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October 27, 2011

Michael Babich, CHAP Project Manager
US Consumer Product Safety Commission
4330 East West Highway
Bethesda, MD 20814

RE: CHAP on Phthalates

Dear Dr. Babich:

ExxonMobil Chemical Company (ExxonMobil) is submitting the enclosed document to support the Chronic Hazard Advisory Panel (CHAP) on Phthalates with its deliberations. The CHAP's charge calls for review and analysis of a very large amount of material. This document addresses at a high level each element of the charge to the CHAP set forth in the CPSIA as it pertains specifically to DINP and DIDP. We address specific issues that have arisen during the course of the CHAP deliberations, but do not repeat all the information contained in prior submissions, relying instead on those prior submissions for more detailed discussions of the robust science available on each compound.

We appreciate the considerable efforts already expended by the CHAP members to meet their charge, and by the CPSC to support the CHAP, and recognize that important work remains to be done. ExxonMobil has and will continue to participate in the CHAP public meetings with the goal of supporting a rigorous and objective scientific assessment of phthalates and phthalate substitutes. The Company is committed to conducting business in a manner that protects human health and the environment, and we support agency assessments of the safety of our products.

We ask that you share this letter and the enclosed document with the CHAP members.

Sincerely,

enclosure

cc: J. Robert Howell, Deputy Executive Director for Safety Operations
Cheryl Falvey, General Counsel

INTRODUCTION

This document serves as a high-level summary that focusses on the charge set forth in the CPSIA to the Chronic Hazard Advisory Panel (CHAP) on Phthalates, as it pertains to DINP and DIDP, and addresses issues that have arisen during the course of the CHAP deliberations. The document explains why the available scientific information, which is quite robust for both phthalates, does not demonstrate any significant health risks to children, pregnant women or other potentially susceptible populations from use of either phthalate in children's products or other consumer products. Accordingly, there is no scientific basis for recommending that either DINP or DIDP be deemed a "banned hazardous substance," nor is there any scientific basis for restricting the use of either phthalate in any products regulated by the Consumer Product Safety Commission.

The conclusions expressed in this document are supported by prior assessments by other regulatory bodies and expert panels in the United States and Europe. Most recently, the Danish EPA has identified DINP and DIDP as cost effective *substitutes* for phthalates classified as Substances of Very High Concern (SVHC).

Further details on the toxicology of DINP and DIDP and citations to studies are available from the prior expert evaluations and prior ExxonMobil submissions to the CPSC for this CHAP (endnote 1). Here we focus on the charge set forth in the CPSIA and specific issues that we believe are of particular concern to the CHAP assessments. We conclude that the data demonstrate that DINP and DIDP should not be recommended to be declared "banned hazardous substances."

Charge 1: Examine all of the potential health effects (including endocrine disrupting effects) of the full range of phthalates. CPSIA § 108(a)(2)(B)(i).

Conclusion: DINP and DIDP pose low concern for risk to human health for all toxicity endpoints.

Each phthalate must be considered and evaluated separately first, as there are clear physical, chemical and toxicological differences among the individual phthalates. The phrase "rat phthalate syndrome" should be used carefully and not in a way that presumes the answer to important questions pertaining to each phthalate, or that causes undue weight to be given to findings that are not clearly treatment-related or that are observed only at very high doses. This point is discussed further later.

DINP and DIDP have been well-tested, including guideline reproductive and developmental toxicity studies and two-year bioassays in rats and mice. Non-human primate data also is available for DINP. The robust database available for each compound supports a conclusion of low toxicity and low risk.

DINP

Animal Data

Two primate studies showed only minor effects at heroic doses (up to 2,500 mg/kg/day for 90 days). These studies should be given significant weight with respect to repeated-dose endpoints since non-human primates are more closely related to humans than are rodents (endnote 2). This is supported by the taxonomic, evolutionary and genetic evidence that places humans in the primate family, and also by toxicokinetic and mechanistic data for phthalates specifically (endnote 3).

No evidence of reproductive toxicity was observed in a guideline two-generation study. Observed post-natal developmental effects on weight were transient and reversible, and likely were due to palatability of the milk. Effects observed in a gestational developmental toxicity study were of questionable biological significance, and were seen only at high, maternally-toxic doses.

A holistic, weight-of-the-evidence review of the DINP database using a framework developed by the OECD and the World Health Organization (WHO) demonstrates that DINP cannot be classified as an endocrine disruptor. That conclusion is supported by the results of studies recently completed by The Hamner Institutes. Those studies indicate that at high doses DINP can cause a reduction in fetal testosterone and marginal, transient effects on anogenital distance (AGD),[1] but this is not accompanied by effects on nipple retention, seminiferous tubule diameter, preputial separation, cryptorchidism, hypospadias, or other male reproductive tract developmental toxicity at doses up to 750 mg/kg/day. No effects on male reproductive tract development or fertility were seen in the apical two-generation reproductive toxicity study.

In systemic toxicity studies, liver and kidney effects are related to mechanisms in rodents that are not relevant to humans. Liver and kidney tumors and increased mononuclear cell leukemia observed in chronic rodent studies also have been demonstrated to not be relevant to humans.

Epidemiology

DINP has been evaluated in only one epidemiological study. The authors reported an association between the DINP metabolite, monoisononyl phthalate, in breast milk and serum luteinizing hormone in infants, but found no association for cryptorchidism, testosterone, or other reproductive hormones. NTP CERHR criticized the study due to confounding and possible contamination of breast milk samples.

Findings of Authoritative Bodies and Expert Panels

CHAP on DINP. A prior CHAP evaluated the potential risks of DINP in children's toys and products and did not find a significant health risk. The CPSC used the CHAP report and additional state-of-the-art exposure studies to assess whether to prohibit use of DINP in children's products. The CPSC found "no demonstrated health risk" for any toxicity endpoint, including developmental and reproductive effects, from DINP-plasticized objects used and mouthed by children.

NTP CERHR. A 16-person expert panel convened by the National Toxicology Program Center for Evaluation of Risks to Human Reproduction concluded that it had "minimal concern" for potential health risks from exposure to DINP. The NTP used the expert panel report and review of subsequent biomonitoring data to conclude there was "minimal concern for DINP causing adverse effects to human reproduction or fetal development" and "minimal concern for developmental effects in children."

European Union. A multi-national committee of scientific experts evaluated the toxicity and environmental fate data for DINP and concluded: "The overall assessment indicates no concern for adults. For infants, combined exposure which is mainly related to exposure from toys and via the environment is not considered of concern." (Emphasis added.) Subsequently, the European Commission (EC), informed by its expert committees, determined that no classification should be given to DINP. That is, the EC does not classify DINP as a carcinogen, a mutagen, or a cause of reproductive or developmental toxicity.

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[1] At 750 mg/kg/day, AGD was decreased in male pups at PND 14, but not at PND 2 or PND 49. Body weights of pups treated with the high dose were significantly less than the controls and this was corrected for via scaling to bodyweight; however, in general the overall size of the pups appeared to be smaller than that of the controls and other treatment groups which may have been a contributing factor to the observed reduction.

DIDP

Animal Data

There was no evidence of reproductive toxicity in a guideline two-generation study, which included measurement of sensitive endpoints of endocrine disruption (e.g., AGD, nipple retention). Observed post-natal developmental effects on weight were transient and reversible, and likely were due to palatability of the milk. Effects seen in a gestational developmental toxicity study are of questionable biological significance, and were seen only at high, maternally-toxic doses.

There is no evidence that DIDP is an endocrine disruptor. In the definitive two-generation reproductive toxicity test, DIDP did not induce hypospadias, cryptorchidism, or alter the androgen sensitive tissues, and it had no effect on male reproductive tract development or fertility.

In systemic toxicity studies, observed liver and kidney effects are related to mechanisms that are not relevant to humans.

Epidemiology

No data are available.

Findings of Authoritative Bodies and Expert Panels

NTP CERHR. A 16-person expert panel concluded it had "minimal" and "negligible" concern for potential reproductive and developmental effects from exposure to DIDP. The NTP used the expert panel report and review of subsequent biomonitoring data to conclude there was "minimal concern for developmental effects in fetuses and children" and "negligible concern for reproductive toxicity in exposed adults."

European Union. A multi-national committee of scientific experts evaluated the toxicity and environmental fate data for DIDP and concluded: "The end products containing DIDP (clothes, building materials) and the sources of exposure (car and public transport interiors, food and food packaging) are unlikely to pose a risk for consumers (adults, infants and newborns) following inhalation, skin contact and ingestion" and that for combined exposures "the overall assessment indicates no concern for adults" and "For infants, combined exposure, which is mainly related to exposure via the environment, is not considered of concern."[2] (Emphasis added.) Subsequently, the European Commission (EC), informed by its expert committees, determined that no classification should be given to DIDP. That is, the EC does not classify DIDP as a carcinogen, a mutagen, or a cause of reproductive or developmental toxicity.

[2] The EU risk assessment expressed concern for newborns and infants if DIDP were substituted for other phthalates in toys, but this was based on a dog study of dubious reliability, as discussed below (Charge 7).

Charge 2: Consider the potential health effects of each of these phthalates both in isolation and in combination with other phthalates. § 108(a)(2)(B)(ii).

Conclusion: There is no basis for concluding that DINP or DIDP will act in combination with the range of phthalates for any toxicological endpoint of relevance to humans.

The potential health effects of DINP and DIDP in isolation are discussed above, under Charge 1.

With respect to DINP or DIDP in combination with other phthalates, no single adverse health effect (e.g. hypospadias, cryptorchidism) has been demonstrated to be commonly induced by all phthalates. The only endpoint that appears to be common across low and high molecular phthalates and for which there is data is peroxisome proliferation in rodents, but this endpoint has been demonstrated not to be relevant to humans. See endnote 1: July 19, 2010 submission and Atts 1-5, 12 & 13.

The hypothesized "rat phthalate syndrome" is applicable only to a subset of phthalates. As discussed above, while DINP at high doses can result in reduced fetal testosterone and transient AGD effects, it does not induce any of the other effects proposed to be part of a "rat phthalate syndrome." At doses up to 750 mg/kg/day, DINP does not cause effects on nipple retention, seminiferous tubule diameter, preputial separation, cryptorchidism, hypospadias, or other male reproductive tract developmental toxicity. DIDP does not induce any of the effects proposed to be part of a "rat phthalate syndrome." This asserted syndrome does not provide a basis for concluding that DINP and DIDP may act in combination with other phthalates in producing health effects. See endnote 1: March 29, 2011 submission.

Charge 3: Examine the likely levels of children's, pregnant women's, and others' exposure to phthalates, based on a reasonable estimation of normal and foreseeable use and abuse of such products. § 108(a)(2)(B)(iii).

Conclusion: Likely levels of children's, pregnant women's, and others' exposure to DINP and DIDP are several orders of magnitude below the LOAELs in animal tests.

Biomonitoring Data

An abundance of biomonitoring data provides information on the likely levels of human exposure to DINP. Conversion of the urine metabolite concentrations to the quantity of phthalates ingested demonstrates that aggregate exposure to DINP from all sources is extremely low – a mean of approximately 1.5 ug/kg/day and a 95th percentile of approximately 10 ug/kg/day. This is true for pregnant women as well as the general population. Exposures for children ages 6-11 are slightly higher, but still very low in the absolute sense – a mean of approximately 3 ug/kg/day and a 95th percentile of approximately 13 ug/kg/day.

Biomonitoring data also is available for DIDP. Conversion of the urine metabolite concentrations to the quantity of phthalates ingested demonstrates that aggregate exposure to DIDP from all sources also is extremely low – a mean of less than 1 ug/kg/day and a 95th percentile of less than 8 ug/kg/day. This is true for pregnant women and children (ages 6-11) as well as the general population.

Physical Properties

For DINP, a generally accepted value for the vapor pressure is 0.00006 Pa at 20 °C, which is equivalent to about 5 x 10^{-7} mm Hg or 6 x 10^{-10} atm. A generally accepted value for water solubility is about 0.6

ug/L. Dermal absorption of DINP is also quite low – in rat dermal studies, absorption after 7 days was only 2 to 4 % of the amount applied to the skin (conditioned or unconditioned).

For DIDP, a generally accepted value for the vapor pressure is 0.000051 Pa at 25 °C, which is equivalent to about 4×10^{-7} mm Hg or 5×10^{-10} atm. A generally accepted value for water solubility is about 0.2 ug/L. Dermal absorption of DIDP is also quite low – in rat dermal studies, only about 2% of dermally applied DIDP was absorbed after 7 days.

These physical/chemical properties inherently limit the degree of exposure reasonably foreseeable for DINP and DIDP in their consumer uses.

Uses

The primary use of DINP and DIDP is to make vinyl products flexible. Each is used in a wide range of products described in previous submissions. To our knowledge, neither is used (or ever has been used) in cosmetics or other personal care products, or in pharmaceuticals, as they do not exhibit the desired properties for these products.

Migration from Vinyl Products

Significant physical forces retain the DINP and DIDP within the molecular matrix of the vinyl, including van der Waals forces and physical entrapment of the DINP and DIDP molecules. Therefore, while migration from vinyl products is possible, it occurs only at a very low rate. In fact, the usefulness of DINP and DIDP depends on each being retained in the vinyl – without the plasticizer, the vinyl would become brittle and subject to cracking or breakage. Thus, not only is exposure inherently limited by the properties of DINP and DIDP themselves, but also by the manner in which they are incorporated into the flexible vinyl end products.

For the prior evaluation of DINP in children's products, the CPSC conducted state-of-the-art migration studies under conditions simulating chewing of DINP-plasticized vinyl. The CPSC also conducted a state-of-the-art observational study on mouthing of toys and other objects by infants. CPSC used these data to estimate DINP exposure. Estimated DINP exposures for soft plastic toys were greatest among children 12-23 months old, for whom the estimated mean exposure was 0.08 ug/kg/d and the 99th percentile was 1.5 ug/kg/d. Estimated average and 99th percentile oral exposures for all age groups and all hypotheticals were below the very conservative ADI of 120 ug/kg/d derived by the CHAP on DINP. Even when the CPSC assumed that all soft plastic objects mouthed by children were made with DINP, or that all toys, teethers and rattles were made with DINP, the 95% upper confidence level of the 99th percentile exposure was still well below the very conservative ADI of 120 ug/kg/day.

Sources of Exposure

The primary purpose of the mandate in section 108 of the CPSIA and the charge to the CHAP is to address potential risks of phthalates in children's toys and products. The assessment previously conducted by the CPSC demonstrates that potential exposure from these sources for DINP is very low. Because the vapor pressure, water solubility and dermal absorption rate are all lower for DIDP than DINP, exposures to DIDP would be even lower if it were used in the same products. In actuality, DIDP typically has not been used in children's toys or other children's products, even prior to the CPSIA.

Exposure to pregnant women and others also would be expected to be very low for each compound, not only from children's products, but also all other products, for the reasons given above. Analysis of data

on DINP and DIDP concentrations in various media and sources indicate that the primary source of the *very low* exposures to each is diet, rather than consumer products.

Potential abuse

It is hard to envision any consumer abuse of products containing DINP or DIDP that would exceed the most conservative mouthing exposure scenarios evaluated by the CPSC and the prior CHAP.

Charge 4: Consider the cumulative effect of total exposure to phthalates, both from children's products and from other sources, such as personal care products. § 108(a)(2)(B)(iv).

Conclusion: DINP and DIDP have no or minimal contribution to any hypothesized cumulative effect.

In its submission prior to the March 2011 CHAP meeting, ExxonMobil explained that the charge to the CHAP does not mandate a quantitative cumulative assessment, but only that the cumulative effect of total exposure to phthalates be considered. Cumulative risk assessment at its current stage of development has significant uncertainty. Any cumulative assessment undertaken by the CHAP should be limited accordingly, and the significance of quantitative results modified by qualitative understanding of the database.

As discussed above (Charge 2), neither DINP nor DIDP can be classified as causing "rat phthalate syndrome." If the CHAP uses that proposed syndrome as a basis for a phthalate cumulative assessment, neither DINP nor DIDP should be included in the assessment.

Two screening-level cumulative assessments of phthalates have been published and each included DINP. In each case, the total risk value was below the derived health benchmark, with DINP contributing a very minor proportion of the total risk estimate—0.5% to 5% of the total risk of phthalates only, and yet less a percentage of the total risk given by all chemicals included in the analysis. While we do not agree with the basis for including DINP in these assessments, they nevertheless demonstrate the low toxicity and low exposure to DINP.

The outcome that phthalates do share in common is weak peroxisome proliferation. Although this is a rodent effect not relevant for human risk assessment, ExxonMobil nevertheless conducted a cumulative assessment based on peroxisome proliferation effects; this has been submitted to CPSC and the CHAP. This assessment again demonstrates that any risk contributed by DINP or DIDP is a very small fraction (6% and 4%, respectively) of the total estimated hazard index value. See endnote 1: July 19, 2010 submission, Att 13.

Charge 5: Review all relevant data, including the most recent, best-available, peer-reviewed, scientific studies of these phthalates and phthalate alternatives that employ objective data collection practices or employ other objective methods. § 108(a)(2)(B)(v).

Conclusion: Rich databases of well-designed, peer-reviewed studies exist for DINP and DIDP, which as a whole demonstrate the low toxicity of each compound.

The very robust databases for DINP and DIDP are summarized above (Charge 1), and greater detail is provided in prior submissions by ExxonMobil (endnote 1), and the prior in-depth reviews of a CHAP and CPSC (DINP only), the NTP CERHR, and the European Commission. These databases provide strong

support for the conclusions that DINP and DIDP have low toxicity and do not pose a concern in their current uses (nor did DINP pose a concern in its former use in children's toys and products).

As the CHAP is aware, The Hamner Institutes recently completed two studies on DINP using a large number of animals, positive controls, and several doses to investigate fetal and post-natal developmental and reproductive effects. We understand that The Hamner Institutes will be submitting the manuscripts for publication within the next few days; acceptance is anticipated by the end of 2011. The charge to review "all relevant data" mandates that the Hamner studies be reviewed and considered by the CHAP in its deliberations.

In carrying out this charge, it is important to consider the quality and reliability of the data being considered. Factors include the size of the study, the purpose of the study design, and the degree of transparency of the research (e.g., are study reports and raw data made publicly available when requested?). For risk assessment, a LOAEL from a small, exploratory study should not be selected over a NOAEL from a well-conducted guideline study. Further, it is important to recognize the difference between a hypothesis-generating study, and a study conducted according to validated test guidelines that were developed by regulatory agencies specifically to ensure that the data obtained are valid, reliable, and useful to support agencies' risk assessment and risk management functions.

Charge 6: Consider the health effects of phthalates not only from ingestion but also as a result of dermal, hand-to-mouth, or other exposure. § 108(a)(2)(B)(vi).

Conclusion: Exposure to DINP and DIDP is very low from all routes.

As stated above (Charge 3), DINP and DIDP have very low dermal absorption, and inhalation exposure is limited by the very low vapor pressure of each compound. The aggregate exposure levels given by biomonitoring are well below conservative health benchmarks, and the major route of exposure appears to be dietary, indicating the contribution of other routes of exposure is minimal.

Clark et al. (2011) have calculated exposures using empirical data on DINP and DIDP concentrations in various sources.[3] The resulting exposure estimates are in good agreement with the exposure values calculated from the NHANES data, and the Clark et al. (2011) findings support a conclusion that diet is the major route of exposure.

Charge 7: Consider the level at which there is a reasonable certainty of no harm to children, pregnant women, or other susceptible individuals and their offspring, considering the best available science, and using sufficient safety factors to account for uncertainties regarding exposure and susceptibility of children, pregnant women, and other potentially susceptible individuals. § 108(a)(2)(B)(vii).

Conclusion – DINP:

An appropriate conservative health-based exposure guidance value for DINP is 880 ug/kg/day. Even using the prior CHAP's overly conservative ADI of 120 ug/kg/day,

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[3] K Clark, R David, R Guinn, K Kramarz, M Lampi, C Staples (2011). Modeling human exposure to phthalate esters: A comparison of indirect and biomonitoring estimation methods. Human and Ecological Risk Assessment: An International Journal, 17:4, 923-965, available at http://dx.doi.org/10.1080/10807039.2011.588157, submitted to M Babich, CPSC via email (Aug. 5, 2011).

there is a reasonable certainty of no harm from exposures of children, pregnant women, and other susceptible individuals and their offspring to DINP.

The prior CHAP calculated an acceptable daily intake (ADI) for DINP of 120 ug/kg/day. This is an overly conservative ADI because:

- The ADI was based on the histopathological effect of spongiosis hepatis observed in the chronic toxicity studies in rats. Spongiosis hepatis (vacuoles in the liver cells) is of unknown biological significance for rats, and of doubtful relevance to humans. See endnote: March 29, 2011 submission, July 19, 2010 submission and Atts A-1 and A-2.
- The ADI was derived by combining data from two studies in an extremely conservative manner to derive a benchmark dose (BMD). The result was a point of departure value four-fold lower than what was a clear NOAEL from the studies themselves.

ExxonMobil believes that a more appropriate, yet still conservative, NOAEL would be 88 mg/kg/day from the chronic toxicity studies.[4] This is conservative because it is from a lifetime study and the LOAEL effects are increased liver weight in the rats, which likely is related to peroxisome proliferation and not relevant to humans, and kidney tubule mineralization, which is due to the alpha-2u-globulin mechanism and not relevant to humans. For the same reasons, the default interspecies extrapolation factor of 10 is conservative. No uncertainty factor for children is necessary because of the available developmental data. Using the conservative interspecies default factor and the default factor of 10 for human variability gives a health-protective exposure level of 880 ug/kg/day.

The biomonitoring data discussed above demonstrate that exposures from all sources are far below this health-protective level of 880 ug/kg/day. Further, prior CHAP and CPSC assessments show that exposures from mouthing children's products would be far below this ADI; other non-mouthed products would pose a yet much lower exposure potential.

Even using the very conservative ADI of 120 ug/kg/day, biomonitoring studies demonstrate that exposures to DINP are well below the ADI.

Conclusion – DIDP:

Appropriate conservative health based exposure guidance values for DIDP are 380 ug/kg/day for pregnant women and 1100 ug/kg/day for children. Even using the CPSC toxicity review overly-conservative ADI of 150 ug/kg/day, there is a reasonable certainty of no harm from exposures of children, pregnant women, and other susceptible individuals and their offspring to DIDP.

The CPSC calculated an ADI of 150 µg/kg/day for DIDP based on a 13-week dietary exposure study in Beagle dogs conducted more than 40 years ago. This study does not provide an appropriate basis for deriving an ADI due to its severe limitations. As described in the study report, gross necropsy examinations did not reveal any consistent compound-related alterations, only minor microscopic changes were noted and there was a lack of significant dose-response in severity and number of animals affected. More significantly, this study was not conducted to a standardized protocol, not conducted according to Good Laboratory Practice (GLP), had only 3 animals per sex per dose, and the results were not subjected to statistical analysis. Using Klimisch criteria for study reliability, this study scores a 3 – Not Reliable.

[4] No observed adverse effect levels from reproductive and developmental toxicity studies are higher.

For pregnant women, a conservative NOAEL for DIDP is 38 mg/kg/day, based on reduced pup weights in the second pup generation of the two-generation reproductive toxicity (endnote 4). With inter- and intra-species uncertainty factors of 10 each, the resulting health protective exposure level is 380 ug/kg/day. For children's exposures, an appropriate NOAEL is 110 mg/kg/day from a chronic bioassay (endnote 5). This is conservative because the effect – increased liver weight – is likely due to a rodent-specific mechanism that is not relevant for humans. Using a conservative interspecies default factor of 10 and the default factor of 10 for human variability gives a health protective exposure level of 1100 ug/kg/day.

The biomonitoring data discussed above demonstrate that exposures of pregnant women and children from all sources are far below these health-protective levels. Even using the CPSC's overly-conservative ADI of 150 ug/kg/day, exposures to DIDP are well below the health-protective level.

Charge 8: Consider possible similar health effects of phthalate alternatives used in children's toys and child care articles. § 108(a)(2)(B)(viii).

Conclusion: DINP and DIDP have low toxicity and compare favorably to the most likely alternatives, and are well tested in the marketplace with respect to functionality for their respective uses. Publicly available data is limited for many potential alternatives, reducing confidence in any conclusions that might be reached concerning potential health effects associated with those substances.

While the major phthalate alternatives do not have the rich databases that DINP and DIDP have, the available data show that DINP and DIDP are on the same order of low toxicity as the most likely alternatives (DINCH, DPHP and DOTP). This is demonstrated in Table 1.

In considering health effects from alternatives, the CHAP should not limit itself to results of toxicological tests. There are other possible hazards from use of alternatives. For example, if the plasticizing function of the alternative is short lived, then the product will become brittle and could pose a choking hazard. In fact, after its prior review of DINP, CPSC staff said, "If DINP is to be replaced in children's products, whether on a mandatory or voluntary basis, the potential risks of the substitutes must be considered. Weaker or more brittle plastics might break and result in a choking hazard."[5]

[5] Babich M, et al. (2004). Risk assessment of oral exposure to diisononyl phthalate from children's products. *Regulatory Toxicology and Pharmacology* 40(2):151-167.

Table 1: Comparison of Toxicity Data for DINP, DIDP and Other Plasticizers

Studies	DINP	DIDP	DINCH	DOTP	DPHP
Acute	Low	Low	Low	Low	Low
Irritation	Slight	Slight	Slight	Slight	Slight
Sensitization	Negative	Negative	Negative	Negative	Negative
Genotoxicity	Negative	Negative	Negative	Negative	Negative
Mutagenicity	Negative	Negative	Negative	Negative	Negative
Repeated Dose[1]	Liver and Kidney Effects	Liver Effects	Thyroid and Kidney Effects	Retinal Degeneration	Liver Effects
Carcinogenicity	Tumor formation NOT relevant to humans		Thyroid Tumor Formation (possibly secondary effect)	Negative	No Data
Reproductive	Negative[2]	Negative[2]	Negative	Negative[3]	Negative
Developmental	Negative Skeletal Variations (1000 mg/kg)	Negative Skeletal Variations (1000 mg/kg)	Negative Slight Decrease AGD/AGI (1000 mg/kg)	Negative Skeletal Variation (747 mg/kg)	Negative High Rate of Resorption; Skeletal Var. (1000 mg/kg)

No effect or effect not relevant to humans
Effect with questionable relevance

[1]The relevance of the listed effects to humans is questionable.
[2]Offspring bodyweight effects/post natal survival (DINP >1100 and DIDP >600 mg/kg/day) are secondary to maternal toxicity. A cross fostering and switched-diet study with DIDP suggest body weight effects are due to milk palatability.
[3]Maternal death post weaning (>1300 mg/kg/day). As described by Faber et al., 2007, possible treatment related effect seen in 2-generation study during a time period when the dose level (mg/kg/day basis) was likely quite large.

Charge 9: Make recommendations regarding any phthalates (or combination of phthalates) [in addition to DEHP, DBP or BBP] or phthalate alternatives that the panel determines should be declared banned hazardous substances. § 108(a)(2)(C).

Conclusion: The CHAP should not recommend that DINP or DIDP be declared a "banned hazardous substance."

A "banned hazardous substance" is a defined term[6] whose meaning depends in turn on the legal definition of "hazardous substance" and "toxic." In summary, the Federal Hazardous Substances Act provides that a substance may be declared a "banned hazardous substance" only if the following criteria are met:

1) it has the capacity to produce personal injury or illness to humans through ingestion, inhalation, or dermal absorption; and
2) 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; and
3) it is contained in a toy or other article intended for use by children "in such manner as to be susceptible of access by a child to whom such toy or other article is entrusted," or it is intended or packaged for household use and "the degree or nature of the hazard involved in the presence or use of such substance in households is such that the objective of the

[6] The full definition of "banned hazardous substance" is found in the FHSA at 15 U.S.C. § 1261(q)(1).

> protection of the public health and safety can be adequately served only by keeping such substance, when so intended or packaged, out of the channels of interstate commerce."

Importantly, this definition refers to a single given substance. While phthalates share a common molecular moiety and nomenclature, their various physical/chemical properties and toxicity endpoints are not uniform. Each phthalate must be evaluated with respect to its particular database and the differentiation among the various phthalates recognized. Equally importantly, the criteria for declaring a substance a "banned hazardous substance" are clearly risk-based, not simply hazard-based. The inquiry is whether the substance could cause substantial personal injury or illness as the result of "customary or reasonably foreseeable handling or use" of a consumer product containing the substance.

As shown earlier in this document, robust hazard information is available for DINP and DIDP, each has low toxicity, and exposures to each are far below levels that ensure a reasonable certainty of no harm to children, pregnant women or other potentially susceptible populations. Neither has the capacity to produce personal injury or illness through foreseeable exposures, including from potential abuse scenarios. Accordingly, neither should be declared a banned hazardous substance. This conclusion is consistent with prior regulatory and expert assessments in the U.S. and Europe.

This document focuses on the available hazard, exposure and risk information for DINP and DIDP. Prior submissions have addressed comparative toxicities of these and several other phthalates, and have shown how regulatory assessments in the United States and Europe have recognized significant differences in toxicities among phthalates, and have classified several as CMRs and listed them as Substances of Very High Concern under REACH, which has not been done for DINP or DIDP. Based on these comparisons, it is apparent that DINP and DIDP might be considered as alternatives for other phthalates that demonstrate greater toxicity. Indeed, the Danish EPA has recently identified DINP and DIDP as cost effective *substitutes* for several other phthalates, noting: "Costs of substitution differ depending on product group and vary from marginal price increases to significant increases. The least expensive option appears to be substitution to non-classified phthalates as DINP and DIDP."[7]

The CPSIA directed the Commission to appoint a CHAP "to study the effects on children's health of all phthalates and phthalate alternatives *as used in children's toys and child care articles."* CPSIA § 108(b)(2)(A), 15 U.S.C. § 2057c(b)(2)(A) (emphasis added). The Commission will use the CHAP report to help it determine whether to "declare any children's product" containing any phthalates to be a "banned hazardous product." CPSIA § 108(b)(3), 15 U.S.C. § 2057c(b)(3). A "child care article" is "a consumer product designed or intended by the manufacturer to facilitate sleep or the feeding of children age 3 and younger, or to help such children with sucking or teething." CPSIA § 108(e)(1)(C), 15 U.S.C. § 2057c(e)(1)(C). These are the very products the prior CHAP evaluated and the Commission previously found to present no demonstrated health risk based on the presence of DINP.

A "banned hazardous product" is defined as a consumer product that presents an unreasonable risk of injury. 15 U.S.C. § 2057. "Risk of injury" means a risk of death, personal injury, or serious or frequent illness. 15 U.S.C. § 2052(a)(14). Because there is a reasonable certainty of no harm from use of DINP and DIDP in children's and other consumer products, there is no unreasonable risk of injury. The available hazard, exposure and risk information does not demonstrate a need to restrict use of DINP or DIDP in children's products or any other consumer products.

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[7] L Høibye, J Maag, E Hansen (2011). Background data for Annex XV dossier - DEHP, BBP, DBP and DIBP. Miljøprojekt Nr. 1362 2011, Danish Environmental Protection Agency, http://www2.mst.dk/udgiv/publications/2011/04/978-87-92708-97-7.pdf.

Further, there is no scientific reason to consider DINP or DIDP a hazardous substance when present in combination with other phthalates. As shown above, the only toxicity endpoint these compounds have in common with other phthalates is peroxisome proliferation, an endpoint that is not relevant to humans. Even if that endpoint were relevant to humans, there is no basis for believing cumulative exposures would ever approach levels where this would be a concern for human risk, and DINP and DIDP would be minor contributors, as shown above. The available data thus does not support including either DINP or DIDP in any cumulative assessment based on any other endpoint, including any endpoint that might be included within the so-called rat phthalate syndrome.

The totality of the data for DINP and DIDP demonstrates that they are safe for use in consumer products, including products intended for use by children, and that the CPSIA interim ban should be lifted.

ENDNOTES

1. Prior submissions to the CPSC and the CHAP are posted on CPSC's website (http://www.cpsc.gov/about/cpsia/chapmain.html) and include the following:

   Approach to Cumulative Risk, March 3, 2010 (slides)
   http://www.cpsc.gov/about/cpsia/docs/CummRiskExxon03232010.pdf

   Plasticizers and the CPSIA, July 16, 2009 (slides)
   http://www.cpsc.gov/about/cpsia/docs/plasticizersExxon07162009.pdf

   Information for the CPSC CHAP, July 19, 2010
   http://www.cpsc.gov/about/cpsia/chap/exxonSub.pdf

   Att 1: DINP Dossier Extract http://www.cpsc.gov/about/cpsia/chap/exxonDINP.pdf
   Att 2: DIDP Dossier Extract http://www.cpsc.gov/about/cpsia/chap/exxonDIDP.pdf
   Att 3: ECPI Toy Reassessment http://www.cpsc.gov/about/cpsia/chap/exxonDBPDEHP.pdf
   Att 4: EU Risk Assessment for DINP (provided on DVD, available at http://www.dinp-facts.com/upload/documents/webpage/document3.pdf)
   Att 5: EU Risk Assessment for DIDP (provided on DVD, available at http://www.didp-facts.com/upload/documents/document5.pdf)
   Att 6: DINP and DIDP (Bachman slides), 2010 http://www.cpsc.gov/about/cpsia/chap/exxonDINPDIDP.pdf
   Att 7: Plasticizers and the CPSIA (slides) http://www.cpsc.gov/about/cpsia/chap/exxonPlast.pdf
   Att 8: Clark Exposure Database, DINP & DIDP http://www.cpsc.gov/about/cpsia/chap0710.html
   Att 9: Estimate of Infant and Toddler Exposure to DINP and DIDP http://www.cpsc.gov/about/cpsia/chap/exxonBabyExp.pdf
   Att 10: Human Exposure to DINP http://www.cpsc.gov/about/cpsia/chap/exxonExpDINP.pdf
   Att 11: DINP & DIDP Are Not Endocrine Disruptors (Hallmark slides) http://www.cpsc.gov/about/cpsia/chap/exxonDINPDIDPEndoc.pdf
   Att 12: Approach to Cumulative Risk (slides) http://www.cpsc.gov/about/cpsia/chap/exxonCummRisk.pdf
   Att 13: Proposed Approach to Conducting a Cumulative Risk Assessment for 6 Phthalates http://www.cpsc.gov/about/cpsia/chap/exxonCummRiskSupp.pdf
   Att A-1: Dr. John Cullen Statement on DINP Liver Effects http://www.cpsc.gov/about/cpsia/chap/exxonCullenDINP.pdf
   Att A-2: Dr. Dawn Goodman Statement on Spongiosis Hepatis http://www.cpsc.gov/about/cpsia/chap/exxonGoodmanDINP.pdf
   Att: A-3: Dr. G. Hard Statement on DINP Kidney Effects http://www.cpsc.gov/about/cpsia/chap/exxonHardDINP.pdf

   Comments to the CHAP on DINP & DIDP Reproductive Toxicity Data and Cumulative Assessment, March 29, 2011 http://www.cpsc.gov/about/cpsia/chap/exxonmobil.pdf

   Comments on the CHAP Deliberative Process http://www.cpsc.gov/about/cpsia/chap/latham.pdf

2. Humans are more closely related to primates than to rodents: *See, e.g.*, Gad S (2009). Drug Safety Evaluation, 2nd ed. John Wiley & Sons, Hoboken, NJ; Fridman E (2002). Medical Primatology: History, Biological Foundations and Applications. Taylor & Francis, London; Mazue G and Richez P (1982). Problems in utilizing monkeys in toxicology. In Animals in Toxicological Research (I. Bartosek et al., eds.), Raven Press, New York, pp. 147-164.

3. Toxicokinetic and mechanistic data for phthalates show humans more closely related to primates than rodents: For example, both humans and primates absorb a lesser fraction of administered phthalate than do rodents. Anderson W, Castle L, Hird S, Jeffery J, Scotter M (2011). A twenty-volunteer study using deuterium labelling to determine the kinetics and fractional excretion of primary and secondary urinary metabolites of di-2-ethylhexylphthalate and di-iso-nonylphthalate. *Food and Chemical Toxicology* 49(9):2022-29; Anderson W, Castle L, Scotter M, Massey R, Springall C (2001). A biomarker approach to measuring human dietary exposure to certain phthalate diesters. *Food Additives & Contaminants* 18(12):1068-174; Pugh G, Isenberg J, Kamendulis L, et al. (2000). Effects of di-isononyl phthalate, di-2-ethylhexyl phthalate, and clofibrate in cynomolgus monkeys. *Toxicological Sciences* 56:181-188; Astill, B. (1989). Metabolism of DEHP: Effects of prefeeding and dose variation and comparative studies in rodents and cynomolgus monkey (CMA studies). *Drug Metabolism Reviews* 21(1):35-53; Rhodes, C, et al. (1986). Comparative pharmacokinetics and subacute toxicity of di(2-ethylhexyl)phthalate (DEHP) in rats and marmosets: Extrapolation of effects in rodents to man. *Environmental Health Perspectives* 65:299-308; Lington, A, et al. (1985). Disposition and metabolism of diisononyl phthalate (DINP) in Fisher 344 rats: multiple dosing studies. *The Toxicologist* 5:238 (abstr. 949).

4. In the second generation, at the second highest dose level (0.2%), there were significant effects on F2 pup survival on post-natal days (PND) 1 and 4, and on female and male pup body weights at PND 14 and 35, respectively. The authors reported no biologically significant effects at the next lower dose level (0.06%) in either generation of treated offspring (F1 and F2). Based on these results, the authors determined that 0.2% DIDP was the Lowest Observed Effect Level (LOEL) 5 and 0.06% was the NOEL for developmental effects in this study. The authors estimated the ingested dose of DIDP for rats fed a diet containing DIDP at a concentration of 0.06% corresponds to between 38 and 44 mg/kg/day during gestation and between 52 and 114 mg/kg/day during lactation.

5. The CPSC calculated an ADI based on this two-year toxicity/carcinogenicity study by Cho et al. (2008), in which Fischer 344 rats were exposed to 0, 400, 2000, and 8000 ppm DIDP. As published in the 2008 article, the daily mg/kg intakes were 0.85, 4.13, 17.37 for males and 0.53, 3.03, and 13.36 for females. However, the author subsequently determined these values to be incorrect and published the correct intake values in 2010. The corrected values are 21.9, 110.3, and 479.2 for males and 22.9, 128.2, and 619.6 mg/kg/day for females. (Note: there were no neoplasms associated with DIDP.)