

SAFE TOYS

PHOTOCOPY
PRESERVATION

Congress of the United States
Washington, DC 20515

November 18, 1998

Hon. William Jefferson Clinton
President of the United States
The White House
1600 Pennsylvania Ave.
Washington, DC 20500

Dear Mr. President:

Recently there have been allegations that the Administration may be attempting to block efforts by the European Union to protect children from a plastic additive used in toys and other products. We are writing to inquire whether these allegations are true.

According to news reports and numerous environmental and health organizations, the Department of Commerce is lobbying to prevent the European Union from banning the sale of toys made with phthalates, a chemical additive used as a softener in plastics. Some studies have indicated that phthalates used in soft polyvinyl chloride (PVC) baby toys leach out when children suck on them. Other studies suggest that in sufficient quantity, phthalate exposure is identified as causing hormonal disturbance, liver and kidney damage, and cancer.

The EU is considering the ban to reduce health risks to children based on studies undertaken by Dutch Ministry of Health, Welfare and Sport, the Netherlands' Health Protection Inspectorate, Greenpeace, and others. In 1998, a risk analysis of phthalates by the Dutch National Institute of Public Health and Environment found that "the resulting uptake by young children was estimated to approximate or exceed the tolerable daily intake," and the Chief Inspector for Health Protection recommended that retailers voluntarily withdraw soft baby toys from the market. A study by Brunel University in the United Kingdom identified other sources of phthalate exposure in food samples, river water, and printing inks and adhesives used in food packaging.

Several individual countries and companies are also acting to minimize risks of PVCs and its chemical additives. Austria, Sweden, Denmark, and Norway have initiated bans on toys containing phthalates. Lego and Nike have pledged a comprehensive phase-out of vinyl in all of their products.

We recognize that the science on phthalates is evolving and there is scientific uncertainty about the risks these compounds pose. Nevertheless, if the reports about the Department of Commerce's actions are accurate, we are very concerned that they represent an unwarranted intrusion into the ability of other countries to make their own decisions about public health risks.

Hon. William Jefferson Clinton
November 18, 1998
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During the 1993 NAFTA debates, U.S. Trade Representative Kantor wrote members of Congress that "each government may establish those levels of protection for human, animal or plant life or health that the government considers to be appropriate." In the context of the General Agreement on Tariffs and Trade negotiations, the Sanitary and Phytosanitary Standards (SPS) Agreement specifically recognizes that "the basic aim of the SPS Agreement is to maintain the sovereign right of any government to provide the level of health protection it deems appropriate," so long as protections are not used to create an unfair trade barrier. Application of these principles to phthalates would seem to require that the United States respect the EU's right to determine for itself an appropriate level of risk.

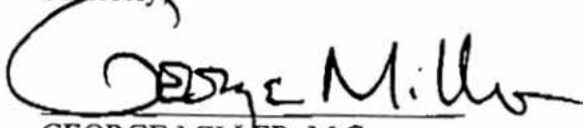
To help us better understand these issues, we ask you to provide the Administration's views on whether toys and other products made with phthalates are potentially hazardous to children's health and whether safe alternatives are available as a replacement. The Consumer Product Safety Commission is undertaking a study of phthalate exposure that will be released shortly. Will the Administration and relevant agencies consider aggregate exposure of phthalates to children in determining appropriate levels of risk and product safety? In addition, we request a detailed account of Administration actions with regard to the EU's proposed ban on toys made with phthalates. Did the Departments of Commerce or State lobby against the proposed ban?

The Administration has taken the lead on protecting children. Executive Order 13045, "Protection of Children from Environmental Health Risks and Safety Risks," which we strongly support, directs each federal agency to "ensure that its policies, programs, activities, and standards address disproportionate risks to children that result from environmental health risks or safety risks." Consistent with this objective, we urge you to take all necessary steps to ensure that children's toys and other products are safe for children.

It is our understanding that the EU and individual countries are considering this ban in order to protect children's health. It would be unfortunate if the United States found itself undermining these efforts for the benefit of toy company profits.

In advance, we appreciate your timely attention to these allegations and the serious nature of this issue.

Sincerely,



GEORGE MILLER, M.C.

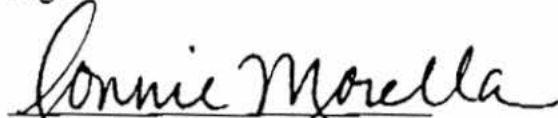
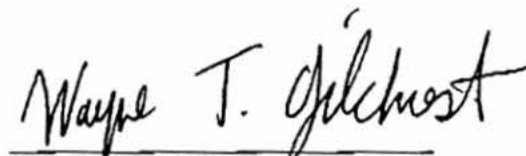
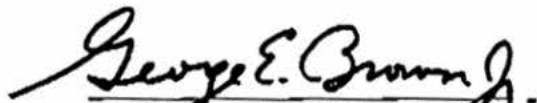
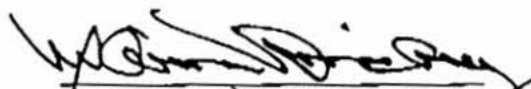
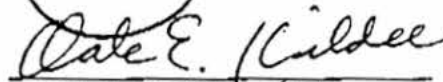
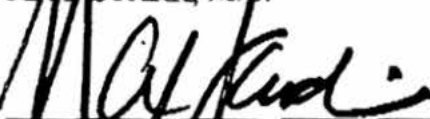
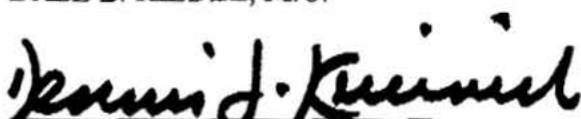
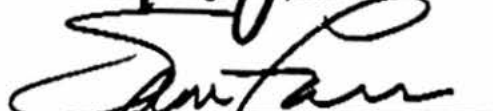
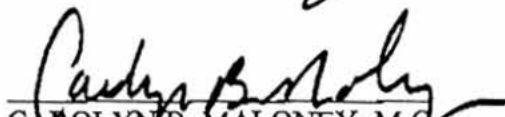
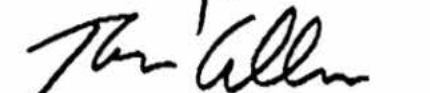
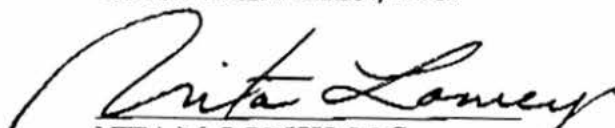
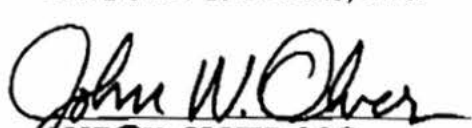
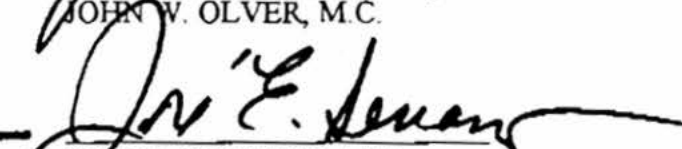
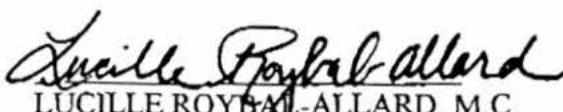


HENRY A. WAXMAN, M.C.

Hon. William Jefferson Clinton

November 18, 1998

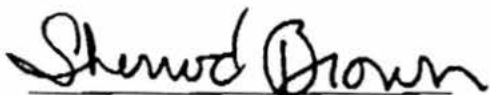
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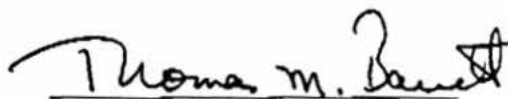

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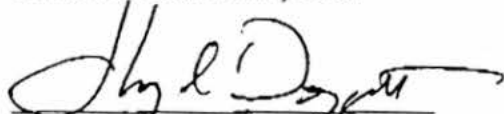
Hon. William Jefferson Clinton

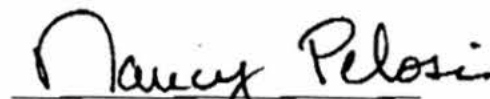
November 18, 1998

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THOMAS M. BARRETT, M.C.


LLOYD DOGGETT, M.C.


NANCY PELOSI, M.C.

cc: Hon. William Daley, Secretary of Commerce
Hon. Ann Brown, Chairman, Consumer Product Safety Commission
Hon. Carol Browner, Administrator, Environmental Protection Agency

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Congress of the United States
House of Representatives
Washington, DC 20515-0507

November 18, 1998

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Hon. William Jefferson Clinton
President of the United States
The White House
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Washington, DC 20500

Dear Mr. President:

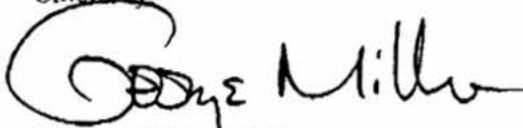
I inadvertently left out two names of Members of Congress who joined me today in writing to you concerning recent allegations that your Administration may be attempting to block efforts by the European Union to protect children from a plastic additive used in toys and other products.

Reps. **Thomas Manton** and **Donna Christian-Green** also agreed to sign the letter.

I regret this oversight and I would appreciate your adding their names to the list of those who signed the letter.

Thank you very much.

Sincerely



George Miller, M.C.

Cc: Hon. William Daley, Secretary of Commerce
Hon. Ann Brown, Chairman, Consumer Product Safety Commission
Hon. Carol Browner, Administrator, Environmental Protection Agency

Letter to Clinton on Toxic Toys 11/18/98

George Miller
Henry Waxman
Connie Morella
Wayne Gilchrest
George Brown Jr.
Maurice Hinchey
Pete Stark
Dale Kildee
Max Sandlin
Dennis Kucinich
Sam Farr
Frank Pallone
Martin Meehan
Carolyn Maloney
Lucille Roybal-Allard
Thomas Allen
Bernard Sanders
Nita Lowey
John Olver
Elizabeth Furse
Jose Serrano
Barbara Lee
Sherrod Brown
Lloyd Doggett
Thomas Barrett
Nancy Pelosi
Thomas Manton
Donna Christian-Green

Office of Congressman George Miller

**Statement by the President on Release of Consumer Product Safety
Commission Report on Phthalates in Toys**
December 2, 1998

I congratulate Chairman Ann Brown and the Consumer Product Safety Commission on the release of a comprehensive and thoughtful report examining the potential exposure and health risks to children from teething rings, pacifiers, rattles and toys containing chemicals called phthalates that are used to soften plastic. The report makes clear that children are not at risk of harmful exposure to these chemicals, provides information to consumers about the safety of these products that may contain phthalates, and outlines the Commission's plans to for further study. I also commend the many manufacturers and retailers who are taking the additional, precautionary measure of discontinuing the sale of products containing the phthalate DINP that are designed for children to put in their mouths. This should allay any remaining fears that families have about these products.

The CPSC report and supporting measures by manufacturers will go a long way toward calming concerns about the safety of products used everyday by our nation's youngest children. It also commits the Consumer Product Safety Commission to pursue additional rigorous work in this area. The Administration will support both the Commission's continued efforts to investigate health issues related to phthalates, as well as governmental and private efforts both here and abroad to take appropriate precautionary measures. .

#

**Questions and Answers on Release of Consumer Products Safety
Commission Report on Phthalates in Toys
December 2, 1998**

Q. What is the Consumer Product Safety Commission (CPSC) releasing today?

- A. The CPSC is releasing a report examining the potential exposure and health risks to children from teethingers, pacifiers, rattles, and toys containing chemicals called phthalates (pronounced fal-ates) that are used to soften plastic. The report concludes that the plastic toys at issue do not release phthalates -- and so children are not exposed to phthalates -- at levels that might be harmful. For this reason, the CPSC has decided not to ban these products.

The CPSC, however, also announced the plans of a number of manufacturers and retailers to discontinue selling certain toys containing DINP and to begin producing toys without this chemical. Manufacturers and retailers have agreed to take these actions out of an abundance of caution and to allay any fears relating to these products.

Q. What is the Administration going to do in response to the CPSC's action, which seem to indicate at least some uncertainty about whether products containing phthalates are harmful to children?

- A. The report shows that, based on all currently available evidence, DINP used in toys, teethingers, and pacifiers is not released at levels that is potentially harmful to children. But because our children's safety is of such paramount importance, the CPSC has committed to doing additional research on this issue and has encouraged manufacturers and retailers to discontinue sale of these products. The Administration will support in every way possible the CPSC's efforts to continue to research DINP, as well as to study alternative methods of softening plastic for use in children's toys.

Q. If this report shows that there is no risk to children, why did the CPSC encourage toy manufacturers and retailers to phase out the use of this chemical and stop selling products containing it?

- A. Although the scientific evidence does not support removal of these products, toy manufacturers and retailers are acting out of an abundance of caution, to remove any risk whatsoever. By taking these voluntary actions, these companies are making clear to their customers that they will take every possible precaution to protect children, even where there appears to be no real risk to their safety.

Q. Environmental groups and others claim that the Commerce and State Departments -- acting at the request of US toy manufacturers -- influenced the European Union's decision not to ban phthalates. Is this true?

A. The report released today states that the Consumer Product Safety Commission does not believe that there is a scientific basis for a ban on phthalates in children's toys and other products. Although the Commerce and State Departments initially expressed concerns about whether the product bans considered (but rejected) by the European Union were scientifically justified, the Administration recognizes that each country has the right to take whatever precautionary measures it deems appropriate to protect public health. The President has made it clear to the Commerce and State Departments that they should respect any precautionary steps that foreign countries believe to be appropriate with respect to these products.



**U.S. CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, D.C. 20207**

Fax Message Cover Sheet

DATE: 12/3/98 TIME: 3:20

FAX TO: NAME: Jennifer Klein

FAX NUMBER: (202) 456-2878

VOICE PHONE NUMBER: _____

FROM: **OFFICE OF THE EXECUTIVE DIRECTOR**

NAME: Pamela Gilbert

VOICE PHONE NUMBER (301) 504-0550

FAX NUMBER: (301) 504-0121

SUBJECT: _____

NUMBER OF PAGES TO FOLLOW: 1



**U.S. CONSUMER PRODUCT SAFETY COMMISSION
WASHINGTON, D.C. 20207**

PHthalATES/CHILDREN'S CHEMICAL HAZARDS

I. Additional Work on Phthalates - \$2.0M

- o Chronic Hazard Advisory Panel (CHAP)
- o Children's Exposure Study *400 instead of 200*
- o Laboratory Test Method Development
- o Laboratory Testing of Products for Phthalate Release
- o Studies to Better Determine Background Levels of Phthalates in Children

II. Evaluation of Chemical Hazards in Children's Products - \$3.5M

- o Market Survey to Identify Products to Evaluate
- o Identify Chemicals Present in Selected Children's Products
- o Perform Chemical Release Studies on Selected Products
- o Conduct Toxicity Reviews
- o Quantify Exposure and Calculate Risks

Messenger to: _____

Jennifer Klein

2nd floor

West Wing

White House

(202) 456-2599

Leave at New Executive Office Building

News from CPSC

U.S. Consumer Product Safety Commission

Office of Information and Public Affairs

Washington, D.C. 20207

For Immediate Release
December 2, 1998
Release # 99-031

Contact: Russ Rader
(301) 504-0580 Ext. 1166

CPSC Releases Study on Phthalates in Teethers, Rattles and Other Children's Products

Washington, D.C. -- The U.S. Consumer Product Safety Commission (CPSC) today released the results of a study of a chemical, diisononyl phthalate (DINP) used to soften some plastic toys and children's products. The study concludes that few if any children are at risk from the chemical because the amount that they ingest does not reach a level that would be harmful. Generally, the amount ingested does not even come close to a harmful level. Therefore, the Commission staff is not recommending a ban on these products.

This study is the most comprehensive evaluation of phthalates in children's products conducted to date. However, the study identified several areas of uncertainty where additional scientific research is needed. As a precaution while more scientific work is done, the CPSC staff requested industry to remove phthalates from soft rattles and teethers. About 90 percent of manufacturers have indicated that they have or will remove phthalates from soft rattles and teethers by early 1999. In addition, until reformulated products are available, major retailers have removed teethers and rattles containing phthalates from store shelves. CPSC staff also has asked the industry to find a substitute for phthalates in other products intended for children under 3 years old that are likely to be mouthed or chewed.

Pacifiers and feeding bottle nipples are made of latex or silicone and do not contain phthalates. However, one pacifier and two models of feeding bottle nipples manufactured by the Gerber Products Company contained a related phthalate. The Gerber pacifier and nipples that contained phthalates are the Clear and Soft lines sold through 1998. Gerber has stopped making these products and is removing phthalates from all future production. Gerber has directed retailers to remove the phthalate-containing pacifier and nipples from store shelves. If you have one of the Gerber Clear and Soft pacifiers or nipples, dispose of them. No other Gerber pacifiers or nipples are involved since they do not contain phthalates.

Existing studies in laboratory animals indicate that in high doses, DINP damages the liver, kidneys and other organs in mice and rats. Other studies indicate that high doses may cause liver tumors in mice and rats. However, scientists do not agree about whether the cancer risk translates to humans.

Up to now, there has been no comprehensive study of how much phthalate can leach out of children's products. The potential for toxic effects in humans depends on the amount of the chemical that comes out of the products when they are mouthed or chewed and the amount of time a child spends each day putting these products in his or her mouth. Even though DINP may be present in a plastic toy or children's product, it must come out in significant amounts to pose a hazard. CPSC's study found that the amount of DINP in a product does not relate to the amount that leaches out.

The CPSC established a level used internationally as an acceptable daily intake level for DINP. For a measure of safety, this level is 100 times less than the amount found not to cause any adverse health effects in laboratory animals. CPSC scientists tested 31 different children's products that contained DINP and found that the amount that is released from the product when mouthed can vary widely, but is generally well below the level that could cause harmful effects. The CPSC used human adult volunteers to help determine how much of the chemical is released when the plastic is chewed or sucked. Using this data and estimating the amount of time children spend mouthing products that may contain DINP, allowed CPSC to estimate the risk to children. Based on this work, the CPSC study concludes that few if any children are at risk from DINP.

CPSC data show that children under the age of one year old are the most likely to mouth or chew soft plastic teethingers, rattles or toys. As a precaution, parents of young children who mouth these products for long periods of time may wish to dispose of them.

The CPSC staff is taking the following steps:

1. Recommending that a Chronic Hazard Advisory Panel made up of independent scientists be formed to carry out an additional scientific assessment of potential risk, including whether phthalates pose a cancer risk to humans.
2. Undertaking further study to determine the amount of time that children mouth products that could contain phthalates.
3. Continuing testing to determine the amount of phthalates released from children's products.

The following manufacturers have stopped or will stop using phthalates in teething and rattles by early 1999:

Chicco	Little Tikes
Disney	Mattel (Fisher-Price, ARCOTOYS, Tyco Preschool)
Evenflo	Safety 1st
The First Years	Sassy
Gerber	Shelcore Toys
Hasbro (incl. Playskool)	Warner Brothers Studio Stores

The following retailers have removed phthalate-containing teething, rattles, pacifiers, and bottle nipples from store shelves:

Toys-R-Us	Walmart
Sears	Target
K-Mart	

The U.S. Consumer Product Safety Commission protects the public from unreasonable risks of injury or death from 15,000 types of consumer products under the agency's jurisdiction. To report a dangerous product or a product-related injury and for information on CPSC's fax-on-demand service, call CPSC's hotline at (800) 638-2772 or CPSC's teletypewriter at (800) 638-8270. To order a press release through fax-on-demand, call (301) 504-0051 from the handset of your fax machine and enter the release number. Consumers can obtain this release and recall information at CPSC's web site at <http://www.cpsc.gov> or via Internet gopher services at gopher.cpsc.gov. Consumers can report product hazards to info@cpsc.gov. To establish a link from your web site to this press release on CPSC's web site, create a link to the following address: <http://www.cpsc.gov/cpscpub/prerel/prhtml99/99031.html>.

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News from CPSC

U.S. Consumer Product Safety Commission

Office of Information and Public Affairs

Washington, D.C. 20207

For Immediate Release
December 2, 1998
Release # 99-031

Contact: Russ Rader
(301) 504-0580 Ext. 1166

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

December 1998

U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

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

Executive Summary

December 1998

U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

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Executive Summary

Overview

1. The U.S. Consumer Product Safety Commission (CPSC) is investigating the potential health risks to children under 3 years of age from teethingers, rattles, and toys made from polyvinyl chloride (PVC) containing a chemical DINP (diisononyl phthalate) used to make the PVC softer.

2. Based on the work the staff has conducted and other scientific studies currently available, the staff concludes that few, if any, children are at risk from liver or other organ toxicity from the release of DINP from these products. This is because the amount they might ingest does not reach a level that would be harmful.

3. The staff believes that uncertainties remain relating to estimations of risk, including the risk of cancer, and that additional studies are needed. The staff recommends CPSC undertake the following additional work:

- Convene a Chronic Hazard Advisory Panel of independent scientists to study issues related to the chronic toxicity and risk, including the risk of cancer, associated with exposure to DINP in children's PVC products.
- Conduct an extensive exposure study to obtain a broader range of data from which to better define the amount of time children mouth products that could contain phthalates.
- Continue work to develop a laboratory test method that better estimates the amount of phthalate released when products are mouthed by children.
- Conduct additional testing of products intended for children under 3 years of age that contain DINP.

Description of Work to Date

CPSC staff has evaluated the potential health risks to children under 3 years of age from teethingers, rattles, and toys made from polyvinyl chloride (PVC) containing DINP.

This evaluation included laboratory testing to simulate the mouthing by young children of products that contain DINP and other phthalates. These tests provided information on the amount and type of phthalate released. CPSC staff also conducted tests using adult volunteers to compare the amount of DINP found in laboratory tests to the amount released when adults sucked or gently chewed on a piece of product.

CPSC staff analyzed the literature and other available information on the health effects of the DINP found in the children's products mentioned above. Staff also evaluated available information on the amount of time children would mouth products such as toys, teethingers, and rattles.

The information obtained from testing and analysis of the literature was used to estimate the potential hazard to children. Staff found the magnitude of the risk is directly related to the amount of DINP released from mouthing and the amount of time children mouth the products.

CPSC Study Findings

A number of important findings resulted from the Commission's study. These include the following:

Phthalates Found in Children's Products

- Based on products tested, DINP is the predominant phthalate used to soften PVC that is contained in some children's products sold in the United States. CPSC staff tested 35 children's PVC products that contained phthalates: 31 contained DINP, two (a pacifier and a baby bottle nipple) contained diisooctyl phthalate (DIOP), one (a soother) contained dinonyl phthalate (DnNP), and one (a child's purse) contained di(2-ethylhexyl) phthalate (DEHP). With pacifiers and baby bottle nipples, only one manufacturer was found to have some models that contained a phthalate. These models have been removed from the market. All other known pacifiers and baby bottle nipples are made from latex or silicone and therefore do not contain phthalates.

Release of DINP from Products

- CPSC laboratory testing of children's products likely to be mouthed by children under 3 years of age showed wide variability in the amount of DINP released. The amount of DINP used to soften the products also varied widely. Importantly, however, the staff found no relationship between the amount of DINP used in the product and the amount released when tested in the laboratory.

Measuring Release of DINP

- CPSC staff found that, based on information currently available, the method used to manufacture the product (e.g., injection or rotational molding or sheeting) does not correlate with the amount of DINP released. The staff also found that there is currently no laboratory test method available to estimate adequately the amount of DINP released during laboratory testing that correlates with the amount released when products are mouthed by humans. Work on developing such a method is proceeding at CPSC and in Europe.

- CPSC staff used 10 adult human volunteers to mouth a piece of a children's toy that contained DINP to determine the release of DINP. The amount of DINP released was higher than the amount released during CPSC laboratory simulation testing. The results indicated that there was a 39.5 fold higher level released during the human subjects testing. Accordingly, the staff applied this factor to increase the DINP release rates measured in the laboratory for the 31 products found to contain DINP.

Data on Children's Exposure

- CPSC staff found that the data available to estimate actual times that children put items that may contain phthalates in their mouths is very limited. The best data comes from a study released by the Dutch Consensus Panel in September 1998. The staff has relied on this data to estimate exposure to children for calculating risk. All previously published estimates of exposure have been based on professional judgment, but not on actual time measurements. The Dutch study found wide variability in the amount of time children spend mouthing. The study also found that children under 1 year of age spend considerably more time mouthing than do children 1 to 3 years of age. Since the Dutch Study was relatively small, CPSC staff recommends a larger observational exposure study in children ranging in age from 3 months to 3 years.

Acceptable Daily Intake

- Animal studies show that DINP causes chronic toxic effects to the liver and other organs. In order to determine the level at which humans are at risk CPSC staff calculated an acceptable daily intake (ADI) for humans. The ADI is a level that is not expected to cause harmful health effects in humans. Using data from the animal studies, staff calculated an acceptable daily intake (ADI) for humans to be 150 micrograms per kilogram of body weight per day. This value is derived by taking the highest level of exposure that did not result in an adverse health effect to animals and applying a 100-fold safety factor to account for possible differences between animals and humans and for differences in the sensitivity among individuals.

Estimated Exposure of Children

- CPSC staff estimated the exposure to DINP from children's teethingers, rattles, and toys. This information is provided in the table below. The data show that none of the daily intake estimates exceed the 150 micrograms per kilogram per day acceptable daily intake (ADI). No estimate of risk is provided for pacifiers or baby bottle nipples because only one manufacturer was found to have models that contained a phthalate (DIOP). This manufacturer has stopped using phthalates.

Estimated Exposure of Children to DINP in Teethingers, Rattles, and Toys

Children's Age	Estimated Daily Intake of DINP ($\mu\text{g/kg/day}$)			
	Geometric Mean	Confidence* Interval (CI)	95th Percentile	Confidence* Interval (CI)
3-12 Months	5.7	2.5-12.9	94.3	50.1-225.6
13-26 Months	0.7	0.3-1.6	7.6	4.4-16.2

*The Confidence Intervals shown in the table are a measure of uncertainty in the estimates of the Geometric Mean and 95th Percentile.

Possible Further Risk from DINP

- One animal study also found that DINP caused an increased incidence of liver tumors (carcinomas and adenomas) in rats and mice. There is uncertainty about the actual mechanism by which compounds such as DINP contribute to cancer in animals and whether this mechanism applies to humans. In addition, there is controversy over what model is appropriate to use to calculate any risk. CPSC staff recommends that a Chronic Hazard Advisory Panel of independent scientists evaluate the available scientific data and advise the Commission on this issue.

Conclusions

The CPSC staff concludes that based on the best available information about the amount of DINP released from the products tested by the staff and relying on the exposure information from the Dutch study, few, if any, children are at risk of liver or other organ toxicity from mouthing teethingers, rattles, and other PVC toys that contain DINP. However, there are a number of significant uncertainties in this assessment including the cancer risk, and further work is necessary to gather better data on which to base the health risk assessment.

Recommended Future Work

CPSC staff recommends the Commission undertake additional work to address the uncertainties that can affect the estimate of the risk to children. The additional work includes:

- Convening a Chronic Hazard Advisory Panel of independent scientists to study issues related to the chronic toxicity and risk, including the risk of cancer, associated with exposure to DINP in children's PVC products.
- Conducting an extensive exposure study to obtain a broader range of data from which to better define the amount of time children mouth products that could contain phthalates.
- Continuing work to develop a laboratory test method that better estimates the amount of phthalate released when products are mouthed by children.
- Conducting additional testing of products intended for children under 3 years of age that contain DINP.



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

December 1998

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Summary

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

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

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

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

I. INTRODUCTION

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

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

II. METHODOLOGY

A. Exposure

1. Impaction Method

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

2. Human Subjects Studies

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

3. Mouthing Activity

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

4. Daily Exposure

The estimated daily oral exposure was calculated by:

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

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

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

B. Chronic Toxicity

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

III. RESULTS

A. Exposure

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

Studies with human subjects were performed using disks with a surface area of approximately 10.3 cm^2 . The ratio between the *in vivo* and impaction methods averaged 39.5,

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

with a range of 22.9 to 72.6 (Table 2). The average (geometric mean) mouthing duration in the 3 to 12-month old group was estimated to be 12.0 minutes per day (Greene, 1998) (Table 3). The average mouthing duration for 13 to 26-months was estimated to be 2.1 minutes per day. These times apply only to toys, teethingers, and rattles, which may contain DINP. The average time for pacifiers, which do not contain DINP, was greater.

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

B. Chronic Toxicity

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

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

IV. DISCUSSION

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

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

A. Exposure

1. Migration Studies

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

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

migration rates (Chen, 1998b). Migration rates, measured by the CPSC staff, using the NERI method ranged from 7.2 to 102 $\mu\text{g}/\text{dm}^2/\text{h}$. Migration rates by the CPSC impaction method ranged from 105 to 133 $\mu\text{g}/\text{dm}^2/\text{h}$ (roughly equivalent to 13 $\mu\text{g}/11\text{ cm}^2/\text{h}$).

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

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

2. Mouthing Duration

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

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

estimated the average mouthing activity for two age groups: 3 to 12 months and 13 to 26 months. These age groups were based on the recommendation of the Division of Human Factors (Kiss, 1998) and are consistent with the results of the Dutch study (Green, 1998).

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

B. Chronic Toxicity

1. Acceptable Daily Intake

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

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

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

Although the studies tested DINP's from different sources, they are considered to be equivalent in their chemical composition and toxicity (Wilkinson, 1998). The background rate of spongiosis hepatitis was higher in the Lington study (about 30 percent) than in the Moore study (about 6 percent). However, the dose response in the Lington study remains more sensitive even after adjusting for background (Figure 3).

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

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

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

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

µg/kg-d. An estimate of the dietary intake of total phthalates in infants in Europe was reported to be 23 µg/kg-d (Janssen et al., 1998).

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

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

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

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

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

method; or assuming that all DAP's are equipotent. If the relative concentrations of different DAP's is unknown, assuming equal potency would be preferred.

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

C. Carcinogenicity

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

1. Carcinogenicity of DINP

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

The dose response observed with DINP is consistent with that of DEHP, another branched chain DAP. The incidence of HCC was significantly elevated in Fischer rats fed DEHP at 1.2 percent, but not at 0.6 percent (NTP, 1982). The incidence of HCC in males and females combined from the three DINP studies and the DEHP study were plotted on the same graph for

comparison (Figure 4). The dose responses from these studies appear to be similar, suggesting that DINP's from different sources may be similar in their cancer dose response. In mice, DEHP was 2 to 3-fold more potent than DINP (not shown). The similar response with DEHP suggests that the key structural feature responsible for carcinogenicity may be the presence of branched chains, rather than the presence of any specific isomers.

2. Mechanism of Action

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

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

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

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

bone marrow cells of F-344 rats in vivo, although the highest dose was only 5.0 mg/kg (Microbiological Associates, 1981e).

At least three mechanisms of action have been proposed for PPC's (Conway et al., 1989; IARC, 1995; Cattley et al., 1998): oxidative stress (oxidative DNA damage), cellular proliferation (mitogenesis), and the preferential growth of preneoplastic cells (tumor promotion). These proposed mechanisms are not mutually exclusive.

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

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

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

certain types of altered hepatic foci may explain why several promotion assays gave negative results (Bentley et al., 1993).

The promotion of spontaneously-initiated cells appears to be the most plausible mechanism of action for PPC's. However, tumor promotion activity has only been demonstrated for a few PPC's; it has not been demonstrated for DINP. Even if this is the predominant mechanism, PPC's are complete carcinogens, that is, administration of PPC's alone leads to tumor formation in animals (Reddy and Rao, 1995). Therefore, it is likely that other mechanisms, possibly including oxidative DNA damage and mitogenesis, also contribute to the carcinogenic process.

a. Peroxisome proliferator-activated receptor

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

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

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

b. Species differences in response to PPC's

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

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

3. Relevance of Animal Tumor Data in Assessing Human Risk

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

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

conditions of the bioassay; and (c) such effects have not been found in adequately designed studies of human systems (IARC, 1995). At this time it is not clear whether these criteria have been satisfied for DINP. For example, although DINP induced PPN under the conditions of the bioassay, it failed to induce chronic hepatocellular proliferation (Moore, 1998a,b).

4. Quantitative Cancer Risk Assessment

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

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

At this time, the choice of the appropriate dose response model for DINP remains unclear. There is ongoing research on the relevance of the tumors in animals to humans. In addition, research on the mechanism of action of PPC's is currently underway (Bucher, 1998; CMA, 1998). The relevant issues are whether a scientific consensus on the mechanism of PPC's exists, and how this applies in the case of DINP. This issue should be explored in an appropriate forum such as a workshop, public hearing, or Chronic Hazard Advisory Panel. The mechanism by

which cancer occurs plays a role in determining the appropriate model to use to calculate a risk. Since scientific consensus does not exist on how DINP causes cancer in animals, quantitative estimates of cancer risk associated with DINP exposure from children's products are not presented here. The issue of cancer risk will be addressed following additional consideration of this issue.

V. CONCLUSIONS

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

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

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

Continued on next page.

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

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

^a Includes only children's products containing DINP.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

^b Number of animals examined.

^c Number of animals with spongiosis hepatitis.

^d Fraction of animals with spongiosis hepatitis.

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

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

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

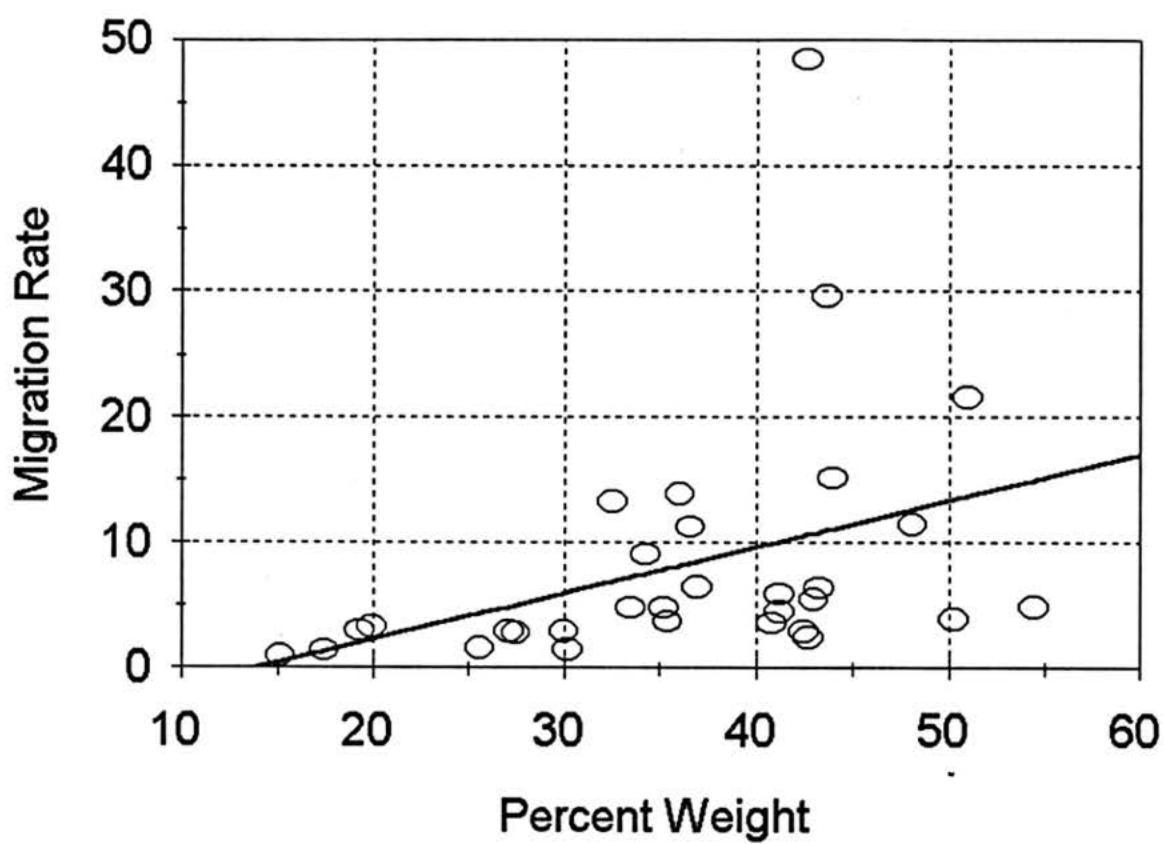


Figure 1. Effect of diisononyl phthalate (DINP) content (percent weight) on the migration rate ($\mu\text{g}/11\text{ cm}^2/\text{h}$) measured by the impaction method (Chen, 1998a). (O) Observed; (—) regression line ($r^2 = 0.14$).

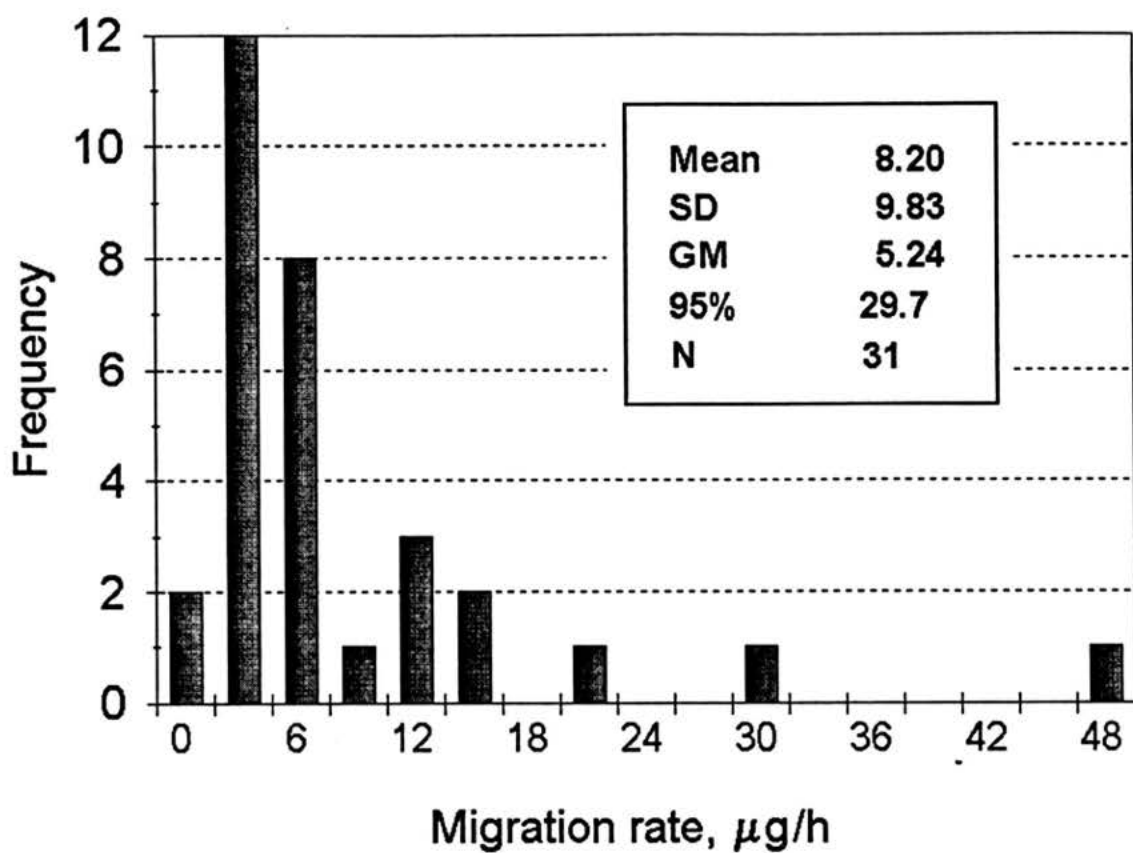


Figure 2. Frequency distribution of diisononyl phthalate (DINP) migration rates for 31 children's products, as measured by the impaction method (Chen, 1998a). The migration rate is in $\mu\text{g/h}$ for an 11 cm^2 area. GM, geometric mean; SD, standard deviation; 95%, 95th percentile value; N, number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

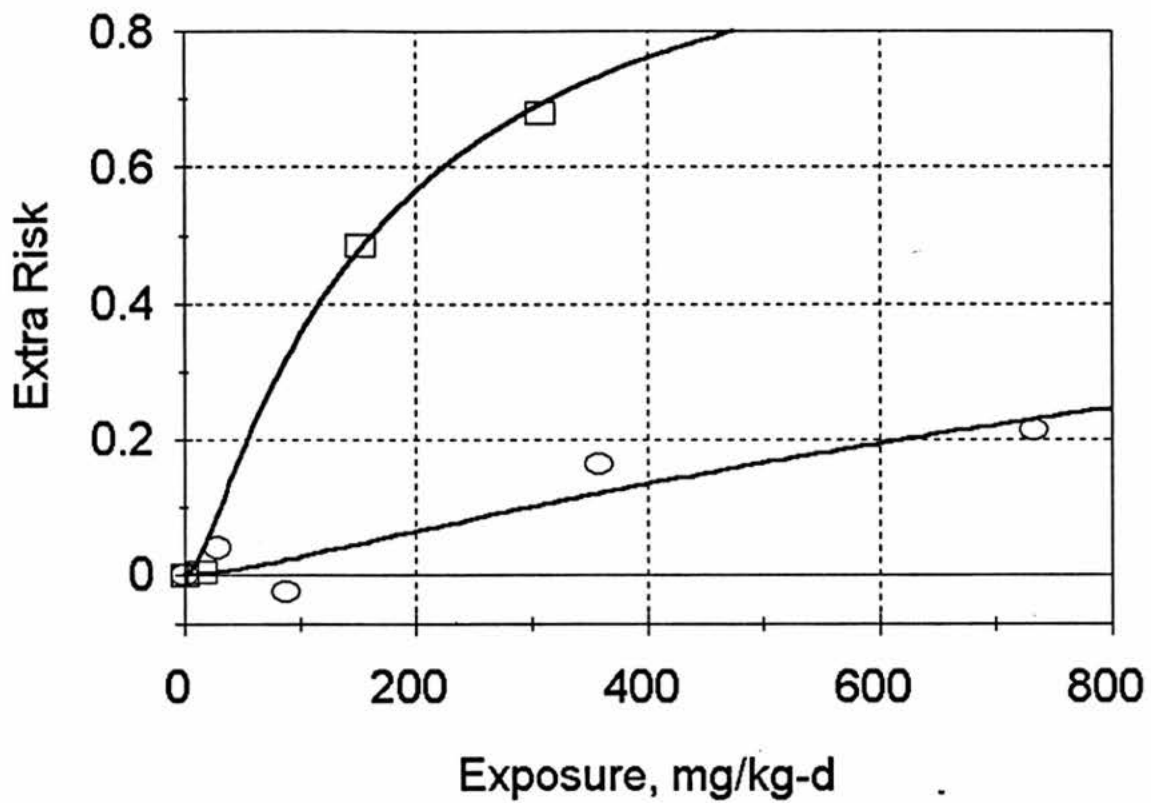


Figure 3. Extra risk of spongiosis hepatitis in male rats fed diisononyl phthalate (DINP) for two years. (□) Lingston et al., 1997; (○) Moore, 1998a; (—) lognormal model for either data set. Data from either study were fitted to a lognormal model as described in (Crump, 1984b).

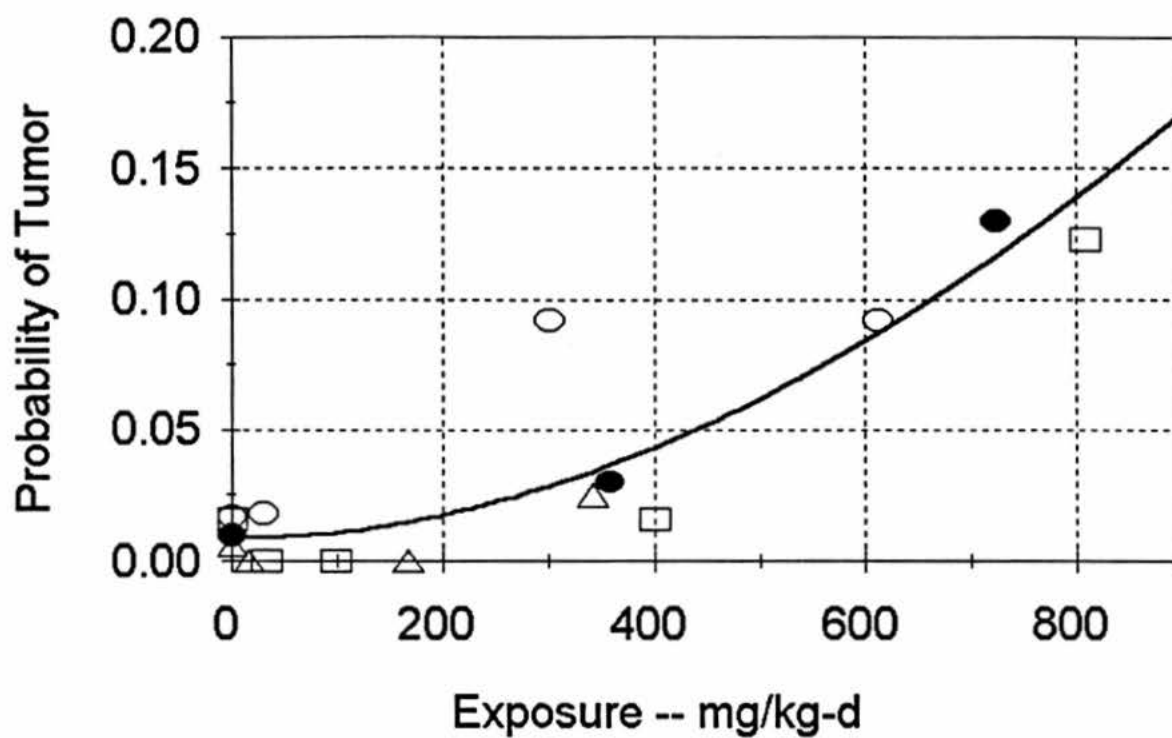


Figure 4. Incidence of hepatocellular carcinoma in rats fed dialkyl phthalates for two years. (●) di-(2-ethylhexyl)phthalate (117-81-7) (NTP, 1982); (○) diisononyl phthalate (71549-78-5) (Bio/dynamics, 1986); (Δ) diisononyl phthalate (68515-48-0) (Lington et al., 1997); (□) diisononyl phthalate (68515-84-0)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

Appendix A

Migration of DINP from Polyvinyl Chloride (PVC) Children's Products

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I. Background

Dialkyl phthalate esters impart flexibility to rigid polyvinyl chloride polymer (PVC). Previous studies by the Inhalation Toxicology Research Institute (ITRI) for the U. S. Consumer Product Safety Commission (CPSC) examined the migration of di 2-ethylhexyl phthalate (DEHP) from teethingers and pacifiers (*Phthalate Ester Migration from Polyvinyl Chloride Consumer Products*, R. L. Hanson, ITRI, 1983). These studies, which use an air driven piston to simulate mouthing and chewing, demonstrate that DEHP migrated from the pacifiers and teethingers. The purpose of the present study is to identify phthalate containing products that are likely to be mouthed by children and to determine the amount of phthalate migration from these products using *in vitro* and *in vivo* tests.

II. Methods

A. Determination of total phthalates from PVC

1. Total phthalates

Samples consisting of thin plastic sheets were cut into small pieces. Thicker samples were cooled by liquid nitrogen and ground to a powder with a micro mill. A weighed portion of the cut sheet or powdered plastic was placed in a Soxhlet extraction thimble and extracted for six hours with 80 ml of hexane. The hexane was evaporated and the percent by weight of phthalates was calculated from the weight of phthalates recovered and the initial weight of the sample extracted.

2. Identification and quantitation of phthalates

Phthalates obtained from the Soxhlet extraction of PVC products were dissolved in hexane and identified by means of gas chromatography/mass spectrometry (GC/MS) by comparison to spectra of known phthalate esters. Comparisons of known with unknown phthalate esters were made by matching retention times of total ion chromatograms and the selective ion chromatograms at mass 149. The mass 149 ion is specific for phthalate esters. Quantitative analysis of phthalates was performed by HP-6890 GC/MS system as follows:

1. GC conditions

Column, J & W DB-1, 0.25 mm ID, 30 m, 0.1 μ m
Oven Temperature, 100 °C for 3 min, 100 °C to 270 °C at 40 °C/min,
270 °C for 30 min
Injector Temperature, 325 °C
Carrier gas, Helium, 1.0 ml/min
Injection, 1 μ l splitless

2. MS analysis

Butyl benzyl phthalate (BBP) was used as an internal standard since it was found as an impurity in DINP at less than 0.5% of total phthalates. Selective ion mode was used in quantitative analysis. Phthalates were quantified by use of the peak area ratio of unknowns and BBP against the calibration curve of the peak area ratios derived from known concentrations of standard phthalates and BBP. The calibration and analyses of unknowns were performed on the same day.

B. *In vitro* phthalate migration

1. Chemicals and apparatus

The apparatus used for *in vitro* simulation of chewing is shown in Figures 1 and 2. This test apparatus allows up to six specimens to be tested simultaneously. The materials and equipment used are as follows:

Shaking water bath capable of maintaining 37 °C

Six 100 ml stainless steel beakers for holding extraction solution and PVC sample

Air driven pistons, 1.58 cm (5/8 inch) hexagon with an area of 2.18 cm² (0.338 in²)

Air compressor with pressure regulation from 258 mm to 3103 mm Hg (10 to 90 pounds per square inch gauge, PSIG)

Programmable controller to activate the pistons, operated at 4 seconds per cycle (2 seconds of applied air pressure, and two seconds of relaxation)

Separatory funnels

Hexane (95%, Mallinckrodt)

Simulated saliva solution - Dulbecco's phosphate buffered saline containing 0.16 percent mucin (pH ≈ 7.2, this is consistent with earlier work done at ITRI)

2. Phthalate migration by shaking

A PVC sample of known surface area was placed in a 250 ml glass stoppered Erlenmeyer flask containing 50 ml of the saliva simulant. The flask was placed in a 37 °C water bath and shaken horizontally for 6 hours at a rate of 60 cycles/min with a travel distance of 2.54 cm (1 in).

3. Phthalate migration by impaction

Samples consisting of thin PVC sheets were cut into disks approximately 7 cm in diameter to prevent significant movement in the stainless steel beaker during impaction. Hollow samples were cut and placed over the piston. Large or odd shaped samples were cut to provide a relatively flat surface. Test specimens smaller than 7 cm tended to move about the beaker and were held in place by a metal rod. Samples were tested intact wherever possible. A Chatillon force gauge measured the force applied by the piston before and after every experiment. Test specimen dimensions were measured and recorded for each experiment.

The normal extraction procedure consisted of adding 50 ml of saliva simulant to the stainless steel beaker holding the item under test. The piston was activated and applied pressure for 2 seconds followed by 2 seconds without pressure. Each test lasted 6 hours at 37 °C. The forces investigated were 0.91 kg, 2.7 kg, and 5.4 kg (2 lbs, 6 lbs, and 12 lbs). The piston sizes were 1.27 cm, 1.59 cm, and 2.54 cm (1/2", 5/8" and 1 ").

4. Extraction of phthalates from saliva simulant using hexane

The test specimen was removed from the beaker and rinsed with a minimum amount of deionized water. The combined aqueous solutions were transferred to a 250 ml glass Erlenmeyer flask. The piston and beaker were rinsed with 50 ml of acetonitrile and combined with the aqueous extraction media. Fifty ml of hexane was then added and the entire mixture was vigorously stirred for 8 minutes and transferred to a separatory funnel. After separation of hexane and aqueous phases, the aqueous phase was extracted with an additional 25 ml of hexane. The combined hexane extracts were allowed to evaporate in an 80 ml beaker at room temperature. The residues were dissolved in approximately 1 ml of hexane and a known amount of butyl benzyl phthalate (BBP) was added as internal standard for GC/MS quantitative analysis.

5. Calculation of migration from impacted and non-impacted surfaces

The area of the surface of an item that was likely to be mouthed when used by a child was assumed to be 11 cm². Since the impaction procedure exposes both impacted and non-impacted areas to the buffer, the migration of phthalate had to be apportioned between the amounts migrating from the impacted areas (chewed) and non-impacted areas (mouthed but not chewed). The tooth/gum contact (chewed) area was assumed to be the area of the piston, 2.18 cm² and the mouthed area was assumed to be 8.82 cm². The apportioning of total release between impacted and non-impacted areas was done algebraically. Knowing the total immersed area, piston area (2.18 cm²), and total phthalate migration, the migration from the impacted area was calculated as the difference between total migration and the migration from the non-impacted area. The calculation, assuming that the migration rate from non-impacted area is same migration rate as determined in the shaking only experiments, resulted in a ratio of 0.0302¹.

C. *In vivo* phthalate migration

The *in vivo* testing used five duck toys that were identical to sample 2.02. These were identified as D1 through D5. Four disks were cut from each duck with a 2.86 cm tubular cutter and identified as D1-1 through D1-4, D2-1 through D2-4, etc. Two disks from each toy were used for human subject testing and the remaining two were used for impaction or other testing. Ten polytetrafluoroethylene disks served as blanks. Prior to testing, all disks were gently washed with warm soapy water, rinsed and allowed to dry at room temperature.

¹The phthalate migration rate ($\mu\text{g}/\text{cm}^2/\text{hr}$) of 6 samples was determined by use of shaking only. The same 6 samples were subjected to the impaction procedure. The calculated apportionment ratio was 0.0302.

The human subjects consisted of three female and seven male CPSC staff volunteers who were not involved with the phthalate project. Each was provided with a polytetrafluoroethylene disk and a disk from the toy duck. Each volunteer was instructed to gently chew/mouth a polytetrafluoroethylene disk for 15 minutes. The subjects were then instructed to repeat the process for four 15 minute intervals on a the disk cut from the toy duck. The subjects were allowed 5 minutes to rest between the periods of active mouthing of the disks. For each 15 minute chewing period the subjects were instructed to collect all their saliva in labeled bottles. The total volume of saliva (ml) and pH of the saliva in each bottle were recorded. All saliva samples were diluted to 50 ml with deionized water and treated with 50 ml of acetonitrile. Extraction of the phthalates from the saliva with hexane was performed as described above. The protocol for the *in vivo* tests was approved by the CPSC human subjects committee.

III. Results and Discussion

This study was conducted in four phases. The first phase was a series of experiments performed to determine the conditions for measuring phthalate migration from the test products. The second phase characterized phthalate release from the PVC products. The third phase was a survey of various PVC children's products for phthalate release. The fourth phase was a human subjects mouthing/chewing test to compare *in vitro* and *in vivo* migration rates.

A. Determining test conditions

A flat and smooth PVC teether containing diisononyl phthalate (DINP) was used to evaluate the test conditions for determining the migration rates of phthalates from children's teethers, toys, and pacifiers. The sample could also be tested without cutting the edge which might affect the rate of phthalate release.

1. Recovery of DINP by acetonitrile/ hexane extraction

DINP (10, 25, 50 and 100 μg) was dissolved in hexane. The solutions were air dried and 50 ml each of saliva simulant and acetonitrile added. The mixture was vigorously stirred, treated with acetonitrile and extracted with hexane as described earlier. The percent recoveries of DINP were 122, 93, 82, and 103 respectively with an average recovery of $100\% \pm 17\%$.

2. Impaction pressure

A comparison of the release rate of DINP versus force applied is shown in Figure 3. Similar results were obtained for either 2.7 kg (6 lbs) or 5.4 kg (12 lbs) of force and both gave substantially higher release rates (approximately 10 $\mu\text{g/hr}$) than were obtained by either by shaking only (approximately 3 $\mu\text{g/hr}$) or with an impaction force of 0.91 kg (2 lbs) (approximately 5 $\mu\text{g/hr}$). An additional experiment was performed on a higher DINP releasing PVC product with similar results. The release rates for this product were 44.67 $\mu\text{g/hr}$ and 37.41 $\mu\text{g/hr}$ respectively for 2.7 kg (6 lbs) and 5.4 kg (12 lbs) of force.

3. Rate of impaction

The impaction controller allows for varying the rate of impaction, however, the total cycle time is always divided into equal periods of impaction and relaxation. A higher absolute release rate ($8.75 \mu\text{g/hr}$) was obtained with a four second cycle than with either a six or an eight second cycle ($2.88 \mu\text{g/hr}$ and $3.88 \mu\text{g/hr}$ respectively). The release rates for cycles of six and eight seconds, when extrapolated to the same number of impactions, however, are similar to the migration rate measured for the four second cycle. The four second cycle impaction rate was chosen to provide the greater number of impacts per unit of time.

4. Extraction time

As shown in Figure 4, the initial migration rates were similar at 2, 4 and 8 hrs but fell off at 24 hrs. After being allowed to stand for one week under ambient laboratory conditions, the samples were retested for an additional 8 hours of impaction. The migration rates were generally similar for this additional period with the highest rate being observed for the sample impacted initially for 8 hrs. Based on these data, an impaction time of 6 hrs appeared to be adequate, for samples with low rates of phthalate migration, to ensure sufficient phthalate for reliable detection and quantitation. Saturation of the simulant with phthalates did not appear to be a problem during the first 8 hrs of extraction.

5. Piston size

Three sizes of hexagonal pistons 1.27 cm, 1.59 cm, and 2.54 cm ($\frac{1}{2}$ ", $\frac{5}{8}$ " and 1") were tested to determine if there is a correlation between the piston area and release rate. The force was adjusted to provide the same applied pressure (1.25 kg/cm^2) to the item under test. Table 1 shows an increase in the absolute migration rates ($\mu\text{g/hr}$) with increasing piston size, however, the rates were equivalent when expressed as rates per square centimeter of piston area ($\mu\text{g/hr/cm}^2$). Since actual tooth contact areas would vary by individual and age, the $\frac{5}{8}$ inch piston was chosen to maintain consistency with the earlier ITRI study.

B. Characterization of phthalate release

1. Constancy of phthalate migration

The data plotted in Figure 5 shows that DINP migration rates for two separate samples remained relatively constant (1.3 ± 0.3 and $1.9 \pm 0.2 \mu\text{g/hr}$ respectively) over four consecutive days of extractions. Phthalate migration could thus continue at the rates initially found over prolonged periods of time.

2. Replication of extraction by impaction

Extraction of two units each from four samples (Toy Fish, Tree House, Tiger Toy, and Pacifier) and extraction of five units each from two samples (Teether#3, and Toy Duck#2) provided data for assessing replication of migration. Table 2 shows that the average percent standard deviation for the combined six items was 17.05 percent (range 9.8 percent to 28.0 percent). Teether #3, which was relatively flat had the least variation (9.8 percent), and was tested intact. The toys and pacifier, however, were not flat and exhibited a greater variation. The greater variation with samples that were not flat may be due to non-uniform application of force over the surface of the item, flexing of the item when impacted, or other unknown factors.

3. Replenishment of saliva simulatant and other migration media

These experiments examined the effect of replenishment on the amount of DINP that migrates from PVC products with various extraction media. Three different media were used, Dulbecco's buffer, Dulbecco's buffer with mucin added, and Dulbecco's buffer with mucin and sodium azide (a bacterial inhibitor). Each experiment listed in Table 3 used a separate unit of Toy Duck#2. The internal air bladder from each unit was cut into six sections, three for the 2 hour replenishment experiments and three for the 6 hour continuous experiments. After each replenishment, the medium that had been removed was treated with 50 ml of acetonitrile. After the third replenishment, the impaction beakers and impactors were washed with acetonitrile and the washings combined with the medium from the third extraction. The combined media and washings for each replenishment period were extracted with hexane. For comparison, a continuous six hour impaction experiment with no replenishment was also performed and the media extracted with hexane as described earlier. As shown in Table 3, the data are variable but the average total migration rate for all replenishment tests combined ($41.4 \mu\text{g/hr}$) is similar to that for all continuous tests ($45.9 \mu\text{g/hr}$) indicating that any replenishment effects, at least at 2 hour intervals, are small. The variability observed may reflect unknown differences in manufacturing or composition of each individual toy. The GC/MS ion chromatograms showed that not all of the products that appeared to be identical had the same distribution of DINP isomers. It is also not clear that the addition of mucin, or mucin and sodium azide increases phthalate extraction over buffer alone.

C. A survey of PVC children's products

A total of thirty five samples of children's products that were likely to be mouthed or chewed, were subjected to impaction in Dulbecco's phosphate buffered saline containing 0.16 percent mucin (Table 4). DINP was present in thirty one, DIOP in two, DEHP in one, and DnNP in one.

The phthalate release rate, calculated for 11 cm^2 , ranged from $1.02 \mu\text{g/hr}$ to $48.40 \mu\text{g/hr}$. Toy Duck #2 had the highest release rate of the thirty five samples tested (Table 4). This release rate was for an internal bladder ($48.4 \mu\text{g/hr}$). The release rate for exterior PVC from Toy Duck #2 was lower ($6.4 \mu\text{g/hr}$). Figure 6 is a plot of the percentage of phthalate versus the release rate for the samples listed in Table 4. It clearly shows a lack of correlation between the release rate

and the amount of phthalate present in the samples. The reason for the lack of correlation is not known.

D. *In vivo* migration of phthalates

Table 5 presents the data from the *in vivo* migration study using PVC disks cut from the exterior of Toy Duck#2. The total quantities of saliva produced in four 15 minute periods of mouthing and chewing ranged from 27 ml to 95 ml. Saliva pH ranged from 6.90 to 7.66 with an average of 7.43. There was no apparent relationship between the amounts of phthalate migrating and the sex of the volunteers, the quantity of saliva produced, and the pH of the saliva. None of the saliva samples obtained from mouthing of the polytetrafluoroethylene control disks contained phthalates. The maximum migration rate for any one individual and time period was 826.48 $\mu\text{g/hr}$ and the minimum was 32.78 $\mu\text{g/hr}$, a ratio of 25.2. Individuals showed better consistency in migration rates with the maximum to minimum migration rate ratios ranging from 1.57 to 3.10. The average migration rates for individuals ranged from 63.22 $\mu\text{g/hr}$ to 596.64 $\mu\text{g/hr}$.

Table 6 presents the migration data obtained by impaction of new and the previously mouthed disks. A comparison of the impaction migration rates from new disks cut from the toy to impaction migration rates from disks used in the *in vivo* study show that the migration rates of the new disks are similar to the migration rates of the previously mouthed disks. The ratio of the geometric means of the *in vivo* migration rates to the *in vitro* migration rates of 39.5 showed that the impaction method substantially underestimates human exposure.

IV. Conclusions

DINP was the predominant phthalate found in children's products likely to be mouthed or chewed. Migration rates from impaction varied from 1 to 48 $\mu\text{g/hr/l cm}^2$ and did not correlate well with phthalate content. The impaction method showed good repeatability overall and did not appear to be sensitive to buffer replenishment. The human subject study showed that the geometric mean migration rate from mouthing/chewing a new disk cut from a PVC children's toy was 39.5 times the geometric mean migration rate from impaction. Migration rates varied substantially from individual to individual.

Table 1. Variation of migration rates based on piston size.

<u>Piston Size</u>	<u>% Phthalate</u>	<u>$\mu\text{g/hr}$</u>	<u>$\mu\text{g/hr/cm}^2$</u>
1.27 cm (0.5 in)	29.96	2.97	2.14
		3.67	2.64
1.59 cm (0.62 in)	29.96	3.32	1.52
		2.41	1.11
		2.76	1.26
2.54 cm (1 in)	29.96	7.13	1.28
		9.07	1.63

Table 2. Replication of migration rates from the impaction method.

Sample	Description	Phthalate	Migration				
			% by wt	$\mu\text{g/hr}$	Avg	Std. Dev.	% Deviation
1-8	Teether #3	DINP	43.28	7.38	8.25	0.81	9.78
1-8				7.88			
1-8				7.80			
1-8				8.98			
1-8				9.24			
2-2	Toy Duck #2	DINP	42.66	37.41	43.61	8.68	19.91
2-2				49.59			
2-2				43.18			
2-2				54.59			
2-2				33.28			
2-4	Toy Fish	DINP	36.95	10.59	11.71	1.58	13.47
2-4				12.82			
2-5	Tree House	DINP	36.05	14.64	13.56	1.53	11.26
2-5				12.48			
1-5	Tiger Toy	DINP	48.10	21.93	18.31	5.13	28.01
1-5				14.68			
1-13	Pacifier	DIOP	32.37	17.22	20.04	3.98	19.87
1-13				22.85			

Average % Deviation = 17.05% (Range 9.78% to 28.01%)

Table 3. Effect of replenishing the buffer vs 6 hours of continuous impaction with Toy Duck#2.

Media	DINP (μ g)								
	Time of Media Change	Migration with each 2 Hour Replenishment				Migration, 6 hours continuous Impaction			
		Sample Number			Average Total Migration	Sample Number			Average Total Migration
		1	2	3		4	5	6	
Dulbecco's	2	4.41	6.39	6.18					
Toy 2.01a	4	3.79	4.93	5.78					
	6	8.71	4.69	9.25					
Total Released		16.91	16.01	21.21	18.04	23.85	16.52	11.74	17.37
Dulbecco's	2	9.83	10.33	10.65					
Repeated	4	10.72	9.71	8.27					
Toy 2.01b	6	14.16	13.52	16.83					
		34.71	33.56	35.75	34.67	72.02	81.49	97.42	83.64
Dulbecco's	2	19.38	19.16	18.57					
and Mucin	4	16.15	21.54	21.82					
Toy 2.01c	6	21.41	20.28	27.29					
Total Released		56.94	60.98	67.68	61.87	61.6	50.48	32.3	48.12
Dulbecco's +	2	19.2	17.1	17.67					
Mucin + Na Azide	4	13.87	14.62	12.57					
Toy 2.01d	6	19.48	15.86	22.77					
Total Released		52.55	47.58	53.01	51.05	32.09	35.38	35.99	34.49
Average all replenishment tests			41.41			Average All Continuous tests			45.91

Table 4. Migration rates and calculated migration rate for 11 cm² of PVC samples.

Sample	Description	Phthalate % by wt	Total Migration $\mu\text{g/hr}$	Area Immersed cm^2	Impact Migration $\mu\text{g/hr/cm}^2$	Non-impact Migration $\mu\text{g/hr/cm}^2$	Calculated Migration Rate ¹ $\mu\text{g/hr/11 cm}^2$
1.01	Handbag	DEHP	19.05	10.84	2.28	0.08	5.68
1.02	Book	DINP	27.45	5.40	1.14	0.0402	2.83
1.03	Teether#1	DINP	36.59	17.50	4.52	0.1599	11.26
1.04	Soother#1	DnNP	26.74	47.09	13.39	0.4734	33.36
1.05	Tiger Toy	DINP	48.1	21.93	4.61	0.1631	11.49
1.06	Toy Dolphin	DINP	43.66	33.45	11.90	0.4209	29.66
1.07	Teether#2	DINP	29.96	5.00	1.18	0.0419	2.94
1.08	Teether#3	DINP	43.28	8.98	2.55	0.0903	6.36
1.09	Teether#4	DINP	33.47	6.06	1.92	0.0677	4.77
1.10	Teether#5	DINP	54.43	7.55	1.95	0.0690	4.86
1.11	Corner Pads	DINP	43.98	18.22	6.10	0.2157	15.20
1.12	Nipple	DIOP	41.88	42.44	16.12	0.5698	40.16
1.13	Pacifier	DIOP	32.37	17.22	5.57	0.1969	13.87
1.14	Toy Food	DINP	51.00	24.35	8.67	0.3064	21.59
2.01	Toy Duck#1	DINP	40.81	3.85	1.44	0.0510	3.59
2.02	Toy Duck#2	DINP	42.66	54.59	19.43	0.6869	48.40
2.03	Teether#6	DINP	50.26	7.37	1.55	0.0548	3.86
2.04	Toy Fish	DINP	36.95	10.59	2.62	0.0925	6.51
2.05	Tree House	DINP	36.05	14.64	5.56	0.1966	13.85
2.07	Squeeze Toy #1	DINP	32.55	15.99	5.35	0.1893	13.34
2.08	Soother#2	DINP	30.17	2.83	0.60	0.0210	1.48
2.09	Teether#7	DINP	25.57	2.89	0.63	0.0223	1.57
2.10	Teether#8	DINP	19.29	3.55	1.19	0.0420	2.96
2.11	Book	DINP	17.45	2.69	0.57	0.0200	1.40
2.12	Bath Toy	DINP	15.14	1.95	0.41	0.0145	1.02
2.13	Toy Turtle	DINP	35.41	4.43	1.48	0.0524	3.69
2.14	Toy Bear	DINP	19.91	3.29	1.34	0.0474	3.33
2.15	Spoon#1	DINP	35.24	4.70	1.91	0.0676	4.76
2.16	Spoon#1	DINP	34.29	9.00	3.66	0.1295	9.12
3.01	Toy Ball	DINP	41.15	6.43	2.45	0.0739	5.93
3.02	Toy Bear	DINP	41.20	4.59	1.83	0.0553	4.46
3.03	Toy	DINP	27.08	2.72	1.16	0.0351	2.86
3.04	Toy Block	DINP	43.03	5.97	2.27	0.0686	5.5
3.05	Toy Car	DINP	42.68	2.47	0.99	0.0299	2.42
3.06	Squeeze Toy #2	DINP	42.49	3.17	1.19	0.0360	2.88

Note: One item tested, a suction cup (Toy # 2.06) with a hook for hanging things on windows is not included since it is not considered a children's product.

¹ The calculated migration rate for the assumed 11 cm² that is mouthed and chewed is the sum of the impact piston area (2.18 cm²) times the impact migration rate and mouthed area (8.82 cm²) times the non-impact migration rate.

Table 5. *In vivo* phthalate migration by mouthing and gentle chewing of 10.3 cm² disks (μg/hr).

Time (min)	Subject									
	D1-1	D1-4	D2-1	D2-4	D3-1	D3-4	D4-1	D4-4	D5-1	D5-4
15	48.22	248.34	510.86	257.60	207.48	101.50	388.74	143.72	250.30	420.98
30	101.54	379.30	371.62	184.34	249.62	109.20	464.00	193.84	152.44	322.62
45	70.36	153.84	559.18	559.18	246.86	67.64	826.48	216.76	272.18	143.26
60	32.78	243.78	336.32	235.76	159.34	81.74	707.34	229.36	214.24	261.24
Maximum	101.54	379.3	559.18	559.18	249.62	109.2	826.48	229.36	272.18	420.98
Minimum	32.78	153.84	336.32	184.34	159.34	67.64	388.74	143.72	152.44	143.26
Max/Min	3.10	2.47	1.66	3.03	1.57	1.61	2.13	1.60	1.79	2.94
Average for all time periods	63.23	256.32	444.50	309.22	215.83	90.02	596.64	195.92	222.29	287.03
Average of all humans	268.10									
Range of averages	63.23 to 596.64									
Saliva in ml	58	55	85	48	44	54	37	27	95	63
Saliva pH	7.13	7.55	7.65	7.61	7.48	7.47	7.21	6.90	7.66	7.62

Table 6. DINP migration by impaction of new and used disks from *in vivo* tests.

Disk number (DN)	Migration Rate			
	New disks		Used disks	
	DN-2	DN-3	DN-1	DN-4
	$\mu\text{g/hr}$	$\mu\text{g/hr}$	$\mu\text{g/hr}$	$\mu\text{g/hr}$
D1	9.53	4.43	4.72	5.02
D2	5.50	14.72	4.99	5.16
D3	4.61	4.86	3.78	5.21
D4	6.82	4.09	4.87	3.13
D5	6.84	2.49	4.84	8.07
Average	6.66	6.12	4.64	5.32

	New Disks	Used Disks
	$\mu\text{g/hr}$	$\mu\text{g/hr}$
Average of all new or used disks	6.39	4.98
Ratio of <i>in vivo</i> :Impaction ¹	39.50	

¹ The ratio is based on the geometric mean as described by M. A. Greene, Statistical methods for estimating average daily intake, U.S. Consumer Product Safety Commission, Washington, DC. December 1998.

Figure 1. Extraction apparatus

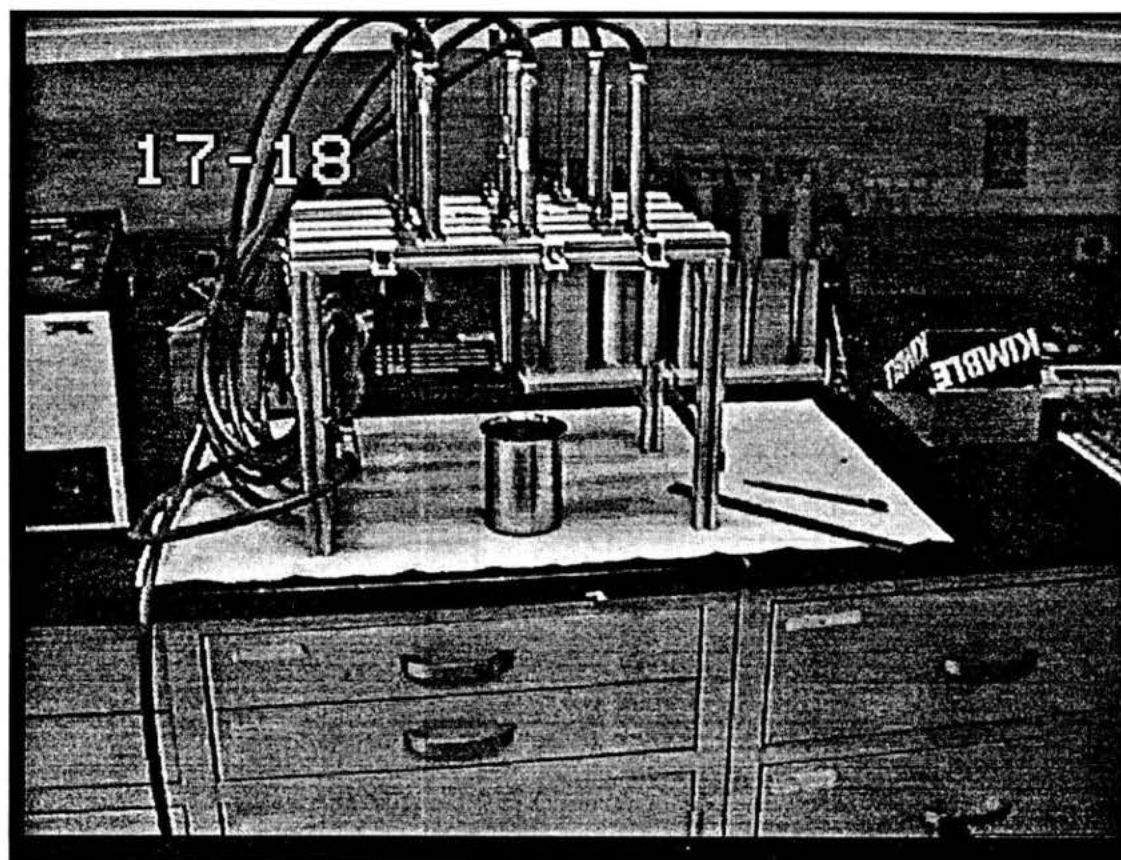


Figure 2. Extraction apparatus piston and hold down bar

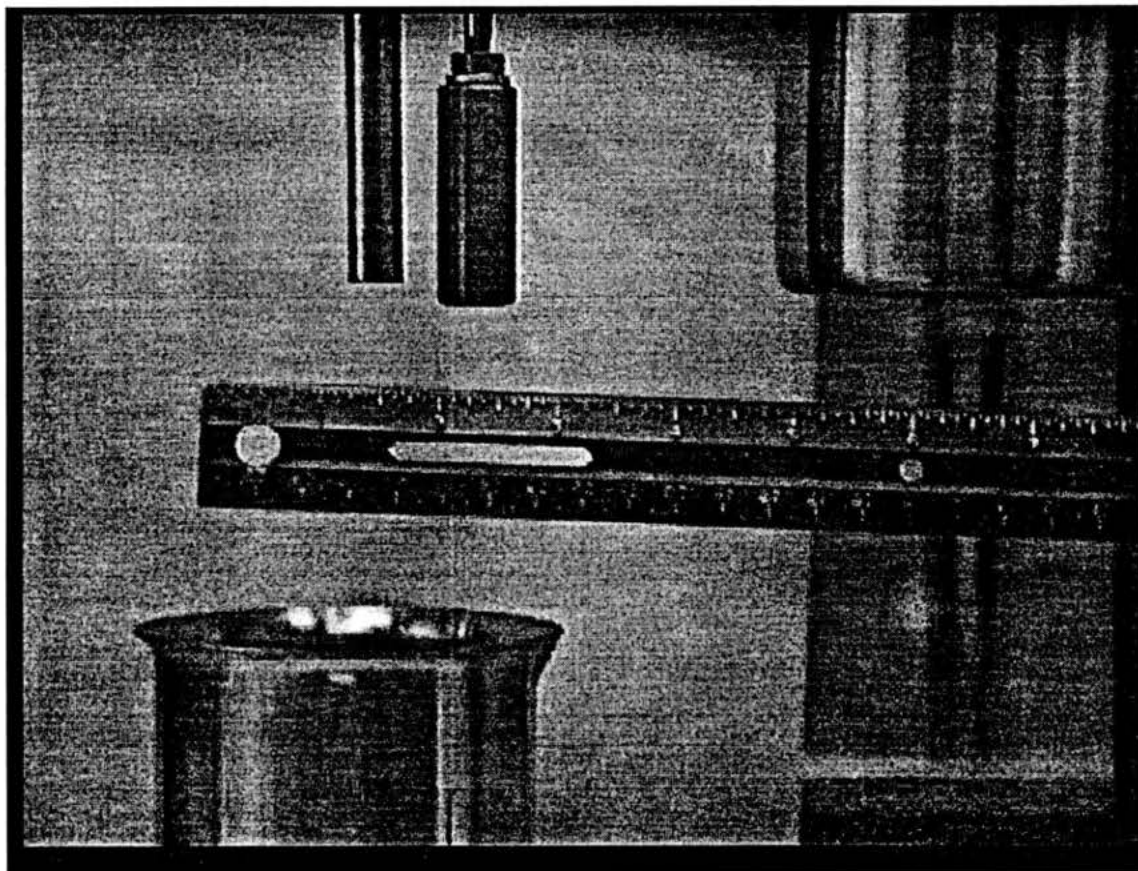


Figure 3. Migration rate vs force

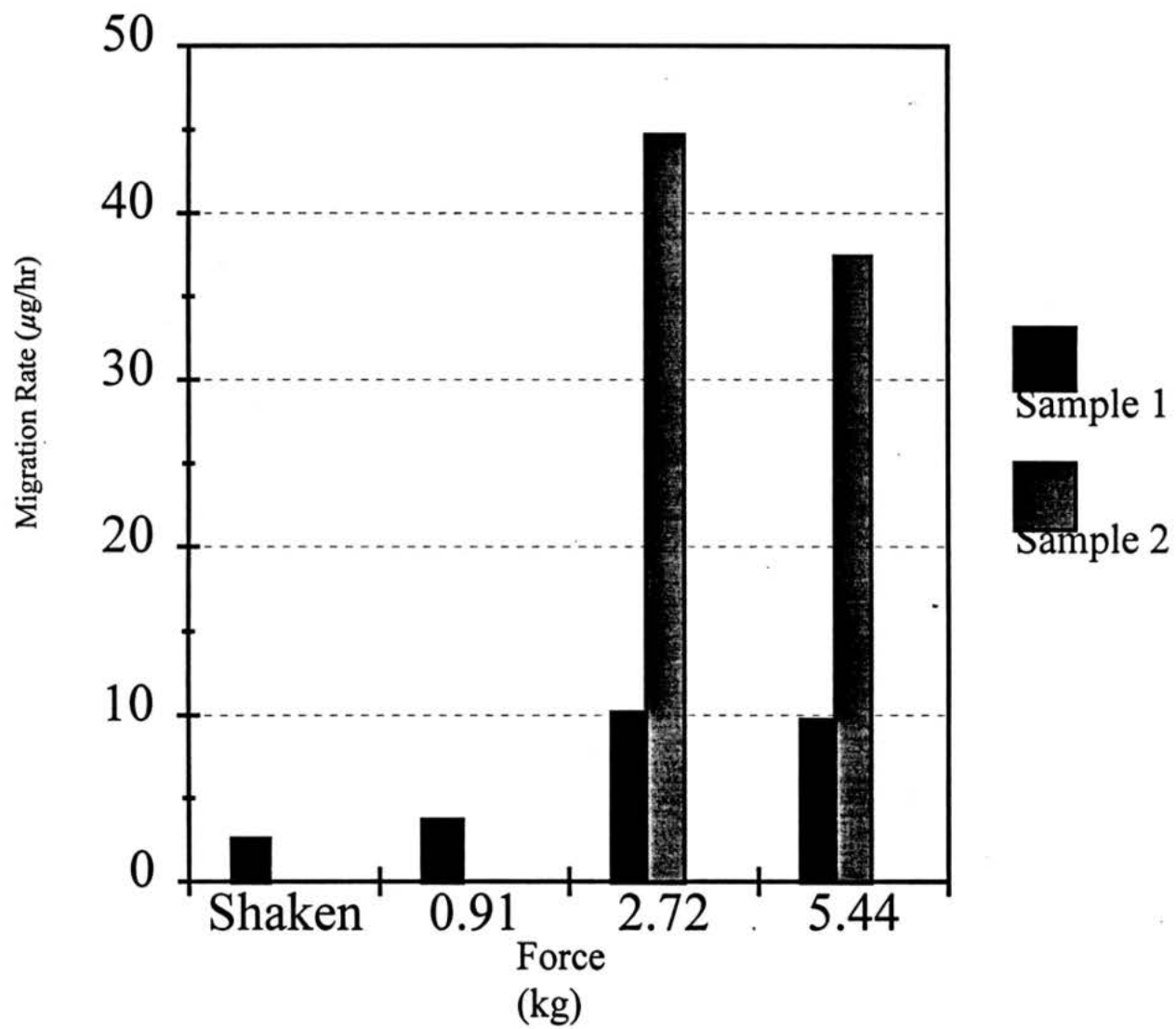


Figure 4. Variation of migration rates by length of impaction time

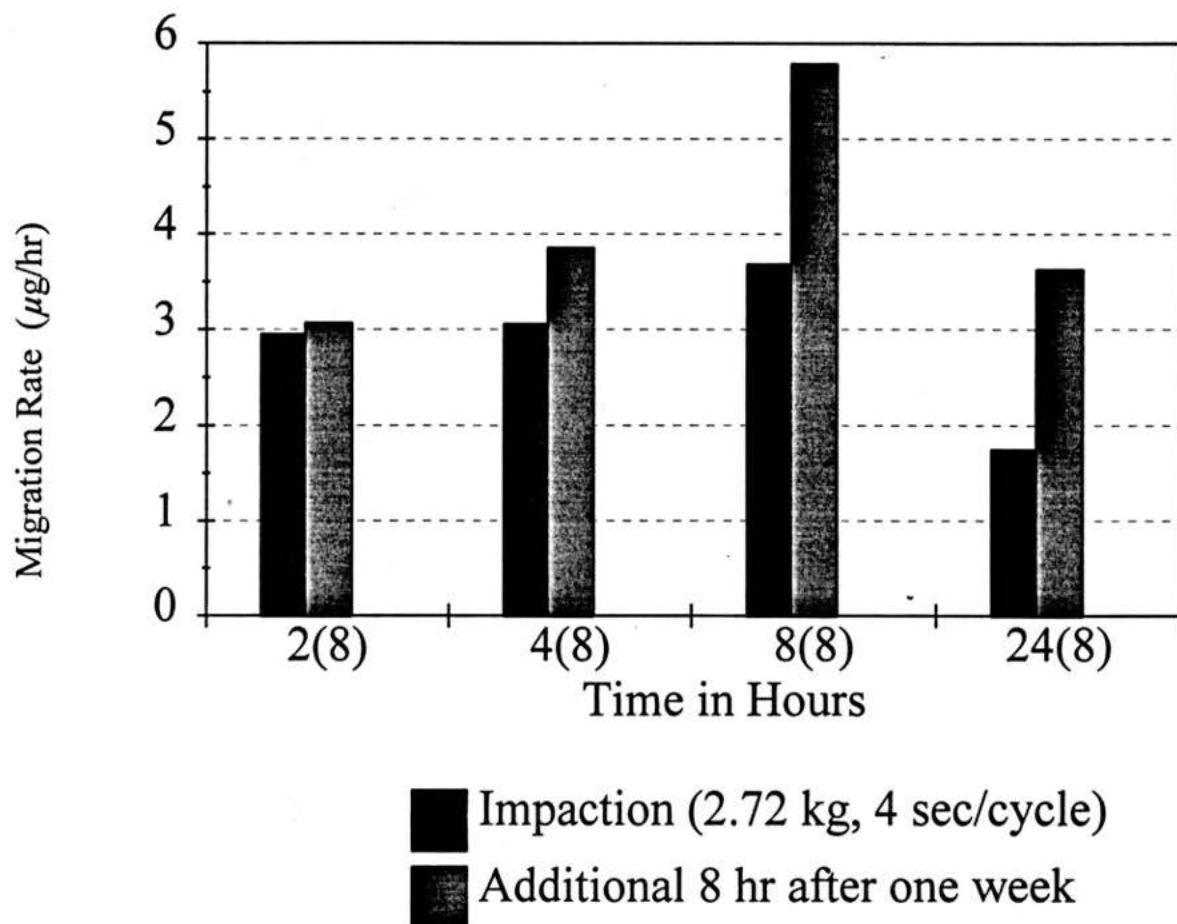


Figure 5. Migration rate on consecutive days, 4 seconds/cycle, 2.72 kg force, 6 hours

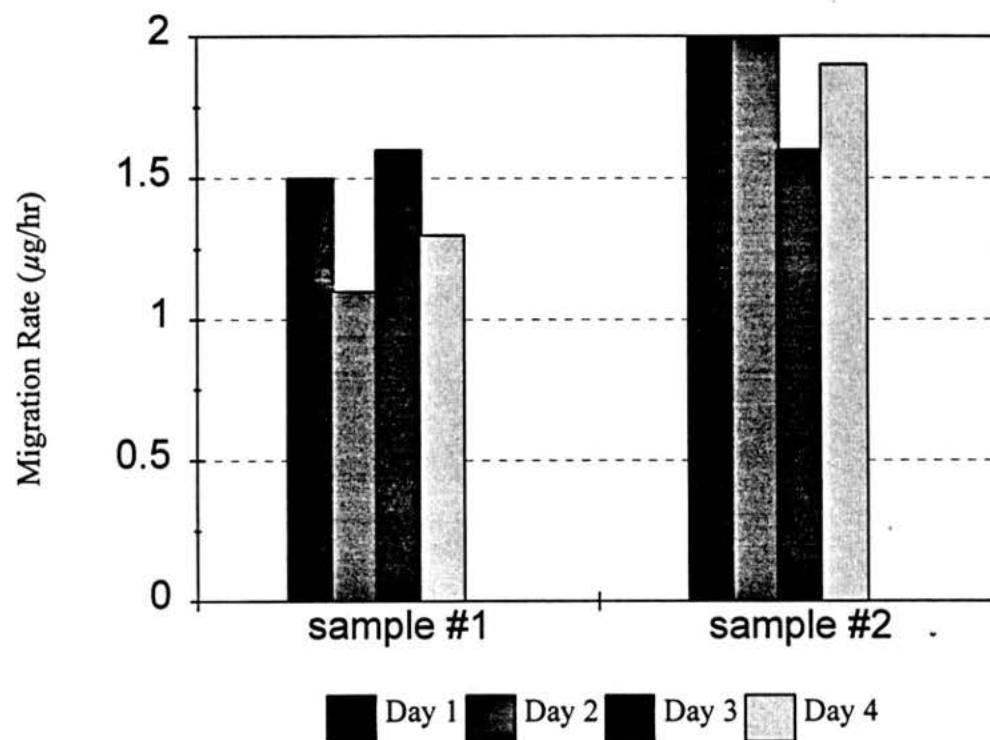
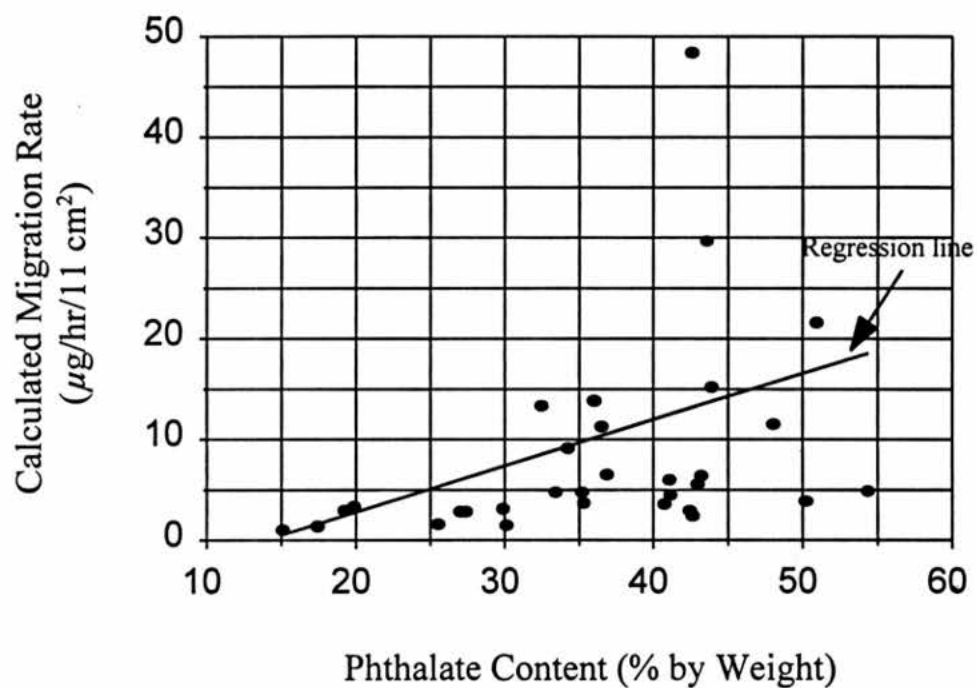


Figure 6. Calculated DINP migration vs % DINP



Note: The regression line has a slope of 0.37, and an R^2 of 0.143.

Appendix B

Statistical Analysis for Prediction of DINP Intake by Young Children

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December 1998

1. Introduction

The purpose of the statistical analysis is to provide estimates for exposure of children up to 26 months of age from diisononyl phthalate (DINP), a chemical found in polyvinyl chloride toys and other children's products.

Exposure, in this paper, was estimated from the product of migration rates from toys and other products, M , given in mass per unit time, and D , the duration or length of time that such products are likely to be in children's mouths. This was then divided by body weight, BW , to form equation (1),

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

See Babich (1998).

Migration rates were estimated from the product of two other quantities, R and S , where R was the migration rate measured *in vitro* from product samples containing DINP and S was a scaling factor obtained from paired *in vitro* and *in vivo* studies using adult volunteers. The procedures used to obtain these measurements are described in Chen (1998). The exposure duration, D , in equation (1) was estimated from observations on toy mouthing behavior on children aged 3-26 months provided by Bea Steenbekkers from Wageningen Agricultural University. Tables developed from these data were published in the European Union's Consensus Report on DINP (Konemann, 1998) and in the full report Groot et al (1998a).

In the statistical analysis leading to estimates of exposure, the migration rate components, R , and S , and the exposure duration, D , were considered to be random variables, that is, quantities that vary over specimens, and individuals. What is the source of the random variation? First, some products, or different pieces of a single product could release DINP at different rates. Second, different human subjects would be expected to extract DINP from the same specimen at different rates. Taken together, the product $RS (=M)$ represents the variability in the amount of DINP in different toys and the rate it is released *in vivo*. Third, the variability in exposure duration, D , would reflect different amounts of time that children put objects in their mouths. This could vary by the age of the child, and for a given child could vary over short periods. Consequently, the daily exposure, DE , would vary between individuals, as the result of the amount of time they engage in chewing, sucking and licking of toys; the rate at which they extract DINP from the toys; and the DINP content of the toys in their environment.

In the analysis described in section 2 of this paper, separate lognormal distributions were fit to each of these random variables. One model was used for *in vitro* migration rates, M , and a second model for scaling, S . With respect to duration, D ,

separate estimates were made for children age 3-12 months and 13-26 months, because the amount of time these children were observed to engage in mouthing behavior was very different. Also, there were different values for mean body weight used for these different age groups.

Parameter estimates were obtained from the means and variances of the logarithms of the observed data. Statistical testing was used to test the goodness of fit of the data to the lognormal distributions.

The separate lognormal distributions were combined to form two lognormal distributions for *DE*, in equation (1), one for each age group. This was used to generate not only the geometric mean daily intake, but also the 95th percentile and the associated confidence interval for that statistic. The geometric mean is a typical measure of the center of a skewed distribution, and in fact, for the lognormal distribution, the geometric mean is an estimate for the median or 50th percentile of the data. The 95th percentile represents the DINP intake for the highest 5% of the children. This would represent children with the longest exposure to products with the greatest migration rates. Confidence intervals as shown in this analysis, represent the amount of uncertainty in the estimates. Confidence intervals for percentiles were from Hahn and Meeker (1991) and verified with parametric bootstrap calculations (Efron and Tibshirani, 1993). These are described in section 3 of the paper.

Section 4 contains a discussion of the results.

2. Fitting Statistical Distributions

This section describes the methods used to fit statistical distributions to the data. Section 2.1 describes fitting the *in vitro* migration rates, *R*. Section 2.2 discusses fitting the scaling distribution, *S*, and section 2.3 fits the exposure distributions to the data in Groot et al (1998b).

The mathematical form of the distributions used in fitting is the lognormal distribution, shown generically in equation (2). The distribution is defined only for positive values and displays a long right hand tail. Mathematically, if *X* is a random variable whose logarithm is normally distributed with parameters (μ, σ^2), then *X* follows a lognormal distribution

$$(2) \quad f(x) = \frac{1}{\sigma x \sqrt{2\pi}} e^{-(\log x - \mu)^2 / 2\sigma^2} \quad 0 < x < \infty, \quad -\infty < \mu < \infty, \quad \sigma > 0$$

This is abbreviated $X \sim LN(\mu, \sigma^2)$.

The product of independent lognormal distributions also follows a lognormal

distribution. If $\log(X_1)$ and $\log(X_2)$ each follow a normal distribution then $\log(X_1) + \log(X_2) \sim N(\mu_1 + \mu_2, \sigma_1^2 + \sigma_2^2)$. Put another way, the product $X_1X_2 \sim LN(\mu_1 + \mu_2, \sigma_1^2 + \sigma_2^2)$. This result is very important because it allows finding the distribution of products of random variables such as found in equation (1) for daily exposure. Once the distribution of the products is available, estimates can be made for the geometric mean daily exposure and 95th percentiles. Closed form interval estimates for the mean and the percentiles are available from the fact that the distribution of means $(1/n_1)\sum \log(X_1) + (1/n_2)\sum \log(X_2) \sim N(\mu_1 + \mu_2, \sigma_1^2/n_1 + \sigma_2^2/n_2)$ with $n_1 + n_2 - 2$ degrees of freedom. It is also interesting to note that exponentiating the mean of the underlying normal distribution is the geometric mean of the original data. Because the underlying distribution is symmetric, the geometric mean is also an estimate for the median of the original data.

The maximum likelihood estimates for the parameters of the lognormal distribution are found by taking the logs of the observations, then using maximum likelihood procedures for the normal distribution. This involves using the mean of the transformed data as the estimate for μ and the variance of the transformed data as the estimate for σ^2 . Exponentiating the estimate for μ (i.e. $\exp[\mu]$) produces a number in the original units that is the geometric mean of the data. (For further details on the lognormal distribution, see Casella and Berger, 1990).

2.1 Migration Rates

The distribution of migration rates for 31 products containing DINP is shown in table 1 below. The intent was to develop a list that would represent the range of toys containing DINP, that a child might put into his/her mouth. The data are the same as found in Table 4 of Chen (1998) except for deletion of four samples that did not contain DINP.

Examination of the histogram of migration rates showed that distribution has a skewed appearance with an arithmetic mean of 8.20, median of 4.8 and standard deviation (SD) of 9.83. The skewness statistic was 2.8. The Shapiro-Wilk W statistic (a test for the fit of the normal distribution) was 0.66 with a p value of less than 0.0001. Transforming to logs produced a mean of 1.66, median of 1.57, SD of 0.91, and a skewness statistic of 0.51. The Shapiro-Wilk W statistic, for the transformed data was 0.97 with a p value of 0.55. The skewness and normality test suggested that the log transformation was successful in fitting a normal distribution. Note that the mean value following the log transformation, corresponded to a geometric mean in the original data of 5.24.

Table 1
Distribution of DINP Migration Rates

Migration Rates	Frequency
0.0-2.4	5
2.5-4.9	13
5.0-7.4	4
7.5-9.9	1
10.0-12.4	2
12.5-14.9	2
15.0-17.5	1
17.5-	3
Total	31

Notes: The data are from Table 4 in Chen (1998) with four samples removed. Migration rates are given in micrograms per hour for an 11 square centimeter area. That size area was chosen because it was believed to be the same surface area as an object likely to be mouthed by a child.

There were some further analyses performed on these data. An analysis was conducted to determine if migration rates differed by type of specimen. Products were classified as teethingers, mouth toys, and others. To determine whether the data could be assumed to come from the same underlying process, a Kolmogorov-Smirnov test was performed on the empirical distributions of the migration rates by product classification. The *p* value for this test was 0.58, which did not provide any statistical justification for separating the analysis by type of product. This meant that there was no evidence to suggest that a particular product class had a greater migration rate than any other product type.

In a second analysis, models were estimated to determine if migration rates could be explained by the characteristics of the products. These characteristics included the percent DINP content by weight, the type of manufacturing process (e.g. injection molding, rotation, etc.) and the thickness of the product. The purpose of this analysis was to determine if there was some way to predict migration rates as related to the percent of phthalate content, manufacturing process, etc. While the graphical analysis showed some positive relationship between migration rate and DINP content, various regression models failed to produce a value of R^2 greater than 0.33. These models were judged to be inadequate to predict DINP migration rates especially given the shrinkage in predictive quality that would be expected from applying the models to new data. Moreover, discussions with CPSC laboratory staff suggested that migration rates were variable even within a single specimen.

2.2 Scaling Factors

To compute the scaling factors that would relate *in vitro* migration rates for the 31 products above to rates that would be expected from human mouthing, CPSC staff obtained migration data using 10 human volunteers. Details of this study are in Chen (1998). The testing used five duck toys that were identical to sample 2.02. Four disks were cut from each duck. Two disks from each toy were used for *in vivo* human subject testing and the remaining two were used for impaction. Each human provided measurements for four fifteen-minute periods for a total of 40 measurements. The data used in this analysis were those found in tables 5 and 6 of Chen (1998) but the *in vivo* and *in vitro* migration rates were divided by 10.3 to produce rates with units of micrograms per square centimeter per hour.

Like the migration rate data discussed above, these *in vivo* measurements also showed considerable skewness. The arithmetic mean was 25.0 micrograms per cm² per hour, with an SD of 16.7. The data were very skewed to the right with a skewness value of 1.46. The Shapiro-Wilk W statistic was 0.88 with a *p* value of 0.0004, confirming that the data did not follow a normal distribution. Transformation to logs provided a mean of 3.01 (geometric mean of 20.3) with a skewness of -0.5 and a value of W of 0.97 (*p* value of 0.5329).

An analysis of variance procedure (ANOVA) was applied to the migration rates to determine if there were any disk effects, gender effects or systematic variation in migration rates over the fifteen minute period. Using the log of the migration rate as the response variable, only the disk effect was statistically significant ($F = 3.85$ with 4 and 31 df, $p=0.0119$). On the basis of this analysis it was determined that even though the disks should have been identical, they should not be considered as replicates.

This information was used in determining how to obtain an average for the scaling factor. Let H_i and I_i denote average migration rates for disk i ($i = 1, 2, \dots, 5$), where H is the human average (two humans with 4 measurements each) and I is the machine impaction average (2 machine readings). Then the two possible ways to compute the average would be $S = \Sigma H_i / \Sigma I_i$ or $S = (1/5) \Sigma (H_i / I_i)$. The first approach is the ratio of the totals while the second is the average of the ratios. The second approach was used because the ANOVA showed that the ratios for each disk were significantly different from each other. If the human and machine observations could have been considered independent replicates, then the first calculation would be more appropriate.

The five ratios were 22.9, 32.3, 32.8, 54.6 and 72.6 with an arithmetic mean of 43.05 and an SD of 20.21. The data showed right skewness with a value of 0.85. The Shapiro-Wilk W statistic was 0.9040, ($p = 0.43$). These statistics did not strongly argue for a log transformation of the data, but because the analysis on the human extraction data above strongly suggested the log transformation for both the *in vivo* and *in vitro* migration rates, the ratios were also used in logarithmic form. Transforming to logs produced a mean of the logs of 3.68 (geometric mean 39.5) and SD of was 0.46. This improved the skewness to 0.46 and the Shapiro Wilk statistic to 0.9423 ($p = .6929$).

2.3 Exposure Analysis

In this last part of the statistical analysis, distributions were estimated for time children spent mouthing toys as reported in Groot et al (1998a, 1998b). Two separate analyses were conducted, one for children 3-12 months and the second 13-26 months. The 3-12 month period corresponds to the time when there is the highest mouthing activity for children and would be likely to result in the highest average daily intake of DINP. The children aged 13 to 26 months had spent much less time mouthing toys and would consequently have a much lower potential for exposure to DINP.

The age categories of 3-12 months and 13-26 months are similar to those in Groot et al (1998a). They reported using overlapping age boundaries (i.e. 3-6 months, 6-12 months, etc.), but inspection of the raw data showed that children at the lower end of the cell boundary were not contained in the particular age group. For example, a child age six months would have been in the 3-6 month group rather than the 6-12 month group. To avoid ambiguity, we characterize the cell boundaries as non-overlapping, so that we use 13-26 months in place of 12-26 months. Also, in this research, the upper boundary of 26 months is used rather than 36 months as reported in Groot et al (1998a). Inspection of the ages as reported in the raw data showed that there were only two children more than two years old, a 26 month old boy and a 35 month old boy. The remaining 9 children in that age category were between 19 and 24 months. Given the variability in the data, it seemed that one observation would be hardly sufficient to estimate the mouthing duration of children 27 months to 36 months, so this observation was omitted from the present reanalysis. Consequently the second part of the analysis only covers 13-26 months. No dosage estimates were made for children over 26 months.

Table 2 shows the data summarized by age group. Several aspects of this table were notable. First, duration was strongly related to age. For example, the two children aged 8 months averaged 78.3 minutes while children 14 months and over averaged 4 minutes or less. Second, not only were there ages where no children were observed, but also there were an unequal number of children observed at each age.

Table 2
Mean Toy Mouthing Time by Child Age

Age (months)	Number of Children	Mean Toy Mouthing Time (minutes)
3	1	12.6
4	2	8.6
5	2	21.8
6	0	-
7	2	42.8
8	2	78.3
9	4	15.7
10	3	25.0
11	1	0.4
12	2	5.1
13	2	9.1
14	1	4.0
15	1	3.8
16	2	4.0
17	2	2.8
18	4	1.1
19	2	0.9
20	0	-
21	3	0.5
22	3	2.5
23	0	-
24	1	0.0
25	0	-
26	1	1.3
27-34	0	-
35	1	0.0

Source: Groot, et al (1998a). Blanks indicate that there were no observations for children in those age categories.

The analyses for the 3-12 month old children and 13-26 months age children are described below.

2.31 3-12 Months

Table 2 shows that the maximum mouthing duration for toys occurred for children age 3 to 12 months. Even more important, the duration was substantially larger than for all other ages, with the maximum duration of 141.2 minutes provided by one of the two 8 month old subjects.

The arithmetic mean mouthing time for the 3-12 month age group was 24.4 minutes, the median was 15.3 and the standard deviation was 32.9. The skewness statistic was 2.85, with the Shapiro Wilk $W = 0.6530$ ($p < .0001$). As noted above, the largest observation was 141 minutes, followed by 70 minutes, 43 minutes and 31 minutes. The four smallest observations were 0.4, 1.8, 1.9 and 4.9 minutes. The extreme skewness suggested a log transformation of the data. The log transformed versions had corresponding statistics of mean = 2.49 and SD = 1.37. The value of the skewness statistic was -0.6840 . The Shapiro Wilk W was 0.9559 ($p = .4976$). From the transformed data, the geometric mean mouthing time was 12.03 minutes with an estimated 95% confidence interval of 6.2 to 23.3 minutes.

While these mouthing times may appear to be low, the data showed that children spent much more time mouthing other objects such as fingers and pacifiers. For 3-12 month old children the average usage of pacifiers was 45 minutes per day and fingers was 11 minutes per day. Mouthing times for pacifiers and other objects were not considered in the estimates for duration and DINP intake because they did not contain DINP. This is discussed in the appendix to this paper.

2.32 13-26 Months

This analysis used the same strategy as 3-12 months. The arithmetic mean mouthing time for children aged 13-26 months was 2.54 minutes with a median of 1.49 minutes, a SD of 2.94 minutes, skewness of 1.4117 and Shapiro Wilk W statistic of 0.8161 ($p = 0.0006$). This distribution was also highly skewed, suggesting the log transformation. The five largest observations were 10.4 minutes, 8.1 minutes, 7.7 minutes, 4.0 minutes and 3.9 minutes, while there were 5 values with zero recorded mouthing time. While the skewness and the very large observations again suggested a log transformation, the five zeroes proved to be worth consideration.

These five zero observations were from a child age 16 months, 2 children at 18 months, one at 19 months, and one at 24 months. One possibility would be to replace them with very small quantities, however this would induce negative skewness, that is, it would create the opposite outlier problem as found with the original values. This strategy was rejected. The remaining two approaches were (1) dropping the 5 cases with zeroes and then transforming to logs and (2) averaging the observations by month of age, before taking the logs. This second strategy had the desired result of reducing the number of zeroes to one for the child age 24 months, but at the cost of artificially lowering the standard deviation of the data.

The first approach of dropping the zeroes before transforming to logs, produced a mean of 0.74, an SD of 1.06, skewness of -0.3176 , and Shapiro Wilk $W = 0.7372$ ($p = .2875$). Averaging ages before taking logs produced a mean of 0.77, an SD of 0.88, skewness of -0.8850 and Shapiro Wilk $W = 0.9620$ ($p = .7964$). Because the means were

very close for both approaches, and because averaging first had the undesirable effect of lowering the SD, the first approach of dropping the zero observations was selected. Using this approach, the geometric mean was estimated at 2.1 minutes with a 95% confidence interval of 1.22 to 3.62 minutes.

3. Estimates for Average Daily Exposure

Equation (1) can be reexpressed in logarithmic terms as

$$(3) \quad \log(DE) = \log(M) + \log(D) - \log(BW)$$

where DE = daily oral exposure, M is migration rate per unit time, D is exposure duration and BW is body weight. Parameter estimates for that model are found in table 3 below.

Table 3
Estimates for Log of Average Daily Exposure for a child 3-12 months
(micrograms per day per 10 kg BW)

Component	Mean	Variance	Sample Size
Migration Rate (M)	1.6565	0.8318	31
Scaling Factor (S)	3.6766	0.2120	5
Exposure (D)	2.4880	1.8695	19
Constants	-6.0822	0.0000	-
Log of Average Daily Exposure (DE)	1.7389	2.9133	-

Notes: See section 2 for parameter estimates. Constants are $-\log(7.3)$ to convert the resulting exposure per kilogram to exposure per 7.3 kg (mean body weight) and $-\log(60)$ to convert from minutes to hours. The average body weight was from Snyder et al (1977). Constants enter additively for logarithmic relationships. The variance is calculated conventionally for M and S and D and described above.

Table 3 shows the log of average daily exposure for a child 3-12 months old. As noted above, these data are assumed to follow a lognormal distribution with parameters, $\mu = 1.7389$ $\sigma^2 = 2.9133$ ($\sigma = 1.7069$). Exponentiating the results provides an estimate of the geometric mean of 5.69 micrograms per 7.3 kg child per day, with a 95% confidence interval of (2.5 to 12.9) micrograms.

The point estimate for the 95th percentile is $\exp(\mu + 1.65\sigma/\sqrt{n})$, which is essentially the same as that for a normal distribution except that the result is exponentiated. The interval estimate for the 95th percentile follows Section 4.4 in Hahn

and Meeker (1991), who provide an interval estimate for the percentile of a normal distribution, and also associated tables. The underlying theory, according to them, involves the noncentral t distribution. To check these intervals, parametric bootstrap confidence intervals were also created (Efron and Tibshirani, 1993). These were very close to the intervals in Hahn and Meeker.

The 95th percentile exposure was 94.3 micrograms with a 95% confidence interval of (50.1 to 225.6).

Table 4 contains values for a child 13-26 months in the same units.

Table 4
Estimates for the Log of Average Daily Exposure for a child 13-26 months
(micrograms per day per 10 kg BW)

Component	Mean	Variance	Sample Size
Migration Rate (M)	1.6565	0.8318	31
Scaling Factor (S)	3.6766	0.2120	5
Exposure (D)	0.7447	1.1185	17
Constants	-6.4246	0.0000	0
Log of Average Daily Exposure (DE)	-0.3868	2.1623	-

Notes: See section 2 for parameter estimates and the notes for table 4. The variance is calculated the same way as table 4. The average body weight used was 10.7 kg (Snyder et al, 1977).

Exponentiating the results in table 4 produced a geometric mean daily exposure of 0.69 micrograms per 10.7 kg per day, with a 95% confidence interval of (0.32 to 1.55). The estimated 95th percentile exposure was 7.6 micrograms with a 95% confidence interval of 4.4 to 16.2 micrograms.

4. Conclusion

This paper has described the method for estimating DINP intake used for children aged 3-12 months and 13-26 months. The approach is similar to that taken by the Dutch Consensus group (van Veen, 1998). Migration rates were developed from in-vitro experiments, then scaled by using migration rate data from paired in-vitro and in-vivo samples. Mouthing durations were obtained from Groot et al (1998a).

These data were combined into an analytic model that used a lognormal distribution for human exposure duration, combining estimates from the separate experiments. Geometric means, 95th percentiles and associated confidence intervals

were estimated.

The results showed a geometric mean average daily intake of 5.7 micrograms per day (95% confidence interval 2.5 to 12.9) for children between ages 3 and 12 months. The distribution was very skewed, with an estimate of 5% of children at 94.3 micrograms or more (95% confidence interval 50.1 to 225.6). The values for children at 13-26 months was considerably lower with a geometric mean of less than 1 microgram per day.

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Appendix

Differences between CPSC research and the Dutch Consensus Group Report

This paper differs from the research by the Dutch Consensus group in the following respects:

1. The Dutch Consensus group used three specimens cut from two products for DINP extraction while we used specimens from 31 different products.
2. Instead of using machine impaction methods and then scaling them with paired *in vitro* and *in vivo* measurements, the Dutch Consensus group obtained migration rates directly from 20 adult human subjects using these three specimens (Meuling and Rijk, 1998).
3. Instead of fitting a probability distribution for migration rates or exposure duration, the Dutch consensus group used a Monte Carlo simulation that sampled from the empirical distribution of migration rates and exposure durations.
4. The Dutch consensus group used a normal distribution for body weight in their simulation, assuming age specific values ranging from 6.25 kg for children 3-6 months to 13.5 kg for children 18-36 months. The analysis in this paper used a constant 7.3 kg body weight for children aged 3-12 months and 10.7 kg for children 13-26 months.
5. Exposure durations used in our analysis were restricted to those from objects labelled as "Mouth Toys" or "Other Toys," in Groot et al (1998a), while the Dutch Consensus group reported using the larger quantity of "all mouthing activities except sucking on dummies (also known as pacifiers)." See van Veen (1998).

The most important distinctions would result from items 1 and 5 above. With respect to item 1, the migration rate estimates, the Dutch Consensus group used three specimens (see Meuling and Rijk, 1998). The first specimen was a standard PVC sample containing 38.5% DINP and was not a consumer product. The second and third were sections from a teething ring; specimen 2 was a "finger," and specimen 3 was from a flat part of the same toy. In contrast we used specimens from 31 different products, including toys and teething rings, with DINP content varying from 15 to 54% (see Chen, 1998, table 4). These products were chosen from toys we believed were likely to be sucked, chewed or mouthed by children.

The other important distinction is item 5 above. While we and the Dutch Consensus group used the same source for the exposure duration, (Groot, et al, 1998b), the Dutch consensus group used total mouthing time for all objects other than pacifiers as an estimate for the time that children would be exposed to DINP. Total mouthing time included observations for children mouthing their fingers and also objects defined as non toys (cloth, cutlery, paper, adult books). See Groot et al, (1998b, appendix 1). The statistical analysis in this paper used only reported mouthing time for toys, which included the two categories of "toys for mouthing," and "other toys." The difference is

substantial. For example, for age group 6-12, the mean mouthing duration was reported as 27.9 minutes for toys and 44 minutes for all objects (Groot, et al, 1998b table 5-13). Resulting, total mouthing time overstates the mean toy mouthing time by a factor of 58 percent. Since fingers and non toys did not contain DINP, it did not appear appropriate to use total mouthing time.

It is doubtful that the differences from items 2, 3 and 4 above would be substantial. There has been much research on different methods for measurement of DINP migration rates and there is still much to be learned about variability inherent in different laboratory methods (see Chen, 1998). In item 3, the use of a Monte Carlo simulation instead of the fitting of analytic models, the difference would turn on how well the models fit the data. If the models fit well, then a large number of Monte Carlo samples would have about the same results as the analytic models. We preferred to use an analytical model whenever possible for analytic tractability and to facilitate obtaining confidence intervals.

Finally, the use of variable body weights instead of a fixed constant of 7.3 or 10.7 kg would be unlikely to make much difference because the variability in body weight would be small, compared to the other sources of variability in these analyses.



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

December 1998

U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

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

Executive Summary

December 1998

U.S. Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

NOTE: This document has not been
reviewed or accepted by the Commission.
Initial rlh Date 12/1/98

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Executive Summary

Overview

1. The U.S. Consumer Product Safety Commission (CPSC) is investigating the potential health risks to children under 3 years of age from teethingers, rattles, and toys made from polyvinyl chloride (PVC) containing a chemical DINP (diisononyl phthalate) used to make the PVC softer.

2. Based on the work the staff has conducted and other scientific studies currently available, the staff concludes that few, if any, children are at risk from liver or other organ toxicity from the release of DINP from these products. This is because the amount they might ingest does not reach a level that would be harmful.

3. The staff believes that uncertainties remain relating to estimations of risk, including the risk of cancer, and that additional studies are needed. The staff recommends CPSC undertake the following additional work:

- Convene a Chronic Hazard Advisory Panel of independent scientists to study issues related to the chronic toxicity and risk, including the risk of cancer, associated with exposure to DINP in children's PVC products.
- Conduct an extensive exposure study to obtain a broader range of data from which to better define the amount of time children mouth products that could contain phthalates.
- Continue work to develop a laboratory test method that better estimates the amount of phthalate released when products are mouthed by children.
- Conduct additional testing of products intended for children under 3 years of age that contain DINP.

Description of Work to Date

CPSC staff has evaluated the potential health risks to children under 3 years of age from teethingers, rattles, and toys made from polyvinyl chloride (PVC) containing DINP.

This evaluation included laboratory testing to simulate the mouthing by young children of products that contain DINP and other phthalates. These tests provided information on the amount and type of phthalate released. CPSC staff also conducted tests using adult volunteers to compare the amount of DINP found in laboratory tests to the amount released when adults sucked or gently chewed on a piece of product.

CPSC staff analyzed the literature and other available information on the health effects of the DINP found in the children's products mentioned above. Staff also evaluated available information on the amount of time children would mouth products such as toys, teethingers, and rattles.

The information obtained from testing and analysis of the literature was used to estimate the potential hazard to children. Staff found the magnitude of the risk is directly related to the amount of DINP released from mouthing and the amount of time children mouth the products.

CPSC Study Findings

A number of important findings resulted from the Commission's study. These include the following:

Phthalates Found in Children's Products

- Based on products tested, DINP is the predominant phthalate used to soften PVC that is contained in some children's products sold in the United States. CPSC staff tested 35 children's PVC products that contained phthalates: 31 contained DINP, two (a pacifier and a baby bottle nipple) contained diisooctyl phthalate (DIOP), one (a soother) contained dinonyl phthalate (DnNP), and one (a child's purse) contained di(2-ethylhexyl) phthalate (DEHP). With pacifiers and baby bottle nipples, only one manufacturer was found to have some models that contained a phthalate. These models have been removed from the market. All other known pacifiers and baby bottle nipples are made from latex or silicone and therefore do not contain phthalates.

Release of DINP from Products

- CPSC laboratory testing of children's products likely to be mouthed by children under 3 years of age showed wide variability in the amount of DINP released. The amount of DINP used to soften the products also varied widely. Importantly, however, the staff found no relationship between the amount of DINP used in the product and the amount released when tested in the laboratory.

Measuring Release of DINP

- CPSC staff found that, based on information currently available, the method used to manufacture the product (e.g., injection or rotational molding or sheeting) does not correlate with the amount of DINP released. The staff also found that there is currently no laboratory test method available to estimate adequately the amount of DINP released during laboratory testing that correlates with the amount released when products are mouthed by humans. Work on developing such a method is proceeding at CPSC and in Europe.

- CPSC staff used 10 adult human volunteers to mouth a piece of a children's toy that contained DINP to determine the release of DINP. The amount of DINP released was higher than the amount released during CPSC laboratory simulation testing. The results indicated that there was a 39.5 fold higher level released during the human subjects testing. Accordingly, the staff applied this factor to increase the DINP release rates measured in the laboratory for the 31 products found to contain DINP.

Data on Children's Exposure

- CPSC staff found that the data available to estimate actual times that children put items that may contain phthalates in their mouths is very limited. The best data comes from a study released by the Dutch Consensus Panel in September 1998. The staff has relied on this data to estimate exposure to children for calculating risk. All previously published estimates of exposure have been based on professional judgment, but not on actual time measurements. The Dutch study found wide variability in the amount of time children spend mouthing. The study also found that children under 1 year of age spend considerably more time mouthing than do children 1 to 3 years of age. Since the Dutch Study was relatively small, CPSC staff recommends a larger observational exposure study in children ranging in age from 3 months to 3 years.

Acceptable Daily Intake

- Animal studies show that DINP causes chronic toxic effects to the liver and other organs. In order to determine the level at which humans are at risk CPSC staff calculated an acceptable daily intake (ADI) for humans. The ADI is a level that is not expected to cause harmful health effects in humans. Using data from the animal studies, staff calculated an acceptable daily intake (ADI) for humans to be 150 micrograms per kilogram of body weight per day. This value is derived by taking the highest level of exposure that did not result in an adverse health effect to animals and applying a 100-fold safety factor to account for possible differences between animals and humans and for differences in the sensitivity among individuals.

Estimated Exposure of Children

- CPSC staff estimated the exposure to DINP from children's teethingers, rattles, and toys. This information is provided in the table below. The data show that none of the daily intake estimates exceed the 150 micrograms per kilogram per day acceptable daily intake (ADI). No estimate of risk is provided for pacifiers or baby bottle nipples because only one manufacturer was found to have models that contained a phthalate (DIOP). This manufacturer has stopped using phthalates.

Estimated Exposure of Children to DINP in Teethingers, Rattles, and Toys

Children's Age	Estimated Daily Intake of DINP ($\mu\text{g}/\text{kg}/\text{day}$)			
	Geometric Mean	Confidence* Interval (CI)	95th Percentile	Confidence* Interval (CI)
3-12 Months	5.7	2.5-12.9	94.3	50.1-225.6
13-26 Months	0.7	0.3-1.6	7.6	4.4-16.2

*The Confidence Intervals shown in the table are a measure of uncertainty in the estimates of the Geometric Mean and 95th Percentile.

Possible Further Risk from DINP

- One animal study also found that DINP caused an increased incidence of liver tumors (carcinomas and adenomas) in rats and mice. There is uncertainty about the actual mechanism by which compounds such as DINP contribute to cancer in animals and whether this mechanism applies to humans. In addition, there is controversy over what model is appropriate to use to calculate any risk. CPSC staff recommends that a Chronic Hazard Advisory Panel of independent scientists evaluate the available scientific data and advise the Commission on this issue.

Conclusions

The CPSC staff concludes that based on the best available information about the amount of DINP released from the products tested by the staff and relying on the exposure information from the Dutch study, few, if any, children are at risk of liver or other organ toxicity from mouthing teethingers, rattles, and other PVC toys that contain DINP. However, there are a number of significant uncertainties in this assessment including the cancer risk, and further work is necessary to gather better data on which to base the health risk assessment.

Recommended Future Work

CPSC staff recommends the Commission undertake additional work to address the uncertainties that can affect the estimate of the risk to children. The additional work includes:

- Convening a Chronic Hazard Advisory Panel of independent scientists to study issues related to the chronic toxicity and risk, including the risk of cancer, associated with exposure to DINP in children's PVC products.
- Conducting an extensive exposure study to obtain a broader range of data from which to better define the amount of time children mouth products that could contain phthalates.
- Continuing work to develop a laboratory test method that better estimates the amount of phthalate released when products are mouthed by children.
- Conducting additional testing of products intended for children under 3 years of age that contain DINP.



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

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Summary

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

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

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

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

I. INTRODUCTION

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

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

II. METHODOLOGY

A. Exposure

1. Impaction Method

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

2. Human Subjects Studies

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

3. Mouthing Activity

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

4. Daily Exposure

The estimated daily oral exposure was calculated by:

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

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

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

B. Chronic Toxicity

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

III. RESULTS

A. Exposure

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

Studies with human subjects were performed using disks with a surface area of approximately 10.3 cm^2 . The ratio between the *in vivo* and impaction methods averaged 39.5,

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

with a range of 22.9 to 72.6 (Table 2). The average (geometric mean) mouthing duration in the 3 to 12-month old group was estimated to be 12.0 minutes per day (Greene, 1998) (Table 3). The average mouthing duration for 13 to 26-months was estimated to be 2.1 minutes per day. These times apply only to toys, teethingers, and rattles, which may contain DINP. The average time for pacifiers, which do not contain DINP, was greater.

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

B. Chronic Toxicity

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

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

IV. DISCUSSION

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

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

A. Exposure

1. Migration Studies

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

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

migration rates (Chen, 1998b). Migration rates, measured by the CPSC staff, using the NERI method ranged from 7.2 to 102 $\mu\text{g}/\text{dm}^2/\text{h}$. Migration rates by the CPSC impaction method ranged from 105 to 133 $\mu\text{g}/\text{dm}^2/\text{h}$ (roughly equivalent to 13 $\mu\text{g}/11\text{ cm}^2/\text{h}$).

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

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

2. Mouthing Duration

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

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

estimated the average mouthing activity for two age groups: 3 to 12 months and 13 to 26 months. These age groups were based on the recommendation of the Division of Human Factors (Kiss, 1998) and are consistent with the results of the Dutch study (Green, 1998).

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

B. Chronic Toxicity

1. Acceptable Daily Intake

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

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

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

Although the studies tested DINP's from different sources, they are considered to be equivalent in their chemical composition and toxicity (Wilkinson, 1998). The background rate of spongiosis hepatitis was higher in the Lington study (about 30 percent) than in the Moore study (about 6 percent). However, the dose response in the Lington study remains more sensitive even after adjusting for background (Figure 3).

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

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

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

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

µg/kg-d. An estimate of the dietary intake of total phthalates in infants in Europe was reported to be 23 µg/kg-d (Janssen et al., 1998).

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

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

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

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

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

method; or assuming that all DAP's are equipotent. If the relative concentrations of different DAP's is unknown, assuming equal potency would be preferred.

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

C. Carcinogenicity

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

1. Carcinogenicity of DINP

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

The dose response observed with DINP is consistent with that of DEHP, another branched chain DAP. The incidence of HCC was significantly elevated in Fischer rats fed DEHP at 1.2 percent, but not at 0.6 percent (NTP, 1982). The incidence of HCC in males and females combined from the three DINP studies and the DEHP study were plotted on the same graph for

comparison (Figure 4). The dose responses from these studies appear to be similar, suggesting that DINP's from different sources may be similar in their cancer dose response. In mice, DEHP was 2 to 3-fold more potent than DINP (not shown). The similar response with DEHP suggests that the key structural feature responsible for carcinogenicity may be the presence of branched chains, rather than the presence of any specific isomers.

2. Mechanism of Action

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

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

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

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

bone marrow cells of F-344 rats in vivo, although the highest dose was only 5.0 mg/kg (Microbiological Associates, 1981e).

At least three mechanisms of action have been proposed for PPC's (Conway et al., 1989; IARC, 1995; Cattley et al., 1998): oxidative stress (oxidative DNA damage), cellular proliferation (mitogenesis), and the preferential growth of preneoplastic cells (tumor promotion). These proposed mechanisms are not mutually exclusive.

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

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

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

certain types of altered hepatic foci may explain why several promotion assays gave negative results (Bentley et al., 1993).

The promotion of spontaneously-initiated cells appears to be the most plausible mechanism of action for PPC's. However, tumor promotion activity has only been demonstrated for a few PPC's; it has not been demonstrated for DINP. Even if this is the predominant mechanism, PPC's are complete carcinogens, that is, administration of PPC's alone leads to tumor formation in animals (Reddy and Rao, 1995). Therefore, it is likely that other mechanisms, possibly including oxidative DNA damage and mitogenesis, also contribute to the carcinogenic process.

a. Peroxisome proliferator-activated receptor

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

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

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

b. Species differences in response to PPC's

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

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

3. Relevance of Animal Tumor Data in Assessing Human Risk

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

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

conditions of the bioassay; and (c) such effects have not been found in adequately designed studies of human systems (IARC, 1995). At this time it is not clear whether these criteria have been satisfied for DINP. For example, although DINP induced PPN under the conditions of the bioassay, it failed to induce chronic hepatocellular proliferation (Moore, 1998a,b).

4. Quantitative Cancer Risk Assessment

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

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

At this time, the choice of the appropriate dose response model for DINP remains unclear. There is ongoing research on the relevance of the tumors in animals to humans. In addition, research on the mechanism of action of PPC's is currently underway (Bucher, 1998; CMA, 1998). The relevant issues are whether a scientific consensus on the mechanism of PPC's exists, and how this applies in the case of DINP. This issue should be explored in an appropriate forum such as a workshop, public hearing, or Chronic Hazard Advisory Panel. The mechanism by

which cancer occurs plays a role in determining the appropriate model to use to calculate a risk. Since scientific consensus does not exist on how DINP causes cancer in animals, quantitative estimates of cancer risk associated with DINP exposure from children's products are not presented here. The issue of cancer risk will be addressed following additional consideration of this issue.

V. CONCLUSIONS

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

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

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

Continued on next page.

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

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

^a Includes only children's products containing DINP.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

^b Number of animals examined.

^c Number of animals with spongiosis hepatitis.

^d Fraction of animals with spongiosis hepatitis.

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

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

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

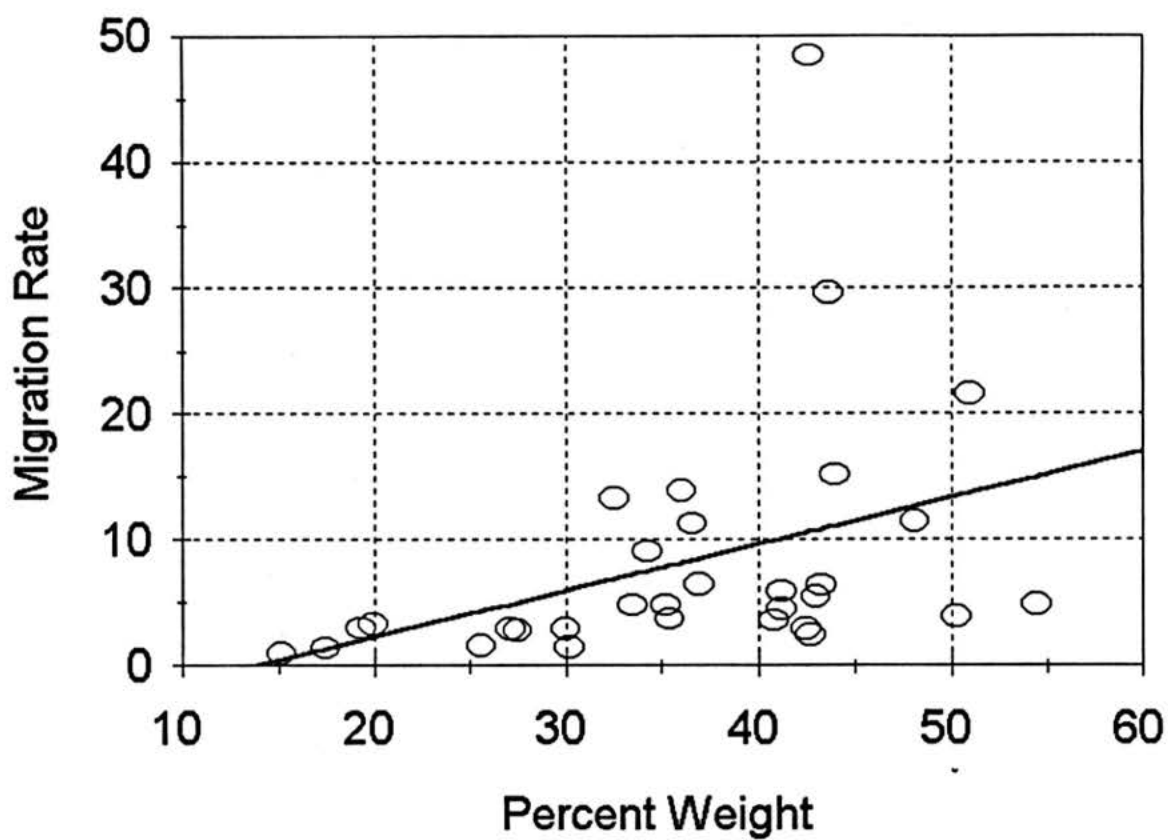


Figure 1. Effect of diisononyl phthalate (DINP) content (percent weight) on the migration rate ($\mu\text{g}/11\text{ cm}^2/\text{h}$) measured by the impaction method (Chen, 1998a). (O) Observed; (—) regression line ($r^2 = 0.14$).

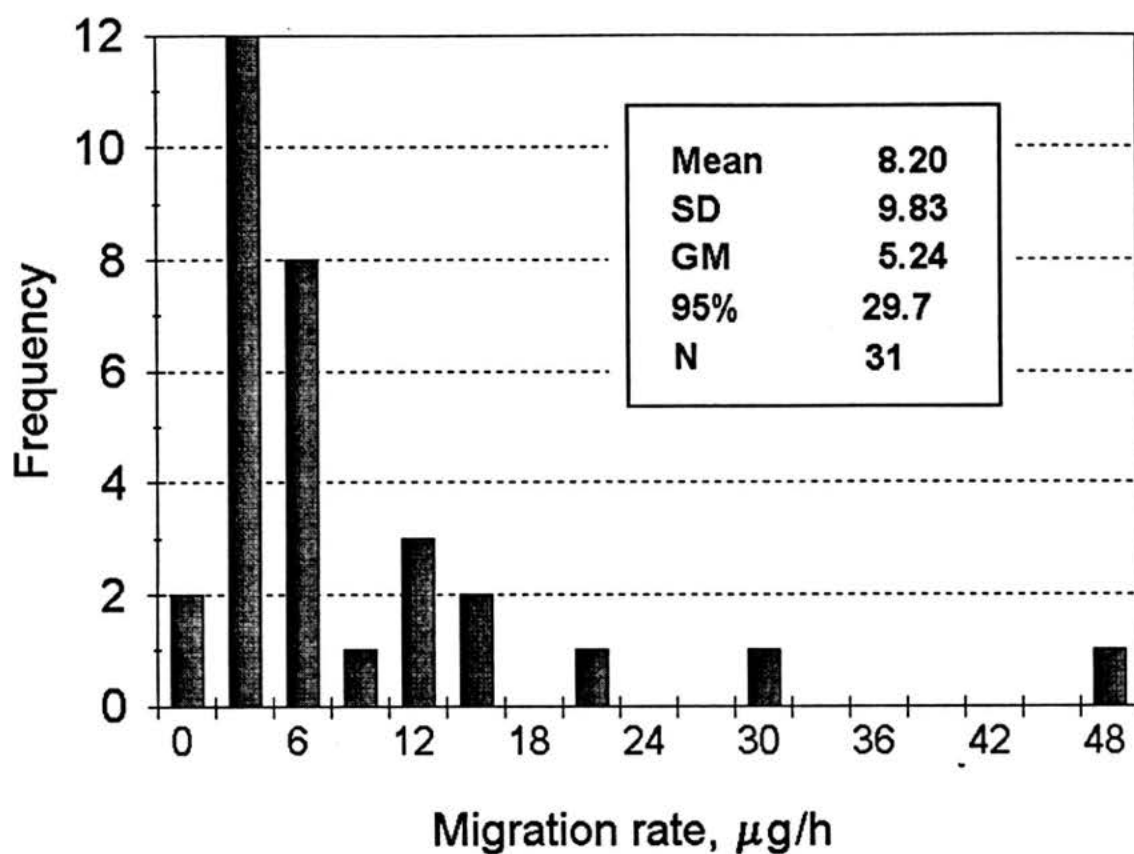


Figure 2. Frequency distribution of diisononyl phthalate (DINP) migration rates for 31 children's products, as measured by the impaction method (Chen, 1998a). The migration rate is in $\mu\text{g/h}$ for an 11 cm^2 area. GM, geometric mean; SD, standard deviation; 95%, 95th percentile value; N, number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

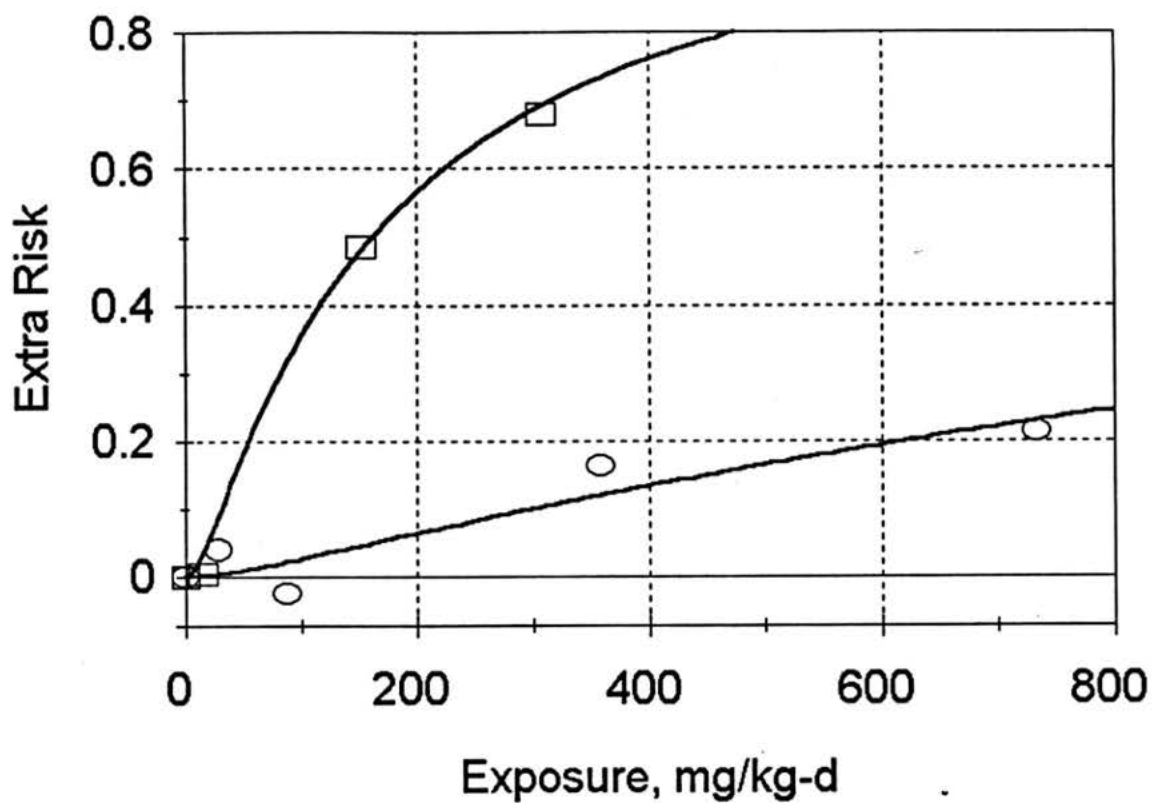


Figure 3. Extra risk of spongiosis hepatitis in male rats fed diisononyl phthalate (DINP) for two years. (□) Lington et al., 1997; (○) Moore, 1998a; (—) lognormal model for either data set. Data from either study were fitted to a lognormal model as described in (Crump, 1984b).

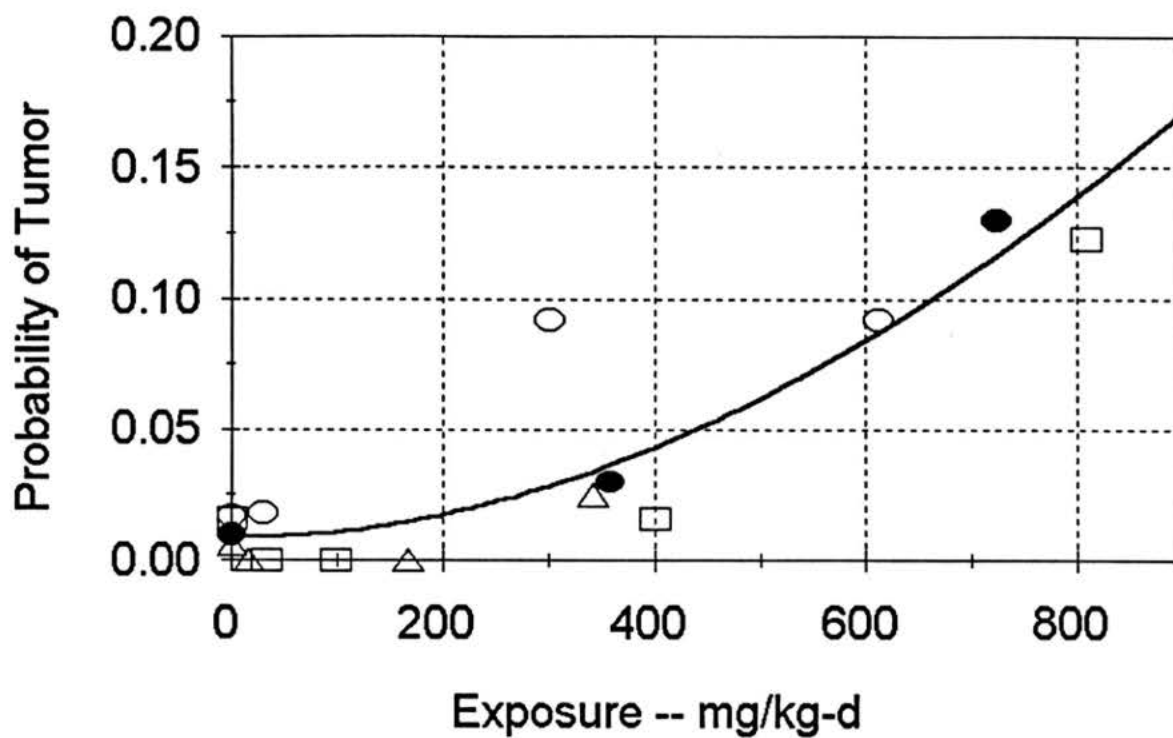


Figure 4. Incidence of hepatocellular carcinoma in rats fed dialkyl phthalates for two years. (●) di-(2-ethylhexyl)phthalate (117-81-7) (NTP, 1982); (○) diisobutyl phthalate (71549-78-5) (Bio/dynamics, 1986); (Δ) diisobutyl phthalate (68515-48-0) (Lington et al., 1997); (□) diisobutyl phthalate (68515-84-0)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

Appendix A

Migration of DINP from Polyvinyl Chloride (PVC) Children's Products

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I. Background

Dialkyl phthalate esters impart flexibility to rigid polyvinyl chloride polymer (PVC). Previous studies by the Inhalation Toxicology Research Institute (ITRI) for the U. S. Consumer Product Safety Commission (CPSC) examined the migration of di 2-ethylhexyl phthalate (DEHP) from teething and pacifiers (*Phthalate Ester Migration from Polyvinyl Chloride Consumer Products*, R. L. Hanson, ITRI, 1983). These studies, which use an air driven piston to simulate mouthing and chewing, demonstrate that DEHP migrated from the pacifiers and teething. The purpose of the present study is to identify phthalate containing products that are likely to be mouthed by children and to determine the amount of phthalate migration from these products using *in vitro* and *in vivo* tests.

II. Methods

A. Determination of total phthalates from PVC

1. Total phthalates

Samples consisting of thin plastic sheets were cut into small pieces. Thicker samples were cooled by liquid nitrogen and ground to a powder with a micro mill. A weighed portion of the cut sheet or powdered plastic was placed in a Soxhlet extraction thimble and extracted for six hours with 80 ml of hexane. The hexane was evaporated and the percent by weight of phthalates was calculated from the weight of phthalates recovered and the initial weight of the sample extracted.

2. Identification and quantitation of phthalates

Phthalates obtained from the Soxhlet extraction of PVC products were dissolved in hexane and identified by means of gas chromatography/mass spectrometry (GC/MS) by comparison to spectra of known phthalate esters. Comparisons of known with unknown phthalate esters were made by matching retention times of total ion chromatograms and the selective ion chromatograms at mass 149. The mass 149 ion is specific for phthalate esters. Quantitative analysis of phthalates was performed by HP-6890 GC/MS system as follows:

1. GC conditions

Column, J & W DB-1, 0.25 mm ID, 30 m, 0.1 μ m
Oven Temperature, 100 °C for 3 min, 100 °C to 270 °C at 40 °C/min,
270 °C for 30 min
Injector Temperature, 325 °C
Carrier gas, Helium, 1.0 ml/min
Injection, 1 μ l splitless

2. MS analysis

Butyl benzyl phthalate (BBP) was used as an internal standard since it was found as an impurity in DINP at less than 0.5% of total phthalates. Selective ion mode was used in quantitative analysis. Phthalates were quantified by use of the peak area ratio of unknowns and BBP against the calibration curve of the peak area ratios derived from known concentrations of standard phthalates and BBP. The calibration and analyses of unknowns were performed on the same day.

B. *In vitro* phthalate migration

1. Chemicals and apparatus

The apparatus used for *in vitro* simulation of chewing is shown in Figures 1 and 2. This test apparatus allows up to six specimens to be tested simultaneously. The materials and equipment used are as follows:

Shaking water bath capable of maintaining 37 °C

Six 100 ml stainless steel beakers for holding extraction solution and PVC sample

Air driven pistons, 1.58 cm (5/8 inch) hexagon with an area of 2.18 cm² (0.338 in²)

Air compressor with pressure regulation from 258 mm to 3103 mm Hg (10 to 90 pounds per square inch gauge, PSIG)

Programmable controller to activate the pistons, operated at 4 seconds per cycle (2 seconds of applied air pressure, and two seconds of relaxation)

Separatory funnels

Hexane (95%, Mallinckrodt)

Simulated saliva solution - Dulbecco's phosphate buffered saline containing 0.16 percent mucin (pH ≈ 7.2, this is consistent with earlier work done at ITRI)

2. Phthalate migration by shaking

A PVC sample of known surface area was placed in a 250 ml glass stoppered Erlenmeyer flask containing 50 ml of the saliva simulant. The flask was placed in a 37 °C water bath and shaken horizontally for 6 hours at a rate of 60 cycles/min with a travel distance of 2.54 cm (1 in).

3. Phthalate migration by impaction

Samples consisting of thin PVC sheets were cut into disks approximately 7 cm in diameter to prevent significant movement in the stainless steel beaker during impaction. Hollow samples were cut and placed over the piston. Large or odd shaped samples were cut to provide a relatively flat surface. Test specimens smaller than 7 cm tended to move about the beaker and were held in place by a metal rod. Samples were tested intact wherever possible. A Chatillon force gauge measured the force applied by the piston before and after every experiment. Test specimen dimensions were measured and recorded for each experiment.

The normal extraction procedure consisted of adding 50 ml of saliva simulant to the stainless steel beaker holding the item under test. The piston was activated and applied pressure for 2 seconds followed by 2 seconds without pressure. Each test lasted 6 hours at 37 °C. The forces investigated were 0.91 kg, 2.7 kg, and 5.4 kg (2 lbs, 6 lbs, and 12 lbs). The piston sizes were 1.27 cm, 1.59 cm, and 2.54 cm (1/2", 5/8" and 1 ").

4. Extraction of phthalates from saliva simulant using hexane

The test specimen was removed from the beaker and rinsed with a minimum amount of deionized water. The combined aqueous solutions were transferred to a 250 ml glass Erlenmeyer flask. The piston and beaker were rinsed with 50 ml of acetonitrile and combined with the aqueous extraction media. Fifty ml of hexane was then added and the entire mixture was vigorously stirred for 8 minutes and transferred to a separatory funnel. After separation of hexane and aqueous phases, the aqueous phase was extracted with an additional 25 ml of hexane. The combined hexane extracts were allowed to evaporate in an 80 ml beaker at room temperature. The residues were dissolved in approximately 1 ml of hexane and a known amount of butyl benzyl phthalate (BBP) was added as internal standard for GC/MS quantitative analysis.

5. Calculation of migration from impacted and non-impacted surfaces

The area of the surface of an item that was likely to be mouthed when used by a child was assumed to be 11 cm². Since the impaction procedure exposes both impacted and non-impacted areas to the buffer, the migration of phthalate had to be apportioned between the amounts migrating from the impacted areas (chewed) and non-impacted areas (mouthed but not chewed). The tooth/gum contact (chewed) area was assumed to be the area of the piston, 2.18 cm² and the mouthed area was assumed to be 8.82 cm². The apportioning of total release between impacted and non-impacted areas was done algebraically. Knowing the total immersed area, piston area (2.18 cm²), and total phthalate migration, the migration from the impacted area was calculated as the difference between total migration and the migration from the non-impacted area. The calculation, assuming that the migration rate from non-impacted area is same migration rate as determined in the shaking only experiments, resulted in a ratio of 0.0302¹.

C. *In vivo* phthalate migration

The *in vivo* testing used five duck toys that were identical to sample 2.02. These were identified as D1 through D5. Four disks were cut from each duck with a 2.86 cm tubular cutter and identified as D1-1 through D1-4, D2-1 through D2-4, etc. Two disks from each toy were used for human subject testing and the remaining two were used for impaction or other testing. Ten polytetrafluoroethylene disks served as blanks. Prior to testing, all disks were gently washed with warm soapy water, rinsed and allowed to dry at room temperature.

¹The phthalate migration rate ($\mu\text{g}/\text{cm}^2/\text{hr}$) of 6 samples was determined by use of shaking only. The same 6 samples were subjected to the impaction procedure. The calculated apportionment ratio was 0.0302.

The human subjects consisted of three female and seven male CPSC staff volunteers who were not involved with the phthalate project. Each was provided with a polytetrafluoroethylene disk and a disk from the toy duck. Each volunteer was instructed to gently chew/mouth a polytetrafluoroethylene disk for 15 minutes. The subjects were then instructed to repeat the process for four 15 minute intervals on a the disk cut from the toy duck. The subjects were allowed 5 minutes to rest between the periods of active mouthing of the disks. For each 15 minute chewing period the subjects were instructed to collect all their saliva in labeled bottles. The total volume of saliva (ml) and pH of the saliva in each bottle were recorded. All saliva samples were diluted to 50 ml with deionized water and treated with 50 ml of acetonitrile. Extraction of the phthalates from the saliva with hexane was performed as described above. The protocol for the *in vivo* tests was approved by the CPSC human subjects committee.

III. Results and Discussion

This study was conducted in four phases. The first phase was a series of experiments performed to determine the conditions for measuring phthalate migration from the test products. The second phase characterized phthalate release from the PVC products. The third phase was a survey of various PVC children's products for phthalate release. The fourth phase was a human subjects mouthing/chewing test to compare *in vitro* and *in vivo* migration rates.

A. Determining test conditions

A flat and smooth PVC teether containing diisononyl phthalate (DINP) was used to evaluate the test conditions for determining the migration rates of phthalates from children's teethers, toys, and pacifiers. The sample could also be tested without cutting the edge which might affect the rate of phthalate release.

1. Recovery of DINP by acetonitrile/ hexane extraction

DINP (10, 25, 50 and 100 μg) was dissolved in hexane. The solutions were air dried and 50 ml each of saliva simulant and acetonitrile added. The mixture was vigorously stirred, treated with acetonitrile and extracted with hexane as described earlier. The percent recoveries of DINP were 122, 93, 82, and 103 respectively with an average recovery of $100\% \pm 17\%$.

2. Impaction pressure

A comparison of the release rate of DINP versus force applied is shown in Figure 3. Similar results were obtained for either 2.7 kg (6 lbs) or 5.4 kg (12 lbs) of force and both gave substantially higher release rates (approximately 10 $\mu\text{g/hr}$) than were obtained by either by shaking only (approximately 3 $\mu\text{g/hr}$) or with an impaction force of 0.91 kg (2 lbs) (approximately 5 $\mu\text{g/hr}$). An additional experiment was performed on a higher DINP releasing PVC product with similar results. The release rates for this product were 44.67 $\mu\text{g/hr}$ and 37.41 $\mu\text{g/hr}$ respectively for 2.7 kg (6 lbs) and 5.4 kg (12 lbs) of force.

3. Rate of impaction

The impaction controller allows for varying the rate of impaction, however, the total cycle time is always divided into equal periods of impaction and relaxation. A higher absolute release rate ($8.75 \mu\text{g/hr}$) was obtained with a four second cycle than with either a six or an eight second cycle ($2.88 \mu\text{g/hr}$ and $3.88 \mu\text{g/hr}$ respectively). The release rates for cycles of six and eight seconds, when extrapolated to the same number of impactions, however, are similar to the migration rate measured for the four second cycle. The four second cycle impaction rate was chosen to provide the greater number of impacts per unit of time.

4. Extraction time

As shown in Figure 4, the initial migration rates were similar at 2, 4 and 8 hrs but fell off at 24 hrs. After being allowed to stand for one week under ambient laboratory conditions, the samples were retested for an additional 8 hours of impaction. The migration rates were generally similar for this additional period with the highest rate being observed for the sample impacted initially for 8 hrs. Based on these data, an impaction time of 6 hrs appeared to be adequate, for samples with low rates of phthalate migration, to ensure sufficient phthalate for reliable detection and quantitation. Saturation of the simulant with phthalates did not appear to be a problem during the first 8 hrs of extraction.

5. Piston size

Three sizes of hexagonal pistons 1.27 cm, 1.59 cm, and 2.54 cm ($\frac{1}{2}$ ", $\frac{5}{8}$ " and 1") were tested to determine if there is a correlation between the piston area and release rate. The force was adjusted to provide the same applied pressure (1.25 kg/cm^2) to the item under test. Table 1 shows an increase in the absolute migration rates ($\mu\text{g/hr}$) with increasing piston size, however, the rates were equivalent when expressed as rates per square centimeter of piston area ($\mu\text{g/hr/cm}^2$). Since actual tooth contact areas would vary by individual and age, the $\frac{5}{8}$ inch piston was chosen to maintain consistency with the earlier ITRI study.

B. Characterization of phthalate release

1. Constancy of phthalate migration

The data plotted in Figure 5 shows that DINP migration rates for two separate samples remained relatively constant (1.3 ± 0.3 and $1.9 \pm 0.2 \mu\text{g/hr}$ respectively) over four consecutive days of extractions. Phthalate migration could thus continue at the rates initially found over prolonged periods of time.

2. Replication of extraction by impaction

Extraction of two units each from four samples (Toy Fish, Tree House, Tiger Toy, and Pacifier) and extraction of five units each from two samples (Teether#3, and Toy Duck#2) provided data for assessing replication of migration. Table 2 shows that the average percent standard deviation for the combined six items was 17.05 percent (range 9.8 percent to 28.0 percent). Teether #3, which was relatively flat had the least variation (9.8 percent), and was tested intact. The toys and pacifier, however, were not flat and exhibited a greater variation. The greater variation with samples that were not flat may be due to non-uniform application of force over the surface of the item, flexing of the item when impacted, or other unknown factors.

3. Replenishment of saliva simulant and other migration media

These experiments examined the effect of replenishment on the amount of DINP that migrates from PVC products with various extraction media. Three different media were used, Dulbecco's buffer, Dulbecco's buffer with mucin added, and Dulbecco's buffer with mucin and sodium azide (a bacterial inhibitor). Each experiment listed in Table 3 used a separate unit of Toy Duck#2. The internal air bladder from each unit was cut into six sections, three for the 2 hour replenishment experiments and three for the 6 hour continuous experiments. After each replenishment, the medium that had been removed was treated with 50 ml of acetonitrile. After the third replenishment, the impaction beakers and impactors were washed with acetonitrile and the washings combined with the medium from the third extraction. The combined media and washings for each replenishment period were extracted with hexane. For comparison, a continuous six hour impaction experiment with no replenishment was also performed and the media extracted with hexane as described earlier. As shown in Table 3, the data are variable but the average total migration rate for all replenishment tests combined ($41.4 \mu\text{g/hr}$) is similar to that for all continuous tests ($45.9 \mu\text{g/hr}$) indicating that any replenishment effects, at least at 2 hour intervals, are small. The variability observed may reflect unknown differences in manufacturing or composition of each individual toy. The GC/MS ion chromatograms showed that not all of the products that appeared to be identical had the same distribution of DINP isomers. It is also not clear that the addition of mucin, or mucin and sodium azide increases phthalate extraction over buffer alone.

C. A survey of PVC children's products

A total of thirty five samples of children's products that were likely to be mouthed or chewed, were subjected to impaction in Dulbecco's phosphate buffered saline containing 0.16 percent mucin (Table 4). DINP was present in thirty one, DIOP in two, DEHP in one, and DnNP in one.

The phthalate release rate, calculated for 11 cm^2 , ranged from $1.02 \mu\text{g/hr}$ to $48.40 \mu\text{g/hr}$. Toy Duck #2 had the highest release rate of the thirty five samples tested (Table 4). This release rate was for an internal bladder ($48.4 \mu\text{g/hr}$). The release rate for exterior PVC from Toy Duck #2 was lower ($6.4 \mu\text{g/hr}$). Figure 6 is a plot of the percentage of phthalate versus the release rate for the samples listed in Table 4. It clearly shows a lack of correlation between the release rate

and the amount of phthalate present in the samples. The reason for the lack of correlation is not known.

D. *In vivo* migration of phthalates

Table 5 presents the data from the *in vivo* migration study using PVC disks cut from the exterior of Toy Duck#2. The total quantities of saliva produced in four 15 minute periods of mouthing and chewing ranged from 27 ml to 95 ml. Saliva pH ranged from 6.90 to 7.66 with an average of 7.43. There was no apparent relationship between the amounts of phthalate migrating and the sex of the volunteers, the quantity of saliva produced, and the pH of the saliva. None of the saliva samples obtained from mouthing of the polytetrafluoroethylene control disks contained phthalates. The maximum migration rate for any one individual and time period was 826.48 $\mu\text{g/hr}$ and the minimum was 32.78 $\mu\text{g/hr}$, a ratio of 25.2. Individuals showed better consistency in migration rates with the maximum to minimum migration rate ratios ranging from 1.57 to 3.10. The average migration rates for individuals ranged from 63.22 $\mu\text{g/hr}$ to 596.64 $\mu\text{g/hr}$.

Table 6 presents the migration data obtained by impaction of new and the previously mouthed disks. A comparison of the impaction migration rates from new disks cut from the toy to impaction migration rates from disks used in the *in vivo* study show that the migration rates of the new disks are similar to the migration rates of the previously mouthed disks. The ratio of the geometric means of the *in vivo* migration rates to the *in vitro* migration rates of 39.5 showed that the impaction method substantially underestimates human exposure.

IV. Conclusions

DINP was the predominant phthalate found in children's products likely to be mouthed or chewed. Migration rates from impaction varied from 1 to 48 $\mu\text{g/hr/l cm}^2$ and did not correlate well with phthalate content. The impaction method showed good repeatability overall and did not appear to be sensitive to buffer replenishment. The human subject study showed that the geometric mean migration rate from mouthing/chewing a new disk cut from a PVC children's toy was 39.5 times the geometric mean migration rate from impaction. Migration rates varied substantially from individual to individual.

Table 1. Variation of migration rates based on piston size.

<u>Piston Size</u>	<u>% Phthalate</u>	<u>$\mu\text{g/hr}$</u>	<u>$\mu\text{g/hr/cm}^2$</u>
1.27 cm (0.5 in)	29.96	2.97	2.14
		3.67	2.64
1.59 cm (0.62 in)	29.96	3.32	1.52
		2.41	1.11
		2.76	1.26
2.54 cm (1 in)	29.96	7.13	1.28
		9.07	1.63

Table 2. Replication of migration rates from the impaction method.

Sample	Description	Phthalate	Migration				
			% by wt	$\mu\text{g/hr}$	Avg	Std. Dev.	% Deviation
1-8	Teether #3	DINP	43.28	7.38	8.25	0.81	9.78
1-8				7.88			
1-8				7.80			
1-8				8.98			
1-8				9.24			
2-2	Toy Duck #2	DINP	42.66	37.41	43.61	8.68	19.91
2-2				49.59			
2-2				43.18			
2-2				54.59			
2-2				33.28			
2-4	Toy Fish	DINP	36.95	10.59	11.71	1.58	13.47
2-4				12.82			
2-5	Tree House	DINP	36.05	14.64	13.56	1.53	11.26
2-5				12.48			
1-5	Tiger Toy	DINP	48.10	21.93	18.31	5.13	28.01
1-5				14.68			
1-13	Pacifier	DIOP	32.37	17.22	20.04	3.98	19.87
1-13				22.85			

Average % Deviation = 17.05% (Range 9.78% to 28.01%)

Table 3. Effect of replenishing the buffer vs 6 hours of continuous impaction with Toy Duck#2.

Media	DINP (μg)									
	Time of Media Change	Migration with each 2 Hour Replenishment				Average Total Migration	Migration, 6 hours continuous Impaction			
		Sample Number			Average Total Migration		Sample Number			Average Total Migration
		Hrs	1	2			3	4	5	
Dulbecco's	2	4.41	6.39	6.18						
Toy 2.01a	4	3.79	4.93	5.78						
	6	8.71	4.69	9.25						
Total Released		16.91	16.01	21.21	18.04	23.85	16.52	11.74	17.37	
Dulbecco's	2	9.83	10.33	10.65						
Repeated	4	10.72	9.71	8.27						
Toy 2.01b	6	14.16	13.52	16.83						
		34.71	33.56	35.75	34.67	72.02	81.49	97.42	83.64	
Dulbecco's	2	19.38	19.16	18.57						
and Mucin	4	16.15	21.54	21.82						
Toy 2.01c	6	21.41	20.28	27.29						
Total Released		56.94	60.98	67.68	61.87	61.6	50.48	32.3	48.12	
Dulbecco's +	2	19.2	17.1	17.67						
Mucin + Na Azide	4	13.87	14.62	12.57						
Toy 2.01d	6	19.48	15.86	22.77						
Total Released		52.55	47.58	53.01	51.05	32.09	35.38	35.99	34.49	
Average all replenishment tests			41.41			Average All Continuous tests			45.91	

Table 4. Migration rates and calculated migration rate for 11 cm² of PVC samples.

Sample	Description	Phthalate % by wt	Total Migration $\mu\text{g/hr}$	Area Immersed cm^2	Impact Migration $\mu\text{g/hr/cm}^2$	Non-impact Migration $\mu\text{g/hr/cm}^2$	Calculated Migration Rate ¹ $\mu\text{g/hr/11 cm}^2$
1.01	Handbag	DEHP	19.05	10.84	2.28	0.08	5.68
1.02	Book	DINP	27.45	5.40	1.14	0.0402	2.83
1.03	Teether#1	DINP	36.59	17.50	4.52	0.1599	11.26
1.04	Soother#1	DnNP	26.74	47.09	13.39	0.4734	33.36
1.05	Tiger Toy	DINP	48.1	21.93	4.61	0.1631	11.49
1.06	Toy Dolphin	DINP	43.66	33.45	11.90	0.4209	29.66
1.07	Teether#2	DINP	29.96	5.00	1.18	0.0419	2.94
1.08	Teether#3	DINP	43.28	8.98	2.55	0.0903	6.36
1.09	Teether#4	DINP	33.47	6.06	1.92	0.0677	4.77
1.10	Teether#5	DINP	54.43	7.55	1.95	0.0690	4.86
1.11	Corner Pads	DINP	43.98	18.22	6.10	0.2157	15.20
1.12	Nipple	DIOP	41.88	42.44	16.12	0.5698	40.16
1.13	Pacifier	DIOP	32.37	17.22	5.57	0.1969	13.87
1.14	Toy Food	DINP	51.00	24.35	8.67	0.3064	21.59
2.01	Toy Duck#1	DINP	40.81	3.85	1.44	0.0510	3.59
2.02	Toy Duck#2	DINP	42.66	54.59	19.43	0.6869	48.40
2.03	Teether#6	DINP	50.26	7.37	1.55	0.0548	3.86
2.04	Toy Fish	DINP	36.95	10.59	2.62	0.0925	6.51
2.05	Tree House	DINP	36.05	14.64	5.56	0.1966	13.85
2.07	Squeeze Toy #1	DINP	32.55	15.99	5.35	0.1893	13.34
2.08	Soother#2	DINP	30.17	2.83	0.60	0.0210	1.48
2.09	Teether#7	DINP	25.57	2.89	0.63	0.0223	1.57
2.10	Teether#8	DINP	19.29	3.55	1.19	0.0420	2.96
2.11	Book	DINP	17.45	2.69	0.57	0.0200	1.40
2.12	Bath Toy	DINP	15.14	1.95	0.41	0.0145	1.02
2.13	Toy Turtle	DINP	35.41	4.43	1.48	0.0524	3.69
2.14	Toy Bear	DINP	19.91	3.29	1.34	0.0474	3.33
2.15	Spoon#1	DINP	35.24	4.70	1.91	0.0676	4.76
2.16	Spoon#1	DINP	34.29	9.00	3.66	0.1295	9.12
3.01	Toy Ball	DINP	41.15	6.43	2.45	0.0739	5.93
3.02	Toy Bear	DINP	41.20	4.59	1.83	0.0553	4.46
3.03	Toy	DINP	27.08	2.72	1.16	0.0351	2.86
3.04	Toy Block	DINP	43.03	5.97	2.27	0.0686	5.5
3.05	Toy Car	DINP	42.68	2.47	0.99	0.0299	2.42
3.06	Squeeze Toy #2	DINP	42.49	3.17	1.19	0.0360	2.88

Note: One item tested, a suction cup (Toy # 2.06) with a hook for hanging things on windows is not included since it is not considered a children's product.

¹ The calculated migration rate for the assumed 11 cm² that is mouthed and chewed is the sum of the impaction piston area (2.18 cm²) times the impaction migration rate and mouthed area (8.82 cm²) times the non-impaction migration rate.

Table 5. *In vivo* phthalate migration by mouthing and gentle chewing of 10.3 cm² disks (μg/hr).

Time (min)	Subject									
	D1-1	D1-4	D2-1	D2-4	D3-1	D3-4	D4-1	D4-4	D5-1	D5-4
15	48.22	248.34	510.86	257.60	207.48	101.50	388.74	143.72	250.30	420.98
30	101.54	379.30	371.62	184.34	249.62	109.20	464.00	193.84	152.44	322.62
45	70.36	153.84	559.18	559.18	246.86	67.64	826.48	216.76	272.18	143.26
60	32.78	243.78	336.32	235.76	159.34	81.74	707.34	229.36	214.24	261.24
Maximum	101.54	379.3	559.18	559.18	249.62	109.2	826.48	229.36	272.18	420.98
Minimum	32.78	153.84	336.32	184.34	159.34	67.64	388.74	143.72	152.44	143.26
Max/Min	3.10	2.47	1.66	3.03	1.57	1.61	2.13	1.60	1.79	2.94
Average for all time periods	63.23	256.32	444.50	309.22	215.83	90.02	596.64	195.92	222.29	287.03
Average of all humans	268.10									
Range of averages	63.23	to		596.64						
Saliva in ml	58	55	85	48	44	54	37	27	95	63
Saliva pH	7.13	7.55	7.65	7.61	7.48	7.47	7.21	6.90	7.66	7.62

Table 6. DINP migration by impaction of new and used disks from *in vivo* tests.

Disk number (DN)	Migration Rate			
	New disks		Used disks	
	DN-2	DN-3	DN-1	DN-4
	$\mu\text{g/hr}$	$\mu\text{g/hr}$	$\mu\text{g/hr}$	$\mu\text{g/hr}$
D1	9.53	4.43	4.72	5.02
D2	5.50	14.72	4.99	5.16
D3	4.61	4.86	3.78	5.21
D4	6.82	4.09	4.87	3.13
D5	6.84	2.49	4.84	8.07
Average	6.66	6.12	4.64	5.32

	New Disks	Used Disks
	$\mu\text{g/hr}$	$\mu\text{g/hr}$
Average of all new or used disks	6.39	4.98
Ratio of <i>in vivo</i> :Impaction ¹	39.50	

¹ The ratio is based on the geometric mean as described by M. A. Greene, Statistical methods for estimating average daily intake, U.S. Consumer Product Safety Commission, Washington, DC. December 1998.

Figure 1. Extraction apparatus

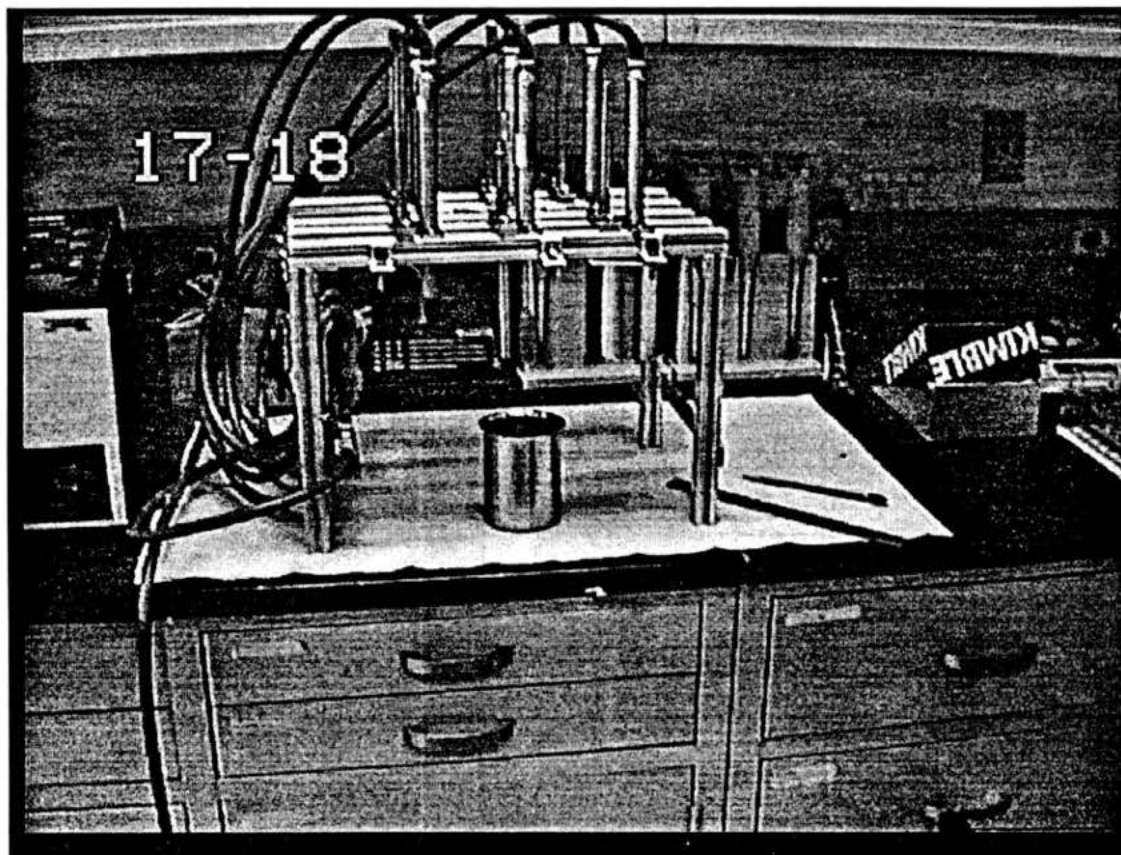


Figure 2. Extraction apparatus piston and hold down bar

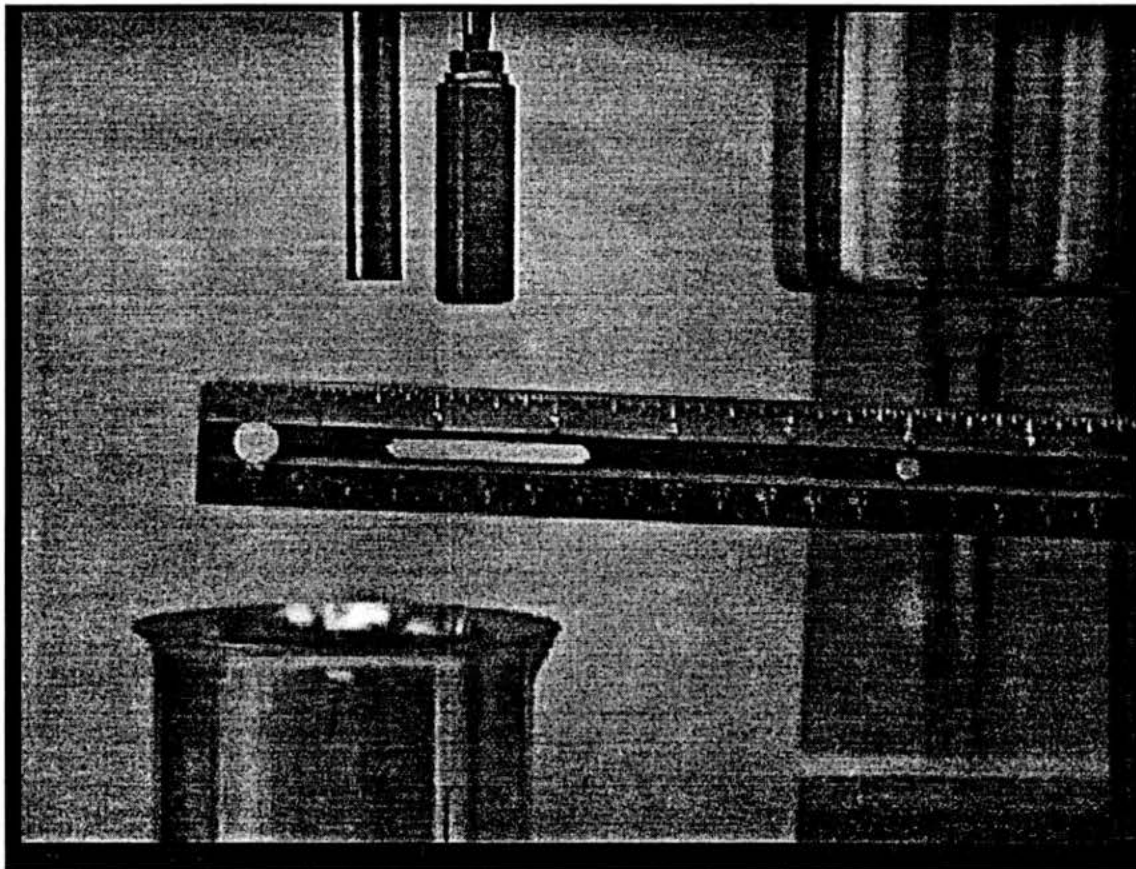


Figure 3. Migration rate vs force

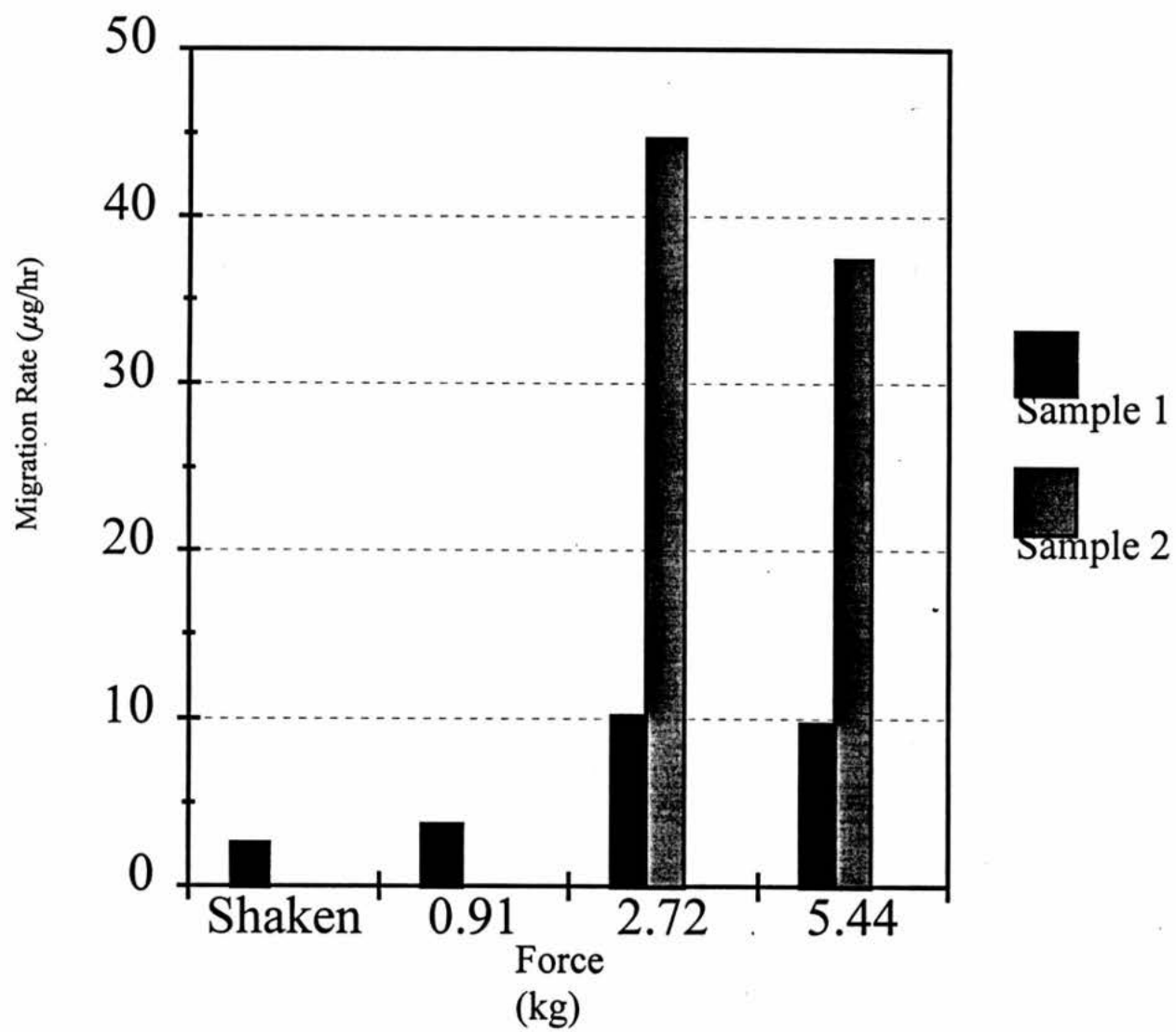


Figure 4. Variation of migration rates by length of impaction time

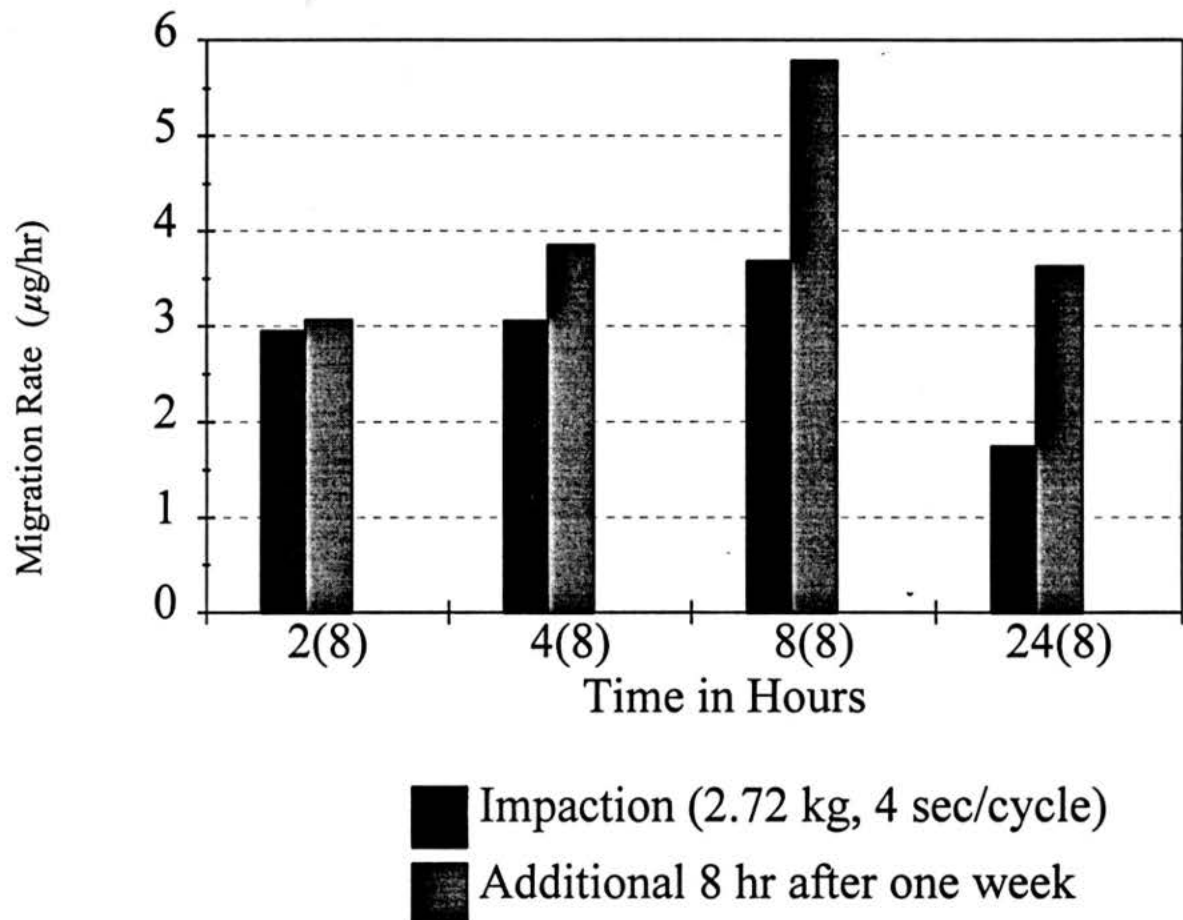


Figure 5. Migration rate on consecutive days, 4 seconds/cycle, 2.72 kg force, 6 hours

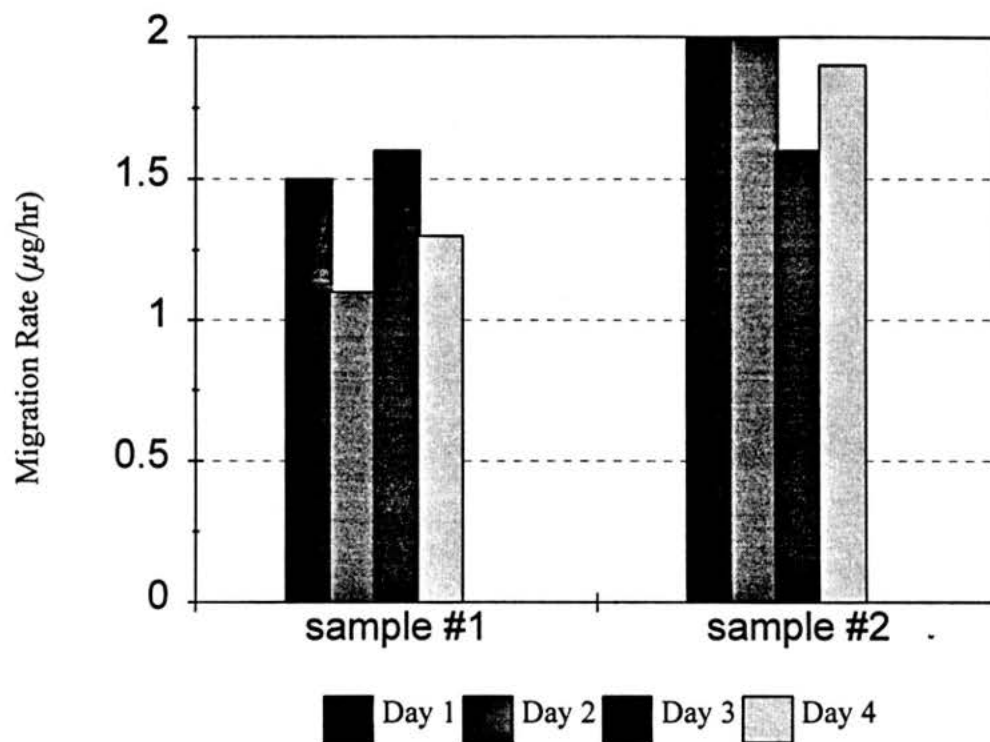
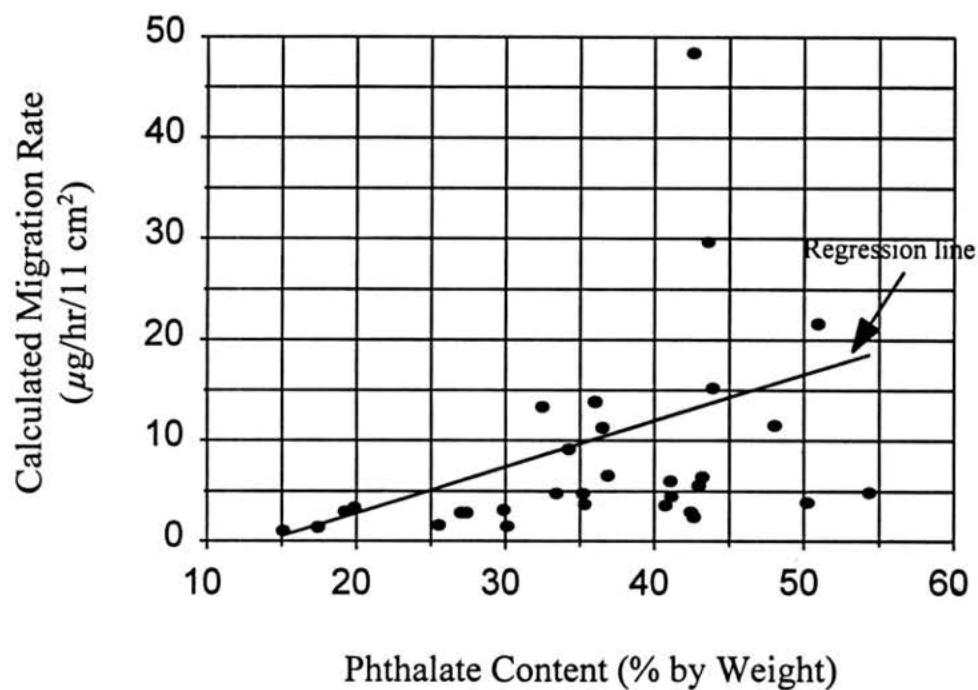


Figure 6. Calculated DINP migration vs % DINP



Note: The regression line has a slope of 0.37, and an R^2 of 0.143.

Appendix B

Statistical Analysis for Prediction of DINP Intake by Young Children

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1. Introduction

The purpose of the statistical analysis is to provide estimates for exposure of children up to 26 months of age from diisononyl phthalate (DINP), a chemical found in polyvinyl chloride toys and other children's products.

Exposure, in this paper, was estimated from the product of migration rates from toys and other products, M , given in mass per unit time, and D , the duration or length of time that such products are likely to be in children's mouths. This was then divided by body weight, BW , to form equation (1),

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

See Babich (1998).

Migration rates were estimated from the product of two other quantities, R and S , where R was the migration rate measured *in vitro* from product samples containing DINP and S was a scaling factor obtained from paired *in vitro* and *in vivo* studies using adult volunteers. The procedures used to obtain these measurements are described in Chen (1998). The exposure duration, D , in equation (1) was estimated from observations on toy mouthing behavior on children aged 3-26 months provided by Bea Steenbekkers from Wageningen Agricultural University. Tables developed from these data were published in the European Union's Consensus Report on DINP (Konemann, 1998) and in the full report Groot et al (1998a).

In the statistical analysis leading to estimates of exposure, the migration rate components, R , and S , and the exposure duration, D , were considered to be random variables, that is, quantities that vary over specimens, and individuals. What is the source of the random variation? First, some products, or different pieces of a single product could release DINP at different rates. Second, different human subjects would be expected to extract DINP from the same specimen at different rates. Taken together, the product $RS (=M)$ represents the variability in the amount of DINP in different toys and the rate it is released *in vivo*. Third, the variability in exposure duration, D , would reflect different amounts of time that children put objects in their mouths. This could vary by the age of the child, and for a given child could vary over short periods. Consequently, the daily exposure, DE , would vary between individuals, as the result of the amount of time they engage in chewing, sucking and licking of toys; the rate at which they extract DINP from the toys; and the DINP content of the toys in their environment.

In the analysis described in section 2 of this paper, separate lognormal distributions were fit to each of these random variables. One model was used for *in vitro* migration rates, M , and a second model for scaling, S . With respect to duration, D ,

separate estimates were made for children age 3-12 months and 13-26 months, because the amount of time these children were observed to engage in mouthing behavior was very different. Also, there were different values for mean body weight used for these different age groups.

Parameter estimates were obtained from the means and variances of the logarithms of the observed data. Statistical testing was used to test the goodness of fit of the data to the lognormal distributions.

The separate lognormal distributions were combined to form two lognormal distributions for *DE*, in equation (1), one for each age group. This was used to generate not only the geometric mean daily intake, but also the 95th percentile and the associated confidence interval for that statistic. The geometric mean is a typical measure of the center of a skewed distribution, and in fact, for the lognormal distribution, the geometric mean is an estimate for the median or 50th percentile of the data. The 95th percentile represents the DINP intake for the highest 5% of the children. This would represent children with the longest exposure to products with the greatest migration rates. Confidence intervals as shown in this analysis, represent the amount of uncertainty in the estimates. Confidence intervals for percentiles were from Hahn and Meeker (1991) and verified with parametric bootstrap calculations (Efron and Tibshirani, 1993). These are described in section 3 of the paper.

Section 4 contains a discussion of the results.

2. Fitting Statistical Distributions

This section describes the methods used to fit statistical distributions to the data. Section 2.1 describes fitting the *in vitro* migration rates, *R*. Section 2.2 discusses fitting the scaling distribution, *S*, and section 2.3 fits the exposure distributions to the data in Groot et al (1998b).

The mathematical form of the distributions used in fitting is the lognormal distribution, shown generically in equation (2). The distribution is defined only for positive values and displays a long right hand tail. Mathematically, if *X* is a random variable whose logarithm is normally distributed with parameters (μ, σ^2), then *X* follows a lognormal distribution

$$(2) \quad f(x) = \frac{1}{\sigma x \sqrt{2\pi}} e^{-(\log x - \mu)^2 / 2\sigma^2} \quad 0 < x < \infty, \quad -\infty < \mu < \infty, \quad \sigma > 0$$

This is abbreviated $X \sim LN(\mu, \sigma^2)$.

The product of independent lognormal distributions also follows a lognormal

distribution. If $\log(X_1)$ and $\log(X_2)$ each follow a normal distribution then $\log(X_1) + \log(X_2) \sim N(\mu_1 + \mu_2, \sigma_1^2 + \sigma_2^2)$. Put another way, the product $X_1X_2 \sim LN(\mu_1 + \mu_2, \sigma_1^2 + \sigma_2^2)$. This result is very important because it allows finding the distribution of products of random variables such as found in equation (1) for daily exposure. Once the distribution of the products is available, estimates can be made for the geometric mean daily exposure and 95th percentiles. Closed form interval estimates for the mean and the percentiles are available from the fact that the distribution of means $(1/n_1)\Sigma\log(X_1) + (1/n_2)\log(X_2) \sim N(\mu_1 + \mu_2, \sigma_1^2/n_1 + \sigma_2^2/n_2)$ with $n_1 + n_2 - 2$ degrees of freedom. It is also interesting to note that exponentiating the mean of the underlying normal distribution is the geometric mean of the original data. Because the underlying distribution is symmetric, the geometric mean is also an estimate for the median of the original data.

The maximum likelihood estimates for the parameters of the lognormal distribution are found by taking the logs of the observations, then using maximum likelihood procedures for the normal distribution. This involves using the mean of the transformed data as the estimate for μ and the variance of the transformed data as the estimate for σ^2 . Exponentiating the estimate for μ (i.e. $\exp[\mu]$) produces a number in the original units that is the geometric mean of the data. (For further details on the lognormal distribution, see Casella and Berger, 1990).

2.1 Migration Rates

The distribution of migration rates for 31 products containing DINP is shown in table 1 below. The intent was to develop a list that would represent the range of toys containing DINP, that a child might put into his/her mouth. The data are the same as found in Table 4 of Chen (1998) except for deletion of four samples that did not contain DINP.

Examination of the histogram of migration rates showed that distribution has a skewed appearance with an arithmetic mean of 8.20, median of 4.8 and standard deviation (SD) of 9.83. The skewness statistic was 2.8. The Shapiro-Wilk W statistic (a test for the fit of the normal distribution) was 0.66 with a p value of less than 0.0001. Transforming to logs produced a mean of 1.66, median of 1.57, SD of 0.91, and a skewness statistic of 0.51. The Shapiro-Wilk W statistic, for the transformed data was 0.97 with a p value of 0.55. The skewness and normality test suggested that the log transformation was successful in fitting a normal distribution. Note that the mean value following the log transformation, corresponded to a geometric mean in the original data of 5.24.

Table 1
Distribution of DINP Migration Rates

Migration Rates	Frequency
0.0-2.4	5
2.5-4.9	13
5.0-7.4	4
7.5-9.9	1
10.0-12.4	2
12.5-14.9	2
15.0-17.5	1
17.5-	3
Total	31

Notes: The data are from Table 4 in Chen (1998) with four samples removed. Migration rates are given in micrograms per hour for an 11 square centimeter area. That size area was chosen because it was believed to be the same surface area as an object likely to be mouthed by a child.

There were some further analyses performed on these data. An analysis was conducted to determine if migration rates differed by type of specimen. Products were classified as teethingers, mouth toys, and others. To determine whether the data could be assumed to come from the same underlying process, a Kolmogorov-Smirnov test was performed on the empirical distributions of the migration rates by product classification. The *p* value for this test was 0.58, which did not provide any statistical justification for separating the analysis by type of product. This meant that there was no evidence to suggest that a particular product class had a greater migration rate than any other product type.

In a second analysis, models were estimated to determine if migration rates could be explained by the characteristics of the products. These characteristics included the percent DINP content by weight, the type of manufacturing process (e.g. injection molding, rotation, etc.) and the thickness of the product. The purpose of this analysis was to determine if there was some way to predict migration rates as related to the percent of phthalate content, manufacturing process, etc. While the graphical analysis showed some positive relationship between migration rate and DINP content, various regression models failed to produce a value of R^2 greater than 0.33. These models were judged to be inadequate to predict DINP migration rates especially given the shrinkage in predictive quality that would be expected from applying the models to new data. Moreover, discussions with CPSC laboratory staff suggested that migration rates were variable even within a single specimen.

2.2 Scaling Factors

To compute the scaling factors that would relate *in vitro* migration rates for the 31 products above to rates that would be expected from human mouthing, CPSC staff obtained migration data using 10 human volunteers. Details of this study are in Chen (1998). The testing used five duck toys that were identical to sample 2.02. Four disks were cut from each duck. Two disks from each toy were used for *in vivo* human subject testing and the remaining two were used for impaction. Each human provided measurements for four fifteen-minute periods for a total of 40 measurements. The data used in this analysis were those found in tables 5 and 6 of Chen (1998) but the *in vivo* and *in vitro* migration rates were divided by 10.3 to produce rates with units of micrograms per square centimeter per hour.

Like the migration rate data discussed above, these *in vivo* measurements also showed considerable skewness. The arithmetic mean was 25.0 micrograms per cm² per hour, with an SD of 16.7. The data were very skewed to the right with a skewness value of 1.46. The Shapiro-Wilk W statistic was 0.88 with a *p* value of 0.0004, confirming that the data did not follow a normal distribution. Transformation to logs provided a mean of 3.01 (geometric mean of 20.3) with a skewness of -0.5 and a value of W of 0.97 (*p* value of 0.5329).

An analysis of variance procedure (ANOVA) was applied to the migration rates to determine if there were any disk effects, gender effects or systematic variation in migration rates over the fifteen minute period. Using the log of the migration rate as the response variable, only the disk effect was statistically significant ($F = 3.85$ with 4 and 31 df, $p=0.0119$). On the basis of this analysis it was determined that even though the disks should have been identical, they should not be considered as replicates.

This information was used in determining how to obtain an average for the scaling factor. Let H_i and I_i denote average migration rates for disk i ($i = 1, 2, \dots, 5$), where H is the human average (two humans with 4 measurements each) and I is the machine impaction average (2 machine readings). Then the two possible ways to compute the average would be $S = \Sigma H_i / \Sigma I_i$ or $S = (1/5) \Sigma (H_i / I_i)$. The first approach is the ratio of the totals while the second is the average of the ratios. The second approach was used because the ANOVA showed that the ratios for each disk were significantly different from each other. If the human and machine observations could have been considered independent replicates, then the first calculation would be more appropriate.

The five ratios were 22.9, 32.3, 32.8, 54.6 and 72.6 with an arithmetic mean of 43.05 and an SD of 20.21. The data showed right skewness with a value of 0.85. The Shapiro-Wilk W statistic was 0.9040, ($p = 0.43$). These statistics did not strongly argue for a log transformation of the data, but because the analysis on the human extraction data above strongly suggested the log transformation for both the *in vivo* and *in vitro* migration rates, the ratios were also used in logarithmic form. Transforming to logs produced a mean of the logs of 3.68 (geometric mean 39.5) and SD of was 0.46. This improved the skewness to 0.46 and the Shapiro Wilk statistic to 0.9423 ($p = .6929$).

2.3 Exposure Analysis

In this last part of the statistical analysis, distributions were estimated for time children spent mouthing toys as reported in Groot et al (1998a, 1998b). Two separate analyses were conducted, one for children 3-12 months and the second 13-26 months. The 3-12 month period corresponds to the time when there is the highest mouthing activity for children and would be likely to result in the highest average daily intake of DINP. The children aged 13 to 26 months had spent much less time mouthing toys and would consequently have a much lower potential for exposure to DINP.

The age categories of 3-12 months and 13-26 months are similar to those in Groot et al (1998a). They reported using overlapping age boundaries (i.e. 3-6 months, 6-12 months, etc.), but inspection of the raw data showed that children at the lower end of the cell boundary were not contained in the particular age group. For example, a child age six months would have been in the 3-6 month group rather than the 6-12 month group. To avoid ambiguity, we characterize the cell boundaries as non-overlapping, so that we use 13-26 months in place of 12-26 months. Also, in this research, the upper boundary of 26 months is used rather than 36 months as reported in Groot et al (1998a). Inspection of the ages as reported in the raw data showed that there were only two children more than two years old, a 26 month old boy and a 35 month old boy. The remaining 9 children in that age category were between 19 and 24 months. Given the variability in the data, it seemed that one observation would be hardly sufficient to estimate the mouthing duration of children 27 months to 36 months, so this observation was omitted from the present reanalysis. Consequently the second part of the analysis only covers 13-26 months. No dosage estimates were made for children over 26 months.

Table 2 shows the data summarized by age group. Several aspects of this table were notable. First, duration was strongly related to age. For example, the two children aged 8 months averaged 78.3 minutes while children 14 months and over averaged 4 minutes or less. Second, not only were there ages where no children were observed, but also there were an unequal number of children observed at each age.

Table 2
Mean Toy Mouthing Time by Child Age

Age (months)	Number of Children	Mean Toy Mouthing Time (minutes)
3	1	12.6
4	2	8.6
5	2	21.8
6	0	-
7	2	42.8
8	2	78.3
9	4	15.7
10	3	25.0
11	1	0.4
12	2	5.1
13	2	9.1
14	1	4.0
15	1	3.8
16	2	4.0
17	2	2.8
18	4	1.1
19	2	0.9
20	0	-
21	3	0.5
22	3	2.5
23	0	-
24	1	0.0
25	0	-
26	1	1.3
27-34	0	-
35	1	0.0

Source: Groot, et al (1998a). Blanks indicate that there were no observations for children in those age categories.

The analyses for the 3-12 month old children and 13-26 months age children are described below.

2.31 3-12 Months

Table 2 shows that the maximum mouthing duration for toys occurred for children age 3 to 12 months. Even more important, the duration was substantially larger than for all other ages, with the maximum duration of 141.2 minutes provided by one of the two 8 month old subjects.

The arithmetic mean mouthing time for the 3-12 month age group was 24.4 minutes, the median was 15.3 and the standard deviation was 32.9. The skewness statistic was 2.85, with the Shapiro Wilk $W = 0.6530$ ($p < .0001$). As noted above, the largest observation was 141 minutes, followed by 70 minutes, 43 minutes and 31 minutes. The four smallest observations were 0.4, 1.8, 1.9 and 4.9 minutes. The extreme skewness suggested a log transformation of the data. The log transformed versions had corresponding statistics of mean = 2.49 and SD = 1.37. The value of the skewness statistic was = -0.6840. The Shapiro Wilk W was 0.9559 ($p = .4976$). From the transformed data, the geometric mean mouthing time was 12.03 minutes with an estimated 95% confidence interval of 6.2 to 23.3 minutes.

While these mouthing times may appear to be low, the data showed that children spent much more time mouthing other objects such as fingers and pacifiers. For 3-12 month old children the average usage of pacifiers was 45 minutes per day and fingers was 11 minutes per day. Mouthing times for pacifiers and other objects were not considered in the estimates for duration and DINP intake because they did not contain DINP. This is discussed in the appendix to this paper.

2.32 13-26 Months

This analysis used the same strategy as 3-12 months. The arithmetic mean mouthing time for children aged 13-26 months was 2.54 minutes with a median of 1.49 minutes, a SD of 2.94 minutes, skewness of 1.4117 and Shapiro Wilk W statistic of 0.3161 ($p = 0.0006$). This distribution was also highly skewed, suggesting the log transformation. The five largest observations were 10.4 minutes, 8.1 minutes, 7.7 minutes, 4.0 minutes and 3.9 minutes, while there were 5 values with zero recorded mouthing time. While the skewness and the very large observations again suggested a log transformation, the five zeroes proved to be worth consideration.

These five zero observations were from a child age 16 months, 2 children at 18 months, one at 19 months, and one at 24 months. One possibility would be to replace them with very small quantities, however this would induce negative skewness, that is, it would create the opposite outlier problem as found with the original values. This strategy was rejected. The remaining two approaches were (1) dropping the 5 cases with zeroes and then transforming to logs and (2) averaging the observations by month of age, before taking the logs. This second strategy had the desired result of reducing the number of zeroes to one for the child age 24 months, but at the cost of artificially lowering the standard deviation of the data.

The first approach of dropping the zeroes before transforming to logs, produced a mean of 0.74, an SD of 1.06, skewness of -0.3176, and Shapiro Wilk $W = 0.7372$ ($p = .2875$). Averaging ages before taking logs produced a mean of 0.77, an SD of 0.88, skewness of -0.8850 and Shapiro Wilk $W = 0.9620$ ($p = .7964$). Because the means were

very close for both approaches, and because averaging first had the undesirable effect of lowering the SD, the first approach of dropping the zero observations was selected. Using this approach, the geometric mean was estimated at 2.1 minutes with a 95% confidence interval of 1.22 to 3.62 minutes.

3. Estimates for Average Daily Exposure

Equation (1) can be reexpressed in logarithmic terms as

$$(3) \quad \log(DE) = \log(M) + \log(D) - \log(BW)$$

where DE = daily oral exposure, M is migration rate per unit time, D is exposure duration and BW is body weight. Parameter estimates for that model are found in table 3 below.

Table 3
Estimates for Log of Average Daily Exposure for a child 3-12 months
(micrograms per day per 10 kg BW)

Component	Mean	Variance	Sample Size
Migration Rate (M)	1.6565	0.8318	31
Scaling Factor (S)	3.6766	0.2120	5
Exposure (D)	2.4880	1.8695	19
Constants	-6.0822	0.0000	-
Log of Average Daily Exposure (DE)	1.7389	2.9133	-

Notes: See section 2 for parameter estimates. Constants are $-\log(7.3)$ to convert the resulting exposure per kilogram to exposure per 7.3 kg (mean body weight) and $-\log(60)$ to convert from minutes to hours. The average body weight was from Snyder et al (1977). Constants enter additively for logarithmic relationships. The variance is calculated conventionally for M and S and D and described above.

Table 3 shows the log of average daily exposure for a child 3-12 months old. As noted above, these data are assumed to follow a lognormal distribution with parameters, $\mu = 1.7389$ $\sigma^2 = 2.9133$ ($\sigma = 1.7069$). Exponentiating the results provides an estimate of the geometric mean of 5.69 micrograms per 7.3 kg child per day, with a 95% confidence interval of (2.5 to 12.9) micrograms.

The point estimate for the 95th percentile is $\exp(\mu + 1.65\sigma/\sqrt{n})$, which is essentially the same as that for a normal distribution except that the result is exponentiated. The interval estimate for the 95th percentile follows Section 4.4 in Hahn

and Meeker (1991), who provide an interval estimate for the percentile of a normal distribution, and also associated tables. The underlying theory, according to them, involves the noncentral *t* distribution. To check these intervals, parametric bootstrap confidence intervals were also created (Efron and Tibshirani, 1993). These were very close to the intervals in Hahn and Meeker.

The 95th percentile exposure was 94.3 micrograms with a 95% confidence interval of (50.1 to 225.6).

Table 4 contains values for a child 13-26 months in the same units.

Table 4
Estimates for the Log of Average Daily Exposure for a child 13-26 months
(micrograms per day per 10 kg BW)

Component	Mean	Variance	Sample Size
Migration Rate (M)	1.6565	0.8318	31
Scaling Factor (S)	3.6766	0.2120	5
Exposure (D)	0.7447	1.1185	17
Constants	-6.4246	0.0000	0
Log of Average Daily Exposure (DE)	-0.3868	2.1623	-

Notes: See section 2 for parameter estimates and the notes for table 4. The variance is calculated the same way as table 4. The average body weight used was 10.7 kg (Snyder et al, 1977).

Exponentiating the results in table 4 produced a geometric mean daily exposure of 0.69 micrograms per 10.7 kg per day, with a 95% confidence interval of (0.32 to 1.55). The estimated 95th percentile exposure was 7.6 micrograms with a 95% confidence interval of 4.4 to 16.2 micrograms.

4. Conclusion

This paper has described the method for estimating DINP intake used for children aged 3-12 months and 13-26 months. The approach is similar to that taken by the Dutch Consensus group (van Veen, 1998). Migration rates were developed from in-vitro experiments, then scaled by using migration rate data from paired in-vitro and in-vivo samples. Mouthing durations were obtained from Groot et al (1998a).

These data were combined into an analytic model that used a lognormal distribution for human exposure duration, combining estimates from the separate experiments. Geometric means, 95th percentiles and associated confidence intervals

were estimated.

The results showed a geometric mean average daily intake of 5.7 micrograms per day (95% confidence interval 2.5 to 12.9) for children between ages 3 and 12 months. The distribution was very skewed, with an estimate of 5% of children at 94.3 micrograms or more (95% confidence interval 50.1 to 225.6). The values for children at 13-26 months was considerably lower with a geometric mean of less than 1 microgram per day.

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Appendix

Differences between CPSC research and the Dutch Consensus Group Report

This paper differs from the research by the Dutch Consensus group in the following respects:

1. The Dutch Consensus group used three specimens cut from two products for DINP extraction while we used specimens from 31 different products.
2. Instead of using machine impaction methods and then scaling them with paired *in vitro* and *in vivo* measurements, the Dutch Consensus group obtained migration rates directly from 20 adult human subjects using these three specimens (Meuling and Rijk, 1998).
3. Instead of fitting a probability distribution for migration rates or exposure duration, the Dutch consensus group used a Monte Carlo simulation that sampled from the empirical distribution of migration rates and exposure durations.
4. The Dutch consensus group used a normal distribution for body weight in their simulation, assuming age specific values ranging from 6.25 kg for children 3-6 months to 13.5 kg for children 18-36 months. The analysis in this paper used a constant 7.3 kg body weight for children aged 3-12 months and 10.7 kg for children 13-26 months.
5. Exposure durations used in our analysis were restricted to those from objects labelled as "Mouth Toys" or "Other Toys," in Groot et al (1998a), while the Dutch Consensus group reported using the larger quantity of "all mouthing activities except sucking on dummies (also known as pacifiers)." See van Veen (1998).

The most important distinctions would result from items 1 and 5 above. With respect to item 1, the migration rate estimates, the Dutch Consensus group used three specimens (see Meuling and Rijk, 1998). The first specimen was a standard PVC sample containing 38.5% DINP and was not a consumer product. The second and third were sections from a teething ring; specimen 2 was a "finger," and specimen 3 was from a flat part of the same toy. In contrast we used specimens from 31 different products, including toys and teething rings, with DINP content varying from 15 to 54% (see Chen, 1998, table 4). These products were chosen from toys we believed were likely to be sucked, chewed or mouthed by children.

The other important distinction is item 5 above. While we and the Dutch Consensus group used the same source for the exposure duration, (Groot, et al, 1998b), the Dutch consensus group used total mouthing time for all objects other than pacifiers as an estimate for the time that children would be exposed to DINP. Total mouthing time included observations for children mouthing their fingers and also objects defined as non toys (cloth, cutlery, paper, adult books). See Groot et al, (1998b, appendix 1). The statistical analysis in this paper used only reported mouthing time for toys, which included the two categories of "toys for mouthing," and "other toys." The difference is

substantial. For example, for age group 6-12, the mean mouthing duration was reported as 27.9 minutes for toys and 44 minutes for all objects (Groot, et al, 1998b table 5-13). Resulting, total mouthing time overstates the mean toy mouthing time by a factor of 58 percent. Since fingers and non toys did not contain DINP, it did not appear appropriate to use total mouthing time.

It is doubtful that the differences from items 2, 3 and 4 above would be substantial. There has been much research on different methods for measurement of DINP migration rates and there is still much to be learned about variability inherent in different laboratory methods (see Chen, 1998). In item 3, the use of a Monte Carlo simulation instead of the fitting of analytic models, the difference would turn on how well the models fit the data. If the models fit well, then a large number of Monte Carlo samples would have about the same results as the analytic models. We preferred to use an analytical model whenever possible for analytic tractability and to facilitate obtaining confidence intervals.

Finally, the use of variable body weights instead of a fixed constant of 7.3 or 10.7 kg would be unlikely to make much difference because the variability in body weight would be small, compared to the other sources of variability in these analyses.