**TAB K**

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**Memorandum**

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TO : Marilyn G. Wind, Ph. D.
Deputy Associate Executive Director
Directorate for Health Sciences

THROUGH: Susan Ahmed, Ph. D. SA
Associate Executive Director
Directorate for Epidemiology

Russell H. Roegner, Ph. D. RR
Division Director
Division of Hazard Analysis

FROM : Michael A. Greene, Ph. D. MAG
Mathematical Statistician
Division of Hazard Analysis

SUBJECT : Oral Intake of DINP Among Young Children

Attached is the report on the Oral Intake of DINP for children 3-36 months old.

# Oral DINP Intake Among Young Children

Michael A. Greene
Mathematical Statistician
Division of Hazard Analysis

## Executive Summary

This paper contains estimates of oral diisononyl phthalate (DINP) intake by young children from mouthing soft plastic toys and other objects. Estimates are based on mouthing behavior from a study of 169 children, migration rates for various soft plastic objects likely to be mouthed and various scaling factors. The analysis includes both point estimates and confidence intervals that take into account variability in migration rates, mouthing times and other factors. Estimated DINP intake is then compared to the Acceptable Daily Intake (ADI) to determine the proportion of children at-risk.

The analysis is based on a new children's observational study, described in Greene (2002) and Kiss (2001). The study involved four hours of direct observation of 169 children in the Chicago and Houston metropolitan areas who were recruited using random digit dialing. Professional observers visiting children in their homes and other locations wrote down detailed descriptions of the objects that were mouthed as well as the mouthing times associated with such objects. These data allowed for the development of daily mouthing time estimates for a variety of different types of objects, including soft plastic toys.

This analysis is also based on new DINP migration rates from the CPSC Directorate for Laboratory Sciences (see Chen, 2002). The procedure followed a new protocol (modified Head over Heels) that was tested in a recent interlaboratory study at the European Commission (Simenou et al, 2001).

The risk assessment builds on the statistical methods in the previous CPSC risk assessment (CPSC, 1998) and the Dutch Consensus Group risk assessment (Konemann, 1998). The full probability distribution of DINP intake is estimated in order to obtain point estimates of the mean, median, $90^{th}$, $95^{th}$ and $99^{th}$ percentile DINP intake for children in three age groups between 3 and 36 months. Confidence intervals for the point estimates are developed using bootstrap resampling.

DINP intake is estimated for various mouthing scenarios. The first is the base case representing an estimate of DINP intake for typical children from mouthing. This scenario is developed from the soft plastic toy mouthing time in the observational study and the migration rates from soft plastic toys tested in CPSC's laboratory. However, not all soft plastic toys contain DINP. To represent this case, we added toys with zero

migration rates to the migration rate dataset so that the proportion of DINP-containing toys to all soft plastic toys would reflect the marketplace.

In the base case (Case 1), mean daily DINP intake from soft plastic toys was estimated at 0.07 micrograms per kilogram per day (95 percent confidence interval 0.03-0.13 micrograms per kilogram per day) for children 3-12 months. The 99$^{th}$ percentile daily intake in this age group was 1.44 microgram per kilogram per day (95 percent confidence interval 0.74 – 2.35). Children 12-24 months had a mean of 0.08 micrograms per kilogram per day (0.04-0.14), and a 99$^{th}$ percentile of 1.50 micrograms per kilogram per day (0.89-2.30). Children 24-36 months had lower estimates than 3-12 and 12-24 month old children with a mean of 0.03 micrograms per kilogram per day (0.01-0.06) and a 99$^{th}$ percentile of 0.56 micrograms per kilogram per day (0.17-1.64). All estimates were well below the acceptable daily intake (ADI) of 120 micrograms per kilogram per day.

These estimates are lower than in previous analyses (Babich, 1998; Konemann, 1998) and than reported by the Chronic Hazard Advisory Panel (CPSC, 2001). One major reason for the difference is that the present study is the first to use empirical estimates for soft plastic toy mouthing time to estimate DINP intake. Other studies used mouthing times for all mouthing toys or for all objects except pacifiers. Since children mouth a wide variety of objects and toys, not all soft plastic, non-pacifier or toy mouthing time overestimates the intake of DINP. Also, the other studies applied migration rates from objects only containing DINP to the mouthing times. Soft plastic objects contain other plasticizers than DINP. This present study reduces migration rates to account for the proportion of soft plastic toy objects that children mouth that actually contain DINP.

The analysis is then extended to consider five hypothetical cases. These include the following:

- Case 2: All soft plastic toys contained DINP
- Case 3: All soft plastic toys, teethers and rattles contained DINP
- Case 4: All soft plastic objects contained DINP
- Case 5: All toys, teethers and rattles contained DINP
- Case 6: All pacifiers contained DINP

Case 2 is different from Case 1, because the zero migration rates representing soft plastic toys that do not contain DINP, are dropped from the migration rate data.

Except for Cases 5 and 6, all cases include mouthing times and migration rates for previous lower numbered cases. Case 5 adds mouthing time for non soft plastic toys, teethers and rattles to the mouthing times in Case 3. Case 6 only uses mouthing times associated with pacifiers. All cases are simulated from data in the children's observational study using mouthing times for the appropriate category of objects mouthed.

The highest estimated DINP intake occurs in the case simulating pacifiers containing DINP. Mean daily DINP intake for children 3-12 months old from pacifiers would be 4.75 micrograms per kilogram per day (95 percent confidence interval 2.21-8.00). The 99$^{th}$ percentile would be 62.35 micrograms per kilogram per day (23.44-101.47). Children in the two older age groups would have lower DINP intake.

The staff concludes from the evidence presented in this paper, that DINP offers little or no risk at present levels of DINP migration rates and mouthing times. Moreover, increased prevalence of DINP in toys would seem unlikely to pose a hazard, providing that migration rates would be at the same level as in the study. However, in view of the amount of time that some children mouth pacifiers, it is possible that a very small number of children might approach the ADI should DINP be used as the plasticizer in pacifiers.

## 1. Introduction

The purpose of this paper is to estimate oral diisononyl phthalate (DINP) intake by young children from mouthing soft plastic toys. Estimates are based on mouthing behavior from an observational study of 169 children (Greene, 2002; Kiss, 2001), migration rates for various objects likely to be mouthed (Chen, 2002) and various scaling factors. The analysis includes both point estimates and confidence intervals. The estimates take into account variability in migration rates, mouthing times and other factors. Estimated DINP intake is then compared to the Acceptable Daily Intake (ADI) to determine the proportion of children at-risk.

The analysis begins with the base case or Case 1, that is intended to estimate the distribution of DINP intake for children under three years of age in the United States. The analysis adds a number of objects with zero migration rates to the objects tested in the lab to approximate the fraction of soft plastic toys containing DINP. Mouthing times used in this analysis are the soft plastic toy mouthing time from the observational study.

The analysis is then extended to consider five hypothetical cases. These include the following:

- Case 2: All soft plastic toys contained DINP
- Case 3: All soft plastic toys, teethers and rattles contained DINP
- Case 4: All soft plastic objects contained DINP
- Case 5: All toys, teethers and rattles contained DINP
- Case 6: All pacifiers contained DINP

Case 2 is different from Case 1, because the zero migration rates representing soft plastic toys that do not contain DINP, are dropped from the migration rate data.

Except for Cases 5 and 6, all cases include mouthing times and migration rates for previous lower numbered cases. Case 5 adds mouthing time for non soft plastic toys, teethers and rattles to the mouthing times in Case 3. Case 6 only uses mouthing times

associated with pacifiers. All cases are simulated from data in the children's observational study using mouthing times for the appropriate category of objects mouthed.

The analysis is based on a new children's observational study, described in Greene (2002) and Kiss (2001). The study involved four hours of direct observation of children in the Chicago and Houston metropolitan areas during 2000 and 2001, who were recruited using random digit dialing. Professional observers visiting children in their homes and other locations wrote down a detailed description of the objects that were mouthed as well as the mouthing times associated with such objects. In addition, parents reported the amount of time children were awake and not eating in a supplementary telephone survey. This time was used to project daily mouthing times from the four hours of observations.

In this analysis, DINP migration rates were obtained from soft plastic objects at CPSC's Directorate for Laboratory Sciences (see Chen, 2002) for objects similar to those mouthed in the observational study. DINP was extracted from objects using the Head-Over-Heels rotator and measured by Gas Chromatography-Mass Spectroscopy (GC-MS). This procedure was recently tested in an interlaboratory study conducted by the Joint Research Center of the European Commission (Simoneau, Geiss, Roncari, Zocchi and Hannaert, 2001). The migration rate data were augmented with a number of items with zero migration rates in the base case to reflect the proportion of soft plastic toys that contained DINP.

Two other data sources were required to scale *in vitro* (laboratory) migration rates to *in vivo* (human) rates. These were (1) migration rates for a 38% DINP standard disk mouthed by human volunteers described in the Dutch Consensus Group (Meuling and Rijk, 1998) and (2) migration rates for the 38% DINP standard disk using the procedure in the Joint Research Center interlaboratory study (Simoneau et al, 2001). Estimated DINP ingestion is then scaled by body weight to produce an estimate in micrograms per day per kilogram of body weight. Estimates of the distribution of children's body weight was from the EPA Exposure Factors Handbook (USEPA, 1997). The DINP intake estimate in micrograms per kilogram of body weight can then be compared with the acceptable daily intake (ADI) to determine if the amount ingested is likely to pose a hazard.

The basic risk analysis methodology extends the methods found in the previous CPSC DINP risk assessment (Greene, 1998; CPSC, 1998) and the Dutch Consensus Group Report (Konemann, 1998). In this present analysis, each of the different components in the risk analysis such as mouthing times, exposure times, migration rates, scaling factors and body weight are treated as random variables. The probability distribution of DINP intake is then estimated as the joint distribution of all these random variables. That probability distribution expresses all the possible values of daily intake. Statistics of interest such as the mean, median, 95$^{th}$ percentile, etc. can be computed from the joint probability distribution. Confidence intervals for these statistics are developed using the bootstrap, a procedure that resamples from the data.

The organization of this paper is as follows: Section 2 describes previous studies, Section 3 describes the data, Section 4 presents the model for estimating oral DINP intake, Section 5 contains results, which are then discussed in Section 6. Computer programs used in the analysis and a description of the input datasets are presented in an appendix.

## 2. Previous Studies

This section reviews three previous studies. These include the Dutch Consensus Group report, CPSC's 1998 risk analysis and the risk analysis in the Chronic Hazard Advisory Panel Report (CPSC, 2001).

### 2.1 Dutch Consensus Group Study (Konemann, 1998)

The Dutch Consensus Group used a Monte Carlo type procedure to estimate means and percentiles of DINP intake. The analysis used the empirical distributions of daily mouthing time from a children's observational study (Groot, Lekkerkerk and Steenbekkers, 1998a, 1998b) and DINP migration rates from adult human volunteers. Body weight was assumed to follow a normal distribution with mean and standard deviation from tabled sources. The Monte Carlo analysis replicated the following procedure:

1. Select a daily mouthing time from the observations on children
2. Select a migration rate from the human volunteer study
3. Select a body weight from the normal distribution
4. Multiply the mouthing time by the migration rate and divide by weight.

This procedure results in a large number of values for estimated DINP intake. Textbook formulas applied to these values result in estimates for the mean, median, 95$^{th}$, 99$^{th}$ percentiles or any other statistics. The procedure does not produce confidence intervals.

In the observational study used for estimating mouthing times, parents observed children for a total of five hours. Groot et al (1998a) also obtained waking times so that daily mouthing times could be estimated by multiplying the amount of mouthing time per hour by the time awake during the day. Mouthing times covering all mouthing activities except for pacifiers were included in the risk analysis even though many of the objects mouthed in the data were not made from PVC and were unlikely to contain DINP.[1]

DINP intake was computed by multiplying mouthing time by DINP migration rates. Migration rates for objects containing DINP were obtained from twenty adult

[1] The authors classified mouthing times into five groups as follows: pacifiers, fingers, toys meant for mouthing, other toys and non toys. The category of non pacifiers included mouthing times from fingers, toys meant for mouthing, other toys and non toys.

human volunteers who mouthed (sucked and bit) three types of objects including a standard disk containing 38% PVC, a finger from a commercially available teething ring and a disk punched from a flat part of the teething ring. Saliva was collected and the quantity of DINP was determined using High Performance Liquid Chromatography. See Meuling and Rijk (1998) for details.

Using this data and the Monte Carlo method, separate estimates of DINP intake were made for the standard PVC sample, the finger and the teething ring disk. Estimates were also separated by the age group of the child. Mean DINP intake ranged from 1 μg/kg per day for children between 18-36 months from the standard PVC sample to 14 μg/kg per day using the teething ring for children 3-6 months old. The 95$^{th}$ percentile DINP intake for children 3-6 and 6-12 months old from the teething ring was estimated at about 40 μg/kg per day (Van Veen ,1998, tables 1-3).

## 2.2 CPSC 1998 Study

The 1998 CPSC risk analysis (Babich, 1998; Greene, 1998) shared some of the data used in the Dutch Consensus Report but used somewhat different methodology.

Mouthing times in the CPSC study also were from Groot et al (1998b), but CPSC used only mouthing time from objects labeled as "Mouth Toys" or "Other Toys." This excluded fingers and "non toy" mouthing times. The reason for excluding fingers and non toy mouthing times is that such objects did not contain DINP.[2]

Rather than using DINP migration rate data from human volunteers directly, CPSC obtained migration rates from toys and other mouthing objects with an impaction device (see Chen, 1998). Comparing migration rates between the impaction method with the human volunteers studies (Meuling and Rijk, 1998; also Steiner, Scharf, Fiala and Washuttl, 1998) showed migration rates from human volunteers were much higher. CPSC then conducted a scaling study with migration rates on the same specimens from human volunteers and the impaction method. This study involved 10 volunteers chewing on disks cut from a yellow duck bath toy. Their saliva was collected and DINP was measured. Migration rates using the impaction method were also obtained from these disks. The ratio of human DINP migration rates to impaction method migration rates was then used as a scaling factor. Migration rates from toys were then multiplied by this factor. See Greene (1998) for details.

Instead of the Monte Carlo approach used by the Dutch Consensus Group, CPSC fit lognormal distributions to mouthing time data, scaling factors and migration rates. As a result, the distribution of daily exposure could be expressed in closed form as the product of lognormal random variables. Means and percentiles of the distribution of

[2] For example, toys for mouthing and other toys were about 35% of the total non pacifier mouthing time for children 3-6 months old and about 65% of the total for children 6-12 months old. The remaining percentages include fingers and non-toys. (Groot et al, 1998b, Figures 5-3 and 5-5).

DINP intake were computed as functions of the mean and standard deviation. The parametric bootstrap was used for confidence intervals (Efron and Tibshirani, 1993).

CPSC's risk assessment calculations produced lower estimates for mean DINP intake than the Dutch Consensus Group but higher estimates for the 95$^{th}$ percentile. The lower mean is generally a result of lower mouthing times as a result of using a more restricted subset of the mouthing times than used in the Dutch Consensus Group assessment. The higher 95$^{th}$ percentile estimate is due to more variability in the CPSC's DINP intake estimation process. This variability includes the toy migration rates and the adult human volunteer study used for the scaling factor. The Dutch Consensus Group did not include any migration rates from toys, rather, as mentioned above, they used the adult human volunteer study for the migration rates. This leaves out variability in their estimates due to variability in the scaling factor.

## 2.3 CPSC Chronic Hazard Advisory Panel (CHAP)

CPSC convened a panel of scientific experts to determine whether DINP in consumer products poses a chronic hazard and, if feasible, indicate the probable harm to human health resulting from exposures to DINP. CPSC's 1998 DINP risk analysis (Babich, 1998) recommended convening such a panel. The Commission voted in December 1998 to convene a CHAP. Seven panel members were selected, met during the summer of 2000 and completed their final report one year later in June, 2001. The activities of the CHAP were conducted in accordance with sections 28 and 31 of the Consumer Product Safety Act (15 U. S. C. 2077, 2080).

The CHAP used different data from either of the previous studies and a different statistical approach (CPSC, 2001).

The CHAP used migration rates from CPSC's 1998 human volunteers mouthing data. Volunteers chewed disks containing DINP. DINP was recovered from their saliva. Mean migration rates from the human volunteers was 26.4 micrograms per square centimeter per hour.[3] From the data an upper 95$^{th}$ percentile was estimated as 60 micrograms per square centimeter per hour.

Mouthing time data was taken from an observational study of children's mouthing behavior in Juberg, Thompson, Alfano and Coughlin (2001). This sample was 107 children under 18 months of age and 110 children 19-36 months. Mouthing observations and object categories were recorded by parents in a diary for either one day or one week of observations. The CHAP referred to a few children under 18 months mouthing non pacifier objects for about 3 hours per day and a few older children with 1 hour per day of mouthing. Based on these observations, it was estimated that DINP intake for "... relatively highly exposed children 0-18 and 19-36 months old would be approximately

[3] CPSC (2001, table IV-2), given as 263.6 micrograms per 11 square centimeters per hour.

280 and 66 μg/kg/day, respectively." [4] This is presented as a "plausible upper bound," although it is unclear what percentile of the risk distribution it represents.

## 3. Data

Data in this risk assessment included (1) mouthing time distributions, (2) daily exposure time, (3) migration rates for soft plastic toys, (4) migration rates for standard disks, and (5) human mouthing data for standard disks and (6) children's weights. The data are discussed in this section.

### 3.1 Mouthing Times

Mouthing times were obtained in an observational study on 169 children between 3 and 36 months of age in Chicago, Illinois and Houston, Texas in 2000 and 2001. The children were selected by random digit dialing. Professional observers went to the children's houses on two separate occasions for two hours of observation in each session. During these sessions, the observers recorded every object the child placed in his mouth and the length of time the object was mouthed. There were a total of 20,807 mouthing events for these children for an average of 123 events per child.

Among the 20,807 observations there were 3,952 distinct combinations of objects and descriptions of objects in the database. Staff reviewed every combination to create a smaller number of usable classifications. This involved developing 51 primitive categories of objects that could appear as single descriptors or in combination with other descriptors. Using these primitive descriptors there were 110 unique combinations of descriptors. Combinations were further mapped into 13 groupings as shown below.

All Objects
- 1. Non Pacifiers
  - 1.1 Soft Plastic Objects
    - 1.11 Soft Plastic Food Contact Items[5]
    - 1.12 Soft Plastic Non Food Contact Items
      - 1.121 Soft Plastic Toys, Teethers and Rattles
        - 1.1211 Soft Plastic Toys
        - 1.1212 Soft Plastic Teethers and Rattles
      - 1.122 Other Soft Plastic[6]
  - 1.2 Anatomy[7]
  - 1.3 Toys, Teethers and Rattles, not soft plastic
  - 1.4 Other Objects[8]
- 2. Pacifiers

[4] Here is how the DINP intake for younger children was calculated. 3 hours per day x 60 μg per centimeter per hour x 11 cm object size / 7 kg body weight = 283 μg/kg/day.
[5] Bottle, Drinking Cup/Straw, Fork.
[6] Clothing, Furniture, Other, unknown
[7] Hair, skin, fingers, hands
[8] Books, clothing, carpet and furniture, non soft plastic food contact items such as spoons and cups.

The rules for grouping objects were as follows:

1. Every object must fall into no more than one grouping at a particular level of the hierarchy.
2. Objects falling into a particular grouping, must also be in the next higher grouping (the grouping above it that is indented to the left)
3. When there are conflicts about where an object will be counted because it appears to be classifiable in two or more groupings at the same level, the object will be assigned to the higher (non-indented) level.[9]

The most important partition is All Soft Plastic Toys (see 1.1211) as these objects are likely to contain a plasticiser such as DINP. Mouthing times associated with these objects are used in the base case to estimate oral DINP intake for these children.

The data were separated by year of age (3-12 months, 12-24 months, 24-36 months), with separate estimates made for each age.[10] The distribution of mouthing times was based on data from 54 children under 1 year, 66 children between 1 and 2 years and 49 children over 2 years of age. Mouthing times for soft plastic toys are shown in table 1 below.

Table 1
Estimated Daily Mouthing Times for Soft Plastic Toys
(Time in Minutes)

| Age | Mean | Median | 95th Percentile | 99th Percentile |
|---|---|---|---|---|
| 3-12 months | 1.3<br>(0.7 - 2.0) | 0.0<br>(0.0 – 0.3) | 7.1<br>(3.9 - 11.0) | 10.5<br>(5.8 - 13.7) |
| 12-24 months | 1.9<br>(1.2 - 2.6) | 0.1<br>(0.0 – 0.6) | 8.8<br>(5.6 - 11.7) | 12.6<br>(9.0 - 16.0) |
| 24-36 months | 0.8<br>(0.3 - 1.6) | 0.0<br>(0.0 – 0.2) | 3.3<br>(1.4 - 16.3) | 12.1<br>(2.0 - 21.0) |

Source: Greene (2002). 95% confidence interval in parentheses.

[9] Examples of rule 1 are as follows: every item must be either in non pacifiers or pacifiers, and every soft plastic item must be in non-food contact or food contact items. As an example of rule 2, every soft plastic toy is also counted in soft plastic non food contact items. As an example of rule 3, suppose an item in the data would be classified as both soft plastic and anatomy. This could occur for example, if a child was mouthing a pacifier and his fingers at the same time. Rule 3 allocates this time only to Anatomy and not to the Pacifier.

[10] Children's ages were computed in days between the observation and their date of birth. Ages were averaged over the two days of observations. The actual age ranges in the three groups in days were as follows: 96.5 – 359.0, 373.5 – 729.0, 738.0 – 1122.5.

### 3.2 Exposure Times

As mentioned above, in addition to mouthing time estimates, exposure times were required to convert mouthing time recorded during four hours of observations to daily mouthing time. During a phone interview parents were asked to list the typical time that the child usually woke up on a weekday and then went to sleep at night. Also requested were the typical length of naps, meals and snacks. Exposure time was defined as the total waking hours (difference between bedtime and waking time less naps) less time spent eating (meals and snacks).

Of the 169 children in the study, there were exposure time values for 109 children.[11] As a result, it was necessary then to model exposure time to provide estimates for children without reported observations. Data for estimating exposure times came from 483 children between 1 and 81 months.[12] After exploring a number of explanatory variables, exposure time was modeled as a function of the child's age. The model is shown in equation (1) below:

$$Exposure = 9.46 + 0.0375\,Age \quad (1)$$

Age in equation (1) is in months.

The root mean square error (standard deviation of the regression) was 1.26 hours, $R^2$ was 0.26, $F(1,481)=166.01$, $p < 0.0001$. The model differs from that presented previously (Greene, 2002) because it does not use the number of children in the family as an explanatory variable. There was no practical difference in fit between the two models.

Equation (1) provides the mean exposure for a given value of the child's age. However, this is not the only likely value of exposure. The probability distribution of exposure can be characterized as a normal distribution with the mean at the value provided in equation (1) and the standard deviation at the root mean square error. For each child, this distribution was represented at intervals of 5%, that is the 5$^{th}$ percentile, the 10$^{th}$ percentile, 15$^{th}$ percentile, ..., 90$^{th}$ percentile, 95$^{th}$ percentile. Since the range of the normal distribution is infinite, it is not possible to represent the 0$^{th}$ percentile or the 100$^{th}$ percentile. Instead, the 0.1$^{th}$ percentile and the 99.9$^{th}$ percentile were also used in the probability distribution to represent the lower and upper extremes of exposure.

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[11] Part of the interview with the parents was discontinued during the study to reduce the burden on participating parents. This was helpful in recruiting more children for the professional observation study. As a result, there were 60 children of the 169 in the study without the telephone interview.

[12] The ages were computed at the time of the telephone survey. Since the time between the telephone survey and the observation study might be different by several months, children in both studies might be represented with different ages in the exposure analysis and the mouthing time analysis. There were 491 children in the telephone survey with useful data for 483 children. Further details of this study are in Greene (2001).

### 3.3 Migration Rates for Soft Plastic Objects

Migration rates for soft plastic objects were provided by Chen (2002). Migration rates were obtained using the Head over Heels Rotator and GC-MS. The procedure followed the Joint Research Center protocol (Simenou et al, 2001).

Objects were selected from the list of objects in the children's mouthing study. The objects used in this analysis are in table 2 below, listed in increasing order of migration rates. Many of the soft plastic items mouthed were play food. Examples include egg, bacon, ice cream, spaghetti and lettuce. Statistics on the migration rates are relative to an object that was 10 square centimeters in area. They were as follows: mean = 4.08 $\mu$g/min/10cm$^2$, median = 3.38 $\mu$g/min/10cm$^2$, standard deviation = 2.72 $\mu$g/min/10cm$^2$.

Table 2
Migration Rates for Soft Plastic Items

| Object Description | DINP migration rate ($\mu$g/min/10cm$^2$) | Object Description | DINP migration rate ($\mu$g/min/10cm$^2$) |
|---|---|---|---|
| Cape | 1.05 | Face | 3.52 |
| Tub Toy | 1.08 | Egg | 3.71 |
| Sheet | 1.50 | Green whale | 4.02 |
| Face | 1.63 | Cushion | 4.20 |
| Bacon | 1.83 | Spaghetti | 4.32 |
| Large reptile | 2.03 | Lettuce | 4.64 |
| Ice Cream | 2.05 | Yellow duck | 6.14 |
| Face | 2.19 | Leg | 6.52 |
| Blue body | 2.73 | Tomato | 6.55 |
| Blue seat | 2.88 | Donut | 6.78 |
| Face | 3.22 | French Fries | 10.78 |
| Green protrusion | 3.23 | Pizza | 11.09 |

Source: Chen (2002)

After examining the toy and object description in the observational study, CPSC staff purchased 41 soft plastic toys from local retail outlets. These were separated into 133 specimens. Specimens were divided into soft plastic and non soft plastic, resulting in 85 soft plastic specimens. Soft plastic specimens were further screened for DINP, resulting in 49 specimens with no detectable DINP and 36 specimens with DINP. Migration rates were then obtained for 24 of the 36 specimens. These 24 migration rates are shown above in table 2.

Migration rates could not be obtained for the remaining 12 specimens because the objects were too small or were not hollow. As a result, migration rates were available for two thirds (24/36) of the objects with DINP. Representing the soft plastic toy population

migration rates with the 24 measured rates and the (85-36=) 49 zeroes, for the non DINP containing soft plastic items, would underestimate the distribution of migration rates, because of the omission of rates from the 12 non-measurable specimens with DINP. To get the right balance of non-DINP containing objects one would need to represent only two-thirds of the 49 them, similar to the two-thirds of the DINP containing objects with migration rates. As a result, (2/3 * 49=) 33 "objects" with zero migration rates were added to the dataset. See Chen (2002) for details.

This augmented dataset with 24 real objects and 33 zeros represented the set of soft plastic toys available to children. Migration rates from this dataset were used to simulate the base case, that is to estimate DINP exposure using the present population of toys and empirically observed mouthing behavior.

In all the other cases, only the migration rates for the 24 real objects were used. For example, case 2 was intended to simulate a situation where all soft plastic toys contain DINP. This scenario would require only DINP containing objects. Other cases modeled scenarios where broader categories of objects contained DINP.

### 3.4 Scaling Factors

A scaling factor is required to convert migration rates using the Head over Heels Rotator to levels that humans would experience, that is from *in vitro* to *in vivo* levels. The numerator of the scaling factor must be from data from the analysis of saliva from volunteers chewing on an object, while the denominator would represent a migration rate from that object using the same procedure for the toy migration rates in table 2 above. The common object was the 38% standard PVC disk. The human volunteer data was from the Dutch Consensus Group's 1998 risk assessment (Meuling and Rijk, 1998).[13] For the laboratory migration rates in the denominator, the JRC procedure was applied to the standard disk at the CPSC Directorate for Laboratory Sciences using the same procedure as in the migration rates studies of toys. Data for the human volunteers is shown in the table below.

[13] The data were provided by M. A. H. Rijk. Note that 38% is a nominal measurement. A sample of 10 disks showed an average measurement of 38.8% and an SD of 0.31%. See Table 1 in Rijk and Ehrlert (1999).

Table 3
Migration Rates from Human Volunteers and 38% Standard PVC Disk
Migration Rates in $\mu$g/min/10cm2

| Subject | Migration Rate | Subject | Migration Rate |
|---|---|---|---|
| 1 | 0.81 | 11 | 1.77 |
| 2 | 1.02 | 12 | 1.22 |
| 3 | 0.52 | *13* | *5.29* |
| 4 | 1.28 | 14 | 1.65 |
| 5 | 0.74 | 15 | 1.03 |
| 6 | 1.44 | 16 | 0.73 |
| 7 | 1.10 | 17 | 2.05 |
| 8 | 1.30 | 18 | 0.89 |
| 9 | 1.04 | 19 | 1.35 |
| 10 | 1.35 | 20 | 0.99 |

Notes: The raw data was provided to us by M. A. H. Rijk.

The mean of the data was 1.38 and the standard deviation was 0.99.

Observation 13 (italics), an obvious outlier that was almost 4 standard deviations above the mean, was then deleted from the dataset. Statistics on the remaining data were mean = 1.17 and standard deviation = 0.38.

Migration rates for the five standard disks are shown in table 4 below.

Table 4
Head over Heels Migration Rates for the Standard PVC Disk
Migration Rates in $\mu$g/min/10cm$^2$

| Specimen | Migration Rate | Specimen | Migration Rate |
|---|---|---|---|
| A | 3.43 | D | 4.17 |
| B | 4.31 | E | 4.62 |
| C | 4.38 | | |

Source: Data from CPSC Directorate for Laboratory Sciences

The mean migration rate was 4.18 $\mu$g/min/10cm$^2$ and the standard deviation was 0.45 $\mu$g/min/10cm$^2$.

### 3.5 Body Weight

DINP oral intake estimates are scaled to body weight for comparison with the ADI. The ADI is given in micrograms per kilogram body weight.

The distribution of body weight was taken from the US Environmental Protection Administration Exposure Factors Handbook (US EPA, 1997, page 7-1 and 7-2). The data came from a 1979 study by a National Center for Health Statistics task force. About 1000 children up to 36 months of age were involved in a longitudinal study with anthropometric data collected at various age intervals. Table 7-1 in the report presents $5^{th}$, $10^{th}$, $25^{th}$, $50^{th}$, $75^{th}$, $90^{th}$ and $95^{th}$ percentile weights for the following age groups: birth, 1, 3, 6, 9, 12, 18, 24, 30 and 36 months. Weights were reported separately for males and females. The percentile data as reported in that publication were smoothed by cubic spline interpolation.

The DINP intake model required weights at a series of equally probable intervals and at ages varying by one month between 3 and 36 months. First the EPA data were averaged over sex. Then cubic spline interpolation was used to provide all multiples of the $5^{th}$ percentile (i.e. adding the $20^{th}$, $30^{th}$, and other percentiles).[14] Cubic spline interpolation was then used to generate the missing months. This resulted in a matrix of 37 rows (birth to age 36 months) by 19 columns ($5^{th}$ to $95^{th}$ percentiles).[15]

## 4. Model

In this section the model of DINP intake is developed. The first section develops the deterministic model and the second extends the development to the probabilistic or bootstrap model. The deterministic model provides point estimates of DINP intake. The probabilistic model introduces sampling variability into the point estimates by using the bootstrap. This then produces confidence intervals.

The parametric approach, i.e. lognormal distributions, from CPSC's 1998 report was not used because the observed distribution of mouthing times in certain important object categories had a large proportion of children with no mouthing time on those objects. For example in the important category of soft plastic toys, 50 percent of the children reported no mouthing times. This was a much larger proportion than in the 1998 data which used a more gross category of "Mouth Toys" or "Other Toys" (Greene, 1998 page B-13). The more refined the category, the more likely there will be many zero mouthing times. Also in the base case, more than half the soft plastic items did not

[14] Data preparation was performed in the SAS® language with release 8.02 for Windows. Spline interpolation used the spline function in R (release 1.4.0). Bootstrap computations were also in R. Information on R is available at http://www.r-project.org/.

[15] More extreme percentiles of the weight distribution could not be computed because it was not possible to extrapolate beyond the data values.

contain DINP, thus they had zero migration rates. Since the lognormal distribution is defined only for positively valued observations, this distribution could not be used.[16]

### 4.1 Deterministic Model

The risk analysis in this paper considers DINP intake as the product of a series of random variables. Define the following random variables:

| | | |
|---|---|---|
| $M$ | = | mouthing times of children |
| $E_a$ | = | daily exposure (conditional on the child's age, $a$) |
| $W_a$ | = | child's weight, also conditional on age |
| $R$ | = | *in vitro* migration rate of soft plastic objects |
| $C$ | = | *in vivo* migration rates, standard disk |
| $I$ | = | *in vitro* migration rates, standard disk |
| $D$ | = | DINP intake. |

Then an estimate for DINP Intake in micrograms per kilogram of body weight is

$$D = \frac{ME_aRC}{W_aI} \tag{2}$$

where the quantity $C/I$ is actually a scaling factor to translate *in vitro* to *in vivo* rates and DINP intake is measured in micrograms per kilogram body weight.

The probability distribution of DINP intake is the set of all possible values of the product given in equation (2) and the associated probability that each such value will occur. If that probability distribution were known, then statistics of interest such as mean DINP intake, 95$^{th}$ percentile intake, etc. could be obtained from the distribution using textbook formulas. This distribution is not known, but can be estimated from data, i.e. the empirical distribution. Estimates for the statistics can then be developed from the estimated distribution, again using textbook formulas.

All the empirical data used for the model are discrete or discretized (i.e. represented at discrete intervals) and equally probable. As a result, the empirical cumulative distribution function of risk is a step function, starting at the minimum and

[16] The lognormal distribution is very convenient in risk analysis because the risk calculation is multiplicative as shown in equation (2). Products of lognormal distributions also follow a lognormal distribution. More complicated distributions including mixtures of, say, lognormal distributions and distributions with some probability mass at zero, do not have closed form expression. Whether to use a parametric distribution or the empirical distribution has often been discussed in the statistical literature. For example "... the parametric bootstrap is useful in problems where some knowledge about the fom of the underlying population is available,..., a main reason for making parametric assumptions in traditional statistical analysis is to facilitate the derivation of text book formulas for standard errors. Since we don't need formulas in the bootstrap approach, we can avoid restrictive parametric assumptions..." (Efron and Tibshirani, 1993, page 56).

rising to the maximum value, with jumps at each observed value, where the probability increases by $1/n$ where $n$ is the relevant sample size for that particular distribution. The discussion below elaborates on this idea.

The empirical distribution of DINP intake arises from the data values as follows:

1. Each of the data values used to represent one of these random variables, except weight and exposure are observations on the marginal or univariate distribution. For example, migration rates for toys, and the standard disk (both in vivo and in vitro) similarly represent marginal distributions.

2. Both body weight and exposure are related to the child's age. The distribution of body weight is contained in the quantiles that were estimated using cubic spline smoothing (see above) for a particular age. The distribution of exposure, given the child's age is centered at the value computed using the regression equation and varies according to the normal distribution.[17] Essentially then, given a child's age, there is a marginal exposure distribution and a marginal weight distribution. Each child then has a vector of body weights spanning the $5^{th}$ to $95^{th}$ percentiles and a vector of exposure times, based on age. Consider then the matrix for a given child where the rows are exposure times, the columns are weight and every entry represents the exposure time in that row divided by the child's weight in that column. Multiply that matrix by mouthing time and the result is a matrix of daily mouthing times per kilogram of body weight for a given child. For all children, this then becomes a three dimensional array where the added dimension is the child's identity. Call this matrix **B**. In terms of the model in equation (2), this is $ME_a/W_a$. The type of operation that builds up all possible combinations of values is called the outer product.

3. Another outer product is also required to complete the empirical distribution. Form the outer product of the scaling factor $C/I$, by taking each human volunteer's data as the columns, each *in vitro* migration rate as the rows, and creating a matrix where the intersection of row and column is the row entry divided by the column entry. Then expand to a three dimensional matrix, by multiplying each entry of the outer product by the migration rates of the soft plastic objects, $R$. The resulting three dimensional matrix contains toy migration rates scaled to *in vivo* levels. Symbolically this is $RC/I$.

4. The full joint distribution is assembled by obtaining the outer product of the matrices in 2 and 3 above.

[17] Under classical regression assumptions, the distribution of the predicted values would be normal with mean zero and variance equal to the mean square error. By repeatedly estimating the regression with bootstrapped age and exposure pairs, we are actually approximating the distribution of the estimated regression coefficients, which might in fact not be normal. In such a case, the distribution of the predicted values would not be normal either.

5. Since all marginal values are equally probable, then each value of the empirical joint distribution is equally probable.[18]

A simplified example is as follows: Suppose the problem was just to develop statistics on the scaling factor *C/I*. Table 5 below contains a part of the joint distribution of the scaling factor. Numbers in the body of the table are the ratio of *in vivo* to *in vitro* migration rates. For example, one subject provided an *in vivo* migration rate of 0.52, and one standard disk provided 3.43. The ratio of these is 0.15.

Table 5
Selected Values of the Joint Distribution of the Scaling Factor
Migration Rates in $\mu$g/min/10cm$^2$

| | Migration Rates from Head over Heels Method | | | | |
|---|---|---|---|---|---|
| Migration Rates from Human Subjects | 3.43 | 4.17 | 4.31 | 4.38 | 4.62 |
| 0.52 | 0.15 | 0.12 | 0.12 | 0.12 | 0.11 |
| 0.73 | 0.21 | 0.18 | 0.17 | 0.17 | 0.16 |
| 0.74 | 0.22 | 0.18 | 0.17 | 0.17 | 0.16 |
| 0.81 | 0.24 | 0.19 | 0.19 | 0.18 | 0.18 |
| -- | -- | -- | -- | -- | -- |
| 2.03 | 0.60 | 0.49 | 0.48 | 0.47 | 0.44 |

Note: Dashes (--) indicate that a number of rows have been left out.

The full scaling factor distribution has (5 x 19=) 95 cells. The probability associated with any pair is 1/95. Other statistics on the scaling factor are as follows: mean 0.28, range 0.11-0.60, standard deviation 0.10.

The full joint distribution of DINP intake (see equation (2)) for each child, aside from mouthing times was 909,720 cells, from 19 *in vivo* rates (the human volunteer study), 5 *in vitro* rates (the standard disk in the laboratory), 24 migration rates (toys), 21 exposure values per child and 19 body weights.[19] To represent the sample of 54 children who were 3 months to 1 year old, the probability distribution would contain 49 million cells. While this dataset could be created on the computer, the packaged statistical procedures for calculating means and percentiles could not handle a dataset this large. As a result, a procedure was developed to randomly sample from the joint distribution.

[18] If the calculation for the joint distribution produces two values at exactly the same number, then both copies are kept.
[19] For the base case with 44 specimens, this becomes 1,667,820 cells.

While this introduces some variability in the estimates, experiments showed the variability was extremely small with the large sample size.[20]

The sampling procedure was as follows:

1. Define the sample size, $n$, as some large number. We used $n$=160,000 cells. This was a compromise between computer time and variability in the estimates.

2. Create the full joint probability distribution of daily mouthing time, exposure, and child's body weight. (Recall that mouthing time, exposure and body weight are conditional on the child's age.) Put this probability distribution into a column vector. Let $v$ be the length of this vector.

3. Replicate this vector $n$ *div* $v$ times where *div* means integer division (i.e. divide and discard the remainder). Then fill the remainder out with a random sample from the vector.[21]

4. Create additional vectors of size $n$, by sampling from the toy migration rates, the *in vivo* standard disk data and the *in vitro* standard disk data *with replacement.*

5. Create the product of the items in 3 and 4. This is a simple element wise product where each element of each vector is multiplied (or divided) against the corresponding element in each other vector.

The result of these calculations is a sample of size $n$ from the full joint distribution, without having to form the actual joint distribution. The appropriate statistics, such as the mean, median, 95$^{th}$ percentile or any other statistic can be obtained from this distribution using textbook statistics formulas. Recall that each entry in the joint probability distribution is equally probable.

### 4.2 Probabilistic model

The construction of the joint distribution provides point estimates for the required statistics. It does not however, include any sampling variability. Sampling variability is introduced using the bootstrap. This involves resampling from *all* marginal distributions, then following the procedure for the deterministic model. All samples have the same

[20] Experiments showed that when the joint distribution was represented by a sample size of 160,000 cells, that the coefficient of variation of the 99th percentile was under 1 percent. CVs for other statistics such as the mean, median, 95$^{th}$ percentile, etc. were lower.

[21] For example, mouthing time for children 3-12 months has 54 cells, exposure has 21 cells and weight has 19 cells. This creates a vector of length 21,546. This would be replicated 7 times to fill out 150,822 cells. An additional sample of 9,178 items would be drawn from the original vector to fill out the 160,000 items.

number of items as the original distribution and are with replacement. Then statistics are tabulated on each resample, using the same procedure as the deterministic model.

The computation proceeds in the following steps:

1. Sample the rows of the mouthing time distribution. This results in a sample of 54, 66 or 49 children depending on the age group. Each sampled element included a mouthing time and an age.

2. Draw a sample from the exposure dataset. (Recall that this dataset was used to construct the regression equation relating child age to exposure.) The regression equation is then computed from this (i.e. bootstrap) sample. The slope, and intercept coefficients and the standard error of the regression are saved for use in constructing the exposure distribution in exactly the same way that the original exposure distribution was constructed. Note that the slope and intercept coefficients will vary as a result of different samples being selected.

3. Draw samples from the migration rates, *in vivo* standard disk data and the *in vitro* standard disk data.

At this point, there is a complete bootstrap sample of all marginal distributions containing a sample of children's mouthing times, exposure and body weight, and all the other elements in the problem. The remainder of a single bootstrap iteration step is identical to the deterministic model. The approximation to the joint distribution is created in the same way except from the bootstrap sample rather than the original data.

This process is then repeated a large number of times, to obtain the distributions of the statistics such as the mean and percentiles. Each repetition produces a mean, a median, a $95^{th}$ percentile, etc. Bootstrap theory holds that the distribution of each of these statistics approximates the sampling distribution of each statistic. The confidence interval for the statistic can then be obtained from the lower and upper percentiles of the bootstrap distribution of that statistic. For example, the 95 percent confidence interval for the median is obtained as the $2.5^{th}$ percentile and the $97.5^{th}$ percentile of the bootstrap distribution of the median. With 2000 bootstrap realizations, the 95 percent confidence interval is formed from the $2.5^{th}$ percentile (interpolating the $50^{th}$ and $51^{st}$ observation from the smallest of the medians) and the $97.5^{th}$ percentile (interpolating the $1950^{th}$ and $1951^{st}$ observation). [22]

## 5.0 Results

Table 6, the base case and tables 7-11, hypothetical cases, contain estimates for daily DINP intake under different scenarios. All the tables are organized in the same way.

[22] We followed the recommendation of 2000 bootstrap samples for estimating probability distributions. See Efron and Tibshirani (1993), chapters 12-14.

The middle panel in the table describes daily DINP intake in micrograms, while the right panel describes daily intake scaled to body weight, that is in micrograms per kilogram. These are the units in which the ADI is expressed so that values in the right panel are to be compared against the ADI. The top panel of the table is for the children from three to 12 months of age, the middle part of the table covers children 12-24 months of age, while the bottom of the table covers children 24-36 months of age. Point estimates come from the deterministic model, while the confidence intervals are from the probabilistic or bootstrap model, based on 2000 iterations.

The base case is presented first, followed by the hypothetical cases. All cases use the same weight distribution, age and exposure data, and scaling factors as the base case. Migration rates and mouthing times are different. The different cases are described below.

### 5.1 Base Case

Table 6 shows estimates of DINP intake from soft plastic toys in the base case. Recall that the data were augmented by adding 33 objects with zero migration rates.

Table 6
Base Case
Estimated Daily Intake of DINP from Soft Plastic Toys

| Age | | Daily Intake (μg) Point Estimate | 95 Percent CI LCL | UCL | Daily Intake Scaled to Body Weight (μg/kg ) Point Estimate | 95 Percent CI LCL | UCL |
|---|---|---|---|---|---|---|---|
| 3-12 (n=54) | Mean | 0.61 | 0.28 | 1.09 | 0.07 | 0.03 | 0.13 |
| | Median | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | 90th Percentile | 1.26 | 0.13 | 3.22 | 0.14 | 0.02 | 0.37 |
| | 95th Percentile | 3.71 | 1.29 | 6.91 | 0.44 | 0.15 | 0.82 |
| | 99th Percentile | 11.96 | 6.22 | 19.22 | 1.44 | 0.74 | 2.35 |
| 12-24 (n=66) | Mean | 0.89 | 0.44 | 1.48 | 0.08 | 0.04 | 0.14 |
| | Median | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | 90th Percentile | 2.29 | 0.50 | 4.79 | 0.21 | 0.05 | 0.45 |
| | 95th Percentile | 5.61 | 2.59 | 9.27 | 0.53 | 0.24 | 0.89 |
| | 99th Percentile | 15.69 | 9.29 | 24.02 | 1.50 | 0.89 | 2.30 |
| 24-36 (n=49) | Mean | 0.36 | 0.11 | 0.80 | 0.03 | 0.01 | 0.06 |
| | Median | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | 90th Percentile | 0.58 | 0.06 | 1.32 | 0.04 | 0.00 | 0.10 |
| | 95th Percentile | 1.54 | 0.59 | 3.00 | 0.12 | 0.04 | 0.23 |
| | 99th Percentile | 7.26 | 2.25 | 21.04 | 0.56 | 0.17 | 1.64 |

Notes: Right endpoint not included in age interval except for the last group that includes several children 36 months old. See footnote 10 for more details on the age distribution. Point estimates and confidence intervals are from the bootstrap procedure. LCL is the lower confidence limit and UCL is the upper confidence limit. Includes 24 objects with non zero DINP migration rates and 33 objects with zero migration rates.

The table shows that the upper confidence limit for the upper percentiles is considerably below the acceptable daily intake (ADI) of 120 micrograms per kilogram per day. For example, for the youngest children, the estimate for the 99$^{th}$ percentile is 1.44 micrograms per kilogram per day (95% confidence interval 0.74 to 2.35 micrograms per kilogram per day), well below the ADI. The statistics are slightly larger for children 12-24 months.

## 5.2 Case 2. All Soft Plastic Toys Contain DINP

Table 7, Case 2 simulates a situation where all soft plastic objects contain DINP. This table and all subsequent tables use only the 24 non zero migration rates.

Table 7

Case 2
Estimated Daily Intake of DINP for Soft Plastic Toys
All Soft Plastic Toys Contain DINP

| Age | | Daily Intake (μg) Point Estimate | 95 Percent CI LCL | UCL | Daily Intake Scaled to Body Weight (μg/kg) Point Estimate | 95 Percent CI LCL | UCL |
|---|---|---|---|---|---|---|---|
| 3-12 (n=54) | Mean | 1.46 | 0.70 | 2.42 | 0.17 | 0.08 | 0.29 |
| | Median | 0.00 | 0.00 | 0.19 | 0.00 | 0.00 | 0.02 |
| | 90th Percentile | 4.50 | 1.93 | 7.73 | 0.53 | 0.23 | 0.92 |
| | 95th Percentile | 7.91 | 3.89 | 12.86 | 0.94 | 0.47 | 1.54 |
| | 99th Percentile | 18.31 | 9.39 | 28.10 | 2.20 | 1.13 | 3.40 |
| 12-24 (n=66) | Mean | 2.27 | 1.21 | 3.33 | 0.22 | 0.11 | 0.32 |
| | Median | 0.07 | 0.00 | 0.51 | 0.01 | 0.00 | 0.05 |
| | 90th Percentile | 7.11 | 3.80 | 10.40 | 0.67 | 0.36 | 0.99 |
| | 95th Percentile | 11.67 | 6.53 | 16.42 | 1.11 | 0.62 | 1.57 |
| | 99th Percentile | 24.53 | 13.76 | 33.39 | 2.36 | 1.32 | 3.21 |
| 24-36 (n=49) | Mean | 0.91 | 0.29 | 1.86 | 0.07 | 0.02 | 0.14 |
| | Median | 0.00 | 0.00 | 0.12 | 0.00 | 0.00 | 0.01 |
| | 90th Percentile | 1.92 | 0.87 | 3.34 | 0.15 | 0.07 | 0.26 |
| | 95th Percentile | 3.47 | 1.59 | 9.22 | 0.27 | 0.12 | 0.72 |
| | 99th Percentile | 16.19 | 3.45 | 34.78 | 1.28 | 0.26 | 2.74 |

Notes: See table 6. Migration rates contain only the 24 objects with non zero rates.

DINP intake in table 7 is almost 3 times higher than in table 6.[23] Even with the assumption that all soft plastic toys contain DINP, upper percentile DINP intake is a small fraction of the ADI.

## 5.3 Case 3. Soft Plastic Toys, Teethers and Rattles Contain DINP

Case 3 uses the same 24 DINP containing-objects as Case 2, but adds mouthing times from soft plastic teethers and rattles to that of soft plastic toys. This case simulates DINP intake from soft plastic toys, teethers and rattles. Results are in table 8 below.

[23] The average migration rate in this case is 2.8 times higher than the base case. In the base case, the average migration rate is total migration rate of objects divided by 68 (44 zero specimens plus 24 non zero specimens), whereas in table 7 the divisor is 24.

Table 8

Case 3
Estimated Daily Intake of DINP
Soft Plastic Toys, Teethers and Rattles

| Age | | Daily Intake (μg) Point Estimate | 95 Percent CI LCL | UCL | Daily Intake Scaled to Body Weight (μg/kg ) Point Estimate | 95 Percent CI LCL | UCL |
|---|---|---|---|---|---|---|---|
| 3-12 (n=54) | Mean | 3.56 | 1.96 | 5.86 | 0.45 | 0.24 | 0.74 |
| | Median | 0.42 | 0.00 | 1.48 | 0.05 | 0.00 | 0.17 |
| | 90th Percentile | 10.44 | 5.83 | 17.24 | 1.29 | 0.70 | 2.16 |
| | 95th Percentile | 16.99 | 9.34 | 26.90 | 2.15 | 1.17 | 3.47 |
| | 99th Percentile | 37.07 | 19.82 | 55.92 | 4.87 | 2.57 | 7.37 |
| 12-24 (n=66) | Mean | 2.31 | 1.31 | 3.63 | 0.22 | 0.12 | 0.34 |
| | Median | 0.11 | 0.00 | 0.61 | 0.01 | 0.00 | 0.06 |
| | 90th Percentile | 7.13 | 3.91 | 11.23 | 0.68 | 0.37 | 1.07 |
| | 95th Percentile | 11.76 | 6.84 | 17.85 | 1.12 | 0.64 | 1.72 |
| | 99th Percentile | 25.14 | 14.51 | 36.53 | 2.41 | 1.40 | 3.47 |
| 24-36 (n=49) | Mean | 1.10 | 0.31 | 2.38 | 0.08 | 0.02 | 0.18 |
| | Median | 0.00 | 0.00 | 0.14 | 0.00 | 0.00 | 0.01 |
| | 90th Percentile | 1.97 | 0.86 | 5.31 | 0.15 | 0.07 | 0.41 |
| | 95th Percentile | 4.33 | 1.60 | 14.78 | 0.33 | 0.12 | 1.09 |
| | 99th Percentile | 22.00 | 3.45 | 41.38 | 1.65 | 0.27 | 3.14 |

Notes: see table 7.

Table 8 shows about a doubling in DINP intake over table 7 among children 3-12 months old, principally because these are the children using teethers and rattles. The changes in DINP intake among older children are generally at the second decimal place. Upper percentiles still remain far below the ADI.

## 5.4 Case 4. All Soft Plastic Objects Contain DINP

Table 9 adds mouthing time from other soft plastic objects, simulating a case where all soft plastic objects contain DINP. Additional objects include forks, drinking cups, straws, plastic furniture, plastic on clothing, etc.

Table 9

Case 4
Estimated Daily Intake of DINP
All Soft Plastic Objects

| Age | | Daily Intake (μg) Point Estimate | 95 Percent CI LCL | UCL | Daily Intake Scaled to Body Weight (μg/kg) Point Estimate | 95 Percent CI LCL | UCL |
|---|---|---|---|---|---|---|---|
| 3-12 (n=54) | Mean | 5.09 | 3.10 | 7.88 | 0.63 | 0.38 | 0.99 |
| | Median | 1.04 | 0.34 | 2.79 | 0.12 | 0.04 | 0.33 |
| | 90th Percentile | 14.87 | 9.06 | 22.69 | 1.84 | 1.09 | 2.83 |
| | 95th Percentile | 23.01 | 14.41 | 34.57 | 2.90 | 1.77 | 4.36 |
| | 99th Percentile | 46.46 | 28.38 | 65.79 | 5.94 | 3.59 | 8.53 |
| 12-24 (n=66) | Mean | 4.35 | 2.70 | 6.45 | 0.41 | 0.26 | 0.60 |
| | Median | 1.62 | 0.74 | 2.91 | 0.15 | 0.07 | 0.27 |
| | 90th Percentile | 11.78 | 7.36 | 17.51 | 1.12 | 0.70 | 1.65 |
| | 95th Percentile | 17.80 | 11.09 | 26.24 | 1.69 | 1.06 | 2.48 |
| | 99th Percentile | 35.41 | 21.17 | 51.01 | 3.36 | 2.01 | 4.81 |
| 24-36 (n=49) | Mean | 4.77 | 2.56 | 7.65 | 0.37 | 0.19 | 0.59 |
| | Median | 1.01 | 0.21 | 2.43 | 0.08 | 0.01 | 0.18 |
| | 90th Percentile | 13.34 | 7.01 | 21.83 | 1.02 | 0.53 | 1.67 |
| | 95th Percentile | 22.01 | 11.38 | 35.14 | 1.70 | 0.87 | 2.73 |
| | 99th Percentile | 49.05 | 24.64 | 74.06 | 3.87 | 1.91 | 5.85 |

Notes: See table 7.

Table 9 shows a small increase over table 8. The largest increase is among the oldest children, but the DINP intake is again well below the ADI.

### 5.5 Case 5. All Toys, Teethers And Rattles Contain DINP

Case 5 reflects a scenario where children only play with toys, teethers or rattles that contain DINP. This means that children do not play with wood, hard plastic or cloth toys. The case is not comparable to case 4 because it does not include mouthing times for non toys. It is comparable to case 3.

Table 10

Case 5
Estimated Daily Intake of DINP
All Toys, Teethers and Rattles

| Age | | Daily Intake (μg) Point Estimate | 95 Percent CI LCL | UCL | Daily Intake Scaled to Body Weight (μg/kg ) Point Estimate | 95 Percent CI LCL | UCL |
|---|---|---|---|---|---|---|---|
| 3-12 (n=54) | Mean | 23.49 | 14.85 | 34.08 | 2.91 | 1.83 | 4.26 |
| | Median | 12.21 | 7.39 | 18.97 | 1.45 | 0.87 | 2.28 |
| | 90th Percentile | 57.48 | 35.97 | 84.49 | 7.13 | 4.42 | 10.63 |
| | 95th Percentile | 85.09 | 52.83 | 125.25 | 10.71 | 6.54 | 16.07 |
| | 99th Percentile | 168.86 | 98.85 | 249.32 | 21.89 | 12.60 | 32.51 |
| 12-24 (n=66) | Mean | 8.86 | 5.55 | 13.00 | 0.84 | 0.52 | 1.23 |
| | Median | 3.54 | 2.00 | 5.96 | 0.33 | 0.18 | 0.55 |
| | 90th Percentile | 23.21 | 14.59 | 34.28 | 2.20 | 1.38 | 3.25 |
| | 95th Percentile | 35.24 | 22.25 | 51.88 | 3.35 | 2.11 | 4.97 |
| | 99th Percentile | 71.31 | 41.84 | 107.77 | 6.88 | 4.01 | 10.64 |
| 24-36 (n=49) | Mean | 3.69 | 1.95 | 5.95 | 0.28 | 0.15 | 0.44 |
| | Median | 1.05 | 0.53 | 1.84 | 0.08 | 0.04 | 0.14 |
| | 90th Percentile | 9.44 | 4.60 | 16.72 | 0.71 | 0.35 | 1.23 |
| | 95th Percentile | 16.72 | 7.85 | 28.13 | 1.25 | 0.59 | 2.08 |
| | 99th Percentile | 40.50 | 19.31 | 63.44 | 3.02 | 1.45 | 4.71 |

Notes: see table 7.

As mentioned above, this case includes all toys, teethers and rattles, which includes objects made from other materials than soft plastic, such as cloth, hard plastic and wood. The mouthing times used to construct table 10 include all the soft plastic, toy and rattle mouthing times from table 8 and also mouthing times for the non soft plastic toys, teethers and rattles such as cloth toys, hard plastic toys, etc.

In this case, DINP intake rises to about one sixth of the ADI for the 99$^{th}$ percentile children, 3-12 months at 21.89 micrograms per kilogram (12.60-32.51). DINP intake would increase by a factor of 5 or 6 for children 3-12 months, and by a factor of 2-4 for children 12-36 months, as compared with case 3. Despite this increase, DINP intake still is below the ADI.

## 5.5 Case 6. DINP in Pacifiers

Case 6 only addresses pacifiers. At the present time pacifiers do not contain DINP. The purpose of this case is to estimate DINP intake from pacifiers if they contained DINP.

Table 11

Case 6
Estimated Daily Intake of DINP
Pacifiers

| Age | | Daily Intake (µg) Point Estimate | 95 Percent CI LCL | UCL | Daily Intake Scaled to Body Weight (µg/kg) Point Estimate | 95 Percent CI LCL | UCL |
|---|---|---|---|---|---|---|---|
| 3-12 (n=54) | Mean | 37.79 | 17.48 | 64.40 | 4.75 | 2.21 | 8.00 |
| | Median | 0.00 | 0.00 | 5.14 | 0.00 | 0.00 | 0.64 |
| | 90th Percentile | 106.11 | 50.82 | 190.66 | 13.51 | 6.38 | 23.82 |
| | 95th Percentile | 193.27 | 92.08 | 332.64 | 24.55 | 11.74 | 41.37 |
| | 99th Percentile | 497.58 | 221.51 | 808.08 | 62.35 | 28.44 | 101.47 |
| 12-24 (n=66) | Mean | 30.92 | 12.89 | 55.23 | 2.82 | 1.19 | 5.00 |
| | Median | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | 90th Percentile | 86.95 | 23.76 | 188.26 | 7.96 | 2.12 | 17.26 |
| | 95th Percentile | 191.06 | 70.26 | 338.19 | 17.44 | 6.44 | 30.84 |
| | 99th Percentile | 502.52 | 242.84 | 769.54 | 45.55 | 22.32 | 69.14 |
| 24-36 (n=49) | Mean | 21.23 | 0.96 | 53.68 | 1.71 | 0.07 | 4.33 |
| | Median | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | 90th Percentile | 0.06 | 0.00 | 115.03 | 0.00 | 0.00 | 9.08 |
| | 95th Percentile | 72.04 | 0.00 | 387.41 | 5.41 | 0.00 | 31.37 |
| | 99th Percentile | 602.27 | 35.77 | 1082.09 | 48.97 | 2.61 | 88.30 |

Notes: See table 7.

As shown in the table, pacifier use is mainly among the children ages 3-24 months, although there are a few older children using pacifiers. Pacifier use tends to be continuous among those who use it, resulting in relatively large mouthing times for users. Note that median DINP intake for pacifier use is zero for all age groups, indicating that at least half the children in the data did not use pacifiers. Also more than 90 percent of the sample children between age 24 and 36 months, did not use pacifiers, as shown by 90$^{th}$ percentile DINP intake at zero.

Table 11 shows mean, median, 90$^{th}$ percentile and 95$^{th}$ percentile DINP intake for pacifiers to be well below the ADI. However, the upper confidence limit for the 99$^{th}$

percentile is more than half the ADI for the older children and estimated at over 100 micrograms per kilogram for the youngest children. It is also worth noting that total DINP intake for all children would be greater than shown in table 11, because this table does not consider intake from soft plastic toys and other items.

## 6. Discussion

The risk analysis in this paper differs from previous CPSC and European efforts in several ways. First, the analysis is based on a new observational study of mouthing behavior in children. The sample was recruited through random digit dialing, and as such, represents a random and demographically balanced sample from two major American metropolitan areas. This study also used trained professional observers rather than parents to record mouthing times. It was possible to ask the professional observers to record every mouthing activity and provide detailed specifications of every object that was mouthed. The risk analysis could then focus on mouthing times associated specifically with soft plastic objects, rather than use broader mouthing time categories (such as mouthing times for all objects except pacifiers) that would result in overestimates of mouthing times and inflated DINP risk.

Second, migration rates in this analysis were from a wide variety rather than a limited selection of objects. It is important to note that migration rates vary among different toys, and that this variation belongs in the risk analysis. This variation does not occur with migration rates from human subject studies using a small number of objects. It seems better to use a variety of different objects and then scale to human levels, in order to capture the best estimate of DINP intake and the variability of that intake. Moreover, with a good set of scaling factors, the risk analysis can be updated easily by testing new toys.

Third, migration rates for toys were from a new set of laboratory procedures. These procedures were tested in a recent large-scale interlaboratory study.

Fourth, migration rates in this study were corrected in the base case for objects that do not contain DINP. It is not accurate to apply mouthing times for soft plastic objects to DINP toy migration rates because not all soft plastic toys contain DINP.

Finally, the paper uses probabilistic risk analysis, providing both point and interval estimates for the percentiles of DINP intake. The source of some of the variability is the variability in migration rates, children's weights, exposure time, mouthing times and other data used in the model. Then using the bootstrap to estimate confidence intervals introduces sampling variability. The intervals provide an estimate as to the range of values that might be likely to occur if different samples were selected.

These differences in data and methodology result in estimates for DINP intake that are considerably smaller than previous estimates. The estimates are more accurate in that they are specific to soft plastic mouthing times and objects containing DINP. The

estimates also build in the variability associated with different mouthing and waking times among children, different scaling ratios and different migration rates from different toys and from sampling.

The base case involving mouthing times for soft plastic toys and migration rates for soft plastic toys (some not containing DINP) showed that DINP intake levels were under 1 microgram per kilogram body weight for all but the 99$^{th}$ percentile. The 95 percent upper confidence limit for this quantity for the youngest children was 2.35 micrograms per kilogram. These are all well below the ADI of 120 micrograms per kilogram.

The base case estimates in this paper are lower than previous analyses. For example, the mean DINP intake for children 3-12 months for soft plastic toys was 0.07 micrograms per kilogram per day, in contrast to CPSC's 1998 estimate of 5.7 micrograms per kilogram per day and the Dutch consensus group estimates between 7-12 micrograms per kilogram per day (6-12 month old children). Neither previous analysis used soft plastic toy mouthing times nor corrected migration rates for soft plastic objects that did not contain DINP. Also, the 99$^{th}$ percentile estimate for the youngest children of 1.44 micrograms per kilogram per day (95 percent confidence interval 0.74-2.35) in the present analysis is considerably below the CHAP upper bound estimate of 280 micrograms per kilogram per day.

After the base cases, other cases were simulated with increasing mouthing times representing scenarios with more objects containing DINP. These cases resulted in higher estimated DINP intake among children. Aside from the pacifier case, the largest DINP intake simulated the use of DINP in all toys, teethers and rattles. This assumes that wood, cloth, metal and other toys would be replaced with soft plastic toys containing DINP. Intake levels were still well below the ADI for this case, with the 99$^{th}$ percentiles for the youngest children at about one sixth of the ADI (at 21.89 micrograms per kilogram per day with the 95% confidence interval 12.6-32.5). But, in the pacifier scenario, the upper confidence limits for the upper percentile estimates for DINP intake approached the ADI. For example, the 99$^{th}$ percentile estimate for pacifiers was 62.4 micrograms per kilogram per day (95% confidence interval 28.4 – 101.5).

The staff concludes based on the evidence in this analysis, that at present levels DINP offers little or no risk to children. Moreover, additional use of DINP in toys would seem unlikely to pose a hazard, providing that DINP migration rates from such objects would be at the same level as those tested in the study. However, in view of the amount of time that some children mouth pacifiers, it is possible that a very small number might approach the ADI if DINP were used as the plasticizer in these objects.

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## Appendix
## Data and Computer Programs for Modelling Exposure

### Datasets

*Exposure (exposure.df)*

2 columns and 483 rows. Column 1 is child age in months, column 2 is daily exposure. Exposure is defined as the time (hours) the child is awake, not napping and not eating, i.e. the time the child can mouth objects. The dataset was obtained from the telephone survey of 491 children. Eight observations were not usable.

The dataset is to used to estimate a regression of the relationship between age and exposure. The regression line is used to estimate exposure time for all children. (Note that 109 of the 169 children in the observational dataset have recorded exposure time.)

*Mouthing Data (mouth.df).*

17 columns and 169 rows. Each row represents a child in the observational study. The data were obtained from the professional observer study of 169 children. Columns are defined in the following table:

| Column Number | Column Name | Definition |
|---|---|---|
| 1 | MASTERID | Child's ID number, e.g.. 00301618 |
| 2 | AGEINMO | Child's age in months, e.g. 3.1704 |
| 3 | SEX | Child's sex. 0=F, 1=M |
| 4 | ALL | Total Mouthing Times for all objects |
| 5 | NOPASS | Non Pacifiers |
| 6 | SOFTPLAS | Soft Plastic |
| 7 | SOFTMFD | Soft Plastic – No food contact items |
| 8 | TTR | Soft Plastic toys, teethers and rattles |
| 9 | TOY | Soft plastic toys |
| 10 | TR | Soft plastic teethers and rattles |
| 11 | OTHSOFT | Other soft plastic items |
| 12 | FOODCON | Soft Plastic Food Contact Items |
| 13 | ANATOMY | Anatomy |
| 14 | TTRNOT | Toys, teethers and rattles, not soft plastic |
| 15 | OTHER | Other objects |
| 16 | PACIFIER | Pacifiers |
| 17 | ALL.TTR | All Toys, teethers and rattles (including non soft plastic items) |

All times in *Mouth.df* are given in minutes per hour.

Column 9 was used for the base case and case 2. Column 8 was used for case 3. Entries in column 8 were the sum of columns 9 and 10. Case 4 used column 6. This column was the sum of columns 7 and 8. Case 5 used column 17, which was the sum of columns 8 and 14. Case 6 used column 16.

*Human Chew and Spit Data (chew.df)*

2 columns and 19 rows. Column 1 is the person index, column 2 is the DINP measured in the person's saliva, in micrograms per 10 $cm^2$ object per minute. Subjects chewed on a standard 38% disk. The data was provided by M.A.H. Rijk. More details about the object and the protocol are in Meuling and Rijk (1998).

*In-vitro extraction rates for the standard disk (Newlab.df).*

5 rows, 2 columns. Each row is a measurement at the CPSC chemistry laboratory on the 38% standard disk. Column 1 contains the disk identifier (A-E), column 2 the migration rate in micrograms per 10 $cm^2$ object per minute. DINP was extracted using the Head over Heels rotator, with quantitation by GC-MS. The procedure was described in the Joint Research Center Interlaboratory study (Simoneau, Geiss, Roncari, Zocchi and Hannaeret, 2001).

*Toy migration rates (mig.df)*

24 rows, 2 columns. Each row is a measurement of migration rates for toys at the CPSC chemistry laboratory using the same procedure as in the standard disks. Column contains the toy name, column 2 contains the migration rate in micrograms per 10 $cm^2$ object per minute.

For the basic factual case that includes objects mouthed that do not contain DINP, the dataset is augmented by 33 additional rows where the migration rates in column 2 are zero. All other cases use the 24 objects only.

**Program**

The program phboot2.f produces statistics and bootstrap confidence intervals. This program is coded in the S language and was run in the R language environment.

The result is returned in a matrix (res), where each row (of 2000) is a bootstrap realization. Column 1 contains the mean, column two contains the median, column 3 contains the $90^{th}$ percentile, column 4 has the $95^{th}$ and column 5 has the $99^{th}$ percentile.

The distribution of any particular statistic can then be obtained using the apply function. For example, the mean of the statistics, used as point estimates is

```
mean  <- apply(res,2,mean)
```

confidence limits are

```
Lcl <- apply(res,2,quantile,0.025)
ucl <- apply(res,2,quantile,0.975)
```

# Phboot2.f

```
sizemat.f <- function(mat,sim.run)
 {
  size  <-  dim(mat)[1] * dim(mat)[2]
  rep.factor <- sim.run %/% size
  add        <- sim.run %% size
  c(rep.factor,add)
  }

phboot2.f <- function(expo.df = exposure.df,age.group=young,
                      toymouth.df=mouth.df,wt.df=weight.df,
                      mig1.df=mig.df,lab1.df=newlab.df,
                      chew1.df=chew.df,mouth.col=9,R=2000,sim.run=160000)

   { #bootstrap analysis for confidence intervals

   res <- matrix(0,R,10)

  for (i in 1:R) {
   sample.rows <- sample(nrow(expo.df),repl=T)
   expo.lm   <- lm(exposure - ageinmo,data=expo.df[sample.rows,])
   intercept <- coef(expo.lm)[1]
   slope     <- coef(expo.lm)[2]
   len       <- length(expo.lm$residual)
   std.err   <- sd(expo.lm$residual) * sqrt((len-2)/(len-1))

   # daily mouthing times
   sample.rows <- sample(age.group,repl=T)
   norm.q      <- std.err * qnorm(c(c(.001,.999),seq(.05,.95,.05)))
   daily.expos <- outer((intercept+slope*toymouth.df[sample.rows,2]),norm.q,FUN="+")
   daily.mouth <- daily.expos * toymouth.df[sample.rows,mouth.col]
   reps        <- sizemat.f(daily.mouth,sim.run)

   #get the indexes for the weight distribution
   kids.age <- trunc(mouth.df[sample.rows,2]+1)
   ourweight.df <- weight.df[kids.age,]

   #divide mouthing by body weight distribution
   #remember rows correspond to a childs age
   mat <- matrix(0,length(kids.age),dim(ourweight.df)[2] * dim(daily.mouth)[2])
   len <- length(kids.age)
   for (j in 1:len)
      { temp1 <- as.numeric(daily.mouth[j,])
        temp2 <- as.numeric(ourweight.df[j,])
        mat[j,] <- as.numeric(outer(temp1,temp2,FUN='/'))
      }

     dmouth  <- as.numeric(daily.mouth)
     mth     <- c(rep(dmouth,reps[1]),sample(dmouth,reps[2],repl=T))
     mig     <- sample(sample(mig1.df[,2],repl=T), sim.run,repl=T)
     chew    <- sample(sample(chew1.df[,2],repl=T),sim.run,repl=T)
     release <- sample(sample(lab1.df[,2],repl=T),sim.run,repl=T)
     res1 <- mth * mig * chew / release

     mth <- sample(as.numeric(mat),sim.run,repl=T)
     res2 <- mth * mig * chew/release
     res[i,] <- c(mean(res1),median(res1),quantile(res1,c(0.9,0.95,.99)),
                  mean(res2),median(res2),quantile(res2,c(0.9,0.95,.99)))
     }
    res
    }
```

# TAB L

# Updated Risk Assessment of Oral Exposure to Diisononyl Phthalate (DINP) in Children's Products

August 26, 2002

Michael A. Babich, Ph.D.
Directorate for Health Sciences
U.S. Consumer Product Safety Commission
Bethesda, MD 20814

## Contents

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## Summary

Dialkyl phthalates have been used as plasticizers in many household products made from polyvinyl chloride (PVC), including children's products such as teethers, rattles, and soft plastic toys. Because plasticizers are not chemically bound to PVC, they may be released when children place PVC products in their mouths. This report updates the 1998 CPSC staff risk assessment of oral DINP exposure from children's products. In 1998, the CPSC staff concluded that DINP exposure from soft plastic teethers and toys was below the acceptable daily intake (ADI), but that there were significant sources of uncertainty in the exposure estimates, as well as in the potential for carcinogenicity in humans. The CPSC staff recommended additional work to address the uncertainties. At the request of CPSC, manufacturers voluntarily removed dialkyl phthalates from teethers and rattles. Since 1998, the CPSC staff convened a Chronic Hazard Advisory Panel (CHAP), conducted an observational study of children's mouthing activity, participated in the development of a candidate standard method for measuring DINP migration, and obtained new DINP migration data.

DINP exposure was toxic to the liver in lifetime feeding studies in the rat. The no observed adverse effect level (NOAEL) in male rats was 15 mg/kg-d. The CHAP used a benchmark dose approach to derive an acceptable daily intake (ADI) value of 120 µg/kg-d. 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, mainly soft plastic toys, using a laboratory method ("head-over-heels") developed by the Dutch Consensus Group and later modified by the European Union Joint Research Center. Ten square-centimeter disks cut from PVC products are immersed in a saliva simulant and tumbled for 30-minutes, then repeated, and the amount of DINP in the saliva simulant is determined. The staff tested 41 soft plastic children's products; 24 were made of PVC and 17 of these contained DINP. None of the teethers tested contained dialkyl phthalates. Some of the products contained multiple pieces or parts made of different plastics. Thus, 36 of 85 (42%) soft plastic articles contained DINP. Migration rates were obtained for 24 articles; some articles could not be tested due to their size or shape. Using the tumbling method, DINP migrated from soft plastic articles at rates ranging from 1.0 to 11.1 µg/10 $cm^2$/minute. As reported in 1998, the migration rate was not correlated with the DINP content, which ranged from 12.9 to 39.4 percent. To estimate exposure, migration rates were adjusted by multiplying by the *in vivo*: *in vitro* ratio obtained from studies with a PVC standard disk. The *in vivo* migration rate was from studies with adult volunteers conducted by the Dutch Consensus Group. The *in vitro* migration rate was measured by the CPSC's Directorate for Laboratory Sciences, Division of Chemistry.

The CPSC staff also conducted an observational study of children's mouthing behavior in 169 children from 3 to 36 months of age. Participants were recruited from the Houston and Chicago metropolitan areas by random digit dialing. Trained observers made 12, 20-minute observations over two days, recording the objects the children mouthed and the duration of each mouthing event, as measured with a stop-watch. Objects mouthed were classified into

13 categories, including soft plastic toys, soft plastic teethers and rattles, and pacifiers. Participants were divided into three age groups. Daily mouthing durations for each object class were extrapolated from the observed mouthing times (minutes per hour) and the exposure duration (amount of time the child was awake and not eating, hours per day), which was reported by parents.

Exposure estimates were derived for three age groups and several object classes. In the basic case, we estimated the exposure from soft plastic toys, adjusting for the prevalence of DINP (42%). The basic case is the best estimate of current oral exposure to DINP in children's products. In hypothetical cases, the prevalence of DINP was assumed to be 100 percent. Hypothetical cases included soft plastic toys; soft plastic toys, teethers, and rattles; all soft plastic objects; all toys, teethers, and rattles; and pacifiers. Hypothetical cases are the exposures that would result if DINP use in soft plastic toys and teethers were to increase. For example, in 1998 about 90 percent of soft plastic toys and teethers contained DINP. No pacifiers contained DINP, although a small number contained diisooctyl phthalate.

Distributions of the daily DINP exposures were estimated by Monte Carlo methods (bootstrap procedure), as described by Greene (2002b). Exposure estimates were derived by sampling from six distributions: migration data with 24 products, *in vitro* data with the standard disk, *in vivo* data with the standard disk, hourly mouthing time, exposure data (hours per day), and body weight. The procedure was implemented in a manner that preserved the dependence of the mouthing, weight and exposure on age, and the independence of the remaining variables. Exposures for all hypothetical cases (100% containing DINP) were based on the migration rates obtained for the 24 soft plastic products (mainly toys) tested by the staff. In the basic case (soft plastic toys, 42% containing DINP), 33 zero migration rates were added to the 24 non-zero rates. The different exposures are primarily due to differences in mouthing duration for the different object classes and age groups and, in the basic case, to the difference in DINP prevalence. Because migration rates were obtained for soft plastic toys, but not teethers, rattles, or pacifiers, caution should be used in interpreting the results for objects other than soft plastic toys.

Estimated exposures generally increased in the order: soft plastic toys < soft plastic toys, teethers, and rattles < all soft plastic objects < all toys, teethers, and rattles < pacifiers. For all object classes, the resulting estimated exposures were lower than the ADI (120 μg/kg-d). For example, in the basic case (soft plastic toys, 42% containing DINP), the mean exposure among 12 to 24-month-olds was 0.08 μg/kg-d, with a 95$^{th}$ percentile of 0.53 μg/kg-d. For the hypothetical case "all toys, teethers, and rattles," exposure was greatest among 3 to 12-month-olds. The mean exposure was 2.9 (1.8 – 4.3) μg/kg-d, while the median was 1.4 (0.87-2.3) μg/kg-d and the 95$^{th}$ percentile exposure was 10.7 (6.5-16.1) μg/kg-d.

The hypothetical exposures from pacifiers were greater, though still below the ADI. Exposure was greatest among 3 to 12-month-olds, where the mean exposure was estimated to be 4.8 (2.2 – 8.0) μg/kg-d. The median was 0.00 (0.0-0.64) μg/kg-d, as 57 percent of children did not mouth pacifiers, and the 95$^{th}$ percentile exposure was 24.6 (11.7-41.4) μg/kg-d. The 99$^{th}$ percentile exposure was 62.4 (28.4-101.5) μg/kg-d. The

staff concluded that oral exposure to DINP from mouthing soft plastic toys is not likely to present a health hazard to children. Currently, teethers, rattles, and pacifiers do not contain dialkyl phthalates. If DINP were to be used in teethers, rattles, or pacifiers, these products would probably not present a health hazard to children. The exposure estimates for these products were based on migration data with soft plastic toys.

As with any risk assessment, this risk assessment includes assumptions and sources of uncertainty. In applying the Monte Carlo procedure, it was assumed that the hourly mouthing duration, exposure duration, and body weight are dependent on the age in months. The daily mouthing duration (product of the hourly mouthing duration and exposure time), product migration rate, human subject migration rate, and laboratory migration rate were assumed to be independent. It was also assumed that the migration rates for soft plastic toys would apply to teethers, rattles, and pacifiers. Sources of uncertainty in the risk assessment include the lack of data on the toxicity of DINP in children or immature animals, and the possibility that DINP could be absorbed through the lining of the mouth.

## List of Abbreviations

| | |
|---|---|
| ADI | Acceptable daily intake |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| BMD | Benchmark dose |
| CDC | Centers for Disease Control and Prevention (U.S.) |
| CERHR | Center for the Evaluation of Risks to Human Reproduction, National Toxicology Program (U.S.) |
| CHAP | Chronic Hazard Advisory Panel |
| CI | Confidence interval |
| CMA | Chemical Manufacturers Association |
| CPSC | U.S. Consumer Product Safety Committee |
| CSTEE | Scientific Committee on Toxicity, Ecotoxicity, and the Environment, European Commission |
| DEHP | Di(2-ethylhexyl) phthalate |
| DINP | Diisononyl phthalate |
| DINP-1 | Diisononyl phthalate, type 1 (68515-48-0) |
| DINP-2 | Diisononyl phthalate, type 2 (28553-12-0) |
| DINP-A | Diisononyl phthalate, type A (71549-78-5) |
| F344 | Fischer 344 |
| FHSA | Federal Hazardous Substances Act |
| GD | Gestational day |
| GJIC | Gap junction intercellular communication |
| JRC | Joint Research Centre, European Commission, Ispra, Italy |
| LOAEL | Lowest observed adverse effect level |
| LOEL | Lowest observed effect level |
| MAFF | Ministry of Agriculture, Fisheries, and Food, United Kingdom |
| MEHP | Mono(2-ethylhexyl) phthalate |
| MINP | Mono(isononyl) phthalate |
| MNCL | Mononuclear cell leukemia |
| NERI | Danish National Environmental Institute |
| NOAEL | No observed adverse effect level |
| NOEL | No observed effect level |
| PND | Postnatal day |
| PPARα | Peroxisome proliferator-activated receptor, alpha isoform |
| PPRE | Peroxisome proliferator response element |
| PVC | Polyvinyl chloride |
| PWG | Pathology working group |
| RIVM | Rijksinstituut voor Volksgesondheid en Milieu (National Institute of Public Health and Environment), the Netherlands |
| SD | Sprague-Dawley |
| TNO | Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek (Netherlands Organisation for Applied Scientific Research) |

I. Introduction

Dialkyl phthalates have been used as plasticizers in many household products made from polyvinyl chloride (PVC), including children's products such as soft plastic teethers, rattles, and toys. Because plasticizers are not chemically bound to PVC, they may be released when children place PVC products in their mouths. Dermal exposure from these products is also possible, but probably to a lesser extent (CPSC 1983; CPSC 2001; France 2001). Significant inhalation exposure is not likely, due to the low vapor pressure of DINP. Until about 1985, di(2-ethylhexyl) phthalate (DEHP) was the predominant dialkyl phthalate in PVC children's products such as teethers, rattles, and soft toys. However, DEHP was found to be carcinogenic in laboratory animals (NTP 1982). Thus, U.S. Consumer Product Safety Commission (CPSC) staff performed a cancer risk assessment of exposure to DEHP in children's products (CPSC 1983), inititated a rulemaking procedure to limit the use of DEHP in children's products, and convened a Chronic Hazard Advisory Panel (CHAP) to review the available information on the possible health effects of DEHP. The rulemaking was later withdrawn when manufacturers voluntarily agreed to remove DEHP from pacifiers, teethers, and rattles (TMA 1986). DEHP was replaced with another phthalate, diisononyl phthalate (DINP).

In 1998, the CPSC staff completed a risk assessment of oral exposure to diisononyl phthalate (DINP) in children's products such as soft plastic teethers and toys (CPSC 1998). DINP was present in 31 of the 35 teethers and soft toys tested. Most pacifiers were manufactured from silicone or latex and, therefore, did not contain phthalates. The estimated 95$^{th}$ percentile exposure to DINP from teethers and soft toys (94 μg/kg-d) was below the acceptable daily intake (ADI) value for chronic organ toxicity (150 μg/kg-d). The staff concluded that few, if any, children were at risk of chronic organ toxicity. However, there were several significant sources of uncertainty in the risk assessment, including the studies and methods used to estimate exposure and the possible cancer risk. The CPSC staff did not perform a cancer risk assessment, due to an ongoing debate about the relevance of animal tumors induced by DINP and other dialkyl phthalates. Rodent liver tumors induced by DINP are associated with peroxisome proliferation, which has been proposed as a mechanism for tumor induction and which has not been demonstrated in humans or monkeys. Therefore, as recommended by the staff, the Commission directed the staff to do the following additional work:

- Convene a CHAP to study issues related to chronic toxicity and risk, including the relevance to humans of liver tumors observed in animals and possible contribution of background exposure to other phthalates.
- Conduct a more extensive observational study of children's mouthing behavior.
- Develop a laboratory method for DINP migration that more accurately predicts the amount of DINP released when children mouth products.
- Conduct additional testing of children's products that contain DINP.

At the request of CPSC, manufacturers voluntarily removed DINP from children's products "intended to be mouthed," including teethers and rattles. Thus, in 1999 manufacturers began manufacturing teethers and rattles with plastics such as

polypropylene that do not require plasticizers. However, manufacturers continued to use DINP in soft plastic toys. In Canada, manufacturers and distributors also voluntarily removed phthalates from children's products intended to be mouthed. The European Union issued a temporary ban of six phthalates (DINP, DEHP, di-n-octyl phthalate, dibutyl phthalate, benzylbutyl phthalate, and diisodecyl phthalate) in children's products intended to be mouthed, which has been extended and remains in effect. Precautionary labeling is required on children's products not intended for mouthing. The European Union is currently considering legislation that would either make the ban permanent or limit phthalate migration from these products. Some individual European states have banned phthalates either in all children's products or products intended for mouthing.

In 1998, the National Environmental Trust and 11 other organizations petitioned the Commission to: (i) ban the use of PVC in toys and other products intended for use by children five years of age and under and (ii) issue "a national advisory on the health risks that have been associated with soft plastic vinyl (PVC) toys to inform parents and consumers about the risks associated with PVC toys currently in stores and homes" (FR 53: 70756, 1998). The petitioners cited concerns about the adverse effects of phthalates, lead, and cadmium additives in PVC. The petition was docketed in December 1998. In June 2001, Greenpeace requested that the Commission broaden the scope of the prior petition to include all household products made from PVC. In July 2001, the request was denied because it did not satisfy the requirements of the Federal Hazardous Substances Act (FHSA) or the Commission's regulations for docketing as a petition for rulemaking (Lemberg 2001).

The CPSC staff has now completed the additional work recommended in the 1998 risk assessment. A CHAP, convened in May 2000 to assess the potential risks associated with DINP, published a final report in June 2001 (CPSC 2001). The CPSC staff undertook and completed an observational study of children's mouthing behavior (Greene 2002a; Kiss 2002). The staff participated in efforts to develop a laboratory method for measuring DINP migration from children's toys (Rijk and Ehlert 1999; Rijk et al. 1999; Simoneau et al. 2001). Finally, the staff conducted additional migration measurements using the new laboratory method (Chen 2002).

The purpose of this report is to reevaluate the risk of chronic toxicity associated with oral exposure to DINP in children's products, including teethers and soft toys. This will include new information provided by the CHAP, the CPSC observational study, and new DINP migration data.

II. Chemistry and Use

DINP (68515-48-0; 28553-12-0) is a mixture of C9-rich, di-C8 to C10, branched chain dialkyl esters of *ortho*-phthalic acid (Hellwig et al. 1997; NLM 2001). Different processes are used to produce the isononyl alcohols used as feedstock in manufacturing DINP. This results in DINP's with different isomeric compositions and multiple CAS numbers. Two commercial processes are currently in use.

DINP-1 (68515-48-0) contains alcohol groups made from octene. At least 95 percent of these alcohol groups comprise roughly equal amounts of 3,4-, 3,5-, 3,6-, 4,5-, 4,6-, and 5,6-dimethyl heptan-1-ol (Hellwig et al., 1997) (Table II-1). DINP-1 is also known by the tradename Jayflex®. DINP-2 (28553-12-0) contains alcohol groups made from *n*-butene, which results mainly in methyl octanols and dimethyl heptanols. DINP-2 is also known by the tradenames Palatinol N® and Palatinol DN® (NLM 2001). DINP-3 (also 28553-12-0) contains alcohol groups made from *n*-butene and *i*-butene, resulting in 60 percent methylethyl hexanols. DINP's generally contain 70% or more nonyl alcohol moieties, with the remainder being octyl or decyl (Madison et al. 2000). According to the American Chemistry Council, the composition of each type of DINP is stable (Center for the Evaluation of Risks to Human Reproduction (CERHR) 2000a). Although their isomeric composition differs, the different types of DINP are considered commercially interchangeable. DINP-3 is no longer produced.

Another form of DINP, Santicizer 900®, (71549-78-5) was never produced on a commercial scale (Menza 1985). However, this product was apparently made from *n*-butene and has an isomeric composition similar to the DINP-2 that is currently produced (Harmon, 2000). This product has been referred to as DINP-A (Smith et al. 2000).

Bis(3,5,5-trimethylhexyl) phthalate (14103-61-8) is a branched-chain dinonyl phthalate that comprises a single isomer. This compound has an annual production of less than 10,000 pounds per year (Madison et al. 2000) and, therefore, is not a commercially significant plasticizer. It is marketed as a laboratory reagent (www.sigma-aldrich.com/).

Physico-chemical properties are summarized in Table II-2. DINP is a very hydrophobic compound with low vapor pressure and low water solubility (reviewed in Staples et al. 1997). Due to its extreme hydrophobic nature, the octanol-water partition coefficient (log $K_{ow}$) and water solubility are not amenable to direct measurement. Thus, a range of estimates for these properties has been reported. The values in the table are as recommended in the CERHR report (CERHR 2000a).

DINP is used as a plasticizer in a variety of products manufactured from PVC, including vinyl flooring, wire and cable, stationery, wood veneer, coated fabrics, gloves, toys, tubing, artificial leather, shoes, sealants, and carpet backing (CERHR 2000a). The use of DINP in toys represents a relatively minor portion of U.S. DINP consumption. Domestic consumption of DINP was estimated to be 178,000 metric tons (392 million pounds) in 1998. DINP represents approximately 10 to 15 percent of total dialkyl phthalate

plasticizer production (Madison et al. 2000). DINP has limited use in food packaging and is not used in medical devices (CERHR 2000a).

**Table II-1.** Chemical composition of diisononyl phthalate (DINP) [a]

| Type | CAS no. | Starting material | Composition of alcohol groups | Production |
|---|---|---|---|---|
| DINP-1 | 68515-48-0 | Octene | ≥95% 3,4-, 3,5-, 3,6-, 4,5-, 4,6-, and 5,6-dimethyl heptan-1-ol | >10,000 lbs./year |
| DINP-2 | 28553-12-0 | *n*-butene | Mainly methyl octanols and dimethyl heptanols | >10,000 lbs./year |
| DINP-A [b] | 71549-78-5 | *n*-butene | Mainly methyl octanols and dimethyl heptanols | Never produced commercially |
| DINP-3 | 28553-12-0 | *n*-butene + isobutene | 60% methylethyl hexanols | Not currently produced |
| NA [c] | 14103-61-8 | NA | 3,5,5-trimethyl hexanol | <10,000 lbs./year |

[a] Sources: Hellwig et al. 1997; Madison et al. 2000; NLM 2001.
[b] This product is reported to be similar in composition to DINP-2 (Harmon 2000).
[c] NA, not applicable.

**Table II-2.** Physico-chemical properties of DINP [a]

| | |
|---|---|
| Molecular formula | $C_{26}H_{42}O_4$ |
| Molecular weight | 418.6 g/mol |
| Melting point | -48 °C |
| Boiling point | 370 °C |
| Vapor pressure | $5 \times 10^{-7}$ mm Hg |
| Specific gravity | 0.97 |
| Water solubility | <0.001 mg/L [b] |
| Log $K_{ow}$ | ~9 [b] |

[a] Sources: CERHR 2000a; Staples et al. 1997.
[b] A range of estimates was reported in the literature. The recommended value is from CERHR 2000a.

III. Toxicokinetics

A. Oral Toxicokinetics

Oral absorption of $^{14}$C-DINP was studied in male albino rats (Hazleton 1972; reviewed in CERHR 2000a and CPSC 2001). Most of the administered dose (85%) was eliminated in the feces within 72 hours. The remainder was eliminated in urine (12%) or remained in the tissues.

In studies performed at the Midwest Research Institute, male and female Fischer 344 rats were given either a single oral (gavage) dose at 50 or 500 mg/kg or five daily doses at 50, 150, or 500 mg/kg of $^{14}$C-DINP (El-hawari et al. 1983; El-hawari et al. 1985; Lington et al., 1985; reviewed in CERHR 2000a and CPSC 2001). Elimination of radioactivity in urine and feces was followed for up to 72 hours. Blood and tissue levels of radioactivity were determined in animals sacrificed at times up to 72 hours.

In rats given a single dose, DINP levels in blood and tissue were generally greatest at one hour following administration. Levels were greatest in the liver, followed by blood and kidney, and very low in fat. At least 49 percent of the applied dose was absorbed at 50 mg/kg and declined at 500 mg/kg (CERHR 2000a), suggesting that absorption was saturated at the high dose. Administered radioactivity was largely recovered in urine and feces within 72 hours. Roughly equal amounts of radioactivity were recovered in urine and feces at the low dose, while at the high dose more radioactivity was recovered in feces. Most of the $^{14}$C-DINP collected in urine was in the form of phthalic acid (PA) or side-chain oxidation products of the monoester. Elimination of PA decreased at the high dose. Feces included up to 41 percent DINP, as well as PA and side-chain oxidation products.

In animals given five daily doses, blood and tissue levels were greatest at one hour following the last dose. DINP levels were highest in the liver, followed by kidney, blood, and skin. Administered radioactivity was largely recovered in urine and feces within 72 hours. Excretion of radioactivity was higher in urine than in feces at all three doses. Most of the $^{14}$C-DINP collected in urine was in the form of PA or side chain oxidation products of the monoester. Elimination of PA decreased at the high dose.

DINP and its metabolites monoisononyl phthalate (MINP) and PA were studied in Fischer 344 rats (0, 0.1, or 1.2% in feed) and B6C3F1 (0.05 or 0.6% in feed) for four weeks (Smith et al. 2000). DINP, MINP, and PA were measured in liver and serum at two and four weeks. DINP levels in the livers of rats and mice were greater at the high dose at two weeks, but not at four weeks; DINP was not detected in serum. The levels of MINP in liver and serum increased over time, and were greater than DINP and PA levels. In rats, PA increased with time in liver and serum. In mice, PA increased with time in liver and serum at the low dose, but not at the high dose. PA concentrations were not dose-dependent in the liver or serum of mice or rats.

In short, when DINP was administered orally to rats, it was rapidly absorbed and eliminated. DINP was de-esterified to the monoester, which was further metabolized either by hydrolysis to phthalic acid or by side-chain oxidation of the ester group (CERHR 2000a; CPSC 2001). As with di(2-ethylhexyl)phthalate (Albro and Thomas 1973), it is likely that DINP is rapidly de-esterified by the intestinal mucosa. Limited data in mice are consistent with the rat data.

B. Percutaneous Absorption

Pecutaneous absorption of $^{14}$C-DINP was studied in male Fischer 344 rats (Stoltz and El-hawari 1983; Stoltz et al. 1985). A volume of either 0.1 mL or 0.2 mL of neat DINP was applied to a 12 cm$^2$ area of skin and occluded. DINP remained on the skin during the 7-day study. Some animals were pre-conditioned by applying non-labeled DINP to the skin for three days prior to applying $^{14}$C-DINP. After seven days, roughly 2 to 4 percent of the applied dose (as $^{14}$C) was recovered in urine, feces, gastrointestinal tract, blood, or tissue, in descending order. More than half of the absorbed dose was recovered in urine. In naïve animals, either 3.1 or 3.7 percent of the applied dose was absorbed, at the low and high dose, respectively. Absorption was 2.0 percent in pre-conditioned animals.

Related dialkyl phthalates have also been studied. Dialkyl phthalates were applied to the skin of male Fischer 344 rats in ethanol at a dose of 5 to 8 mg/kg (Elsisi et al. 1989). Approximately 5 percent of the applied dose of DEHP was excreted in five days. Only 0.5 percent of the applied dose of diisodecyl phthalate was excreted in seven days.

Percutaneous absorption of DEHP was also studied in humans *in vivo* and in the isolated perfused porcine skin flap (IPPFS) system (Wester et al. 1998). In humans, 1.8 percent of the applied dose was absorbed, compared to 2.4 percent in the IPPFS system.

Deisinger et al. (1998) studied the percutaneous absorption of $^{14}$C-DEHP from PVC film containing 40 percent DEHP. A 15 cm$^2$ piece of PVC containing about 400 mg DEHP was applied to the skin and occluded, then removed after 24 hours. Excretion was monitored for seven days. From 0.064 to 0.126 percent of the applied DEHP was transferred to the skin in 24 hours. Approximately 0.01 percent of the applied dose (261.5 to 505.6 μg) was absorbed in seven days.

Percutaneous absorption of DEHP was also studied in two *in vitro* studies. Barber et al. (1992) reported a permeability constant of $4.3 \times 10^{-7}$ cm/h for full-thickness rat skin. The permeability constant was $1.05 \times 10^{-7}$ cm/h with human stratum corneum (Barber et al. 1992). Scott et al. (1987) reported permeability constants of $2.28 \times 10^{-5}$ cm/h and $0.57 \times 10^{-5}$ cm/h using rat and human epidermis, respectively.

## IV. Systemic Health Effects

The non-neoplastic systemic effects of DINP have been reviewed in detail elsewhere (CERHR 2000a; CPSC 2001). DINP-1 (68515-48-0) was tested in a two-year study in Fischer 344 rats at doses of 0, 0.03, 0.3, and 0.6 percent in feed (Lington et al. 1997). DINP-1 from a different supplier was tested in Fischer 344 rats at doses of 0, 0.05, 0.15, 0.6, and 1.2 percent in feed (Moore 1998a) and in B6C3F1 mice at doses of 0, 0.05, 0.15, 0.4, and 0.8 percent (Moore 1998b). The studies by Moore are also referred to as the Covance studies (CPSC 1998; CPSC 2001). DINP-A (71549-78-5), which is believed to be similar to DINP-2, was tested in Sprague-Dawley rats at doses of 0, 0.05, 0.5, and 1.0 percent in feed (Bio/dynamics 1986). In addition, rodent studies from 1 to 13 weeks in duration have been reported (reviewed in CERHR 2000a and CPSC 2001). Two studies in primates of 2 weeks and 13 weeks in duration have also been reported (Hall et al. 1999; Pugh et al. 2000).

### A. Liver

#### 1. Hepatomegaly

Hepatomegaly is an early observable effect of DINP exposure in rodents. Increases in absolute and relative liver weights have been reported in studies ranging from 1 week to 2 years in duration (Table IV-1). In Fischer rats exposed to DINP-1 for 2 years, the no observed effect level (NOEL) was 0.15 percent in feed (88 mg/kg-d) (Moore 1998a), while the lowest observed effect level (LOEL) was 0.3 percent (307 mg/kg-d) (Lington et al. 1997). Hepatomegaly was somewhat reversible. In animals fed 1.2 percent DINP for 79 weeks followed by a 26 recovery period, liver weights returned to near control levels (Moore 1998a). In mice exposed to DINP-1 for two years, the NOEL was 0.15 percent (276 mg/kg-d) in males (Moore 1998b). Liver weight increases were also reversible in recovery group animals. In females, the increase in absolute and relative liver weights was not statistically significant. In Sprague-Dawley rats exposed to DINP-A for two years, liver weights were significantly increased in males at the mid and high doses and females at the high dose. Thus, the NOEL was 0.05 percent (33 mg/kg-d) and the LOEL was 0.5 percent (331 mg/kg-d) (Bio/dynamics 1986).

Hepatomegaly was reported following one week of exposure in SV129 wild type mice, but not in PPAR-α null mice (Valles et al. 2000). The PPAR-α protein (alpha isoform of the peroxisome proliferator activated receptor) is believed to mediate many of the effects of DINP and other peroxisome proliferators (Lee et al. 1995; Peters et al. 1997a; Ward et al. 1998). Hepatomegaly was not observed in cynomolgus monkeys exposed to 500 mg/kg-d DINP by gavage for 14 days (Pugh et al. 2000). Non-statistically significant increases in liver weight were observed in marmosets exposed to 100, 500, or 2,500 mg/kg-d DINP by gavage for 13 weeks, the greatest increase occurring at the low dose (Hall et al. 1999). The primate studies are limited by the small number of animals (4) per dose/sex group.

2. Histopathology and Clinical Chemistry

a. Rats

Lington study. Lington et al. (1997) found several non-neoplastic lesions in Fischer 344 rats exposed to DINP for two years, including focal necrosis, spongiosis hepatis, hepatopathy associated with leukemia, and a slight centrilobular to midzonal hepatocellular enlargement. The authors attributed these lesions to the presence of mononuclear cell leukemia (MNCL). In high dose males, the incidences of focal necrosis ($p=0.0018$), spongiosis hepatis ($p=7.3x10^{-10}$), hepatopathy associated with leukemia, and hepatocellular enlargement were significantly elevated (Table IV-2). In mid dose males, spongiosis hepatis and hepatopathy associated with leukemia were significantly elevated, while focal necrosis was non-significantly elevated ($p=0.13$). In high dose females, hepatopathy and hepatocellular enlargement were significantly elevated, while focal necrosis was non-significantly elevated. In mid-dose females, focal necrosis ($p=0.15$) and hepatopathy ($p=0.093$) were non-significantly elevated. The hepatocellular enlargement (hypertrophy) is probably related to the occurrence of hepatomegaly (see above) and peroxisome proliferation (below). In male rats, the severity of spongiosis was minimal to moderate and exhibited a modest dose response (Brown 2000). The average number of foci per animal was more strongly dose dependent, ranging from 1.45 in the controls to 4.26 at the high dose (Brown 2000).

Some statistically significant increases in serum enzymes associated with liver function were reported in the 6, 12, and 18-month interim sacrifices. At 24 months, alkaline phosphatase was significantly increased in mid and high dose males. The no observed effect level (NOEL) for liver effects in this study was 0.03 percent DINP (15 mg/kg-d).

Covance study. In the Covance rat study in Fischer 344 rats, diffuse hepatocellular enlargement, centrilobular to midzonal hepatocellular enlargement, and increased cytoplasmic eosinophilia were observed in rats sacrificed as early as week 1 (Moore 1998a, p. 41). In males exposed to 1.2 percent DINP, the incidences of several lesions were significantly elevated, including: individual cell degeneration/ necrosis ($p=0.0029$), spongiosis hepatis ($p=0.0051$), hepatocellular enlargement ($p=3.1x10^{-14}$), and increased cytoplasmic eosinophilia ($p=4.4x10^{-17}$) (Moore 1998a, Table 10E; see Table IV-3). Spongiosis hepatis was also significantly elevated in males at 0.6 percent DINP ($p=0.0068$). In females exposed to 1.2 percent DINP, focal necrosis, hepatocellular enlargement, and increased cytoplasmic eosinophilia were significantly elevated. Focal necrosis was observed in a few animals at 0.05, 0.15, and 0.6 percent DINP, but did not reach statistical significance. The incidences of the various liver histopathological lesions generally declined in the recovery group, in which animals were exposed to 1.2 percent for 78 weeks, then allowed to recover for 26 weeks. However, the incidence of spongiosis hepatis remained significantly elevated in males in the recovery group ($p=0.037$). At terminal sacrifice, spongiosis hepatis was generally of low severity (grades 1 and 2), with only one animal in the high dose at grade 5 (Moore 1998a, Table 10C). The average grade among animals with spongiosis hepatis did not increase with increasing dose (CPSC 2001).

**Table IV-1**. Increased liver weight following DINP exposure [a]

| Species/strain | Duration | Doses | Effect | NOEL [b] | Reference |
|---|---|---|---|---|---|
| Rat, F344 | 2, 4 weeks | 0, 0.1, 1.2 % in feed | Yes [c] | 0.1 % | Smith et al. 2000 |
| Rat, F344 | 3 weeks | 0, 0.06, 0.12, 0.25 % in feed<br>(M: 0, 639, 1192, 2195 mg/kg-d<br>F: 0, 607, 1198, 2289 mg/kg-d) | Yes | ND [d] | BIBRA 1985<br>Barber et al. 1987 |
| Rat, F344 | 4 weeks | 0, 0.2, 0.67, 2.0 % in feed | Yes | 0.2 % | Shellenberger et al. 1983 |
| Rat, F344 | 13 weeks | 0, 0.1, 0.3, 0.6, 1.0, 2.0 % in feed<br>(0, 50, 150, 320, 530, 1260 mg/kg-d) | Yes | 0.1 % | Bird et al. 1986 |
| Rat, F344 | 13 weeks | 0, 0.25, 0.5, 1.0, 2.0 % in feed<br>(M: 0, 146, 292, 584, 1168 mg/kg-d<br>F: 0, 182, 364, 728, 1456 mg/kg-d) | Yes | 0.25 % | Myers 1991 |
| Rat, F344 | 2 years | 0, 0.03, 0.3, 0.6 % in feed<br>(M: 0, 15, 152, 307 mg/kg-d<br>F: 0, 18, 184, 375 mg/kg-d) | Yes | 0.03 % | Lington et al. 1997 |
| Rat, F344 | 2 years | 0, 0.05, 0.15, 0.6, 1.2 % in feed<br>(M: 0, 29, 88, 359, 733 mg/kg-d<br>F: 0, 36, 109, 442, 885 mg/kg-d) | Yes | 0.15 % | Moore 1998a |
| Rat, SD | 2 years | 0, 0.05, 0.5, 1.0 % in feed<br>(M: 0. 27, 271, 553 mg/kg-d<br>F: 0, 33, 331, 672 mg/kg-d) | Yes | 0.05 % | Bio/dynamics 1986 |
| Mouse, B6C3F1 | 1 week | 0, 0.8 % in feed | Yes | ND | Valles et al. 2000 |
| Mouse, SV129 wt | 1 week | 0, 0.8 % in feed | Yes | ND | Valles et al. 2000 |
| Mouse, SV129 (-/-) [e] | 1 week | 0, 0.8 % in feed | No | 0.8 % | Valles et al. 2000 |
| Mouse, B6C3F1 | 2, 4 weeks | 0, 0.05, 0.6 % in feed | Yes | 0.05 % | Smith et al. 2000 |

**Table IV-1**. Increased liver weight following DINP exposure (continued)

| Species/strain | Duration | Doses | Effect | NOEL [b] | Reference |
|---|---|---|---|---|---|
| Mouse, B6C3F1 | 13 weeks | 0, 0.15, 0.4, 1.0, 2.0 % in feed<br>(M: 0, 340, 904, 2365, 5472 mg/kg-d<br>F: 0, 389, 1041, 2834, 6070 mg/kg-d) | Yes | 0.4 % | Bankston 1992<br>Moore 2000 |
| Mouse, B6C3F1 | 2 years | 0, 0.05, 0.15, 0.4, 0.8 % in feed<br>(M: 0, 90, 276, 742, 1560 mg/kg-d)<br>F: 0, 112, 336, 910, 1888 mg/kg-d) | Yes | 0.15 % [f] | Moore 1998b |
| Cynomolgus monkey | 14 days | 0, 500 mg/kg-d by gavage | No | 500 mg/kg-d | Pugh et al. 2000 |
| Marmoset | 13 weeks | 0, 100, 500, 2500 mg/kg-d by gavage | ND [g] | 2,500 mg/kg-d | Hall et al. 1999 |

[a] Adapted from CPSC 2001 with changes. Where there were differences between sexes, the NOEL is for the more sensitive sex.
[b] NOEL, no observed effect level; ND, not determined.
[c] Positive at 4 weeks only.
[d] Data presented in graphical form. Statistical significance not reported.
[e] PPAR-α null.
[f] Males only.
[g] Non-statistically significant increases in liver weight were reported, with the greatest increase at 100 mg/kg-d.

Beginning at week 52, increased levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were found in males and females exposed to 0.6 or 1.2 percent DINP (Moore 1998a, p. 45). In males, these enzymes remained elevated in the recovery group. This suggests that these increases in liver-specific enzymes were not reversible, at least in the high dose group males.

The no observed effect level (NOEL) for liver effects in this study was 0.15 percent DINP (88 mg/kg-d).

Bio/dynamics study. The Bio/dynamics study (1986) was a two-year bioassay of DINP-A in Sprague-Dawley rats. In males, the incidence of focal necrosis was significantly elevated at the low ($p=0.0042$) and high ($p=0.0001$) doses, while the mid dose was non-significantly elevated ($p=0.086$) (Table IV-4). Spongiosis hepatis was significantly elevated at the mid and high dose. In females, spongiosis hepatis was elevated at the high dose, with borderline statistical significance ($p=0.051$). A NOAEL was not established in this study. The lowest observed adverse effect level (LOAEL) in males was 0.05 percent DINP in feed or 27 mg/kg-d.

Serum glutamic oxaloacetic transaminase values were elevated in the mid and high dose males at 6, 12, and 18 months and in the high dose males at 24 months. Serum glutamic pyruvic transaminase values were elevated in the mid and high dose males at 6 and 12 months, and in the high dose males at 24 months. Serum alkaline phosphatase was elevated in the mid and high dose males at 6 and 12 months only. The LOEL for liver effects in this study was 0.05 percent DINP (27 mg/kg-d), the lowest dose tested.

Subchronic studies. Hepatocellular enlargement was reported in a 13-week study in male and female Fischer 344 rats given 2.0 percent DINP in feed (Myers 1991).

Spongiosis hepatis. Spongiosis hepatis, also described as cystic or microcystic degeneration, is a focal degeneration of the perisinusoidal (Ito) cells of the liver. It is classified as a degenerative lesion (CPSC 2001). Spongiosis hepatis is characterized by the appearance of cystic spaces or vacuoles between hepatocytes that are not lined by endothelium and contain granular or flocculent eosinophilic material or fluid (Boorman 1997; EPL 1999; Hardisty 2000). The vacuoles may also be filled with erythrocytes. Spongiosis hepatis is typically associated with strong liver carcinogens, such as nitrosamines, and has been observed in fish (i.e., medaka) (e.g., Bannasch et al. 1981; Boorman et al. 1997; Brown-Peterson et al. 1999) and rats (Braunbeck et al. 1992; Zerban and Bannasch 1983). Spongiosis hepatis was also observed in a chronic study with DEHP in Fischer 344 rats (David et al. 2000). Spongiosis hepatis (cystic degeneration) has been reported in Fischer 344 rats in several NTP studies, including: tetrafluoroethylene, methyleugenol, malonaldehyde (sodium salt), benzyl acetate, anthraquinone, 3,3'-dimethylbenzidine dihydrochloride, C.I. pigment red 3, pentachlorophenol, chlorendic acid, and 3,3'-dimethoxybenzidine dihydrochloride (Maronpot 2000). Among the compounds tested by NTP, tetrafluoroethylene, methyleugenol, 3,3'-dimethylbenzidine dihydrochloride, chlorendic acid, and 3,3'-

dimethoxybenzidine dihydrochloride were hepatocarcinogens in rats (i.e., clear evidence of carcinogenicity). To our knowledge, none of these compounds has been reported to be a peroxisome proliferator.

**Table IV-2.** Incidence of selected liver lesions in Fischer rats exposed to DINP for two years—all deaths (Lington et al. 1997)[a]

| Lesion | Percent DINP in Feed | | | |
|---|---|---|---|---|
| | 0 | 0.03 | 0.3 | 0.6 |
| **Males** | | | | |
| Number examined | 81 | 80 | 80 | 80 |
| Focal necrosis | 10 | 9 (0.51) | 16 (0.13) | 26 (0.0018) |
| Spongiosis hepatis | 24 | 24 (0.55) | 51 ($1.2 \times 10^{-5}$) | 62 ($7.3 \times 10^{-10}$) |
| Hepatopathy associated with leukemia | 22 | 17 (0.25) | 34 (0.030) | 33 (0.043) |
| Centrilobular to midzonal hepatocellular enlargement | 1 | 1 (0.75) | 1 (0.75) | 9 (0.0084) |
| **Females** | | | | |
| Number examined | 81 | 81 | 80 | 80 |
| Focal necrosis | 13 | 11 (0.41) | 19 (0.15) | 21 (0.082) |
| Spongiosis hepatis | 4 | 1 (0.18) | 3 (0.51) | 4 (0.63) |
| Hepatopathy associated with leukemia | 16 | 18 (0.42) | 24 (0.093) | 33 (0.0025) |
| Centrilobular to midzonal hepatocellular enlargement | 1 | 0 (0.50) | 0 (0.50) | 11 (0.0024) |

[a] Numbers in parentheses are Fisher's exact p-values for pair-wise comparisons with controls.

**Table IV-3.** Incidence of selected liver lesions in Fischer rats exposed to DINP for two years—all deaths (Moore 1998a, Table 10E) [a]

| Lesion | Percent DINP in Feed | | | | | |
|---|---|---|---|---|---|---|
| | 0 | 0.05 | 0.15 | 0.6 | 1.2 | 1.2 [b] |
| **Males** | | | | | | |
| Number examined | 80 | 50 | 50 | 65 | 80 | 50 |
| Individual cell degeneration/necrosis | 0 | 0 | 0 | 1 (0.45) | 5 (0.0029) | 0 |
| Focal necrosis | 3 | 1 | 0 | 0 | 3 (0.69) | 4 (0.27) |
| Spongiosis hepatis | 5 | 5 | 2 | 14 (0.0068) | 21 (0.0051) | 9 (0.037) |
| Diffuse hepatocellular enlargement | 0 | 0 | 0 | 0 | 37 ($3.1\times10^{-14}$) | 0 |
| Increased cytoplasmic eosinophilia | 0 | 0 | 0 | 0 | 43 ($4.4\times10^{-17}$) | 0 |
| **Females** | | | | | | |
| Number examined | 80 | 50 | 50 | 65 | 80 | 50 |
| Individual cell degeneration/necrosis | 0 | 0 | 0 | 0 | 1 (0.50) | 0 |
| Focal necrosis | 1 | 3 (0.17) | 4 (0.078) | 4 (0.13) | 7 (0.034) | 3 (0.17) |
| Spongiosis hepatis | 0 | 0 | 0 | 1 (0.45) | 2 (0.25) | 0 |
| Diffuse hepatocellular enlargement | 0 | 0 | 0 | 0 | 52 ($6.6\times10^{-22}$) | 0 |
| Increased cytoplasmic eosinophilia | 0 | 0 | 0 | 0 | 45 ($4.3\times10^{-18}$) | 0 |

[a] Numbers in parentheses are Fisher's exact p-values for pair-wise comparisons with controls.
[b] Treated for 78 weeks, followed by a 26-week recovery period.

**Table IV-4.** Incidence of selected liver lesions in Sprague-Dawley rats exposed to DINP-A for two years—all deaths (Bio/dynamics 1986, Volume II, page 11)[a]

| Lesion | Percent DINP in Feed | | | |
|---|---|---|---|---|
| | 0 | 0.05 | 0.5 | 1.0 |
| **Males** | | | | |
| Number examined | 70 | 69 | 69 | 70 |
| Focal necrosis | 5 | 17 (0.0042) | 11 (0.086) | 23 (0.0001) |
| Spongiosis hepatis | 16 | 11 (0.89) | 30 (0.0079) | 32 (0.0036) |
| **Females** | | | | |
| Number examined | 70 | 70 | 70 | 70 |
| Focal necrosis | 10 | 15 (0.19) | 7 | 10 (0.60) |
| Spongiosis hepatis | 4 | 3 | 6 (0.38) | 11 (0.051) |

[a] Numbers in parentheses are Fisher's exact p-values for pair-wise comparisons with controls.

Spongiosis hepatis was observed in the two lifetime feed studies in Fischer 344 rats (Lington et al. 1997; Moore 1998a). However, the study by Lington et al. (1997) exhibited a more pronounced dose response for this effect (Figure IV-1). The no-observed-adverse-effect level (NOAEL) was 15 mg/kg-d in the Lington study and 88 mg/kg-d in the Moore study. Because of the difference in dose response, it is not clear which study is more appropriate for deriving an acceptable daily intake (ADI) value. Both studies used Fischer 344 rats, and both used the same type of DINP (DINP-1), although the DINP was from two different suppliers. The CPSC staff used the Lington study, which is more sensitive (Babich 1998; CPSC 1998; Lee 1998). Using the most sensitive study is consistent with the CPSC chronic hazard guidelines (CPSC 1992). Others have argued that the Moore study, which exhibits a less sensitive dose response, should be used because it includes two dose levels between the NOAEL and the lowest-observed-adverse-effect level (LOAEL) in the Lington study (CMA 2000; EPL 1999; France 2001; Wilkinson and Lamb 1999).

The Chemical Manufacturers Association (currently known as the American Chemistry Council) convened a pathology working group (PWG) to review histological slides from both studies (CMA 2000). The PWG attributed the disparity between the two studies to differences in methodology (EPL 1999). According to the PWG, Lington et al. routinely prepared sections from each liver lobe plus gross lesions, resulting in 4 to 5 sections per liver. The number of liver sections routinely examined was not specified in the methods sections of either study. In contrast, Moore routinely reviewed only one section from

each liver plus gross lesions. Because the spongiosis hepatis was generally a microscopic lesion, Lington et al. had a higher probability of finding a lesion if one existed. The difference in methodology makes it difficult to compare the two studies.

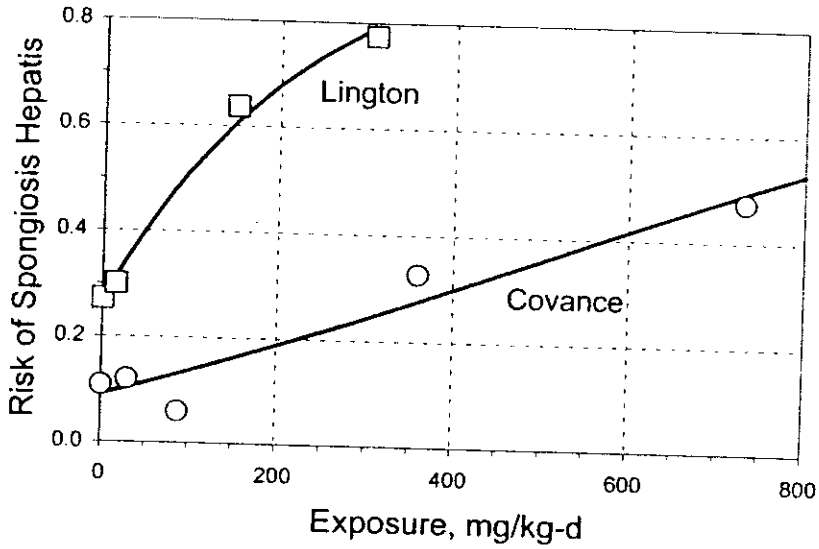


**Figure IV-1**. Risk of spongiosis hepatis in male F344 rats fed diisononyl phthalate (DINP) for two years: squares, Lington et al. 1997; circles, Moore 1998a (Covance); lines, polynomial (multistage) model for either data set (EPA 2000). Incidence data at terminal sacrifice are as revised by the pathology working group (EPL 1999).

Although there is no way to ascertain what results would have been obtained if Moore had reviewed four slides from each liver, the effect of reviewing additional slides can be modeled (Babich and Greene 2000). Assuming that Moore looked at exactly one slide from each liver examined, then the risk of spongiosis hepatis in the Moore data set represents the probability $p_M(D)$ of finding a lesion on one slide, at a given dose level D. Then, the risk of finding a lesion on four slides $p_4(D)$ is:

$$p_4(D) = 1 - [1 - p_M(D)]^4 \qquad \text{(IV.1)}$$

Thus, the data from the Moore (1998) study were scaled to make them roughly comparable to the Lington et al. (1997) study (Table IV-5). The only dose level common to both studies is zero dose. The zero dose incidence in the Moore study (6 of 55) was scaled to 20 of 55. This is not significantly different from the zero dose incidence in the Lington study (22 of 81) by a two-tailed Fisher's exact test (P=0.34). This observation tends to support the validity of the scaling process.

With the Moore data scaled to 4 slides, the two dose responses appear to be comparable (Figure IV-2). A marginal fit to the pooled data is obtained with a polynomial model (P=0.0075) (models are described below). A considerably better fit was obtained when the observation at 88 mg/kg-d, an apparent outlier, was ignored (P=0.64).

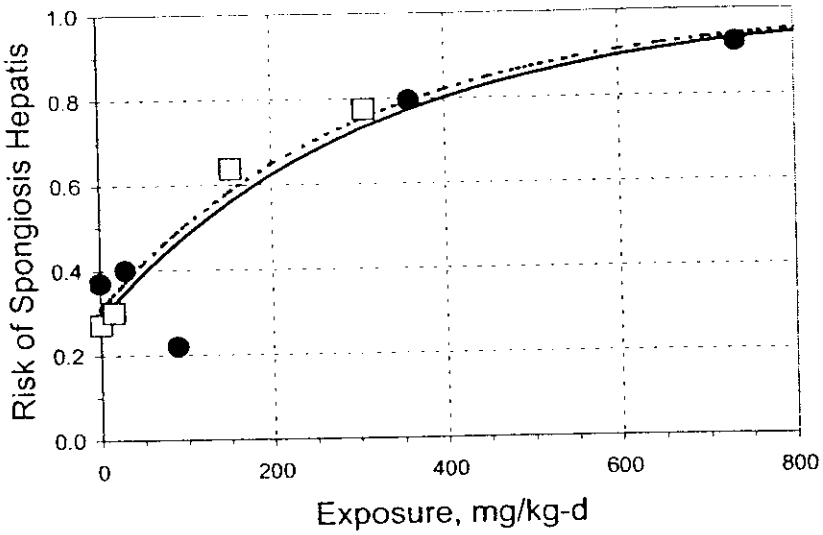


**Figure IV-2.** Risk of spongiosis hepatis--scaled data (see text): squares, Lington et al. 1997; filled circles, Moore 1998a scaled to 4 slides with equation (IV.1); solid line, polynomial (multistage) model for the pooled data (EPA 2000); broken line, polynomial model sans the observation at 88 mg/kg-d.

The Lington data can also be scaled to one slide per liver:

$$p(D) = 1 - [1 - p_L(D)]^{1/4} \qquad \text{(IV.2)}$$

where: $p_L$ is the probability of finding a lesion by viewing 4 slides.

This also makes the two dose responses comparable (not shown) (see Babich and Greene 2000). It should be noted that the number of slides viewed affects the incidence of spongiosis hepatitis in both the control and treated animals. Thus, viewing more than 4 slides could result in a higher background incidence than was observed in the Lington et al. study.

The sponsor of the Lington study also commissioned a reevaluation of slides from this study (Brown 2000). Slides from male rats diagnosed with spongiosis hepatis were evaluated to determine the number of slides with spongiosis hepatis, the number of foci per slide, and the severity of the effect. The purpose of the reevaluation was to further investigate the effect of the number of slides per liver on incidence. The dose responses for each liver lobe are plotted in Figure IV-3. These dose responses are roughly consistent with the dose response for the Lington study scaled to one slide. The observed incidence of spongiosis hepatis was slightly greater in the left and right lobes than in the median and claudate lobes.

The preceding analyses are consistent with the conclusion of the pathology working group that the difference in dose response between the two studies can be attributed to differences in methodology, that is, the number of slides from each liver that were examined microscopically. Furthermore, the observed incidence at the NOAEL in the Moore study is apparently an outlier (Figure IV-1). These findings support the use of the more sensitive study, that is, Lington et al., to establish a NOAEL (15 mg/kg-d) for liver effects.

Lington et al. concluded that spongiosis hepatis and other non-neoplastic liver lesions were associated with MNCL (Lington et al. 1997). However, the pathology working group found that about half of the animals with spongiosis hepatis did not have MNCL (EPL 1999, see p. 16 and Tables 11-12; see also Brown 2000). Therefore, they concluded that, although spongiosis hepatis was somewhat associated with MNCL, it was not a consequence of MNCL. Furthermore, spongiosis hepatis and hepatic necrosis were also observed in the Bio/dynamics study with DINP-A, in which hematological neoplasms were not reported (Bio/dynamics 1986). Therefore, it seems reasonable to conclude that spongiosis hepatis may be induced by chronic exposure to DINP independently of MNCL (CPSC 2001; EPL 1999; Lee 1998).

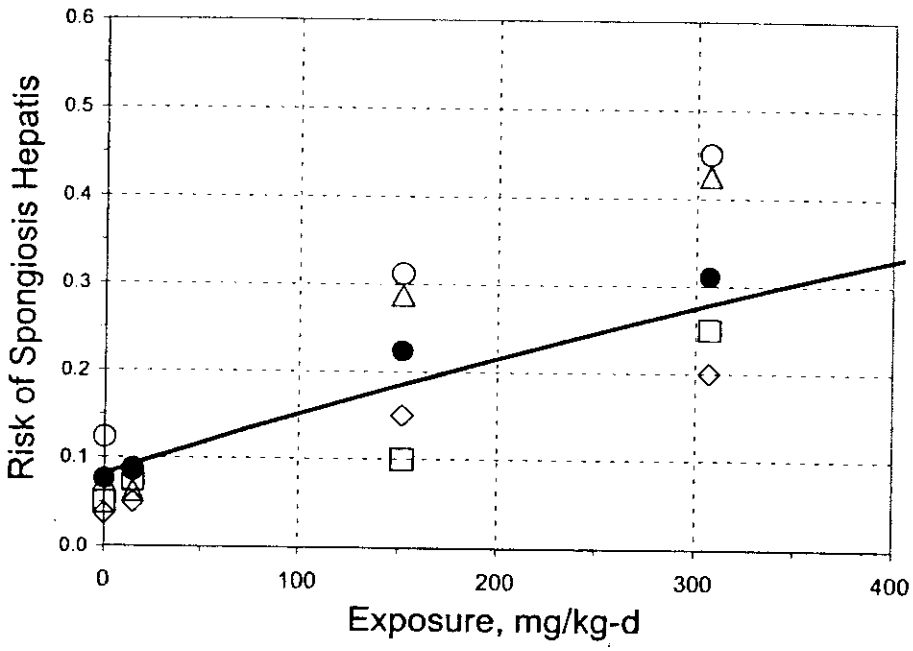


**Figure IV-3.** Risk of spongiosis hepatis by liver lobe (see text): filled circles, Lington et al. 1997 scaled to 1 slide with equation (IV.2); open circles, Lington et al. left lobe; squares, Lington et al. median lobe; triangles, Lington et al. right lobe; diamonds, Lington et al. caudate lobe; line, polynomial (multistage) model for pooled data, one slide for liver (see text) (EPA 2000). Lobe-specific incidence data from Brown (2000).

One may also consider whether spongiosis hepatis was associated with liver tumors or peroxisome proliferation. Spongiosis hepatis was sometimes associated with liver

tumors, but frequently was not (Moore 1998a). Spongiosis hepatis was found primarily in male rats, whereas peroxisome proliferation is induced in both sexes of mice and rats (see below). Therefore, the CHAP concluded that spongiosis hepatis likely occurred independently of liver tumors and peroxisome proliferation (CPSC 2001).

As discussed above, spongiosis hepatis is a focal, degenerative liver lesion found in aging male rats. The incidence (Lington et al. 1997; Moore 1998a) and number of lesions per animal (Brown 2000) increased in a dose-dependent manner following exposure to DINP. Spongiosis hepatis is considered to occur independently of the occurrence of liver neoplasms (Moore 1998a), MNCL (CPSC 2001; EPL 1999; Lee 1998), and peroxisome proliferation (CPSC 2001). The more sensitive study (Lington et al. 1997) may be used to establish a NOAEL for liver effects (Babich and Greene 2000; CPSC 1998; CPSC 2001; CSTEE 2001; Lee 1998).

**Table IV-5.** Incidence of spongiosis hepatis in male rats at terminal sacrifice—pooled data when 4 slides are viewed (Babich and Greene 2000).

| Dose mg/kg-d | Study | N | Observed [a] | | 4 Slides per liver [b] | |
|---|---|---|---|---|---|---|
| | | | X | P | X' | P' |
| 0 | Lington | 81 | 22 | 0.272 | 22 [c] | 0.272 |
| 0 | Moore | 55 | 6 | 0.109 | 20 [c] | 0.364 |
| 15 | Lington | 80 | 24 | 0.300 | 24 | 0.300 |
| 29 | Moore | 50 | 6 | 0.120 | 20 | 0.400 |
| 88 | Moore | 50 | 3 | 0.060 | 10 | 0.200 |
| 152 | Lington | 80 | 51 | 0.638 | 51 | 0.638 |
| 307 | Lington | 80 | 62 | 0.775 | 62 | 0.775 |
| 359 | Moore | 55 | 18 | 0.327 | 43 | 0.782 |
| 733 | Moore | 55 | 26 | 0.473 | 50 | 0.909 |

Dose, dose in feed, milligrams per kilogram per day; Study, Lington et al. (1997) or Moore (1998a) (Covance); N, number of animals at risk; X, observed number of animals with spongiosis hepatis at terminal sacrifice; P, observed fraction of animals with spongiosis hepatis, that is, P = X / N; X', number of animals with spongiosis hepatis assuming 4 slides per liver; P'; fraction of animals with spongiosis hepatis assuming 4 slides per liver.

[a] Incidence data are as reevaluated by the Pathology Working Group (EPL 1999).
[b] Data from Moore (1998a) were adjusted according to equation (IV.1) (see text).
[c] The two incidences at zero dose are not significantly different by a two-tailed Fisher's exact test (P=0.34).

b. Mice

In the Covance study in B6C3F1 mice, focal necrosis, diffuse hepatocellular enlargement, and cytoplasmic eosinophilia were significantly elevated in both males and females at 0.8 percent DINP (Moore 1998b, Table 11D). The incidences of the focal necrosis

declined to background levels in the recovery group, in which animals were exposed to 0.8 percent DINP for 78 weeks, then allowed to recover for 26 weeks. The incidences of hepatocellular enlargement and cytoplasmic eosinophilia also declined dramatically, although not to background levels.

In a 13 week study in B6C3F1 mice, diffuse hepatocelluar enlargement and individual cell necrosis were reported in male and female mice at feed levels of 1.0 and 2.0 percent, respectively (Bankston 1992; Moore 2000). The NOEL for liver histopathological effects in mice was 0.4 percent (Moore 1998b).

c. Primates

No histopathological, clinical chemistry or hematological changes were reported to occur in the two primate studies. However, these studies are limited by the small numbers of animals (4) per dose/sex group and somewhat by their short duration. Cynomolgus monkeys were treated with 500 mg/kg-d for 14 days (Pugh et al. 2000), while marmosets were treated with up to 2500 mg/kg-d for 13 weeks (Hall et al. 1999). For comparison, histopathological effects were reported to occur in rats treated for 13 weeks at doses of at least 584 mg/kg-d (Myers 1991).

B. Kidney

Effects of DINP exposure on the kidney are summarized in Table IV-6 (reviewed in CERHR 2000a; CPSC 2001). Increased kidney weights were reported in rats following as little as 3 weeks exposure (BIBRA 1985). In a 13 week study, increased kidney weights and blood urea nitrogen levels were found in both sexes, with microscopic lesions occurring only in males, at a dietary level of 0.25 percent DINP or greater (Myers 1991). In the 2-year Lington study, increased kidney weights were reported in both sexes beginning at 6 months at 0.3 and 0.6 percent DINP (Lington et al. 1997). In the Covance study in rats, increased kidney weights and blood urea nitrogen were found in males and females at 0.6 and 1.2 percent DINP (Moore 1998a). Kidney weights returned to control levels in the recovery group animals, but blood urea nitrogen remained elevated in recovery group males. Increases in mineralization of renal papillae and pigmentation of tubular cells were found in males at 0.6 and 1.2 percent DINP, which were not reversed in the recovery group. Urine volume was increased and urine electrolytes decreased in males at 1.2 percent DINP and in the recovery group.

In the 2-year Covance study in mice, kidney weights were significantly decreased in males given 0.15 percent or more DINP (Moore 1998b). The decrease in kidney weight was somewhat reversible in the recovery group. Increased incidence and severity of chronic progressive nephropathy was reported in females at 0.8 percent DINP. Increased urine volume and decreased electrolytes were found in males at 0.4 and 0.8 percent, and in females at 0.8 percent, which the authors attributed to an alteration in the concentrating ability of the renal tubule epithelium. In the 13-week pre-chronic study, kidney weights decreased in males, but increased in females (Moore 2000). Tubular nephrosis was found in males at 2.0 percent DINP.

**Table IV-6.** Kidney effects following DINP exposure [a]

| Species/ strain | Duration | Doses | Effect | NOEL [b] | Reference |
|---|---|---|---|---|---|
| Rat, F344 | 3 weeks | 0, 0.06, 0.12, 0.25 % in feed (M: 0, 639, 1192, 2195 mg/kg-d F: 0, 607, 1198, 2289 mg/kg-d) | Increased relative kidney weight | ND [c] | BIBRA 1985 |
| Rat, F344 | 13 weeks | 0, 0.1, 0.3, 0.6, 1.0, 2.0 % in feed (0, 50, 150, 320, 530, 1260 mg/kg-d) | Increased kidney weight (both sexes); nephrotic and regenerative changes (males) | 0.1 % | Bird et al. 1986 |
| Rat, F344 | 13 weeks | 0, 0.25, 0.5, 1.0, 2.0 % in feed (M: 0, 146, 292, 584, 1168 mg/kg-d F: 0, 182, 364, 728, 1456 mg/kg-d) | Increased kidney weight, BUN, (both sexes); microscopic lesions (males) | 0.25 % | Myers 1991 |
| Rat, F344 | 2 years | 0, 0.03, 0.3, 0.6 % in feed (M: 0, 15, 152, 307 mg/kg-d F: 0, 18, 184, 375 mg/kg-d) | Increased relative kidney weights (both sexes); increased urine volume (high dose males); increased tubular cell pigmentation associated with MNCL | 0.03 % | Lington et al. 1997 |
| Rat, F344 | 2 years | 0, 0.05, 0.15, 0.6, 1.2 % in feed (M: 0, 29, 88, 359, 733 mg/kg-d F: 0, 36, 109, 442, 885 mg/kg-d) | Increased kidney weight and BUN (both sexes); mineralization of renal papillae, increased pigmentation of tubular cells, increased urine volume, decreased electrolytes (males) | 0.15 % | Moore 1998a |
| Rat, SD | 2 years | 0, 0.05, 0.5, 1.0 % in feed (M: 0. 27, 271, 553 mg/kg-d F: 0, 33, 331, 672 mg/kg-d) | Increased kidney weight (high dose males; mid and high dose females); increased mineralization at high dose (significant in males) | 0.05 % | Bio/dynamics 1986 |

**Table IV-6**. Kidney Effects following DINP exposure (continued)

| | | | | | |
|---|---|---|---|---|---|
| Mouse, B6C3F1 | 13 weeks | 0, 0.15, 0.4, 1.0, 2.0 % in feed (M: 0, 340, 904, 2365, 5472 mg/kg-d F: 0, 389, 1041, 2834, 6070 mg/kg-d) | Increased kidney weights (females, 2.0%); decreased kidney weights (males, ≥0.4%); tubular nephrosis (males, 2.0%). | 0.15 % | Bankston 1992 Moore 2000 |
| Mouse, B6C3F1 | 2 years | 0, 0.05, 0.15, 0.4, 0.8 % in feed (M: 0, 90, 276, 742, 1560 mg/kg-d) F: 0, 112, 336, 910, 1888 mg/kg-d) | Decreased kidney weights (males, ≥0.15%); increased urine volume (males, 0.04%, both sexes, 0.8%); increased progressive nephropathy (females, 0.8%) | 0.05 % | Moore 1998b |

[a] Adapted from CPSC 2001 with changes.
[b] NOEL, no observed effect level.
[c] ND, not determined.

C. Other Effects

Hematology. In the Lington study, erythrocyte count, hemoglobin, and hematocrit were reduced in animals fed 0.3 or 0.6 percent DINP, but were only statistically significant in males at 0.6 percent DINP (Lington et al. 1997). In the Covance study in rats, erythrocyte count, hemoglobin, and/or hematocrit were significantly reduced at certain doses and time points in rats of both sexes at 0.15, 0.6, or 1.2 percent DINP and in recovery group animals (Moore 1998a). However, these were only consistently reduced at doses of 0.6 percent or greater. At 104 weeks, hemoglobin (1.2 %) and hematocrit (0.6%) were significantly reduced in males, while erythrocytes, hemoglobin, and hematocrit were significantly reduced in females at 0.6 and 1.2 percent DINP. These effects were apparently reversed in the recovery group animals. The NOAEL for hematological effects was 0.3 percent DINP (Lington et al. 1997).

Endocrine Effects. DINP was inactive in an *in vitro* assay that measured binding of phthalates to estrogen receptors (Zacharewski et al. 1998) or in an *in vitro* assay of estrogen-induced gene expression (Harris et al., 1997). DINP did not increase uterine wet weight or vaginal epithelial cell cornification in immature or mature ovariectomized rats (Zacharewski et al. 1998). Perinatal exposure to DINP and other phthalates causes reproductive malformations in male rats by an antiandrogenic mechanism (Gray et al. 2000; see below, part V, Reproductive and Developmental Effects). These effects are apparently the result of lowered testosterone levels during development rather than a direct effect of the phthalate on the androgen receptor (Parks et al. 2000).

Reduced testicular weights, in the absence of histopathological effects, were reported in B6C3F1 mice (Bankston 1992) and in Fischer 344 rats (Myers 1991) given ≥1.0 percent DINP in feed for 13 weeks. Small numbers of immature or abnormal sperm were also present at 1.0 percent DINP in mice (Bankston 1992). Reduced testicular weights without histopathological effects were also reported in chronic studies in B6C3F1 mice at ≥0.4 percent (Moore 1998b), but not in rats at doses up to 1.2 percent (Lington et al. 1997; Moore 1998a). Relative adrenal gland weights were slightly increased at 0.6 percent DINP at terminal sacrifice in the Lington study in Fischer 344 rats (Lington et al. 1997). Spleen weights were increased in female rats at ≥0.6 percent at terminal sacrifice in the Covance study (1998a).

D. Summary of Systemic Effects

Non-cancer systemic health effects are summarized in Table II-7. Liver is the most sensitive organ site for the toxic effects of DINP, with male rats being the most sensitive species and sex. Thus, liver effects in the rat have been considered to be the critical endpoint for assessing the systemic effects of DINP (Babich 1998; CPSC 1998; CPSC 2001; CSTEE 2001; France 2001; Wilkinson and Lamb 1999). At dietary doses of 0.6 percent DINP or more, adverse effects in the liver include spongiosis hepatis, focal necrosis, and hepatomegaly (Lington et al. 1997; Moore 1998a). These effects are accompanied by increases in serum enzymes indicative of liver damage and hematological changes. Therefore, the CPSC staff concludes that DINP is probably toxic

to humans, as defined under the FHSA and implementing regulations, based on sufficient evidence of chronic toxicity in experimental animals (CPSC 1992).

The LOAEL for liver effects was 152 mg/kg-d in the Lington study, at which increased incidence of spongiosis hepatis, a degenerative lesion of the perisinusoidal cells, and increased serum alkaline phosphatase were found. The LOAEL in the Covance study was 359 mg/kg-d, where increased incidence of spongiosis hepatis and increased serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were found. As discussed above, the more sensitive study will be used to determine a NOAEL for systemic effects. Therefore, the NOAEL for systemic effects is 15 mg/kg-d, which is based on increased incidence of spongiosis hepatis and increased serum enzyme levels in male rats (CPSC 1998; CPSC 2001; CSTEE 2001; Lee 1998).

DINP-A (71549-78-5) is a diisononyl phthalate that was never commercialized (see part II). It is believed to be similar to DINP-2. This product was tested in a lifetime feeding study in male and female Sprague-Dawley rats (Bio/dynamics 1986). Hepatic necrosis, as well as spongiosis hepatis, were reported at the LOAEL of 27 mg/kg-d. In comparison, the LOAEL in the Lington study was 152 mg/kg-d. This apparent difference in the toxic potency between the Bio/dynamics study and the Lington study may be due to either differences in toxicity between the two DINP's or to the use of different rat strains. Dose selection may also contribute to the different LOAEL values. Furthermore, the observation of hepatic necrosis at the LOAEL may represent a greater toxicological concern than spongiosis hepatis (CPSC 2001). However, it should be noted that the incidence of necrosis was not dose-dependent. The incidence was significantly different from the control at the low and high doses, but not at the mid dose (see Table IV-4).

DINP-A was never commercialized, and it cannot be established with certainty at this time whether this DINP is, in fact, identical to DINP-2 (compare CSTEE 2001). It may be prudent to presume that currently-used DINP's would give similar results if tested in Sprague-Dawley rats. However, given the potential regulatory implications, it would be difficult to justify deriving a NOAEL value from a bioassay with a substance that was never in commerce. Therefore, the NOAEL from the Lington study will be used for risk assessment purposes (CPSC 2001; CSTEE 2001). If it is determined in the future that DINP-A is identical to DINP-2, then the use of the Bio/dynamics study may be appropriate.

**Table IV-7.** Summary of non-cancer systemic effects in 2-year feeding studies [a]

| Effect | Most sensitive species/sex | NOEL [b] mg/kg-d | LOEL mg/kg-d | Reference |
|---|---|---|---|---|
| **Liver** | | | | |
| Spongiosis hepatis | Male rat | 15 | 152 | Lington et al. 1997 |
| | | 88 | 359 | Moore 1998a |
| Focal necrosis | Male rat | 152 | 307 | Lington et al. 1997 |
| Hepatomegaly | Male rat | 88 | 359 | Moore 1998a |
| Liver-specific serum enzymes | Male rat | 15 | 152 | Lington et al. 1997 |
| **Kidney** | | | | |
| Mineralization of renal papillae | Male rat | 88 | 359 | Moore 1998a |
| Progressive nephropathy | Female mouse | 910 | 1888 | Moore 1998b |
| Kidney weight change | Male rat | 152 | 307 | Lington et al. 1997 |
| **Hematological Changes** | Male rat | 152 | 307 | Lington et al. 1997 |
| | | 88 | 359 | Moore 1998a |

[a] Adapted from CPSC 2001 with changes.
[b] NOEL, no observed effect level; LOEL, lowest observed effect level.