content, manufacturing process, or wall thickness.

Studies with adult volunteers were conducted to compare the migration rate measured *in vivo* with those measured by impaction method. Using disks cut from identical toys, the *in vivo* migration rate was, on average, 39.5 times greater than the rate measured by impaction. Therefore, a factor of 39.5 was applied to the migration rates measured by impaction. Data from the Dutch Consensus Group child observation study were used to estimate the duration of mouthing activity. The combined mouthing time for "toys intended for mouthing" and "other toys" was used as a measure of the number of minutes per day that children's PVC products may be mouthed. For 3 to 12-month-old children, the average daily exposure was estimated to be 5.7 µg/kg-d, with a 95th percentile value of 94.3 µg/kg-d. For 13 to 26-month-old children, the average daily exposure in this group was estimated to be 0.7 µg/kg-d, with a 95th percentile value of 7.6 µg/kg-d.

I. INTRODUCTION

Various dialkyl phthalates (DAP's) are used as plasticizers in products made from polyvinyl chloride (PVC), including children's products such as teething rings, rattles, and squeeze toys. Because DAP's are not covalently bound to the PVC, they may be released from the children's products when children place them into their mouths, leading to ingestion of the DAP (CPSC, 1983; Chen, 1998a). Dermal exposure may also occur, although to a lesser extent (CPSC, 1983).

In the present study, diisononyl phthalate (DINP) (CAS no. 68515-48-0; 28553-12-0) was the primary DAP identified in children's products (Chen, 1998a). DINP is a mixture of as many as 100 isomers of primarily branched chain DAP's (Hellwig et al., 1997; NLM, 1997; Wilkinson, 1998). The composition of isomeric mixtures may vary depending on the manufacturing process. Oral exposure of rats and mice to DINP resulted in toxic effects in the liver and other organs, as well as increased incidence of liver adenoma and carcinoma (reviewed in Babich, 1998; Lee, 1998). The rate of DINP release into a saliva simulant from children's products was measured by CPSC's Directorate for Laboratory Sciences staff (Chen, 1998a). The purpose of this report is to assess the risk of chronic organ toxicity associated with exposure to DINP in children's products.

II. METHODOLOGY

A. Exposure

1. Impaction Method

The migration of DINP's from PVC products into artificial saliva was measured (Chen, 1998a) by essentially the same method CPSC used previously for di-(2-ethylhexyl)phthalate (DEHP) (CPSC, 1983). Briefly, the product to be tested was held in place in a stainless steel beaker and immersed in 50 milliliters of saliva simulant composed of Dulbecco's phosphate buffered saline (PBS) at pH 7.2 supplemented with 0.16 percent mucin. Intact products were used where possible. Otherwise, they were cut to a size small enough to fit in the beaker. A hexagonal pneumatic piston with a surface area of 2.18 cm² impacted the sample at a rate of 15 times per minute with a force of 6 pounds (27 Newtons). The product was extracted for 6 hours. A subset of products was also extracted by gentle shaking with no impaction by the piston. Extracts were analyzed for DAP's by gas chromatography-mass spectroscopy. The migration rates without and with the piston were used to estimate the portions of migration due to diffusion, which depends on the sample surface area, and the action of the piston, respectively (as described in Chen, 1998a; compare also CPSC, 1983). This information was used to calculate the migration rate (micrograms per hour, µg/h) for the portion of the product (11 cm²) that can fit in a child's mouth (as in CPSC, 1983).

2. Human Subjects Studies

Migration rates were also measured with 10 adult volunteers by a method essentially similar to that of the Dutch Consensus Group (EU, 1998a). Briefly, four disks 2.54 cm (1 inch) in diameter were cut from 5 identical PVC toys (Chen, 1998a). The disks were gently washed with warm water and mild detergent and rinsed according to the toy manufacturer's instructions. Two disks from each toy were tested by human subjects (two different individuals) and two were tested by impaction. Subjects were instructed to move the disks about in their mouths, draw upon, apply pressure with the tongue, or lightly chew the disks, during which all saliva was collected in a wide mouth bottle. However, they were asked not to chew heavily or grind the disks so as to break them into smaller pieces. Subjects tested a polytetrafluoroethylene disk (analytical blank) for 15 minutes, followed by a 5 minute rest period. Then the PVC disks were tested for four 15 minute periods, separated by 5 minute breaks. Samples were rinsed with distilled water between tests. After recording the saliva volume, the saliva samples were diluted to a constant volume and analyzed for DINP as described elsewhere (Chen, 1998a).

3. Mouthing Activity

The observational study conducted by the Dutch Consensus Group was used as the basis for estimating the amount of time each day that a child would mouth the products under discussion (EU, 1998a; Groot et al., 1998). The consensus group studied mouthing behavior in 42 children ranging in age from 3 to 36 months. They recorded the time that various objects were mouthed, including pacifiers, toys "intended for mouthing" (that is, teething rings and rattles), other toys, and total mouthing time. The combined mouthing time for "toys intended for mouthing" and "other toys" was used as a measure of the number of minutes per day that children's PVC products, including teething rings, rattles, and toys, may be mouthed. Since it is not believed that any pacifiers containing DINP are currently being marketed in the United States, mouthing times of pacifiers were not included in these calculations. Data from the Dutch Consensus Group study were used to estimate the mouthing duration for the 3 to 12-month-old and 13 to 26-month old children (Greene, 1998). Since there was only one subject in the 27 month to 36 month group and one observation would not be sufficient to estimate the mouthing duration of that whole age group, this observation was eliminated from our staff analysis and, therefore, an upper boundary of 26 months was used.

4. Daily Exposure

The estimated daily oral exposure was calculated by:

$$DE = \frac{M \times R \times D}{60 \times BW} \quad (1)$$

where: DE, is the daily oral exposure, micrograms per kilogram of body weight per day, $\mu\text{g}/\text{kg}\cdot\text{d}$; M, migration rate for an 11 cm^2 area by the impaction method, micrograms per hour, $\mu\text{g}/\text{h}$; R, the ratio of the migration rate with human subjects to that by impaction, unitless; D, duration of mouthing, minutes per day, min/d ; 60, to convert from minutes to hours, min/h ; and BW, body weight, kg.

Data for migration rates (impaction method), the ratio between the migration rate with human subjects to that by impaction, and the duration of mouthing were fitted to lognormal distributions, and the geometric means and variances were estimated (Greene, 1998). The geometric means and variances of these distributions were used to estimate the geometric mean and 95th percentile values of the daily exposure, as well as 95 percent confidence limits for the mean and 95th percentile exposure. Average body weights of 7.3 kg and 10.7 kg were assumed for the 3 to 12-month-old and 13 to 26-month-old age groups, respectively.

B. Chronic Toxicity

The acceptable daily intake (ADI) for chronic organ toxicity was derived by dividing the no-observed-adverse-effect level (NOEL) in animals by an overall uncertainty factor of 100, which is the product of two factors: 10 for interspecies variation and 10 for interindividual variation (CPSC, 1992). The ADI represents a level at which we would expect humans not to experience harmful effects.

III. RESULTS

A. Exposure

DINP was present in 31 of 35 PVC children's products tested¹ (Chen, 1998a). The DINP content ranged from about 15 percent (bath toy, sample 2-12) to 54 percent (teether, sample 1-10) (Table 1). DINP migration rates by the impaction method ranged from 1.0 to $48.4\ \mu\text{g}/\text{h}$ for an area of 11 cm^2 . The highest migration rate was with a squeeze toy (sample 2-2). Migration rates did not correlate with DINP content (Figure 1). The correlation coefficient (r^2) was 0.14. There was no correlation between the migration rate and the manufacturing process or sample thickness (Greene, 1998). The frequency distribution of migration rates was consistent with a lognormal distribution (Greene, 1998). For the 31 DINP-containing children's products, the mean migration rate was $8.2\ \mu\text{g}/11\text{ cm}^2/\text{h}$, with a standard deviation of 9.83 (Figure 2). There was no significant difference in migration rates between toys and teethers (Greene, 1998).

Studies with human subjects were performed using disks with a surface area of approximately 10.3 cm^2 . The ratio between the *in vivo* and impaction methods averaged 39.5, with a range of 22.9 to 72.6 (Table 2). The average (geometric mean) mouthing duration in the 3

¹ Other DAP's identified were diisooctyl phthalate (27554-26-3) (a pacifier and a bottle nipple), di-nonyl phthalate (117-84-0) (a soother), and DEHP (117-81-7) (a toy handbag).

to 12-month old group was estimated to be 12.0 minutes per day (Greene, 1998) (Table 3). The average mouthing duration for 13 to 26-months was estimated to be 2.1 minutes per day. These times apply only to toys, teethingers, and rattles, which may contain DINP. The average time for pacifiers, which do not contain DINP, was greater.

Estimated oral exposures were calculated from the migration rate (Table 1), body weight, and mouthing duration (minutes per day) (Table 3) using equation 1. The mouthing duration is applicable to teethingers, rattles, and toys. The average daily exposure for 3 to 12-month-olds was estimated to be 5.7 $\mu\text{g}/\text{kg}\text{-d}$ (95 percent confidence interval 2.5 to 12.9) (Table 4). The 95th percentile value was estimated to be 94.3 $\mu\text{g}/\text{kg}\text{-d}$. The average daily exposure for 13 to 26-month-olds was 0.7 $\mu\text{g}/\text{kg}\text{-d}$ (95 percent confidence interval 0.3 to 1.6), with a 95th percentile value of 7.6 $\mu\text{g}/\text{kg}\text{-d}$ (Table 4). Although the average mouthing duration for pacifiers was higher than for toys, teethingers and rattles, this mouthing duration was not included since pacifiers do not contain DINP.

B. Chronic Toxicity

Exposing rats or mice to DINP in two-year feeding studies resulted in histopathological effects in the liver, kidney, and other organs (Lington et al., 1997; Moore, 1998a,b). Male rats were the most sensitive sex and species. In the study by Lington et al., a NOEL of 15 mg/kg-d and a lowest-observed-adverse-effect-level (LOEL) of 152 mg/kg-d were observed in male rats, which were somewhat more sensitive than the females (Lington et al., 1997; see also Lee, 1998) (Table 5). Moore reported a NOEL of 88 mg/kg-d in male rats. Although both studies were with F-344 rats, Lington et al. observed a more sensitive dose response (Figure 3). Therefore, to be cautious, the ADI was derived from the NOEL of 15 mg/kg-d in the Lington et al. study. To obtain the ADI, the NOEL was divided by an overall uncertainty factor of 100, which is the product of two factors: 10 for interspecies variation and 10 for interindividual variation (CPSC, 1992). Thus, the ADI for DINP is 0.15 mg/kg-d or 150 $\mu\text{g}/\text{kg}\text{-d}$ (Lee, 1998).

The risk of non-cancer health effects may be assessed for DINP-containing products. For the 3 to 12-month-old group, the average exposure was 5.7 $\mu\text{g}/\text{kg}\text{-d}$ (Table 4), which is well below the ADI of 150 $\mu\text{g}/\text{kg}\text{-d}$. The estimated 95th percentile exposure, 94.3 $\mu\text{g}/\text{kg}\text{-d}$, is also well below the ADI. For the 13 to 26-month old group, the average exposure was 0.7 $\mu\text{g}/\text{kg}\text{-d}$, with a 95th percentile of 7.6 $\mu\text{g}/\text{kg}\text{-d}$, both well below the ADI.

IV. DISCUSSION

Under the Federal Hazardous Substances Act (FHSA), a product or substance may be considered "hazardous" if it may cause "substantial personal injury or substantial illness during or as a proximate result of any customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion by children." 15 USC 1261 (f)(1)(A). Whether a substance such as DINP presents a hazard depends not only on whether it may cause injury (that is, whether it is toxic), but also on the dose response, bioavailability, and exposure. Toxicity includes both acute

and chronic toxicity. Chronic toxicity refers to carcinogenicity, neurotoxicity, reproductive/developmental toxicity, or any other persistent effect such as organ toxicity. 16 CFR 1500.3(c)(2)(ii). Under the CPSC Chronic Hazard Guidelines, a substance may be regarded as “toxic” based on “sufficient” evidence of toxicity in animals or “limited” evidence in humans (CPSC, 1992). Generally, “sufficient” evidence in animals means that a substance produces adverse effects in at least two species, at two doses, or by two routes of administration (CPSC, 1992). For noncancer endpoints, a safety factor approach is generally used to derive an ADI (see above), which is considered to be a level at which humans would not experience harmful effects. A quantitative assessment of exposure and bioavailability is performed. A product intended for use by children that contains a hazardous substance is a banned hazardous substance. 15 U.S.C. § 1261(q)(1)(a).

A. Exposure

1. Migration Studies

A laboratory method was used to study the migration of DINP from children’s products made of PVC. Test samples were impacted by a pneumatic piston in the presence of a saliva simulant. A similar method was used previously to estimate exposure to DEHP (CPSC, 1983). The use of the piston and saliva simulant are intended to approximate the effects of a child’s biting or chewing. The pH of adult human saliva ranges from 5.5 to 7.5, with an average of 6.7 (Afonsky, 1961). The pH of the simulant (7.2) is within the range reported for human saliva. The average mucin content of human saliva is 0.25 percent (Afonsky, 1961). However, in previous experiments with DEHP-containing products, migration rates obtained with 0.16 percent mucin (in PBS or Hank’s balanced salt solution) more closely matched those obtained with adult human saliva (CPSC, 1983). In the present work, increasing the force applied by the piston from 6 to 12 pounds or periodic replenishment of the saliva simulant did not significantly increase the migration rate (Chen, 1998a). Changing the size of the piston, while keeping the pressure constant, did not significantly increase the migration rate per square centimeter (Chen, 1998a).

Various other laboratory methods of measuring DAP migration have been used, including shaking, ultrasound, and impaction, leading to a broad range of results (Rastogi et al., 1997; EU, 1998a; Earls et al., 1998; Steiner et al., 1998; see also Babich, 1998). While CPSC measured migration rates from 1 to 48 $\mu\text{g}/11\text{ cm}^2/\text{h}$ with an impaction method, ultrasound generally gave greater rates. A variety of agitation methods have given migration rates both less than and greater than the CPSC method. However, there have been few attempts to test similar products in different laboratories, making it difficult to make direct comparisons among methods. In the past year, the Danish National Environmental Research Institute (NERI) reported a migration rate of 23,260 $\mu\text{g}/\text{dm}^2/\text{h}$ (equivalent to 2,560 $\mu\text{g}/11\text{ cm}^2/\text{h}$) with a disk cut from a particular toy, by a shaking method (Rastogi et al., 1997). Samples from the same toy, obtained from Dr. Rastogi, were tested by CPSC using both the CPSC and NERI methods, resulting in lower migration rates (Chen, 1998b). Migration rates, measured by the CPSC staff, using the NERI method ranged

from 7.2 to 102 $\mu\text{g}/\text{dm}^2/\text{h}$. Migration rates by the CPSC impaction method ranged from 105 to 133 $\mu\text{g}/\text{dm}^2/\text{h}$ (roughly equivalent to 13 $\mu\text{g}/11 \text{ cm}^2/\text{h}$).

Recently, migration experiments using adult human volunteers were performed in the Netherlands (EU, 1998a). In the Dutch Consensus Group study, DINP migration was measured with specially prepared 10 cm^2 disks, a toy, and a 10 cm^2 disk cut from the same toy (EU, 1998a). The average migration rate was 1.8 $\mu\text{g}/10 \text{ cm}^2/\text{min}$ (range 1.4 to 2.4) or about 120 $\mu\text{g}/11 \text{ cm}^2/\text{h}$. In comparison, the migration rates measured by CPSC averaged 8.7 $\mu\text{g}/11 \text{ cm}^2/\text{h}$ (range 1 to 48) (Table 1). Because the migration rates measured *in vivo* were greater than those measured with the CPSC impaction method, the CPSC staff conducted tests with human subjects so that the two methods could be compared using the same test article. Ten volunteers tested disks cut from five identical toys. The average migration rate in these tests was 241.3 $\mu\text{g}/11 \text{ cm}^2/\text{h}$, which was 39.5 times greater than the average rate obtained by impaction with disks cut from the same five toys. Therefore, a correction factor of 39.5 was applied to the migration rates measured by impaction. Although the use of the correction factor is reasonable in this case, it is preferable to have a laboratory method that better mimics *in vivo* behavior. The CPSC staff plans to work toward the development of a test method that correlates more closely with the *in vivo* results.

It is likely that adults may apply more force in chewing the test article, which would tend to overestimate a child's exposure. On the other hand, during the *in vivo* studies or actual use, some DINP may adhere to the oral mucosa where it will be absorbed or ingested. Therefore, both potential sources of error may tend to mitigate one another (EU, 1998a). At this time, this is the best available approach for assessing exposure to children.

2. Mouthing Duration

Previously, the CPSC staff used assumptions for the duration of mouthing activity that were based on professional judgment, because data on the mouthing activities of children were not available (CPSC, 1983; Kiss, 1998). Recently, however, an observational study of mouthing activity was conducted for the Dutch Consensus Group (EU, 1998a; Groot et al., 1998). In this study, parents observed and recorded the mouthing activity of their children for ten 15-minute periods over 2 days. Mouthing activity was categorized into various groups, such as: dummies (that is, pacifiers), toys intended to be mouthed (teethers and rattles), other toys, fingers, and non-toys.

Data from the Dutch Consensus group study (Groot et al., 1998) were obtained by the CPSC staff for analysis (Greene, 1998). Based on the recommendation of CPSC's Division of Human Factors (Kiss, 1998), the mouthing times for "toys intended to be mouthed" and "other toys" were combined to estimate the total possible mouthing time for teethers, rattles, and toys. Pacifiers were not included in this analysis, because only one PVC pacifier was found in stores and it contained diisooctyl phthalate. Because mouthing activity varies with age, the staff estimated the average mouthing activity for two age groups: 3 to 12 months and 13 to 26 months.

These age groups were based on the recommendation of the Division of Human Factors (Kiss, 1998) and are consistent with the results of the Dutch study (Green, 1998).

Recently, CPSC's Division of Human Factors completed an observational study of mouthing activity in 1 to 8-year-old children (Smith and Kiss, 1998). Although CPSC's study was designed for a different purpose and did not include 3 to 12-month-olds, it tends to support the results of the Dutch study. CPSC's Division of Human Factors concludes that the Dutch study represents the best available data for estimating the duration of mouthing activity for the purpose of estimating exposure to phthalates in infants and toddlers (Kiss, 1998). However, the Dutch study was relatively small. Therefore, CPSC staff recommends a larger observational study be conducted in children ranging in age from 3 to 36 months.

B. Chronic Toxicity

1. Acceptable Daily Intake

DINP was toxic to the liver and other organs of mice and rats fed DINP for periods of time ranging from 10 days to 2 years (reviewed in Babich, 1998; Lee, 1998). The ADI (Lee, 1998), which is the dose at which one would not expect harmful effects in humans (CPSC, 1992), was based on liver histopathological effects in a two-year bioassay (Lington et al., 1997). The ADI was derived by applying uncertainty factors to the NOEL in the study (15 mg/kg-d). The uncertainty factors include a factor of 10 for potential differences in toxicity between animals and humans and another factor of 10 for potential differences among individuals (CPSC, 1992; Lee, 1998). An essentially similar approach was employed by the European Union's Scientific Committee on Toxicity, Ecotoxicity, and the Environment (EU, 1998b).

It has been suggested that the LOEL in the animal studies (150 mg/kg-d) (Lington et al., 1997) should be regarded as a NOEL, because the effects seen at this dose (for example, hepatomegaly) are "adaptive" in nature and are not truly adverse health effects (Wilkinson, 1998). However, histopathological changes including spongiosis hepatitis, a perisinusoidal cell degeneration, were also observed at 150 mg/kg-d (Lington et al., 1997; compare also Moore, 1998a; reviewed in Lee, 1998). The hepatomegaly and histopathology may be part of a continuum of effects that include hepatocellular necrosis at higher doses. Other agencies including the EU Scientific Committee (EU, 1998b) have considered 150 mg/kg-d as the LOEL and 15 mg/kg-d as the NOEL in the Lington study.

Recently, a second lifetime feeding study became available that reported a NOEL of 0.15 percent DINP in feed (88 mg/kg-d in males, 108.6 mg/kg-d in females) (Moore, 1998a) (Table 5). Using this NOEL would result in an ADI of 880 μ g/kg-d, rather than 150 μ g/kg-d. However, the previous study (Lington et al., 1997) reported a much more sensitive dose response (Figure 3). Therefore, the more sensitive study was used as the basis for computing the ADI. The reason for this difference between the two studies is unknown. Both studies employed F-344 rats. Although the studies tested DINP's from different sources, they are considered to be equivalent in their

chemical composition and toxicity (Wilkinson, 1998). The background rate of spongiosis hepatitis was higher in the Lington study (about 30 percent) than in the Moore study (about 6 percent). However, the dose response in the Lington study remains more sensitive even after adjusting for background (Figure 3).

Although the 0.15 percent dose level was considered a NOEL by the author (Moore, 1998a), there were some statistically significant changes in clinical hematology values at this level (108.6 mg/kg-d) in the females. The erythrocyte count was low at 26 weeks, the hematocrit was elevated from 26 to 78 weeks, and the mean cell hemoglobin concentration was elevated at 52 weeks. Some changes in clinical chemistry were also observed in males and females at 0.15 percent or lower doses. Serum levels of aspartate aminotransferase (78 weeks), albumin (52 weeks), and globulin (52 to 78 weeks) were elevated, while glucose was low (52 and 104 weeks) at the 0.15 percent dose in females. Total serum bilirubin was elevated and glucose was low at 0.05 percent (36.4 mg/kg-d) in males. Clinical hematology and chemistry effects were reported at 0.3 percent, but not at 0.03 percent, in the Lington study (Lington et al., 1997). Although these clinical hematology and chemistry effects did not persist over the course of the study and they were not accompanied by histopathological effects, it is debatable whether the 0.15 percent dose level can be accurately characterized as a NOEL in the study by Moore.

2. Background Exposure to Dialkyl Phthalates (DAP's)

DAP's are used in many different products made from PVC and other plastics, including vinyl flooring, building materials, automobile interiors, medical devices, and children's products. DINP is used in vinyl upholstery, wire and cable, coated fabrics, and children's products (Wilkinson, 1998). Some of the more common phthalates -- DEHP, dibutyl phthalate, and butyl benzyl phthalate -- may be found in food (ATSDR, 1993; MAFF, 1996a; Yin and Su, 1996; Giam and Wong, 1997), infant formula (Baczynskyj, 1996; MAFF, 1996b), water (ATSDR, 1993; Yin and Su, 1996), ambient air (ATSDR, 1993), indoor air (Ølie et al., 1997), and soil (ATSDR, 1993). Exposure to DEHP from medical devices also has been reported (Barry et al., 1989; Plonait et al., 1993). DINP was detected at low, non-quantifiable levels in infant formula (MAFF, 1996b) and was a minor component in some samples of sedimented dust in residences (Ølie et al., 1997).

Food is believed to be the primary source of exposure to DAP's (ATSDR, 1993). DAP's are not generally used in food packaging in the U.S. The primary source of the DAP's in food is believed to be general environmental contamination, rather than food packaging (ATSDR, 1993; MAFF, 1996a,b). The average exposure to DEHP was estimated as 0.27 mg/person/day (ATSDR, 1993), which is roughly equivalent to 3.8 µg/kg-d. Total intake of DEHP in Canada was estimated to range from 8 to 19 µg/kg-d for various age groups, with the greatest exposure in the 0.5 to 4-year-old group (Meek and Chan, 1994). The average dietary intake of total DAP's in the U.K. was estimated to range from 0.1 to 0.8 mg/person/day (MAFF, 1996a), or 1-to-11 µg/kg-d. An estimate of the dietary intake of total phthalates in infants in Europe was reported to be 23 µg/kg-d (Janssen et al., 1998).

DINP has rarely been reported in food or the environment and, when present, it is at very low levels. However, DINP currently accounts for roughly 10 to 15 percent of total DAP production (CMA, 1998). Therefore, it is not clear why DINP was rarely detected in environmental samples and in food (see above). Possibly, the production and use of DINP is increasing relative to other DAP's. Environmental exposure to DINP from sources other than children's products is likely to be 10 to 15 percent of total DAP exposure (CMA, 1998).

Few data on background DAP exposure in infants are available. A Canadian study estimated the average DEHP exposure to be 19 µg/kg-d in 0.5 to 4-year-old children, based on a food basket survey (Meek and Chan, 1994). In a study by the U.K. Ministry of Agriculture, Fisheries, and Food, total DAP levels in unreconstituted infant formulae ranged from 1.2 to 10.2 µg/g (MAFF, 1996b). Based on these levels, the average intake of total DAP's from infant formula was estimated to be 130 µg/kg-d at birth and 100 µg/kg-d at 6 months of age (MAFF, 1996b). However, infant formulae in the U.S. appear to have lower DAP levels (Baczynski, 1996). Total DAP levels ranged from 0.011 to 0.051 µg/g in ready to use formulae and from 0.007 to 0.032 µg/g in powdered formulae (Baczynski, 1996). These levels roughly correspond to exposures ranging from 0.05 to 5 µg/kg-d in 5 to 12-month-old infants.²

It has been proposed that background DAP exposures should be considered in assessing the potential risk from DAP's in children's products (EU, 1998a,b). This approach assumes that the toxicological effects of DAP's are additive. The various DAP's differ in their toxic endpoints and potency. For example, some, but not all DAP's are carcinogenic, teratogenic, or reproductive toxins in animals. One common feature of DAP's is their ability to effect changes in the liver, especially hepatomegaly and other effects associated with peroxisome proliferation (ATSDR, 1990; ATSDR, 1993; NTP, 1995; NTP, 1997; reviewed in EU, 1998b). Given the structural similarity of DAP's, it is likely that these liver effects are due to a similar mechanism. However, there are no data to demonstrate that DAP's effects are additive. Even if they act through a common mechanism, their effects would not necessarily be additive.

If it is assumed that the effects of other DAP's are additive, then the DINP exposure from children's products would be in addition to the background DAP exposure. To quantitatively assess the impact of background exposure requires: (a) a method of adjusting for potency differences among the different DAP's, and (b) an estimate of the background exposure in infants. There are several different ways to adjust for the potency of different DAP's, including toxic equivalency factors, such as those used for dioxin congeners; a fractional equivalent dose method; or assuming that all DAP's are equipotent. If the relative concentrations of different DAP's is unknown, assuming equal potency would be preferred.

² Assumes 125 grams of powder per quart (1.14 liters) of reconstituted formula, which is typical of manufacturers' instructions. Also assumes 3 to 4 feedings per day at 210 to 240 mL per feeding (Nelson et al., 1996, p. 162) and a body weight of 10 kg.

Estimates of background exposure in the general population range from 1 to 23 µg/kg-d (see above). The highest estimate (23 µg/kg-d) is 15 percent of the ADI value for DINP (150 µg/kg-d) and is greater than the average exposure from teething and toys (5.7 µg/kg-d at 3 to 12 months). Since there are uncertainties regarding the amount of background exposure to DAP's, whether they act by a common mechanism, and the relative potency of the various DAP's, background levels have not been incorporated into the calculations of exposures.

C. Carcinogenicity

DINP is a member of a class of structurally dissimilar compounds known as peroxisome proliferating compounds (PPC's) or peroxisome proliferators (Barber et al., 1987). PPC's include other DAP's, herbicides, and hypolipidemic (cholesterol lowering) drugs (reviewed in Reddy and Lalwai, 1983; Bentley et al., 1993; IARC, 1995). The relevance of tumors induced by PPC's in assessing human risk has been debated for over a decade. The primary issues include the actual mechanism by which PPC's induce cancer and what is the most appropriate method of assessing human risk. A considerable amount of research has been conducted on the mechanism of action of PPC's. This research and the implications for estimating the risk to humans are discussed in detail below.

1. Carcinogenicity of DINP

When Fischer 344 rats were fed commercially available DINP (68515-48-0), the incidence of hepatocellular carcinoma (HCC) was significantly increased in males, and the risk of HCC or hepatocellular adenoma (HCA) was significantly increased in both males and females (Moore, 1998a; see also Bankston, 1994; Bankston, 1995a,b). DINP from the same source also led to significant increases in HCC, as well as HCC or HCA, in B6C3F₁ mice (Moore, 1998b; see also Bankston, 1995c; Bankston, 1996a,b). Another form of DINP (71549-78-5), that was never produced commercially, induced HCC in female, but not male Sprague Dawley rats (Bio/dynamics, 1986). Previously, it was reported that DINP (68515-48-0) did not induce liver tumors in Fischer 344 rats at doses up to 0.6 percent in the feed (Lington et al., 1997). The incidences of HCC, neoplastic nodules, or total liver neoplasms were not significantly different from the controls in either males or females. However, in the positive studies, increased HCC incidence was consistently observed only at doses of at least 1 percent in the feed (about 600 mg/kg-d). Therefore, the earlier negative results (Lington et al, 1997) may be explained by the selection of doses.

The dose response observed with DINP is consistent with that of DEHP, another branched chain DAP. The incidence of HCC was significantly elevated in Fischer rats fed DEHP at 1.2 percent, but not at 0.6 percent (NTP, 1982). The incidence of HCC in males and females combined from the three DINP studies and the DEHP study were plotted on the same graph for comparison (Figure 4). The dose responses from these studies appear to be similar, suggesting that DINP's from different sources may be similar in their cancer dose response. In mice, DEHP was 2 to 3-fold more potent than DINP (not shown). The similar response with DEHP suggests

that the key structural feature responsible for carcinogenicity may be the presence of branched chains, rather than the presence of any specific isomers.

2. Mechanism of Action

PPC's are characterized by their ability to induce an increase in the size and number of peroxisomes, which are subcellular organelles that contain fatty acid β -oxidation activity (IARC, 1995). Peroxisome proliferation (PPN) is also accompanied by hepatomegaly; induction of the peroxisomal β -oxidation system, certain cytochrome P₄₅₀ type (microsomal) isozymes (CYP4A), and microsomal and cytosolic epoxide hydrolase; stimulation of protein kinase C; reduction of the activities of glutathione peroxidase, glutathione S-transferase, and superoxide dismutase; and lipofuscin accumulation. The hepatomegaly (liver enlargement) is due to both hepatocyte hyperplasia (increased cell number) and hypertrophy (increased cell size). The induction of oxidative enzymes may result in increased hydrogen peroxide production and increased metabolism of fatty acids. Protein kinase C is associated with cell proliferation. Glutathione S-transferase and superoxide dismutase help to protect the cell against oxidative damage.

As with other DAP's, DINP is metabolized to the monoester and alcohol (MWRI, 1983). The monoester has been shown to be a PPC (Benford et al., 1986). In the case of DEHP, both the monoester and a metabolite of the alcohol group (2-ethylhexanoic acid) contribute to peroxisome proliferation (Bentley et al., 1993; IARC, 1995). No data on the ability of isononyl alcohol or its metabolites to induce PPN were available.

Although PPC's have been studied extensively, the mechanism by which they induce tumors in animals has not been elucidated (reviewed in Reddy and Lalwai, 1983; IARC, 1995; Cattley et al., 1998). Tumors induced by PPC's generally are observed only at doses where PPN is also observed; however, the presence of PPN is not always associated with tumor formation. Species such as the hamster and guinea pig are relatively resistant to PPN and to tumor induction by PPC's. *In vitro* studies have shown no evidence of PPN in primate or human liver.

PPC's generally exhibit little or no evidence of genotoxicity in standard assays. DINP was not mutagenic in *Salmonella* (Zeiger et al., 1985) or mouse lymphoma cells (Cifone, 1986). DINP did not induce unscheduled DNA repair in primary rat hepatocytes (Litton Bionetics, 1981a). It did not induce phenotypic transformation of BALB/C-3T3 mouse cells in one experiment with metabolic activation (Microbiological Associates, 1981a) and in five experiments without activation (Litton Bionetics, 1981b,c; Litton Bionetics, 1985; Microbiological Associates, 1981b,c), although one such experiment without metabolic activation gave a small, but statistically significant positive effect (Microbiological Associates, 1981d). In addition, DINP did not increase the frequency of chromosomal aberrations in the bone marrow cells of F-344 rats *in vivo*, although the highest dose was only 5.0 mg/kg (Microbiological Associates, 1981e).

At least three mechanisms of action have been proposed for PPC's (Conway et al., 1989; IARC, 1995; Cattley et al., 1998): oxidative stress (oxidative DNA damage), cellular

proliferation (mitogenesis), and the preferential growth of preneoplastic cells (tumor promotion). These proposed mechanisms are not mutually exclusive.

PPN results in the production of excess hydrogen peroxide that, in the presence of metal ions, may lead to the production of highly reactive oxygen species such as hydroxyl radicals or superoxide. These oxygen species may cause oxidative DNA damage and strand breaks, resulting in mutations or cell death. However, PPC's are generally nongenotoxic in standard assays, and oxidative DNA damage has not been consistently associated with PPN. Therefore, it is considered that, while oxidative stress may contribute to carcinogenesis, it is not the primary mode of action for PPC's (IARC, 1995; Cattley et al., 1998).

During the first several days of exposure in rats or mice, PPC's stimulate the proliferation of hepatocytes, resulting in an increase in cell number, in a process described as acute cell proliferation. If exposure continues, a chronic cell stimulation results, in which increased cell proliferation is presumably balanced by a concomitant increase in apoptosis (programmed cell death) (Marsman et al., 1992). This sustained, low level of cell proliferation is considered to increase the probability that spontaneous DNA damage would be converted into mutations (IARC, 1995). Acute cell proliferation (increase in labeling index) was observed with the hypolipidemic drug Wy-14,643, clofibric acid, and DEHP (Marsman et al., 1988, 1992). Chronic cell proliferation was observed with Wy-14,643 (Marsman et al., 1988, 1992). The chronic cell proliferation induced by Wy-14,643 was not limited to preneoplastic foci (see below) and was accompanied by an increase in apoptosis (Marsman et al., 1988). However, chronic cell proliferation was not observed with clofibric acid or DEHP at doses that were tumorigenic in animals (Marsman et al., 1988, 1992). Chronic stimulation of hepatocellular proliferation was not observed in the cancer bioassays with DINP (Moore, 1998a,b). Because at least three PPC's failed to induce chronic cell proliferation at doses that were tumorigenic, it is likely that chronic cell proliferation is not a prerequisite for the tumorigenicity of PPC's.

Enzymatically or histologically altered hepatic foci are believed to be indicative of preneoplastic cells. Some PPC's have been shown to promote the growth of specific subtypes of altered hepatic foci. The hypolipidemic drug Wy-14,643 promoted the growth of ATPase-deficient foci in rats previously exposed to the initiator diethylnitrosamine (Cattley and Popp, 1989). Thus, it was proposed that PPC's may selectively stimulate the growth of preneoplastic foci. The drug nafenopin promoted the growth of liver tumors in rats initiated with aflatoxin B₁ and led to an increase in the number of hepatic foci characterized by weak basophilia and a lack of γ -glutamyltranspeptidase activity (Kraupp-Grasl et al., 1990). DEHP inhibited the formation of γ -glutamyltranspeptidase-positive foci (Carter et al., 1992), but promoted the number of ATPase-deficient foci (reviewed in Bentley et al., 1993). That PPC's appear to promote only certain types of altered hepatic foci may explain why several promotion assays gave negative results (Bentley et al., 1993).

The promotion of spontaneously-initiated cells appears to be the most plausible mechanism of action for PPC's. However, tumor promotion activity has only been demonstrated for a few

PPC's; it has not been demonstrated for DINP. Even if this is the predominant mechanism, PPC's are complete carcinogens, that is, administration of PPC's alone leads to tumor formation in animals (Reddy and Rao, 1995). Therefore, it is likely that other mechanisms, possibly including oxidative DNA damage and mitogenesis, also contribute to the carcinogenic process.

a. Peroxisome proliferator-activated receptor

A peroxisome proliferator-activated receptor (PPAR) has been identified in several species, including mouse, rat, and human (reviewed in IARC, 1995; Gonzalez, 1997; Cattley et al., 1998). At least three isoforms of PPAR, which is a member of the steroid hormone nuclear receptor superfamily, have been identified, although only PPAR α mediates PPN (Gonzalez, 1997). PPAR α expression in rats is stimulated by glucocorticoids. It has been proposed that a heterodimeric receptor complex comprised of PPAR α and the retinoid X receptor is activated by PPC's and 9-*cis*-retinoic acid (Cattley et al., 1998). The activated complex binds to a specific base sequence, or response element, located in the promoters of PPC-responsive genes. The same response element is recognized by other nuclear hormone receptors, which may modulate the effects of PPAR α on gene expression. Although humans express PPAR α at a lower level than mice, the human PPAR α was shown to function normally in mouse cells *in vitro* (Cattley et al., 1998).

The mouse PPAR α gene has been isolated and a strain of PPAR α -null mice, the so-called "knockout" mice incapable of expressing PPAR α , has been developed (Lee et al., 1995). The PPAR α -null mice were characterized by elevated serum cholesterol levels (Peters et al., 1997a), the presence of lipid-containing vesicles in the liver, increased body fat (Lee et al., 1995), and reduced expression of mitochondrial fatty-acid metabolizing enzymes (Aoyama et al., 1998). The constitutive levels of peroxisomal and microsomal enzymes were similar to those of wild-type mice (Aoyama et al., 1998). However, PPAR α -null mice did not exhibit the typical responses associated with PPN, including hepatomegaly, increased number or size of peroxisomes, and induction of target peroxisomal or mitochondrial enzymes, when exposed to hypolipidemic drugs (Lee et al., 1997).

When PPAR α mice were fed 0.1 percent Wy-14,643 for 11 months, no liver tumors were observed, whereas the tumor incidence was 100 percent in homozygous wild-type mice (Peters, et al., 1997b). It is unknown whether the PPAR α -null mice would have developed tumors if the exposure had been continued until two years. In contrast, DEHP induced maternal toxicity, embryoletality, and teratogenicity in both PPAR α -null and wild-type mice (Peters et al., 1997c). These studies suggest that PPAR α is required for the expression of PPN and tumorigenesis, but not reproductive and developmental toxicity.

b. Species differences in response to PPC's

While rats and mice are responsive to PPC's, Syrian hamsters are moderately responsive, and guinea pigs, dogs, and primates are generally nonresponsive *in vivo* and *in vitro* (Lake, 1995; IARC, 1995; Cattley et al., 1998). However, two drugs were reported to induce PPN in monkeys. PPC's generally failed to induce PPN in human hepatocytes *in vitro*. Limited studies of humans taking hypolipidemic drugs generally reported no evidence of PPN. However, clofibrate and ciprofibrate were reported to have small effects on peroxisome number or size, respectively.

Few carcinogenicity studies of PPC's in species other than the mouse or rat have been reported (IARC, 1995; Cattley et al., 1998). Some hypolipidemic drugs were studied in monkeys, although the durations of the studies and doses probably were insufficient to produce a detectable increase in cancer incidence. A few studies of limited duration in humans taking hypolipidemic drugs failed to show an increased risk of cancer.

3. Relevance of Animal Tumor Data in Assessing Human Risk

Animal carcinogens are generally regarded as potential human carcinogens in the absence of convincing evidence to the contrary (CPSC, 1992; IARC, 1987). In the case of PPC's, it has been argued that the tumors are a secondary effect of PPN, primates and humans are less sensitive than the mice and rats in which PPN-induced tumorigenesis is observed, and, therefore, PPC's do not present a cancer hazard in humans (Cattley et al., 1998). That PPC-induced tumors are generally only observed at doses where PPN occurs and the finding that the receptor PPAR α is required for both tumorigenesis and PPN are frequently cited as evidence that PPC-induced tumorigenesis is a secondary effect of PPN (Cattley et al., 1998; Wilkinson, 1998). However, at this time the mechanism by which PPC's induce tumors is uncertain (IARC, 1995; Cattley et al., 1998). The database in primates and humans is small, many of the studies relating to the mechanisms of action of PPC's are with hypolipidemic drugs, rather than DAP's, and there have been few studies with DINP. Humans possess the same receptor (PPAR α) for PPC's as the mice and rodents, and this receptor is expressed in the lung and kidney, as well as in the liver.

The primary issue in determining whether PPC-induced tumors are relevant to humans is the relationship between tumorigenesis and PPN. Scientists at the U.S. Environmental Protection Agency (Lai, 1996) and the National Institute for Environmental Health Sciences (Bucher, 1998) regard PPC-induced tumors as relevant to humans. The International Agency for Research on Cancer (IARC) concluded that PPC's should be evaluated on a case-by-case basis, and outlined specific criteria for determining their relevance to humans (IARC, 1995). Specifically, when it can be adequately demonstrated that tumorigenesis occurs only as a secondary effect of PPN, then it would be appropriate to consider PPC-induced liver tumors as not relevant in assessing human risk, provided that: (a) alternative mechanisms can be reasonably excluded; (b) PPN and hepatocellular proliferation have been demonstrated under the conditions of the bioassay; and (c) such effects have not been found in adequately designed studies of human systems (IARC, 1995).

At this time it is not clear whether these criteria have been satisfied for DINP. For example, although DINP induced PPN under the conditions of the bioassay, it failed to induce chronic hepatocellular proliferation (Moore, 1998a,b).

4. Quantitative Cancer Risk Assessment

Although the relevance of tumors induced by PPC's to humans continues to be debated, the primary issue is the method of dose response assessment (Cattley et al., 1998). The multistage model (Howe and Crump, 1983; Crump, 1984a) produces cancer risk estimates that are a linear function of dose at low doses. It is the default model used by CPSC and other federal agencies, that is to be used in the absence of convincing evidence that another procedure is more appropriate (CPSC, 1992, p. 46654). The use of linear extrapolation is supported, in part, by the assumption that the exposure in question may act by adding to background processes or exposures (Crump et al., 1976; CPSC, 1992). In contrast, threshold distribution models such as the independent logistic (logit) and independent lognormal (probit) models generally produce cancer risk estimates that are nonlinear and much lower than the multistage model. These nonlinear models are appropriate for cases where there is sufficient evidence to conclude that a linear dose response does not apply. It has been proposed that a linear dose response would not apply to PPC's, because PPC-induced tumors are a secondary effect of PPN, PPN is a threshold phenomenon, and, therefore, PPN-associated tumors must also be a threshold phenomenon (Cattley et al., 1998). When it can be adequately demonstrated that PPC-induced tumorigenesis occurs only as a secondary effect of PPN and other mechanisms can be reasonably excluded, then it would be appropriate to use an alternative method for high-to-low dose extrapolation, such as a threshold distribution model or uncertainty factors.

The knowledge that a carcinogen is nongenotoxic or acts by a receptor-mediated process is, in itself, insufficient to abandon the default procedure for high-to-low dose extrapolation. Extensive study of the effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on gene expression suggests that receptor-mediated mechanisms may result in either linear or nonlinear responses at low doses (Lucier et al., 1993; Portier et al., 1993). However, studies of the interaction of PPC's with PPAR α may help to resolve the issue of which dose response assumption is more appropriate. If the early steps in the PPAR α -mediated tumorigenesis pathway can be identified, then a study of the dose response for these steps could be used in selecting the most appropriate dose response model or in developing a biologically-based dose response model for quantifying the cancer risks.

At this time, the choice of the appropriate dose response model for DINP remains unclear. There is ongoing research on the relevance of the tumors in animals to humans. In addition, research on the mechanism of action of PPC's is currently underway (Bucher, 1998; CMA, 1998). The relevant issues are whether a scientific consensus on the mechanism of PPC's exists, and how this applies in the case of DINP. This issue should be explored in an appropriate forum such as a workshop, public hearing, or Chronic Hazard Advisory Panel. The mechanism by which cancer occurs plays a role in determining the appropriate model to use to calculate a risk. Since scientific consensus does not exist on how DINP causes cancer in animals, quantitative estimates of cancer

risk associated with DINP exposure from children's products are not presented here. The issue of cancer risk will be addressed following additional consideration of this issue.

V. CONCLUSIONS

DINP was the principal plasticizer found in children's products, including teething rings, rattles, and soft toys. It was not found in any pacifiers. The acceptable daily intake (ADI) value, which is based on liver toxicity, is 150 $\mu\text{g}/\text{kg}\cdot\text{d}$. The ADI is the dose at which we would not expect humans to experience harmful effects. However, whether DINP in a particular product presents a hazard depends on a number of factors, including the migration rate and the duration of mouthing activity. Daily exposures for children from 3 to 12 months old were estimated to average 5.7 $\mu\text{g}/\text{kg}\cdot\text{d}$, with a 95th percentile value of 94.3 $\mu\text{g}/\text{kg}\cdot\text{d}$. As with any risk assessment, there are several sources of uncertainty. The exposure estimates could be improved by additional data on the mouthing activity of children from 3 to 36 months old, and the development of a laboratory method for measuring migration rates that correlates more closely with *in vivo* data. Further consideration of the most appropriate method for assessing cancer risk is needed.

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Table 1. Migration of DINP from polyvinyl chloride children's products measured by the impaction method (Chen, 1998a).

Sample no.	Product ^a	DINP content ^b (%)	Estimated migration ^c rate (µg/h)
1-2	Toy Book	27.5	2.8
1-3	Teether	36.6	11.3
1-5	Toy Tiger	48.1	11.5
1-6	Toy Dolphin	43.7	29.7
1-7	Teether	30.0	2.9
1-8	Teether	43.3	6.4
1-9	Teether	33.5	4.8
1-10	Teether	54.4	4.9
1-11	Corner Pads	44.0	15.2
1-14	Toy Food	51.0	21.6
2-1	Toy Duck	40.8	3.6
2-2	Toy Duck	42.7	48.4
2-3	Teether	50.3	3.9
2-4	Toy Fish	37.0	6.5
2-5	Toy Treehouse	36.1	13.9
2-7	Squeeze Toy	32.6	13.3
2-8	Soother	30.2	1.5
2-9	Teether	25.6	1.6
2-10	Teether	19.3	3.0

Continued on next page.

Table 1. Migration of DINP from polyvinyl chloride children’s products measured by the impaction method -- Continued.

Sample no.	Product ^a	DINP content ^b (%)	Estimated migration ^c rate (µg/h)
2-11	Toy Book	17.5	1.4
2-12	Bath Toy	15.1	1.0
2-13	Toy Turtle	35.4	3.7
2-14	Toy Bear	19.9	3.3
2-15	Spoon	35.2	4.8
2-16	Spoons	34.3	9.1
3-1	Ball	41.2	5.9
3-2	Toy Bear	41.2	4.5
3-3	Toy	27.1	2.9
3-4	Toy Block	43.0	5.5
3-5	Toy Car	42.7	2.4
3-6	Squeeze Toy	52.5	2.9

^a Includes only children’s products containing DINP.

^b Content, percent by weight of DINP in the product.

^c Estimated migration rate for an 11 cm² portion of the product in micrograms per hour, measured at 37°C using a saliva simulant, Dulbecco’s phosphate buffered saline with 0.16 percent mucin, while the sample was impacted by a pneumatic piston.

Table 2. Comparison of DINP migration rates measured by the impaction method and with human subjects (Chen, 1998a).

Sample	Migration rate, $\mu\text{g/h}$ ^a		Ratio ^d
	Impaction method ^b	Human subjects ^c	
1	7.0	159.8	22.9
2	10.1	305.4	32.8
3	4.7	204.1	32.3
4	5.5	383.6	72.6
5	4.7	181.1	54.6
G.M. ^d	6.1	241.3	39.51

^a Migration rate in micrograms per hour for a disk-shaped sample with a surface area of 10.3 cm² (Chen, 1998a).

^b Each value is the mean of two tests on two disks taken from the sample toy.

^c Each value is the mean of two tests with different human subjects using disks taken from the same toy used for the impaction method.

^d The ratio of the geometric mean migration rate with human subjects to the mean migration rate by impaction.

Table 3. Mouthing of teethers, rattles, and toys.

Age range months	<u>Minutes per day mouthing teethers, rattles, or toys</u> ^a	
	Geometric mean	Standard deviation
3 -- 12	12.0	2.55
13 -- 26	2.1	1.75

^a Estimated from data in the Dutch Consensus Group study (Groot et al., 1998), as described in (Greene, 1998).

Table 4. Estimated daily oral exposure to DINP in polyvinyl chloride teethers and toys.

Age Range	<u>Exposure, µg/kg-d</u> ^a	
	Average ^b	95th percentile ^c
3 to 12 months	5.7 (2.5 -- 12.9)	94.3 (50.1 -- 225.6)
13 to 26 months	0.7 (0.3 -- 1.6)	7.6 (4.6 -- 16.8)

^a The daily oral exposure in micrograms per kilogram of body weight per day, calculated with equation 1.

^b The numbers in parentheses are the 95 percent confidence intervals (Greene, 1998).

^c The 95th percentile value reflects the variance in the migration rate (impaction method), the ratio of the migration rate in human to that by impaction, and the duration of mouthing activity. The numbers in parentheses represent 95 percent confidence intervals (Greene, 1998).

Table 5. Incidence of spongiosis hepatitis in male Fischer 344 rats fed diisononyl phthalate (DINP) (68515-48-0) for two years.

Dose ^a mg/kg-d (%)		N ^b	Incidence ^c	Risk ^d	Extra Risk ^e
Lington et al., 1997					
0	(0)	81	24	0.296	0
15	(0.03)	80	24	0.300	0.005
152	(0.3)	80	51 **	0.638	0.485
307	(0.6)	80	62 **	0.775	0.680
Moore, 1998a					
0	(0)	80	5	0.062	0
29.2	(0.05)	50	5	0.100	0.040
88.3	(0.15)	50	2	0.040	-0.024
358.7	(0.6)	65	14 **	0.215	0.163
733.2	(1.2)	80	21 **	0.262	0.213

^a The dose in milligrams per kilogram per day, mg/kg-d, with the percent by weight in feed in parentheses.

^b Number of animals examined.

^c Number of animals with spongiosis hepatitis.

^d Fraction of animals with spongiosis hepatitis.

^e The extra risk is $(P - P_0) / (1 - P_0)$, where P is the fraction responding and P₀ is the response in the controls.

* Incidence is significantly different from the control, P≤0.05, one-tailed Fisher's exact test.

** Incidence is significantly different from the control, P≤0.01, one-tailed Fisher's exact test.

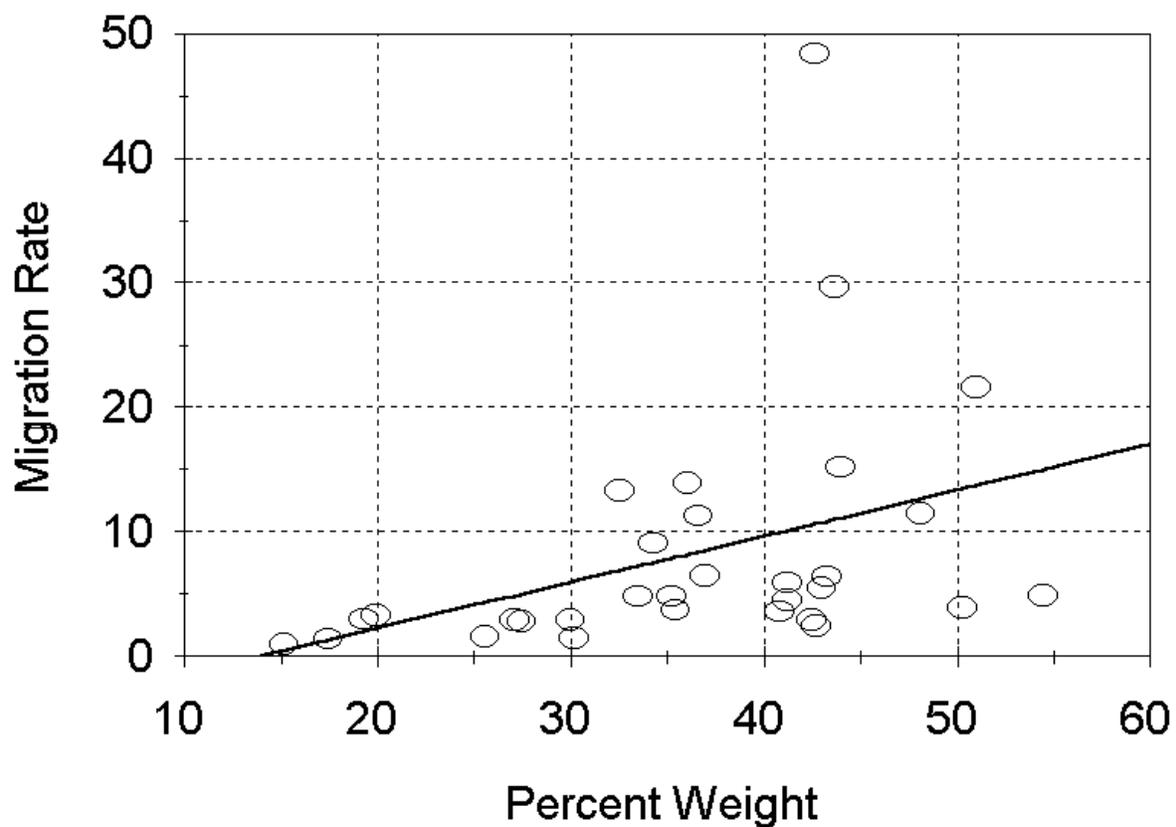


Figure 1. Effect of diisononyl phthalate (DINP) content (percent weight) on the migration rate ($\mu\text{g}/11 \text{ cm}^2/\text{h}$) measured by the impaction method (Chen, 1998a). (F) Observed; (—) regression line ($r^2 = 0.14$).

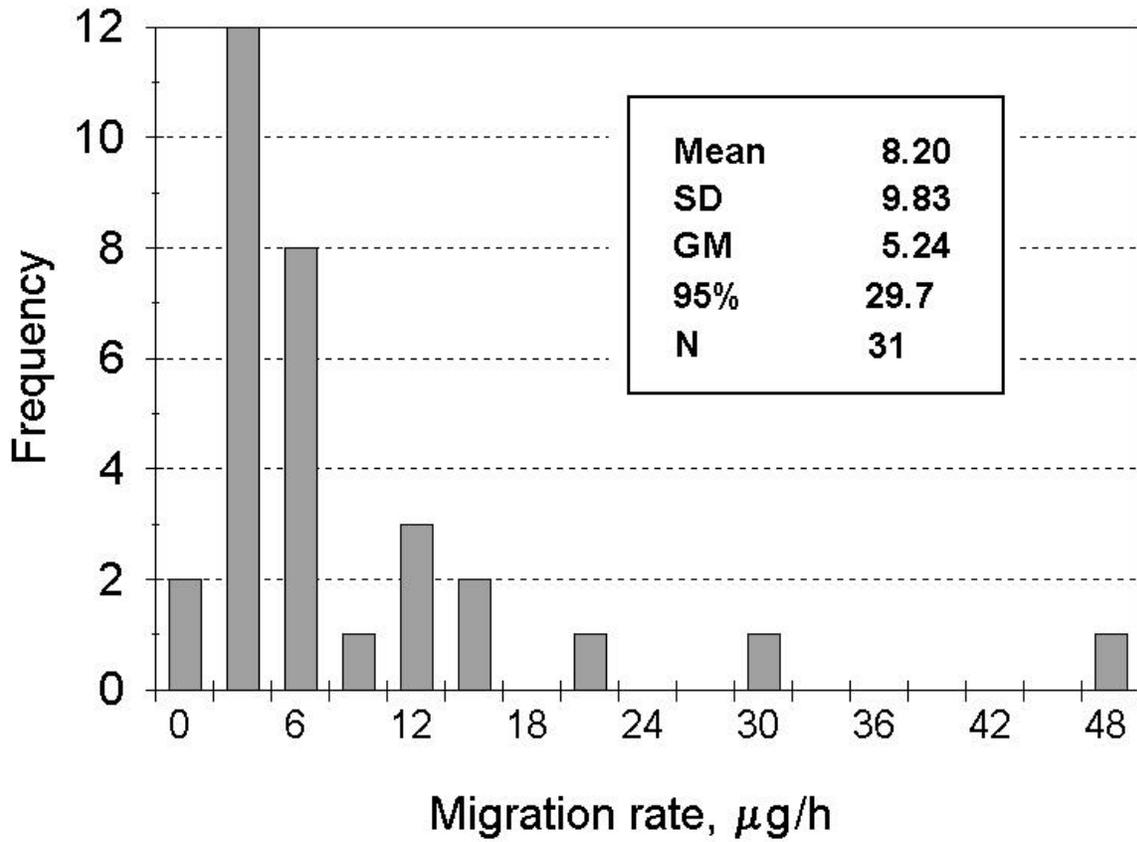


Figure 2. Frequency distribution of diisononyl phthalate (DINP) migration rates for 31 children's products, as measured by the impaction method (Chen, 1998a). The migration rate is in $\mu\text{g/h}$ for an 11 cm^2 area. GM, geometric mean; SD, standard deviation; 95%, 95th percentile value; N, number of products tested.

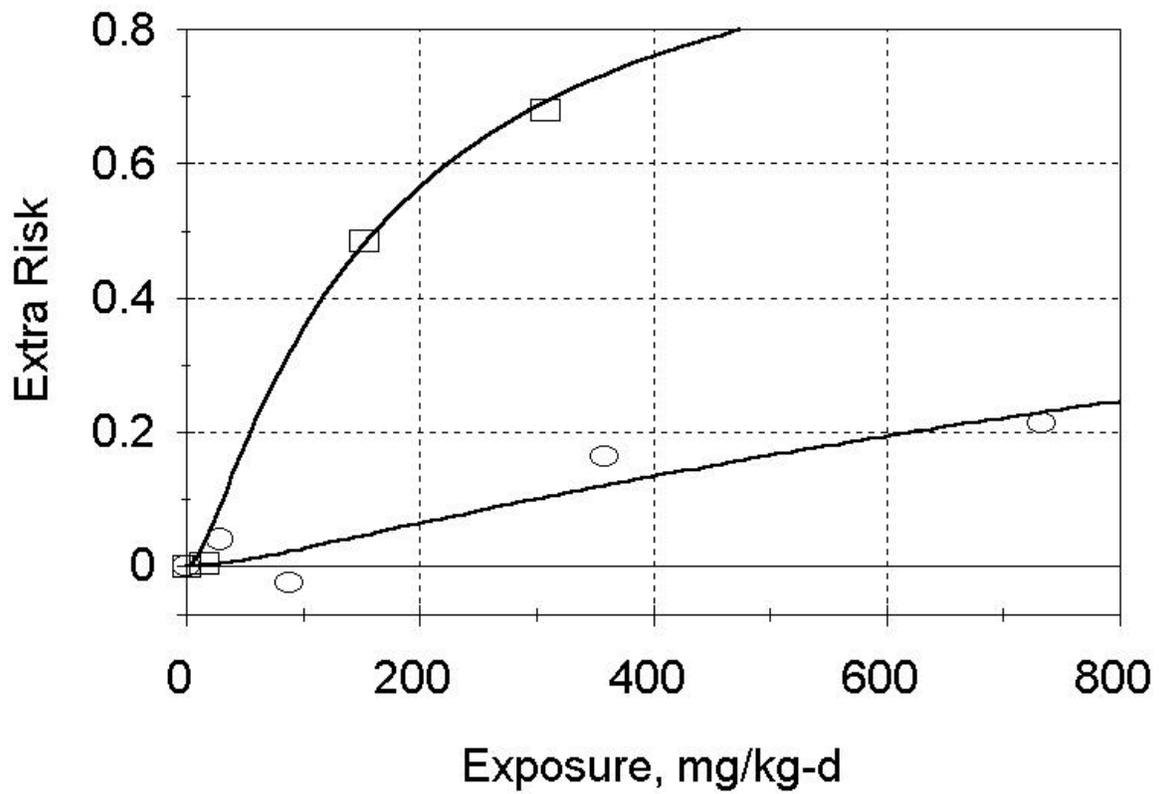


Figure 3. Extra risk of spongiosis hepatitis in male rats fed diisononyl phthalate (DINP) for two years. (G) Lington et al., 1997; (F) Moore, 1998a; (—) lognormal model for either data set. Data from either study were fitted to a lognormal model as described in (Crump, 1984b).

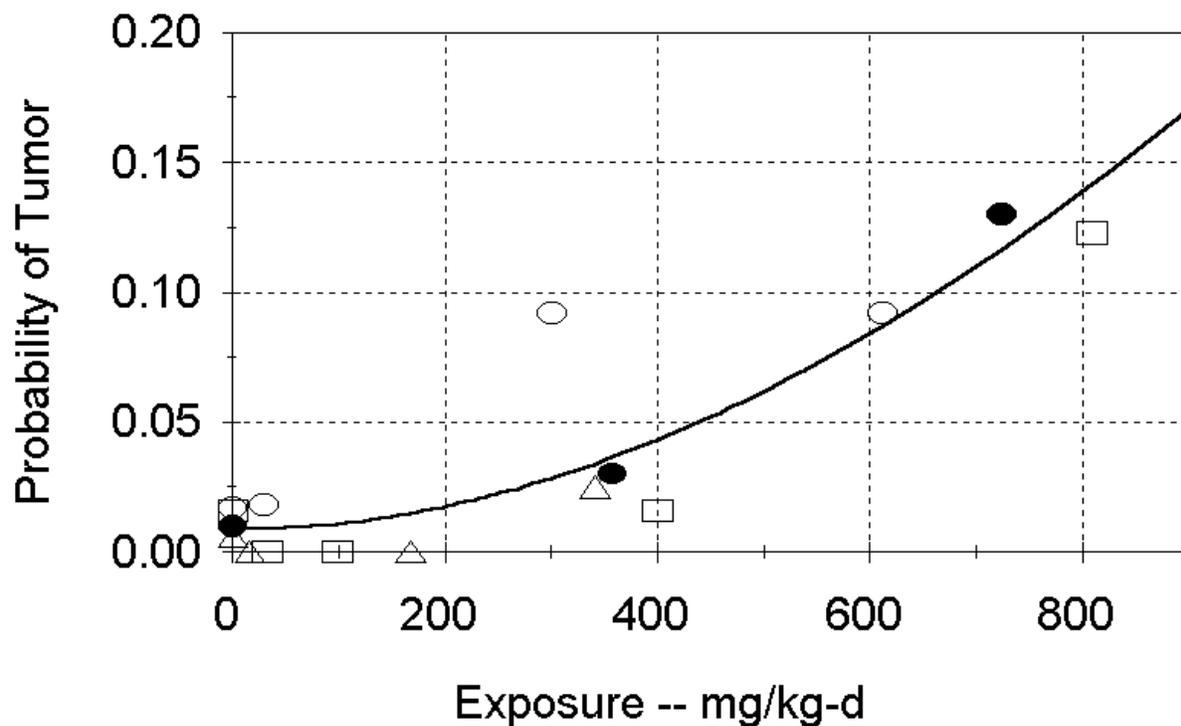


Figure 4. Incidence of hepatocellular carcinoma in rats fed dialkyl phthalates for two years. (M) di-(2-ethylhexyl)phthalate (117-81-7) (NTP, 1982); (F) diisononyl phthalate (71549-78-5) (Bio/dynamics, 1986); (Δ) diisononyl phthalate (68515-48-0) (Lington et al., 1997); (G) diisononyl phthalate (68515-84-0) (Moore, 1998a); (—) best fit of all studies using Global 83.