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Via Courier and Email: cpsc-os@cpsc.gov

ExxonMobil
Chemical

Office of the Secretary
Consumer Product Safety Commission
4330 East-West Highway
Bethesda, Maryland 2081

RE: CHAP on Phthalates

ExxonMobil Chemical Company (ExxonMobil) is providing this package of information in response to the request of the Consumer Product Safety Commission (CPSC) Chronic Hazard Advisory Panel (CHAP) for comment on issues relating to the hazard, exposure, and risk posed by phthalates and phthalate substitutes from all sources of exposures, especially children's products.¹ ExxonMobil commercially produces diisononyl phthalate (DINP; CASRN 68515-48-0), diisodecyl phthalate (DIDP; CASRN 68515-49-1) and other high-molecular weight (HMW) phthalates. These comments relate specifically to DINP and DIDP, which are the two commercial HMW phthalates currently subject to restrictions under the Consumer Product Safety Improvement Act (CPSIA).²

The attached comments first identify several summaries of DINP and DIDP data which can be consulted for information on the uses of, toxicity of and exposure to these compounds. It then provides information for each of the 12 issues on which the CHAP is seeking comment. Overall, we believe that the data for DINP and DIDP show them to be low toxicity compounds with very low exposures, such that they can be safely used in toys and children's articles.

ExxonMobil appreciates the opportunity to provide this information. We would be pleased to answer questions or provide additional materials that would assist the CHAP in its deliberations. Please contact the undersigned with any questions or requests.

Sincerely,



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¹ Notice of Meeting of Chronic Hazard Advisory Panel on Phthalates and Phthalate Substitutes and Opportunity for Public Comment, 75 Fed. Reg. 31426 (June 3, 2010).

² Section 108 of the Consumer Product Safety Improvement Act of 2008, Pub. L. 110-314, 122 Stat. 3016 (August 14, 2008).

**INFORMATION FOR THE CONSUMER PRODUCT SAFETY COMMISSION
CHRONIC HAZARD ADVISORY PANEL ON PHTHALATES
July 19, 2010**

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**INFORMATION FOR THE CONSUMER PRODUCT SAFETY COMMISSION
CHRONIC HAZARD ADVISORY PANEL ON PHTHALATES
July 19, 2010**

ExxonMobil Chemical Company (ExxonMobil) is providing this package of information in response to the request of the Consumer Product Safety Commission (CPSC) Chronic Hazard Advisory Panel on Phthalates (CHAP) for comment on issues relating to the hazard, exposure, and risk posed by phthalates and phthalate substitutes from all sources of exposures, especially children's products.¹ ExxonMobil commercially produces diisononyl phthalate (DINP; CASRN 68515-48-0), diisodecyl phthalate (DIDP; CASRN 68515-49-1) and other high-molecular weight (HMW) phthalates. These comments relate specifically to DINP and DIDP, which are the two commercial HMW phthalates currently subject to restrictions under the Consumer Product Safety Improvement Act (CPSIA).²

Comprehensive Reviews of DINP and DIDP

DINP and DIDP have been registered under the European Union (EU) REACH regulation.³ Attachments 1 and 2 provide extracts from the dossiers submitted to the European Chemicals Agency (ECHA) to support the REACH registration of DINP and DIDP.⁴ Key information from the registration dossiers has been posted to the Internet by ECHA.⁵ This information can be accessed by the public; however, to make it more easily accessible to the CHAP, we have printed out each webpage of the DINP and DIDP entries and then scanned them into pdf documents.⁶ In addition, we are providing some summaries of the toxicity data that were included in the dossier submission to ECHA.⁷

¹ Notice of Meeting of Chronic Hazard Advisory Panel on Phthalates and Phthalate Substitutes and Opportunity for Public Comment, 75 Fed. Reg. 31426 (June 3, 2010).

² Section 108 of the Consumer Product Safety Improvement Act of 2008, Pub. L. 110-314, 122 Stat. 3016 (August 14, 2008).

³ Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), O.J. L 396, 30.12.2006, pp. 1-849.

⁴ The dossiers were prepared in accordance with the REACH regulations and with ECHA guidance. See ECHA, Guidance Documents, http://guidance.echa.europa.eu/guidance_en.htm.

⁵ ECHA, Search for information on registered substances, <http://apps.echa.europa.eu/registered/registered-sub.aspx>. To access the information, search on the CAS registry number (DINP - 68515-48-0; DIDP - 68515-49-1).

⁶ For DINP, we have provided the information submitted under CASRN 68515-48-0, which is the number for ExxonMobil's product. All information submitted for DIDP is for CASRN 68515-49-1.

⁷ The website and our package do not provide the full dossiers for DINP and DIDP and do not include certain production and analysis information that was claimed as Confidential Business Information in accordance with European Union law and REACH guidance. See ECHA (2007), Guidance on data sharing, Chapter 11: Confidential Business Information (CBI), European Chemicals Agency, Guidance for the Implementation of REACH, http://guidance.echa.europa.eu/docs/guidance_document/data_sharing_en.pdf.

The REACH dossiers represent the most current comprehensive summary of information on DINP and DIDP. Another recent summary of DINP has been produced by the European Council for Plasticisers and Intermediates (ECPI) to the assist in the reconsideration of the EU restrictions on DINP in toys and children's articles (referred to herein as ECPI Toy Reassessment). It has been submitted to CPSC and is posted to its website, and is provided here as Attachment 3.⁸

Very comprehensive and detailed summaries of DINP and DIDP are also provided by the EU risk assessments of these chemicals, provided as Attachments 4 and 5 and also available on the Internet.⁹

The CPSC staff has reviewed DINP and DIDP in the context of the Federal Hazardous Substances Act (FHSA); those reviews are posted on the CPSC CHAP webpage.¹⁰ Appendices A and B of these comments provide comments on those toxicity reviews.

ExxonMobil intends to make a presentation at the July 26, 2010 CHAP meeting that summarizes a spectrum of toxicity, exposure and risk assessment information for DINP and DIDP. A copy of the slides for that presentation is provided as Attachment 6.

Overall, DINP and DIDP have very robust databases, with respect to both toxicity data and exposure data. These data demonstrate that these are low toxicity compounds with very low exposures. To the extent that effects are seen in rodent studies, they are seen at high doses (100 or more mg/kg/day). The weight of the evidence also indicates that effects observed in rodent studies likely are not relevant to humans – a conclusion that is supported by primate studies showing no adverse systemic effects even at the extremely high dose of 2,500 mg/kg/day of

⁸ ECPI (2009). Review of Recent Scientific Data on Di-isononyl Phthalate (DINP) and Risk Characterisation for its use in Toys and Childcare articles (CAS No. 68515-48-0 / EINECS No. 271-090-9, 1,2-benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich; CAS No. 28553-12-0 / EINECS No. 249-079-5 di-isononyl phthalate). European Council for Plasticisers and Intermediates, Technical Report 2009-0601-DINP, <http://www.cpsc.gov/about/cpsia/docs/DINPToysExxon062009.pdf>.

⁹ ECB (2003). 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich and di-“isononyl” phthalate (DINP), CAS Nos: 68515-48-0 and 28553-12-0, EINECS Nos: 271-090-9 and 249-079-5, European Union Risk Assessment Report, PL-2 35, EUR 20784 EN, European Chemicals Bureau, available at http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/dinpreport046.pdf;

ECB (2003). 1,2-Benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich and di-“isononyl” phthalate (DINP), CAS Nos: 68515-49-1 and 26761-40-0, EINECS Nos: 271-091-4 and 247-977-1, European Union Risk Assessment Report, PL-2 36, EUR 20784 EN, European Chemicals Bureau, available at http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/didpreport041.pdf.

¹⁰ CPSC Health Sciences (2010). Toxicity Review of Diisononyl) Phthalate (DINP). Memo from M. Babich and C. Osterhout to M. Danello, April 11, <http://www.cpsc.gov/about/cpsia/toxicityDINP.pdf>.

CPSC Health Sciences (2010). Toxicity Review of Di(isodecyl) Phthalate. Memo from C. Osterhout to M. Babich, April 7, <http://www.cpsc.gov/about/cpsia/toxicityDIDP.pdf>.

DINP for 13 weeks. The contributions of DINP and DIDP to a cumulative risk assessment of phthalates are very low. ExxonMobil therefore strongly believes that the available data demonstrate that DINP and DIDP can be used safely in children's articles and toys as well as other consumer products.

The following provides information in response to the 12 issues for which the CHAP has requested comment.

1. Information on current and anticipated future uses of phthalates and phthalate substitutes in products, including market data, production levels, and the range of uses of specific phthalates and phthalate substitutes in different product types.

Tables 1 and 2 of these comments provide information on consumption of DINP and DIDP in the United States in 1998 and are the most complete breakdown of their uses of which we are aware. The information is also provided graphically in Figures 1 and 2. SRI (2009) reports that DINP consumption in 2008 was 155 metric tons and DIDP consumption that year was 90 metric tons.¹¹ SRI projects annual growth to 2013 of 1.5% for DIDP and 1.6% for DINP. The SRI report does not have a consumption breakout for DINP; for DIDP, it reports 33% of total consumption use for wire and cable, 15% for film and sheet, 5% for automotive undercoating, and 30% for "other."

Information on uses of phthalates and other plasticizers was presented to the CPSC last year; the slides of that presentation are posted on the CPSC CHAP webpage and are provided here as Attachment 7 – see in particular slides 5-7.¹²

Information on the uses of DINP and DIDP also is included in the REACH dossier information provided as Attachments 1 and 2; *see* section 3.7 of each dossier, and in the EU risk assessments provided as Attachments 4 and 5; *see* Sections 2.3 and 4.1.1.3 of each assessment.

As concerns have arisen over the use of DEHP, replacement of DEHP with DINP and DIDP has increased. An advantage of DINP and DIDP is that they are essentially "drop in" replacements of DEHP in many applications; that is, they can be substituted into the manufacturing process with minimal need for formulation and process adjustments. At the same time, DINP and DIDP provide very low toxicity profiles.

Future uses of phthalates and of alternatives will of course depend to some extent on the outcome of this CHAP and other initiatives being undertaken by various government authorities. It is important to understand, however, that replacement of a plasticizer in general is not a simple matter of a formulator buying one plasticizer rather than another. There currently are about 80 PVC plasticizers available in the United States of which about one-quarter are phthalates. Only

¹¹ SRI (2009). CEH Marketing Research Report: Plasticizers. By S. Bizzari, M Blagoev, A Kishi, Chemical Economics Handbook—SRI Consulting.

¹² ExxonMobil, Plasticizers and the CPSIA, presented to the U.S. Consumer Product Safety Commission (July 16, 2009), <http://www.cpsc.gov/about/cpsia/docs/plasticizersExxon07162009.pdf>.

some of the phthalates are suitable as general purpose plasticizers (DEHP, DINP, DIDP and DPHP). The remaining plasticizers are not simple drop in alternatives for the general purpose phthalates; they are specialty products developed to provide specific performance for particular applications and come at a premium price. Replacement of a plasticizer generally requires significant resources and time to develop and test an acceptable alternative formulation, manufacturer new molds, and make other necessary equipment changes.

**Table 1. Calculated 1998 U.S. Consumption of DIDP
(thousands of metric tons)**

End Use	Subtotal	Total
Film and Sheet		20
Skins – Unsupported	7	
Pool Lining	9	
Other	4	
Artificial leather		20
Coated Fabrics		1
Dip Coating/Slush Molded		4
Toys	2	
Traffic Cones	<2	
Other	~1	
Tubings		9
Wire and Cables		45
Under-Body Coating		36
GRAND TOTAL		135

Source: Comments of the Chemical Manufacturers Association Phthalate Esters Panel in response to request for public input on seven phthalate esters, submitted to National Toxicology Program Center for the Evaluation of Risks to Human Reproduction, July 7, 1999.

**Table 2. Calculated 1998 U.S. Consumption of DINP
(thousands of metric tons)**

End Use	Subtotal	Total
Film and Sheet		13
Stationary and Wood Veneer	6	
Pool Liners	1	
Other	6	
Flooring		48
Tiles	23	
Sheets	25	
Artificial leather		3
Coated Fabrics		21
Tarps	16	
Conveyor Belts	1	
Other	4	
Dip Coating/Slush Molded		30
Gloves	15	
Toys	6	
Traffic Cones	<1	
Other	~9	
Tubings and Profiles		7
Profiles	5	
Garden Hoses	2	
Wire and Cables		32
Shoes/Shoe Soles		9
Under-Body Coating		7
Sealants (carpet backing)		8
GRAND TOTAL		178

Source: Comments of the Chemical Manufacturers Association Phthalate Esters Panel in response to request for public input on seven phthalate esters, submitted to National Toxicology Program Center for the Evaluation of Risks to Human Reproduction, July 7, 1999.

Fig. 1 DIDP Consumption, 1998

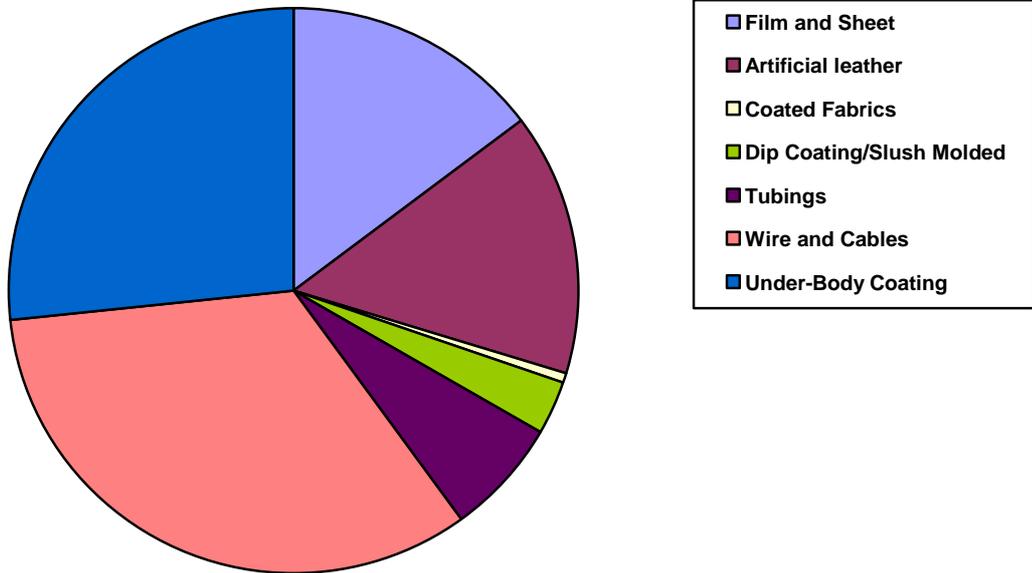
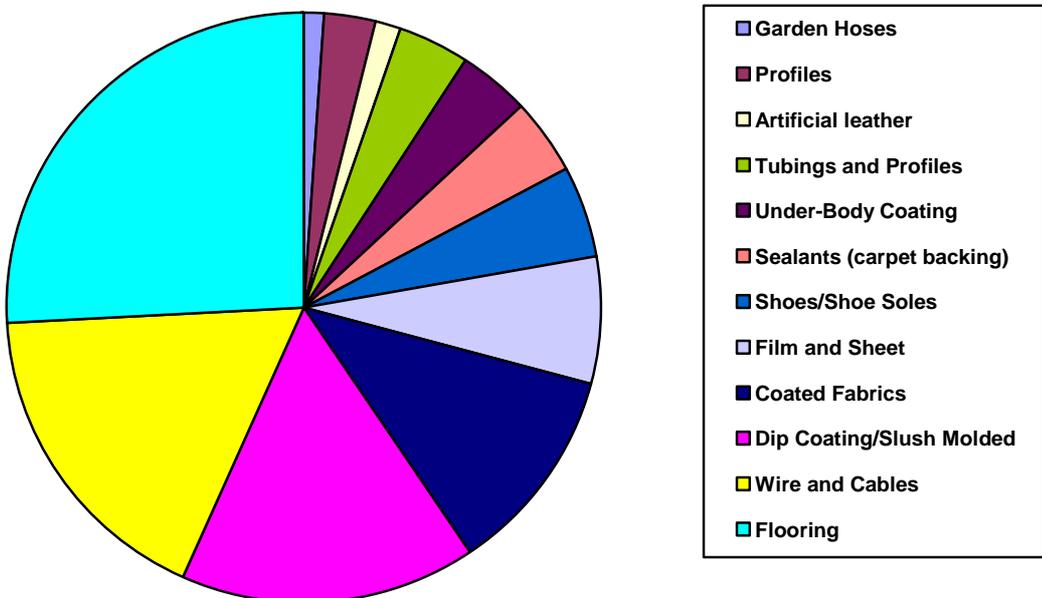


Fig. 2 DINP Consumption, 1998



2. Data on the types and levels of phthalates and phthalate substitutes found in consumer products, cosmetics, pharmaceutical drugs, medical devices, food, food supplements, food packaging, and pesticides.

Data on uses of DINP and DIDP are provided in the EU risk assessments (Attachments 4 and 5) – see Section 2.3 of each assessment. Consumer uses are specifically discussed in Section 4.1.1.3 of each assessment. Tables 1 and 2 of these comments, above, provide information on the uses for which DINP and DIDP were consumed in the United States in 1998. Note that the values in Attachments 4 and 5 and Tables 1 and 2 do not necessarily represent the proportions of DINP and DIDP in toys and children's articles imported into the United States.

The vast majority of uses for DINP and DIDP are as plasticizers of polyvinyl chloride (PVC). To our knowledge, DINP and DIDP are not used in any cosmetics, pharmaceutical drugs or food supplements. Use in pesticides would be primarily, perhaps exclusively, as plasticizer for a PVC component of a pesticidal device.

Since the late 1980's, DINP has been the primary phthalate used in soft vinyl toys; its use in toys that can be mouthed is now subject to the interim restriction of the CPSIA. As of 1998, manufacturers and retailers in the US have voluntarily excluded use of phthalates, including DINP and DIDP, from pacifiers and rattles.¹³

Levels of DINP and DIDP in consumer products depend on the desired physical properties of the consumer product. We note, however, that for risk assessment the question is not what the levels are in the consumer product, but the amount that can be released and thus enable exposure to the chemical. While the phthalates are not covalently bonded to the PVC, they are tightly fused with the PVC matrix by mechanical intertwining and Van der Waals bonding. Once fused, the compound of PVC resin and plasticizer is extremely stable. Migration rates from mouthing of vinyl has been well studied by the CPSC, showing that even under relatively severe conditions of mechanical stress, migration rates are very low.

3. Information on the relative importance of different sources, routes, and pathways of exposure to phthalates in the general population, expectant mothers, and children.

Detailed analyses of exposure pathways for DINP and DIDP, including specifically exposures of infants and young children, are provided in Part 4 of each EU risk assessment (Attachments 4 and 5). Dr. Kathryn Clark of BEC Technology Inc. has compiled a comprehensive database of published data on DINP, DIDP and other phthalate levels in the environment. This database (Clark database) has been provided to CPSC by the American Chemistry Council (ACC) Phthalate Esters Panel and is posted on the CPSC CHAP website.¹⁴ Attachment 8 provides the DINP and DIDP portions of the Clark database. The ACC Phthalate Esters Panel has also

¹³ See CPSC Releases Study on Phthalates in Teethers, Rattles and Other Children's Products, CPSC Press Release # 99-031, Dec. 2, 1998, <http://www.cpsc.gov/CPSCPUB/PREREL/PRHTML99/99031.html>.

¹⁴ Concentration database – Other PEs 2009, <http://www.cpsc.gov/about/cpsia/docs/otherPEs2009.pdf>

provided to CPSC a manuscript by Dr. Clark and her colleagues.¹⁵ This manuscript has been submitted to *Human and Ecological Risk Assessment* and provides discussion of the sources of exposure for DINP and DIDP.

Exposures to DINP and DIDP are limited by their inherent physical properties. They have extremely low water solubilities and vapor pressures and are not readily absorbed through skin. Therefore, nearly all exposure to these phthalates occurs via ingestion of food.¹⁶ However, exposures via this pathway are extremely low. As shown in the Clark database (Attachment 8), DIDP has not been reported as detected in foodstuffs, and monitoring for DINP in foodstuffs has resulted in few values above the limit of detection.

The pre-CPSIA use of DINP in vinyl toys and children's articles that can be mouthed provides another potential pathway for exposure of children. As summarized in the CPSC staff toxicity review of DINP, this pathway has been extensively studied by the CPSC and shown to result in very low exposures even with the application of very conservative assumptions. In addition, the ECPI Toy Reassessment (Attachment 3) provides a risk characterization of use of DINP in toys in the EU. It calculates margins of safety of at least 1000 based on the most conservative exposure data.

The very low exposures to DINP and DIDP from *all* routes are confirmed by biomonitoring data. As discussed in the response to issue 7, below, that data indicates that exposures to DINP and DIDP are on the order of 1 ug/kg/day or less.

4. Data on consumer use patterns including the use of cosmetics and consumer products that may contain phthalates.

Information pertaining to this issue is described in the response to the previous three issues. To our knowledge, DINP and DIDP are not used in cosmetics. As shown in Table 2, above, the majority of DIDP is used for wire and cable (in the flexible PVC sheathing) and automotive underbody coating, uses to which the general population has little exposure.

5. Data on children's activity patterns, including mouthing activity, exposure to household dust, dermal exposure to toys, and other potential child-specific exposure pathways.

The most thorough work on these issues has been conducted by the CPSC in its state-of-the-art studies. The ECPI Toy Reassessment (Attachment 3) also provides formation on mouthing activity and exposure of children to DINP.

¹⁵ K Clark, R David, R Guinn, K Kramarz, M Lampi, C Staples (2010). Modelling human exposure to phthalate esters: A comparison of indirect and biomonitoring estimation methods.

¹⁶ Because of the very low vapor pressures of DINP and DIDP, detections in air would be due to suspended particles on which the phthalates are absorbed or in which the phthalate is incorporated (that is, abraded PVC particles).

Attachment 9 provides estimates of exposure of infants and toddlers to DINP and DIDP, other than from toys, which the ACC Phthalate Esters Panel submitted to the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) in 1999. The estimates consider exposures from air, water, dust, food, and flooring, using conservative values for each. For DINP, the total exposure estimate for DINP is 3.2 ug/kg/day for infants and 2.9 ug/kg/day for toddlers. For DIDP, the total exposure estimate is 2.6 ug/kg/day for infants and 2.1 ug/kg bw/day for toddlers.

6. Information relating to human exposure to phthalates and phthalate substitutes, including migration data, levels in environmental media (ambient and indoor air, water, soil, household dust), dermal exposure, oral exposure, and bioavailability.

Wittassek et al. (2010) have recently published a comprehensive review of biomonitoring data for phthalates.¹⁷ Attachment 10 is a document ExxonMobil prepared for the California Office of Environmental Health Hazard Assessment (OEHHA) that provides calculations of the exposures indicated by those results.¹⁸ Biomonitoring – whether of the monoester or of oxidative metabolites – indicates that the median exposure to DINP from all sources is less than 1 ug/kg/day and the 95th percentile less than 10 ug/kg/day.

Silva et al. (2007) reported that the DIDP monoester was not detectable in urine from 129 adult volunteers.¹⁹ Concentrations of DIDP oxidative metabolites were lower than concentrations of analogous DINP and DEHP oxidative metabolites (Wittassek et al., 2010). Given the very low exposures to DINP, it follows that exposures to DIDP also are very low.

DINP and DIDP detected in air and in dust may be due to particles of abraded PVC. It is not known whether the DINP or DIDP in such particles would be bioavailable, or whether the phthalate would remain in the PVC until expelled from the lungs or gastrointestinal system.

7. New, unpublished, or soon-to-be published data on the types and levels of phthalates, phthalate substitutes, or their metabolites in human urine, blood, milk, or other biological media.

ExxonMobil is aware of the following data that will soon be available or published:

- As discussed above, the ACC Phthalate Esters Panel has provided a manuscript of Clark et al. (2010) to the CPSC.

¹⁷ M Wittassek, H Koch, J Angerer, T Brüning (2010). Assessing exposure to phthalates - The human biomonitoring approach. *Mol Nutr Food Res*. Vol. 54 (in press, DOI 10.1002/mnfr.201000121).

¹⁸ The document was prepared before release of the Centers for Disease and Prevention (CDC) fourth national exposure report. Values for DINP were lower in the 4th Report than in previous reports. <http://www.cdc.gov/exposurereport>.

¹⁹ M Silva, J Reidy, K Kato, J Preau, L Needham, A Calafat (2007). Assessment of human exposure to di-isodecyl phthalate using oxidative metabolites as biomarkers. *Biomarkers* 12:133-144.

- A study has been conducted in the EU by ECPI concerning the rate and extent of conversion of isotopically labelled DINP and DEHP into their primary and secondary metabolites in blood and urine following administration to human volunteers (referred to herein as the ECPI Biomonitoring Study). These data will be directly relevant to pharmacokinetics, biomarkers, and effects on biochemical and physiological processes in humans. The data also will enable refinement of calculation of DINP/DIDP exposure from biomonitoring results. Publication of the results of this study is anticipated this year.
- The Hamner Institute, under the direction of Drs. Mel Anderson and Rebecca Klewell, is conducting mechanistic studies of DINP administered to pregnant dams, examining the distribution of DINP and its major metabolites in the maternal and fetal rat across doses, enabling direct correlation of fetal metabolite concentrations to fetal effects. This kinetic data also will allow extrapolation of a previously published phthalate PBPK model to DINP.
- We understand that the Centers for Disease Control and Prevention (CDC) has oxidative metabolite data for DINP and plans to publish it this year. Dr. Antonia Calafat would be a primary contact at CDC concerning this data.

8. Information relating to metabolism or pharmacokinetic modeling that could be used to estimate human exposure from biomonitoring studies.

Estimation of human exposure from biomonitoring studies is discussed in Attachment 10, in Clark et al. (2010) (submitted to CPSC), and in the literature.²⁰ In addition, the ECPI Biomonitoring Study discussed in the response to Issue 7 will help to refine values used in the calculations.

9. Toxicity data on the full range of phthalates and phthalate substitutes in commercial use, especially unpublished or soon-to-be-published studies.

The toxicity data for DINP and DIDP have been thoroughly reviewed by the CPSC staff, the industry (Attachments 1, 2 and 3), the EU chemical management authorities (Attachments 4 and 5), and other expert bodies. Appendices A and B to this document provide comments on the CPSC staff toxicity reviews, including corrections and additional information that should be considered. As well as its general discussion of toxicity (Attachment 6), ExxonMobil/ECPI intends to make a presentation at the July 26, 2010 CHAP specifically on the issue of endocrine disruption with respect to DINP and DIDP, showing that the evidence shows they are not

²⁰ Wittassek et al. (2010), note 17; page 9; R David (2000). Exposure to phthalate esters. Environ Health Perspectives 108:A440, available at <http://ehpnet1.niehs.nih.gov/docs/2000/108-10/correspondence.html#exp>; M Kohn, F Parham, S Masten, C Portier, M Shelby, J Brock, L Needham (2000). Human exposure estimates for phthalates. Environ Health Perspect 108:A440-A442, available at <http://ehpnet1.niehs.nih.gov/docs/2000/108-10/correspondence.html#exp>.

endocrine disruptors under international definitions (see response to Issue 11, below). The slides for that presentation are provided here as Attachment 11.

We urge the CHAP and CPSC to keep their evaluations of DINP and DIDP toxicity within the follow contexts:

- Significant differences exist among the phthalates with respect to toxicity outcomes. DINP and DIDP must be evaluated on their own merits, not by potentially incorrect extrapolation from other phthalate data.
- An overall concern in toxicology is the extent to which the rodent model accurately reflects the likely response of humans. In the case of DINP, peer-review studies of primates are available and show no systemic toxicity at very high doses. These studies strongly support a conclusion that effects seen in rodents are not relevant to humans, especially at the extremely low levels to which humans are exposed.
- Effects observed in rodent studies of DINP and DIDP occur only at relatively high doses. Thus, even if such effects are relevant to human risk assessment, there is very little likelihood that such effects would occur at the extremely low levels to which humans are exposed.
- In cumulative risk assessments of phthalates conducted to date, DINP and DIDP are very minor contributors to the overall risk.

10. Human data on the toxicity of phthalates, including epidemiological and clinical studies, especially unpublished or soon-to-be published studies.

ExxonMobil has no epidemiological or clinical data other than that published in the literature. We would point out several issues that the CHAP and CPSC should keep in mind when evaluating that data:

- To date, only one clinical study has evaluated exposure to DINP, and no studies are available that have examined DIDP. There is no basis to attribute the correlations reported for other phthalates to DINP or DIDP.
- Evaluation of a large number of endpoints against a number of chemicals is likely to produce some correlations by pure chance.
- Association is not causation. The human studies conducted on phthalates that look for an association of biomonitoring data with effects are screens that can point to areas for further research; they are not results from which a conclusion can be drawn regarding whether the chemical causes an effect in humans.
- The one study that considered DINP was Main et al. (2006). The study authors reported a “subtle” association between neonatal exposure to phthalate monoesters in milk and

reproductive hormone levels in those neonates. This study was evaluated by the NTP CERHR Phthalate Expert Panel in its update evaluation of DEHP.²¹ The Panel indicated a number of weaknesses including confounding due to possible contamination of breast milk samples.²² It indicated that further studies that use larger populations and address confounding are necessary to draw conclusions.

11. Information on the relative sensitivity of potentially vulnerable populations, including the fetus, young children, and expectant mothers, and whether there are any other vulnerable populations that should be considered.

There is no evidence of reproductive toxicity from DINP exposure. In fact, the NTP CERHR concluded that the available evidence (one each of one-generation and two-generation reproductive studies) suggests that DINP has *no* reproductive effects.²³ As described in the CPSC staff toxicity review of DINP, there is evidence of minor developmental effects (skeletal variations; dilated renal pelves at maternally toxic doses) in fetal and newborn rats. However, in a number of studies, the doses that elicited such effects were generally quite high – in the range of 500 to 1000 mg/kg/day (in an outlier study, effects were seen at 143-285 mg/kg/day) (see Tables 6-5 and 6-6 of the CPSC staff toxicity review, pp. 45 and 49). The CPSC staff derived a developmental ADI of 1.0 mg/kg/day, which is three orders of magnitude higher than the exposures to DINP indicated by biomonitoring. (Due to the lack of reproductive effects, no reproductive ADI was calculated.) These data suggest that the fetus, young children and expectant mothers are not highly vulnerable to effects from DINP at plausible levels of exposure.

DIDP treatment of rats resulted in minor development effects of questionable biological significance. CPSC staff derived a developmental NOAEL of 0.4 mg/kg/day based on a study in which there were no effects at 40 mg/kg/day and were effects at the next dose level of 200 mg/kg/day. Note, however, that there was also a developmental study with a NOAEL of 100 mg/kg/day (see Table 8 of the CPSC staff toxicity review). As that NOAEL value fits within the range between the NOAEL of 40 mg/kg/day and LOAEL of 200 mg/kg/day, it could be used for derivation of an ADI of 1.0 mg/kg/day. In either case, the developmental ADI is approximately three orders of magnitude above the likely levels of DIDP exposure indicated by biomonitoring. The reproductive ADI derived by CPSC staff (2.3 – 6.5 mg/kg/day) is yet further above likely exposures. These data suggest that the fetus, young children and expectant mothers are not highly vulnerable to effects from DIDP at plausible levels of exposure.

²¹ NTP CERHR Expert Panel Update on the Reproductive and Developmental Toxicity of Di(2-ethylhexyl) Phthalate, NTP-CERHR-DEHP-05, November 2000 pp. 54-55, http://cerhr.niehs.nih.gov/evaluations/chemicals/phthalates/dehp/DEHP_Report_final.pdf.

²² See A Calafat A Slakman, M Silva, A Herbert, L Needham (2004). Automated solid phase extraction and quantitative analysis of human milk for 13 phthalate metabolites J Chromatogr B 805:49–56.

²³ NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Diisononyl Phthalate (DINP), NIH Publication No. 03-4484, March 2003, p. 2, http://cerhr.niehs.nih.gov/evaluations/chemicals/phthalates/dinp/DiNP_Monograph_Final.pdf.

There has been concern expressed that DINP and DIDP may be antiandrogenic and that fetuses and children therefore may be vulnerable to these compounds. Such concern is not borne out by the current evidence (see Attachment 11). Importantly, DINP and DIDP did not cause adverse effects on reproduction in two-generation studies. Some anti-androgenic-like effects (reduced testosterone synthesis, nipple retention, reduced AGD) have been seen in male rats given a very high doses by gavage (600-750 mg/kg/day), but the data are limited and inconsistent:

- DINP and its monoester metabolite, MINP do not bind to androgen receptors *in vitro*.
- Consistent with *in vitro* assessments of androgen-receptor binding,²⁴ an *in vivo* study found that DINP did not meet the criteria established by OECD for classification as an androgen antagonist.²⁵
- In studies designed to see malformation of the male rat reproductive tract, minor effects have been observed following gavage exposure at very high doses,²⁶ but no effects on androgenic sensitive endpoints have been observed at even higher levels of exposure via the diet.²⁷

Collectively, the data for antiandrogenicity of DINP are based on limited study designs with no or only minor effects being observed at very high gavage doses with no dose response observed. Based on the comprehensive 2-generation reproductive, sub-chronic, and chronic studies, DINP does not meet criteria for classification as an endocrine disrupter under the Weybridge, IPCS and REACH guidance definitions.²⁸

²⁴ A summary of androgen-receptor binding tests of DINP, DIDP, and other phthalates is provided in R McKee, J Butala, R David, G Gans (2004). NTP center for the evaluation of risks to human reproduction reports on phthalates: addressing the data gaps. *Reprod Toxicol* 18:1-22.

²⁵ B Lee, H Koo (2007). Hershberger assay for antiandrogenic effects of phthalates. *J Toxicol Environ Health, Part A* 70:1365-1370;

²⁶ L Gray, J Ostby, J Furr, M Price, D Veeramachaneni, L Parks (2000). Perinatal exposure to phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. *Toxicol Sci* 58:350-365; U Hass, M Filinska, T Kledal (2003). Antiandrogenic effects of diisononyl phthalate in rats. *Reprod Toxicol* 17:493-4; J Borch, O Ladefoged, U Hass, A Vinggaard (2004). Steroidogenesis in fetal male rats is reduced by DEHP and DINP, but endocrine effects of DEHP are not modulated by DEHA in fetal, prepubertal and adult male rats. *Reprod Toxicol* 18:53-61.

²⁷ N Masutomi, M Shibutani, H Takagi, C Uneyama, M Takahashi, M Hirose (2003). Impact of dietary exposure to methoxychlor, genistein, or diisononyl phthalate during the perinatal period on the development of the rat endocrine/reproductive systems later in life. *Toxicol* 192:149-170; A Adamsson, V Salonen, J Paranko, J Toppari (2009). Effects of maternal exposure to diisononylphthalate (DINP) and 1,1,-dichloro2,2-bis(p-chlorophenyl)ethylene (p,p'-DDE) on steroidogenesis in the fetal rat testis and adrenal gland. *Reprod Toxicol* 28:66-74.

²⁸ European Commission (1997). European Workshop on the Impact of Endocrine Disrupters on Human Health and Wildlife, 2-4 December 1996, Weybridge, UK, Report of the Proceedings. DG XII Report EUR 17549, April 16, 1997; IPCS (International Programme on Chemical Safety) (2002). Global Assessment of the State-of-the-Science of Endocrine Disruptors. WHO/PCS/EDC/02.2. Geneva, Switzerland: World Health Organization,

12. Information relating to assessing the cumulative (combined) risk from multiple phthalates, including dose response data, methodology, which health endpoint (or endpoints) is the most relevant to human risk assessment, and which phthalate substitutes or other compounds may contribute to the combined risk.

ExxonMobil has submitted a cumulative risk assessment for DBP, BBP, DnOP, DEHP, DINP and DIDP; it is posted on the CPSC website and is provided here as Attachment 12.²⁹ A more detailed explanation of that cumulative risk assessment is provided as Attachment 13. The endpoint used for the assessment was increased liver weight and increased Palmitoyl CoA activity. This endpoint was selected because it is the only endpoint for which an effect clearly is observed for all six phthalates. The results show that DINP and DIDP make only a very minor contribution to the cumulative risk.

Benson (2009) and Kortenkamp and Faust (2010) have published assessments of the cumulative risk of DBP, DiBP, BBP, DEHP and DINP.³⁰ Both assessments used antiandrogenic endpoints. As discussed in the response to Issue 11, under the current evidence it is not appropriate to consider DINP an antiandrogen.³¹ However, even doing so, DINP again is only a very minor contributor to the overall risk.

Comments by the European chemical industry on the State-of-the-Art report on mixtures toxicity by Kortenkamp, Backhaus and Faust, contracted by the European Commission, and provided as Attachment 14 and address important issues regarding cumulative risk assessment.

A cumulative risk assessment of course makes sense only when chemicals share a common endpoint. A given phthalate should not be shoehorned into a cumulative risk assessment simply for the sake of having a cumulative number – the resulting risk estimate would be scientifically unsound and misleading. The mere fact of having a data point on a chemical showing a given type of effect should not justify inclusion of that chemical in a CRA of that effect where the data

http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en; ECHA (European Chemicals Agency) (2007) Guidance for the preparation of an Annex XV dossier on the identification of substances of very high concern. Guidance for the implementation of REACH, http://guidance.echa.europa.eu/docs/guidance_document/svhc_en.pdf.

²⁹ Approach to Cumulative Risk, Presentation by ExxonMobil Chemical Company to the US Consumer Product safety Commission, March 23, 2010, <http://www.cpsc.gov/about/epsia/docs/CummRiskExxon03232010.pdf>.

³⁰ R Benson (2009). Hazard to the developing male reproductive system from cumulative exposure to phthalate esters--dibutyl phthalate, diisobutyl phthalate, butylbenzyl phthalate, diethylhexyl phthalate, dipentyl phthalate, and diisononyl phthalate. Regul Toxicol Pharmacol. 53(2):90-101; A Kortenkamp, M Faust (2010). Combined exposures to anti-androgenic chemicals: steps towards cumulative risk assessment. Int J Androl 33(2):463-74.

³¹ A report of the National Research Council (NRC) recommended to EPA that a risk assessment be conducted using anti-androgenicity as an endpoint (NRC (2008). Phthalates and Cumulative Risk Assessment: The Task Ahead, The National Academies Press, http://www.nap.edu/catalog.php?record_id=12528). However, from the NRC report, it appears the authors simply accepted stated conclusions of anti-androgenicity for DINP and DIDP; they did not critically evaluate the basis for those assertions.

point is inconsistent, questionable or contrary to the weight of the evidence. The CHAP should weigh carefully whether the evidence for DINP and DIDP truly is sufficient to include these substances in a phthalate cumulative risk assessment using a given endpoint.

Appendix A

Review of the CPSC “Toxicity Review of Di(isononyl) Phthalate”

This appendix provides comments by ExxonMobil Chemical Company on the toxicity review of DINP produced by CPSC staff and posted to the CPSC website (conforming changes also should be made to the CPSC staff Overview of Phthalates Toxicity).¹ Unless otherwise noted, page citations are to that document. If a document cited in our comments is among the references to the toxicity review, we do not repeat that citation here. Additional references are given at the end of the section in which they are cited.

Overall Remarks

The toxicology review is comprehensive with respect to the DINP database. However, it also includes tangential information on other phthalates and even other un-related chemicals. This is inappropriate since the purpose of the document is to address “potential toxicity associated with diisononyl phthalate (DINP)”. The extraneous information adds an additional layer of complexity that can be misinterpreted, leading to inaccurate conclusions on DINP.

Chemistry and Use

Chemistry

The second sentence of the second paragraph of the Chemistry subsection (p. 4) states: “DINP-1 is also known by the trade name Jayflex®.” The Jayflex line includes a variety of plasticizer products and, while a trademark, the name is not registered. The sentence should read: “DINP-1 is also known by the trade name Jayflex™ DINP.”

Acute Toxicity, Skin and Eye Irritation

Sensitization

The second paragraph of the Sensitization subsection (p. 8) states that there was no evidence of dermal irritation in the human repeated insult patch test (HRIPT) for DINP. It should be noted that there also was no evidence of sensitization.

Toxicokinetics

Oral Toxicokinetics

The subsection on human oxidative metabolites states: “In earlier biomonitoring studies, MINP was non-detectable in most individuals, which led to the conclusion that human exposure to DINP was low. However, studies based on MINP may underestimate human exposure. OH_MINP and CO₂-MINP are more sensitive and should lead to more accurate estimates of

¹ CPSC Health Sciences (2010). Toxicity Review of Diisononyl) Phthalate (DINP). Memo from M. Babich and C. Osterhout to M. Danello, April 11, <http://www.cpsc.gov/about/cpsia/toxicityDINP.pdf>; CPSC Health Sciences (2010). Toxicity Review of Diisononyl) Phthalate (DINP). Memo from M. Babich to M. Danello, April 12, <http://www.cpsc.gov/about/cpsia/phthalover.pdf>.

exposure” (pp. 11-12, citations omitted). The logic in these statements is faulty. The fact that oxidative metabolites are more sensitive does not necessarily mean that the MINP studies have underestimated exposure. Because of the addition of oxygen atoms to the metabolic forms, the oxidative metabolites from a given aliquot of DINP will give a higher concentration of oxidative metabolites, in micrograms per liter of urine, than of MINP. If the detection level in ug/L is the same for both types of metabolites, then the oxidative metabolites are more likely to be detected, but it does not follow that the DINP exposures are higher than those indicated by MINP. In fact, conversion of oxidative metabolite concentrations to the associated DINP exposures gives exposure levels very similar to those indicated by MINP concentrations. While the oxidative metabolites have enabled quantification of DINP exposure in a larger percentage of the population, those quantified values are very similar to those obtained using MINP, and they still show that that exposure is very low. *See* Attachment 10 (Human Exposure to Diisononyl Phthalate (DINP)), Tables 1-3, which provides exposures estimated from both MINP and oxidation metabolite data.

Percutaneous Absorption

Given the data available for DINP, the inclusion of discussion of “Other Phthalates” is not necessary and therefore not appropriate. The Elsis et al. (1989) study demonstrated that dermal absorption decreases with increasing alkyl chain length and that absorption of DIDP is ten-fold less than that of DEHP. DINP was not studied by Elsis et al., but the indication is that dermal absorption of DINP would be between that of DEHP and DIDP. This is born out by the results of the Stoltz and El-hawari studies of DINP discussed in this subsection.

Systemic Health Effects

Overall comment on primate data

The toxicity review includes a mention of the primate studies on DINP in the subsection on liver effects. However, these studies deserve more comprehensive discussion with respect to systemic effects in general. The 14-day oral study in monkeys (Pugh et al., 2000) and 13-week oral study in marmosets (Hall et al., 1999) show that orally administered DINP has no serious adverse systemic effects in primates at concentrations up to 2500 mg/kg/day. In particular, there were no changes in the liver or kidney weights and no treatment-related changes in histopathology. Systemic effects unquestionably would have occurred in rodents at such doses.

Although the primate studies used a small number of animals and were no longer than 13 weeks, they nevertheless provide valuable information about the likelihood that effects observed in rodents would occur in humans exposed to DINP. First, primates are much more closely related to humans than are rats (e.g., Lindblad-Toh, 2004). Thus, the lack of effects in primates is highly probative evidence that humans are refractory to systemic effects from DINP. Second, a 13-week, or even 2-week, study is sufficient to observe systemic effects in rodents. For example, liver and kidney weights were increased in a 28-day study of rats (BIBRA, 1985). Liver weight increases were seen as early as 1 week after the beginning of treatment in the rat chronic bioassay (Moore, 1998a). Thus, the primate studies were of sufficient length to assess the potential for DINP treatment to influence liver and kidney weights. That such effects were not seen in the primates at doses and durations that would cause such effects in rodents strongly indicates that humans likely would not be affected by DINP in the manner of rodents.

Because the primate data are highly relevant in assessing the potential toxicity of DINP to humans, those data should be more completely and prominently discussed in the toxicity review.

K. Lindblad-Toh (2004). Genome sequencing: Three's company. *Nature* 428, 475-476, Figure 2 (Mammalian evolution and genome sequencing), http://www.nature.com/nature/journal/v428/n6982/fig_tab/428475a_F2.html.

Spongiosis Hepatis

While a good discussion of spongiosis hepatitis is presented, two key pieces of information are overlooked. First, Karbe and Kerlin (2002), and Anthony (2001) provide evidence that spongiosis hepatitis is a spontaneous degenerative change seen in aging rats without a counterpart in human hepatic pathology. Careful review of rodents over the last twenty or more years by the National Toxicology Program has led to only a rare incidence of neoplasms arising from stellate cells in mice (13 cases from more than 90,000 mice), but these lesions differ morphologically from spongiosis hepatitis. There was no evidence of a lesion resembling spongiosis hepatitis in a review of 163 human livers (Su et al., 1997). Indeed, in the chapter on liver neoplasia from a definitive text on human liver disease, *Pathology of the Liver*, edited by MacSween et al., the authors state: "To the best of our knowledge no human counterpart of the spongiotic pericytoma [spongiosis hepatitis] has ever been described" (Anthony, 2001). Reports of lesions with similar characteristics in humans or non-human primates also are not found in the literature. This lesion or lesions with similar appearances are not described in any of a number of standard texts on neoplasia or systemic pathology in domestic animals, and there are no reports of this lesion in dogs. The only other species in which this lesion has been reported is the teleost fish (Couch, 1991). Given the large number of laboratory dogs and primates that have been exposed to a broad variety of chemicals over a considerable number of years, the absence of descriptions of this lesion would support the view that spongiosis hepatitis is primarily confined to male rats and teleost fish.

Attachments A-1 and A-2 are evaluations by two separate experts in liver pathology, Dr. John Cullen and Dr. Dawn Goodman. Drs. Cullen and Goodman provided these evaluations to the ACC Phthalate Esters Panel with respect to a toxicity review of DINP conducted by the US Environmental Protection Agency.² After reviewing the relevant information, both Drs. Cullen and Goodman conclude that spongiosis hepatitis is not a serious liver effect, even in rats. Dr. Cullen's opinion also addresses liver enlargement and liver enzyme induction in rats treated with DINP.

As discussed on page 21 of the CPSC toxicity review, the studies by Lington et al.(1997) and Moore (1998a), contain methodological difference such that the Lington et al.(1997) had an inherently higher probability of finding spongiosis hepatitis in a pathological assessment; thus making the comparison of the studies difficult. As per Babich and Green (2000), the studies can

² The Cullen and Goodman opinions were included in comments on the EPA's toxicological review of DINP, submitted to EPA in 2005 by the Phthalate Esters Panel, in response to EPA's notice of opportunity for comment (70 Fed. Reg. 34437 (June 14, 2005)). To date, EPA has not issued a revised toxicological review nor responded to the comments received in response to its notice.

be modeled in a manner that normalizes the methodological differences. As demonstrated in Table 5-5 of the toxicity review (p. 25), when the Lington and Moore studies are scaled to a commonality of 4 slides per liver, it is clear that the NOAEL is at least 88 mg/kg/day, such that use of 15 mg/kg/day as a NOAEL is very conservative.

J Couch (1991). Spongiosis Hepatis: Chemical Induction, Pathogenesis, and Possible Neoplastic Fate in a Teleost Fish Model. *Toxicol Pathol* 19(3):237-250.

P Anthony (2001). Tumours and tumour-like lesions of the liver and biliary tract. In: R MacSween, A Burt, B Portman, K Ishak, P Scheuer, P Anthony (editors). *Pathology of the Liver*. 4th edition, Churchill Livingstone, London.

Q Su, A Benner, W Hofmann, G Otto, R Pichlmayr, P Bannasch (1997). Human hepatic preneoplasia: phenotypes and proliferation kinetics of foci and nodules of altered hepatocytes and their relationship to liver cell dysplasia. *Virchows Arch* 431:391-406

Primates

As noted above, the limitations of the primate studies do not negate the valuable information the primate studies provide. The toxicity review notes that “histopathological effects were reported to occur in rats treated for 13-weeks at doses of at least 584 mg/kg/day (Myers, 1991)” but does not discuss the implication of that statement. The lack of liver effects in the primates even at 2500 mg/kg/day for that same length of time indicates that humans are unlikely to experience liver effects even at DINP exposures far in excess of likely exposures.

Endocrine Effects – Animals

The statement on page 30 that “reduced testicular weights, in the absence of histopathological effects, were reported in B6C3F1 mice (Bankston, 1992) and in Fischer 344 rats (Myers, 1991) given \geq 1.0 percent DINP in feed for 13 weeks” is incorrect. In the aforementioned rat study, there was no decrease in testis weight. Further, an *increase* in absolute testis weight in the absence of histopathological findings has been more commonly reported for rats (Lington et al., 1997).

As discussed in Attachment 3 (ECPI Toy Reassessment), the Lee and Koo (2007) study data overall indicate that DINP does not meet the OECD criteria for an androgen antagonist.

Summary

The second paragraph (p. 35) concludes that the NOAEL for systemic effects is 15 mg/kg/day, based the Lington study. However, as discussed above, the combination of the Lington and Moore studies clearly shows that 88 mg/kg/day is a NOAEL.

Reproductive and Developmental Effects

Developmental Effects

On pages 40-43, there is a lengthy discussion on *ortho*-dialkyl phthalates. This information is better suited to the introduction document on phthalates and should be removed since it does not provide information specific to DINP, the purpose of this document.

Gray et al. (2000) and Ostby et al. (2000, 2001)

Gray et al. (2000) conducted a study on the effects of fetal exposure during the late gestational period to DINP and several other phthalates. Timed-pregnant rats were gavaged daily with a single dose of 750 mg/kg/d in corn oil as vehicle from gestational day 14 through postnatal day 3. Data for DINP indicated that at 13 days of age, male pups with retained areolas were observed at an incidence of 22% compared with controls. However, in this study the control incidence for areola retention was reported to be zero, whereas in a subsequent study, control values are reported as 14% (Ostby et al., 2001).

Some of the adult males exposed perinatally to DINP (4/52 pups) had malformations of testis, epididymis, accessory reproductive organs and external genitalia. The low incidence of reported effects was without any dose response and with effects of unclear significance using a small number of rats.). No single endpoint (nipple retention, epididymal agenesis, fluid filled testes, and testes weight) on its own was significantly different from control values. Only by pooling of these different effects, giving a 7.7% incidence, was statistical significance demonstrated. This type of data manipulation is not routinely performed in toxicological safety evaluations, nor is it considered good statistical practice. It should also be noted that Gray et al. (2000) did not see any effects on anogenital distance or on reduction of testosterone levels in the blood with DINP treated animals. Based on the above points, the significance of the reported findings is questionable.

Hass et al. (2003)

This should not be included in the review of DINP since it is only an abstract given at a scientific meeting. The data were never published or made available for review. Furthermore, the abstract states that when birth weight was included as a covariate, AGD was significantly decreased only at the extremely high dose of 900 mg/kg/day.

Borch et al. (2003, 2004)

In a study designed to test effects on testosterone synthesis, 32 pregnant female rats were exposed to either 300 mg/kg-bw DEHP or 750 mg/kg-bw DINP, alone or in combination, from gestation day 7 to gestation day 21 (Borch et al., 2004). The dams were sacrificed on gestation day 21 and the pups were harvested for analysis of testicular testosterone production, testicular testosterone content, plasma testosterone levels, and plasma luteinizing hormone (LH) levels. The results indicated that testicular testosterone production and testicular testosterone content were significantly decreased in the DINP-exposed pups while plasma testosterone and plasma LH levels were unaltered. However, no mechanism of toxicity can be determined from this paper since it is limited by several confounding factors. First, there were no adverse phenotypic effects reported in the study. Second, the authors sampled testosterone levels on gestation day 21, a time point after the developmental surge of testosterone that occurs during gestation day 16-18 in the rat. After gestation day 18, plasma testosterone levels are naturally declining in the fetal rat. Therefore it is unclear if the decrease in testosterone content is in fact a toxicologically significant response. Compare the results of Adamsson et al. (2009) (no significant increase in testosterone levels with dosage on days 13.5 through 17.5).

Swan et al. (2005)

It is inappropriate to include this study since it does not deal with DINP. Furthermore, this report has been heavily criticized by scientists and statisticians (e.g. McEwen and Renner, 2006). In evaluating Swan et al. (2005) in a recent review of DEHP, an expert panel of the NTP CERHR considered the AGI measurement developed by Dr. Swan to be a “novel index” whose relevance in humans “has not been established” (CERHR, 2005). To date, Dr. Swan’s results have not been repeated by other researchers and Dr. Swan has declined requests by other scientists to review her data.

From a toxicological perspective, there is a difficulty in that the strongest association was with diethyl phthalate – a substance which when tested in rats had no effects on the development of the male reproductive system. From a clinical perspective, the attempt to convert AGD into a kind of index for adverse human health effects is not recognized in human biology. Further there are questions regarding the legitimacy of the AGD measurements in this study, particularly whether there was adequate compensation for the wide variations in age and weight of the measured infants (assuming that the infants could be accurately measured in the first place). As McEwen and Renner (2006) note: “Because little is known about AGD in human infants and its variation, no conclusion can be drawn whether the reported values are normal or abnormal. The range of AGD values seen among study subjects likely represents typical biologic variation that would be expected to occur among normal study subjects.”

Recently, in an updated study, Swan used a revised mathematical analysis for measuring changes in AGD and applied this new methodology to a further population of infant boys. Interestingly, the new data set resulted in contradictory results to some of the previous findings, adding further doubt to the validity of the studies (Swan, 2008).

CERHR (2005). NTP CERHR Expert Panel Update on the Reproductive and Developmental Toxicity of Di(2-ethylhexyl) Phthalate, NTP-CERHR-DEHP-05, November 2005, p. 97,
<http://cerhr.niehs.nih.gov/evaluations/chemicals/phthalates/dehp/dehp.html>.

G McEwen, G Renner (2006). Validity of Anogenital Distance as a Marker of in Utero Phthalate Exposure. *Environ Health Perspect* 114:A19-A20.

S Swan (2008). Environmental phthalate exposure in relation to reproductive outcomes and other health endpoints in humans. *Environ Res* 108(2):177-84.

Zhang et al.(2009)

It is inappropriate to include this study since it does not deal with DINP and there is no basis on which to extrapolate the findings to DINP.

Main et al.(2006)

This study evaluated exposure to DINP in an attempt to associate phthalate monoester levels with reproductive hormone levels and cryptorchidism in male infants, although no such association was observed. Pooled milk samples were obtained from each of 130 women when their children were 1-3 months old. Milk was analyzed using HPLC-MS for the monoesters of

di-(2-ethylhexyl) phthalate, di-methyl phthalate, di-n-butyl phthalate, butylbenzyl phthalate and DINP. There were no significant differences in milk phthalate concentrations between the 62 mothers of sons with cryptorchidism and the 68 controls. The children had venous blood sampled at 3 months of age for determination of sex hormone-binding globulin, total and free testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), and inhibin B. Individual hormone levels were used to calculate LH/testosterone, LH/free testosterone, and FSH/inhibin B ratios. MINP was found in all milk samples.

Of the parameters tested, MINP was significantly associated with increased serum LH levels. The authors implied that testosterone levels were likely decreased relieving the negative feedback to the pituitary and thereby increasing LH levels. However, no alteration in free or total testosterone was observed (in fact an increase in free testosterone was observed). Further, this association could simply have been a statistical consequence of multiple comparisons to a common control. Overall, the authors concluded that there were “subtle, but significant, dose-dependent associations between neonatal exposure to phthalate monoesters in breast milk and levels of reproductive hormones in boys at three months of age.”

In 2005, the NTP CERHR evaluated this study and indicated a number of weaknesses including confounding and possible contamination of breast milk samples (CERHR, 2005). According to Calafat et al. (2004b), a special treatment of the milk is required upon sample collection to denature milk enzymes and avoid overestimating the concentrations of phthalate metabolites in milk caused by contamination from the ubiquitous phthalate contaminants that may have been incorporated in the milk during the collection, storage, and measurement process. These considerations limited the usefulness of this study in the NTP CERHR evaluation process.

CERHR (2005). NTP CERHR Expert Panel Update on the Reproductive and Developmental Toxicity of Di(2-ethylhexyl) Phthalate, NTP-CERHR-DEHP-05, November 2005, pp. 7, 55,
<http://cerhr.niehs.nih.gov/evaluations/chemicals/phthalates/dehp/dehp.html>.

Toxic Effects of DINP

Liver

The toxicity review states, “DINP is considered to be ‘probably toxic in humans’” on the basis of liver effects observed in the rodent studies (p. 118). However, the weight of the evidence indicates that the liver effects in rodents are not relevant to humans. As discussed above and in the opinions of Drs. Cullen and Goodman (Attachments A-1 and A-2), spongiosis hepatitis is not a serious liver effect, even in rats, and has been reported only in rats and fish, never in other mammals, including humans. As noted in the toxicity review (p. 118), hepatomegaly and increased cell number and size are likely due to peroxisome proliferation. As discussed on pages 61-81 of the toxicity review, peroxisome proliferation is not readily induced in humans, if at all, and therefore it is unlikely that the liver and kidney effects observed in animal tests are relevant to humans. Liver enlargement and increase in peroxisomal enzyme levels are classic signs of peroxisome proliferation (Klaunig et al., 2003; Cattley et al., 1998). In primates, no statistically significant liver effects were observed even at doses of 2500 mg/kg/day for 13 weeks – a dose

that unquestionably would have caused liver effects in rodents. Therefore, the liver weight changes observed in rodents studies of DINP are likely not relevant to humans.

Kidney

The toxicity review (p. 119) concludes that DINP is “probably toxic” in humans with respect to chronic kidney toxicity. However, no adverse effects have been seen in the highly relevant primate studies at doses up to 2500 mg/kg/day (Hall et al. 1999; Pugh et al., 2000). The effects observed in rats and mice can be attributed to species-specific effects in rodents – peroxisome proliferation and alpha-2u-globulin, and therefore are not likely relevant to humans. Attachment A-3 is a statement by Dr. Gordon C. Hard, an internationally recognized expert in kidney carcinogenesis, renal toxicology, and toxicologic renal pathology.³ Dr. Hard concludes: “In my expert judgment, the kidney-related findings discussed above are not a consequence of toxicity of DINP to the kidney, except for the association between alpha-2u-globulin and pigmentation and linear papillary mineralization. Therefore, in my view there is not sufficient evidence to establish that DINP can reasonably be anticipated to cause serious or irreversible renal effects in humans.”

DINP is an inducer of peroxisome proliferation. Increased kidney weights are a consequence of peroxisomal proliferation and, like increased liver weights, a common observation in studies of peroxisomal proliferation. Woodward (1990) summarized the observations of a number of investigators relating to renal changes induced in rodents by peroxisomal proliferating agents including phthalates. The objective of his summary was to investigate whether cystic lesions in dialysis patients could be the consequence of exposure to DEHP. Woodward found no evidence to support such a link, concluding that “the limited data available seem to suggest that humans are not susceptible to the cystogenic effects of phthalate. . . .”

Huber et al. (1996) extended this analysis, concluding that “DEHP and several other [peroxisomal proliferators] led to clear peroxisomal proliferation in rat and mouse kidneys.” The authors noted that the expression of peroxisomal proliferation, including increased weight and increased levels of peroxisomal proliferation-enzymes, in rodent kidneys was less than that observed in rodent livers. The basis for this was demonstrated by Ward et al. (1998). Using mice deficient in the peroxisomal proliferator-activated receptor α (PPAR α knock out mice), they showed that PPAR α “mediates the subacute-chronic toxicity of DEHP in liver, kidney and testis.” Thus, the kidney weight effects of DINP in rat kidneys can be explained through a PPAR α mechanism.

Ward et al. (1998) noted that there were also PPAR α -independent mechanisms of kidney toxicity. Dr. Hard discusses in his statement (Attachment A-3) two such mechanisms that could explain the increased relative kidney weights. One is that infiltration of MNCL cells into the kidney would increase the kidney weight. As discussed on p. 82 of the toxicity review, MNCL is a lesion that occurs spontaneously and almost exclusively in the F344 rat (the species used in both Lington et al. and Moore et al.), and which is not relevant to humans.

³ As for the statements of Drs. Cullen and Goodman, Dr. Hard’s statement was made for the ACC Phthalate Esters Panel in conjunction with comments on the 2005 EPA toxicological review of DINP. See note 2, page A-3.

For the male rat, alpha-2u-globulin nephropathy also likely contributed to the increase in relative kidney weights. As discussed on pages 82-83 of the toxicity review, the male rat kidneys showed evidence of alpha-2u-globulin nephropathy, a mechanism not relevant to humans. As well as Dr. Hard, Phillips and Cockerell (1984) and Phillips and Egan (1984) also found that increased kidney weights in male rats are associated with induction of alpha-2u-globulin.

W Huber, B Grasl-Kraupp, R Schulte-Hermann (1996). Hepatocarcinogenic potential of di(2-ethylhexyl)phthalate in rodents and its implications on human risk. *Crit Rev Toxicol* 26:365-481.

R Phillips, B Cockerell (1984). Effect of certain light hydrocarbons on kidney function and structure in male rats. *Adv Modern Environ Toxicol* 7. M. Mehlman, C. Hemstreet, J. Thorpe, N. Weaver, eds. Princeton Scientific Publishers, Inc. pp. 89-105.

R Phillips, G Egan (1984). Effect of C10-C11 isoparaffinic solvent on kidney function in Fischer 344 rats during eight weeks of inhalation. *Toxicol Appl Pharmacol* 73:500-510.

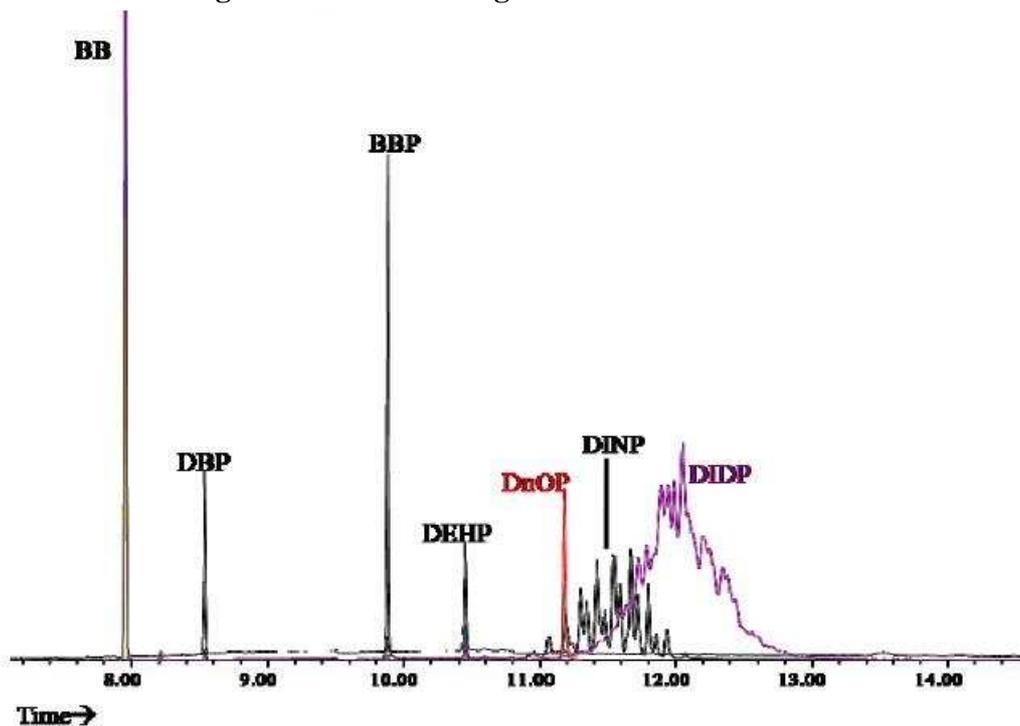
Appendix B Review of the CPSC “Toxicity Review of Di(isodecyl) Phthalate”

This appendix provides comments by ExxonMobil Chemical Company on the toxicity review of DIDP produced by CPSC staff and posted to the CPSC website (conforming changes also should be made to the CPSC staff Overview of Phthalates Toxicity).¹ Unless otherwise noted, page citations are to that document. If a document cited in our comments is among the references to the toxicity review, we do not repeat that citation here. Other references are given at the end of the section in which they are cited.

Overall Comment on DIDP Composition

As noted under Physiochemical Properties, commercial DIDP is a mixture of branched C9-11 isomers, but consists primarily of C10 isomers. Likewise, commercial DINP is a mixture of C8-10 isomers, consisting primarily of C9 isomers. Thus, analysis of an item made with commercial DINP will show peaks on the readout corresponding to C10. See Figure A-3, which is taken from the CPSC protocol for testing of phthalates,² and which shows the isomer distributions for DINP and DIDP and their overlap, as they appear on a chromatogram. Verification that commercial DIDP was used requires detection of C11. *Note that it is the commercial products on which toxicity testing has been conducted.*

Figure A-3. Chromatogram of Various Phthalates



¹ CPSC Health Sciences (2010). Toxicity Review of Di(isodecyl) Phthalate. Memo from C. Osterhout to M. Babich, April 7, <http://www.cpsc.gov/about/cpsia/toxicityDIDP.pdf>

² Test Method: CPSC-CH-C1001-09.3 – Standard Operating Procedure for Determination of Phthalates, April, 1, 2010, <http://www.cpsc.gov/about/cpsia/CPSC-CH-C1001-09.3.pdf>.

Toxicokinetics

The first paragraph of this section of the toxicity review (p. 3) correctly indicates that DIDP is absorbed at a very low level through the skin. However, the citations are to studies of other phthalates. DIDP dermal absorption was studied by Elsisi et al. (1989). In 7 days, only 2% of dermally applied ¹⁴C-DIDP was recovered in other tissues or excretia. In that study, dermal absorption of phthalates decreased with increasing side chain length beyond four carbons (Elsisi et al., 1989).

A Elsisi, D Carter, I Sipes. (1989). Dermal absorption of phthalate diesters in rats. *Fund Appl Toxicol* 12:70-77.

The last paragraph of the section (p. 4) hypothesizes that DIDP was present in the DINP formulation used in Silva et al. (2006). As noted above in the Overall Comment, page B-1 above, this could be due to C10 in the DINP formulation.

Exposure

The statement straddling pages 4 and 5 states that the “manufacturer’s exposure limit for DIDP is five mg/m³ based on a value recommended by the American Conference of Governmental Industrial Hygienists (ACGIH).” Note that ACGIH established that value for DEHP; it is conservatively used also for DIDP.

In the Silva et al. (2007) paper discussed in the Exposure section (p. 5), detection of C10 metabolites may have been to C10 isomers that were part of the DINP used in the study. See Overall Comment, page B-1 above.

Systemic Effects

Page 8 of the CPSC toxicity review includes a synopsis of a 13-week diet study in Beagle dogs (Hazelton, 1968b); this study later is used as the key study for derivation of an acceptable daily intake (ADI). 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 manifesting these effects. More significantly, this study was not conducted to a standardized protocol and was not conducted according to GLP, and the results were not subjected to statistical analysis due to the small study size. Due to these limitations, this study is inappropriate for risk characterization, such as development of an ADI.

A more appropriate study for risk characterization of systemic effects is the rat study conducted by Hazelton Laboratories (1968), discussed on page 8 of the toxicity review. It involved four groups of 10 male and 10 female rats exposed to DIDP at dietary levels of 0.05%, 0.3% and 1% (approximately 25, 150 and 500 mg/kg/d, respectively) for 13 weeks. No compound-related effects were observed at any dietary level with regard to physical appearance, behavior or survival. Growth of the test rats was not significantly affected. Body weight gains for the two highest levels in males were lower than controls (but not significantly different) and the two test groups were comparable through the ninth week. Overall, weight gains at 13 weeks for the male test groups showed a dose-related, although slight, decrease. Body weight gains for the high dose females were only slightly lower than the controls – not a statistically significant difference. Food consumption values were comparable to the

controls. The clinical laboratory values for the test groups showed no significant compound-related differences from control values.

Observations at necropsy revealed the livers of the high dose group animals, particularly the males, to be markedly larger than those of the control rats. Statistical analysis showed the liver weights and liver/body weight ratios for the high dose group males and females to be significantly higher than those for the corresponding controls. No other consistent gross changes were noted in the liver. Histologically, the liver showed no compound-induced alterations. The kidney/body weight ratios but not the absolute weights in the high and intermediate dose group males were significantly higher than those for the corresponding controls. Histologically, the kidneys showed no compound-induced alterations.

A minimal increase in thyroid activity, possibly a compensatory response related to an increased rate of thyroid hormone metabolism due to the overall increased metabolic capacity in the liver, was observed at the highest dose. It can be concluded from this study that the NOAEL is 0.3% (approximately 150 mg/kg/day)³ based on the observation that the highest dose leads to minor liver and thyroid effects.

The Systemic Effects section concludes that DIDP is a probable toxicant based on increased liver weight, increased peroxisomal enzyme levels and histological changes, and increased kidney weight. It is likely that all these effects are the result of peroxisome proliferation, induced via the PPAR α mechanism. As discussed in the toxicity review for DINP (pp. 61-81), peroxisome proliferation is not readily induced in humans, if at all, and therefore it is unlikely that the liver and kidney effects observed in animal tests are relevant to humans.

As discussed in the Genotoxicity/Carcinogenicity section of the DIDP toxicity review, DIDP is a limited peroxisome proliferator. This can account for the liver effects observed in rodent studies of DIDP. Liver enlargement and increase in peroxisomal enzyme levels are classic signs of peroxisome proliferation (Klaunig et al., 2003; Cattley et al., 1998). Therefore, the liver weight changes observed in rodents studies of DIDP are likely not relevant to humans. The hepatocyte swelling and vacuolation were observed only in the dog study; as discussed above, there was not a dose-response for these effects and there were other limitations that indicate that study should not be used for risk assessment.

Similarly, increased kidney weights are a consequence of peroxisomal proliferation and, like increased liver weights, a common observation in studies of peroxisomal proliferation. Woodward (1990) summarized the observations of a number of investigators relating to renal changes induced in rodents by peroxisomal proliferating agents including phthalates. The objective of his summary was to investigate whether cystic lesions in dialysis patients could be the consequence of exposure to DEHP. Woodward found no evidence to support such a link, concluding that “the limited data available seem to suggest that humans are not susceptible to the cystogenic effects of phthalate. . . .”

Huber et al. (1996) extended this analysis, concluding that “DEHP and several other [peroxisomal proliferators] led to clear peroxisomal proliferation in rat and mouse kidneys.” The authors noted that the expression of peroxisomal proliferation, including increased weight and increased levels of peroxisomal proliferation-enzymes, in rodent kidneys was less than that observed in rodent livers. The basis for this was demonstrated by Ward et al. (1998). Using mice deficient in the peroxisomal

³ Table 4 of the CPSC toxicity review gives the dose value as 170 mg/kg/day.

proliferator-activated receptor α (PPAR α knock out mice), they showed that PPAR α “mediates the subacute-chronic toxicity of DEHP in liver, kidney and testis.” Thus, the kidney weight effects of DIDP in rat kidneys can be explained through a PPAR α mechanism, indicating that they are not relevant to humans.

Cattley, R.C., DeLuca, J., Elcombe, C. et al. (1998). Do peroxisome proliferating compounds pose a hepatocarcinogenic hazard to humans? *Regul Toxicol Pharmacol* 26:47-60.

Huber, W.W., Grasl-Kraupp, B., and Schulte-Hermann, R. (1996). Hepatocarcinogenic potential of di(2-ethylhexyl)phthalate in rodents and its implications on human risk. *Critical Reviews in Toxicology* 26:365-481.

Klaunig, J., Babich, M., Baetcke, K., Cook, J., Corton, J., David, R., DeLuca, J., Lai, D., McKee, R., Peters, J., Roberts, R., and Fenner-Crisp, P. (2003). PPAR α agonist-induced rodent tumors: Modes of action and human relevance. *Critical Reviews in Toxicology*, 33(6):655–780.

Ward, J.M., Peters, J.M., Perella, C.M., and Gonzalez, F.J. (1998). Receptor and non-receptor-mediated organ-specific toxicity of di(2-ethylhexyl)phthalate (DEHP) in peroxisome proliferators-activated receptor α -null mice. *Toxicologic Pathology* 26:240-246.

Woodward, K. (1990). Phthalate esters, cystic kidney disease in animals and possible effects on human health: A review. *Human and Experimental Toxicology* 9:397-401.

Developmental Effects

This section concludes that DIDP is a probable toxicant based on developmental effects, including increased incidences of minor skeletal variations (pp. 17-18). The skeletal variations were supernumerary cervical and rudimentary lumbar ribs, for which the increase was statistically significant only on a per litter basis at the high dose. These skeletal variations are developmental variants commonly found in developmental toxicity studies that are usually reversed later in life and are generally regarded as not having toxicological significance. Rudimentary ribs in particular are a common finding in rat fetuses and may be related only to transient maternal stress. In addition, the statistical methods used in developmental studies typically do not account for the fact that multiple comparisons are made, leading to the possibility that these apparently statistically significant differences are in fact due to chance.

Table 5 of the CPSC staff Overview of Phthalates Toxicity indicates that male sexual development for DIDP has not been determined. DIDP has been examined for adverse effects in male sexual development. In a guideline, 2-generation reproduction and developmental toxicity study, there were no effects on anogenital distance, nipple retention, changes in male reproductive organ weights, or fertility (Hushka et al., 2001). Therefore, “no effects” should be noted in the table for DIDP

Genotoxicity/Carcinogenicity

We agree with the conclusion that DIDP is not carcinogenic. However, corrected data have been published, resulting in different NOAELs. In the two-year toxicity/carcinogenicity study by Cho et al. (2008), Fischer 344 rats were exposed to 0, 400, 2000, and 8000 ppm DIDP. As published in 2008,

the daily mg/kg intakes were 0.85, 4.13, 17.37 for males and 0.53, 3.03, and 13.36 for female. However, these values were deemed to be calculated incorrectly in the original submission. An updated table has been published (Cho et al., 2010a); the corrected values are shown in Table A-1.

Table A-1. Corrected Exposures for Cho et al. (2008)

Daily average food intake (g)	DIDP %	mean daily DIDP intake (mg)	mean bw (g)	mean daily DIDP intake (mg/kg/day)
21.07 - male	0	0.00	382.31	0
21.33 - male	0.04	8.54	390.46	21.9
21.53 - male	0.2	43.06	390.58	110.3
21.70 - male	0.8	173.66	362.39	479.2
14.37 - female	0	0.00	229.25	0
13.36 - female	0.04	5.34	233.19	22.9
15.15 - female	0.2	30.30	236.40	128.2
16.69 - female	0.8	133.59	215.60	619.6

Based on these corrected values, the NOAEL is 479 mg/kg/day for males and 619 mg/kg/day for females since no treatment related neoplastic lesions were observed in internal organs.

Since the writing of the CPSC staff toxicity review, Cho et al. have published a 6-month carcinogenicity study in CB6F1-rasH2 transgenic mice in which increased tumor formation was observed in the high dose males (Cho et al. (2010b). However, the utility of the rasH2-hemizygous transgenic mouse for assessing carcinogenic potential of non-genotoxic compounds (e.g., DIDP) is limited. In addition, transgenic mouse models are screens used when a 2-year bioassay is not available. In this case, the bioassay has been published and serves as the definitive test of the carcinogenic potential of DIDP; it found that DIDP is not carcinogenic (Cho et al., 2008).

W-S Cho, B Seok Hana, B Ahnb, K Taek Nama, M Choia, S Yeon Oha, S Hee Kima, J Jeonga, D Deuk Janga (2010). Corrigendum to “Peroxisome proliferator di-isodecyl phthalate has no carcinogenic potential in Fischer 344 rats” [Toxicol. Lett. 178 (2008) 110–116]. Toxicology Letters 197(2):156.

W-S Cho, J Jeong, M Choi, S Nie Park, B Seok Han, W-C Son (2010b). 26-Week carcinogenicity study of di-isodecyl phthalate by dietary administration to CB6F1-rasH2 transgenic mice. Archives of Toxicology, DOI 10.1007/s00204-010-0536-6.

Discussion

In the discussion of the hazard of DIDP, a series of Acceptable Daily Intakes (ADIs) were calculated.

For subchronic effects, “An ADI based on liver effects calculated from the lowest NOAEL (15 mg/kg/day) divided by a safety factor of 100 [10 (animal to human) x 10 (sensitive populations)] is 0.15 mg/kg DIDP”. In this instance, the NOAEL is from a 13-week diet study in Beagle dogs. As discussed previously, this study is limited and not suitable for risk characterization. The most appropriate NOAEL for subchronic risk characterization is 150 mg/kg/day. Applying the same uncertainty factors of 10 and 10, an ADI of 1.5 mg/kg/day is derived.

The ADI based on the two-year chronic toxicity/carcinogenicity study is currently based on incorrect daily intake data and must be updated to reflect the NOAEL of 479 mg/kg/day. See the comments on the Genotoxicity/Carcinogenicity section, above. With this point of departure divided by uncertainty factors of 10 and 10, an ADI of 4.79 mg/kg/day is derived.

The reproductive/developmental toxicity ADI is calculated incorrectly. The key study selected was a one-generation screening study in which rats were exposed to 40, 200, or 1000 mg/kg DIDP. The NOAEL of 40 mg/kg/day was identified on the basis of fetal variations at 200 mg/kg; although the biological significance of fetal variations such as cervical supernumerary ribs remains uncertain. A second one-generation study is also available in which rats were exposed to 0, 100, 500, or 1000 mg/kg/day DIDP in which fetal variations were also noted. The NOAEL of this study was 100 mg/kg/day. When both studies are considered together, it is clear that the true NOAEL is somewhere between 100 mg/kg/day and 200 mg/kg/day, which is consistent with the benchmark doses identified by the update to the Waterman et al., (1999) study report. Thus, for risk characterization purposes, a NOAEL of 100 mg/kg/day is more appropriate than 40 mg/kg/day; adjusted with the total uncertainty factor of 100, an ADI of 1 mg/kg/day is derived.

Based on these data and their correct interpretation, the lowest ADI calculated is 1 mg/kg/day. In conjunction with exposure data, a substantial margin of safety exists between current exposures and the lowest ADI calculated, indicating the continued safe use of DIDP.

List of Attachments

- Attachment 1** **DINP Dossier Extract**
1a Mammalian and Environment Toxicity Summaries and Table of Contents for Data Summaries available on the ECHA Website and on a DVD Submitted to CPSC
(ATT 1a REACH DINP Tox Studies.pdf)
<http://apps.echa.europa.eu/registered/registered-sub.aspx>
1b Contents of the ECHA Registration Website for DINP
(16 pdfs in Folder “Att 1B DINP REACH Data” on DVD)
- Attachment 2** **DIDP Dossier Extract**
1a Mammalian and Environment Toxicity Summaries and Table of Contents for Data Summaries available on the ECHA Website and on a DVD Submitted to CPSC
(ATT 2a REACH DIDP Tox Studies.pdf)
<http://apps.echa.europa.eu/registered/registered-sub.aspx>
1b Contents of the ECHA Registration Website for DIDP
(13 pdfs in Folder “Att 2b DIDP REACH Data” on DVD)
- Attachment 3** **ECPI Toy Reassessment**
(Att 3 ECPI Toy Reassessment.pdf)
<http://www.cpsc.gov/about/cpsia/docs/DINPToysExxon062009.pdf>
- Attachment 4** **EU Risk Assessment Report for DINP**
(Att 4 EU RA DINP.pdf – provided on DVD only)
http://ecb.jrc.ec.europa.eu/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/dinpreport046.pdf
- Attachment 5** **EU Risk Assessment Report for DIDP**
(Att 5 EU RA DIDP.pdf – provided on DVD only)
http://ecb.jrc.ec.europa.eu/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/didpreport041.pdf
- Attachment 6** **DINP & DIDP Presentation (A. Bachman)**
(Att 6 DINP DIDP Presentation Bachman.pdf)
- Attachment 7** **ExxonMobil Presentation to CPSC: Plasticizers and the CPSIA**
(Att 7 ExxonMobil Plasticizers Presentation.pdf)
<http://www.cpsc.gov/about/cpsia/docs/plasticizersExxon07162009.pdf>
- Attachment 8** **Clark Database (DINP and DIDP only)**
(Att 8 Clark database DINP DIDP.pdf)
<http://www.cpsc.gov/about/cpsia/docs/otherPEs2009.pdf>
- Attachment 9** **Estimate of Exposures of Infants and Toddlers to DINP and DIDP**
(Att 9 Baby Exp Est.pdf)

- Attachment 10** **Human Exposure to Diisononyl Phthalate (DINP)**
(Att 10 DINP Exposure.pdf)
- Attachment 11** **DINP & DIDP Not Endocrine Disruptors Presentation (N. Hallmark)**
(Att 11 ED Presentation Hallmark.pdf)
- Attachment 12** **Approach to Cumulative Risk Presentation**
(Att 12 Cumm Risk Exxon slides.pdf)
<http://www.cpsc.gov/about/cpsia/docs/CummRiskExxon03232010.pdf>
- Attachment 13** **Supplement with Detail on Cumulative Risk Approach**
(Att 13 Cum Risk Supp.pdf)
- Attachment 14** **Comments on State-of-the-Art report on mixtures toxicity**
(Att 14 Mix Tox Comments.pdf)
- Attachment A-1** **Statement of Dr. John M. Cullen regarding DINP Liver Effects**
(Att A-1 Cullen DINP Opinion.pdf)
- Attachment A-2** **Statement of Dr. Dawn G. Goodman regarding Spongiosis Hepatis**
(Att A-2 Goodman DINP Opinion.pdf)
- Attachment A-3** **Statement of Dr. Gordon C. Hard regarding Kidney Effects**
(Att A-3 Hard DINP Opinion.pdf)