September 16, 2009

Sent via email (Studies provided on a CD sent via mail)

Dr. George Alexeeff Office of Environmental Health Hazard Assessment 1001 I Street, Sacramento, CA 95814 Post Office Box 4010 Sacramento, CA 95812-4010

Dear Dr. Alexeeff:

ExxonMobil Chemical Company (ExxonMobil) is providing this package of information on human exposure data for diisononyl phthalate (DINP) to assist the Office of Environmental Health Hazard Assessment (OEHHA) in its prioritization of DINP for development of Hazard Identification material. We are providing copies of pertinent studies on a separate CD; a summary of the information provided by these studies is given in the text and tables of this letter.

If OEHHA staff have questions, or if we can provide further information, please contact the undersigned at laura.n.winks@exxonmobil.com, (281) 870-6439, or any of the scientists listed below.

Bob Barter, Ph.D., robert.a.barter@exxonmobil.com, (908) 730-2153

Rick McKee, Ph.D., DABT, richard.h.mckee@exxonmobil.com, (908) 730-1037

Michael Bird, Ph.D., michael.g.bird@exxonmobil.com, (908) 730-1060

We appreciate the opportunity to present this information.

Sincerely,

Laura N. Winks

cc: Dr. David A. Eastmond

INTRODUCTION AND OVERVIEW

At the Carcinogen Identification Committee (CIC) meeting on May 29, 2009, the CIC recommended to OEHHA prioritization categories for 38 chemicals, including DINP. Dr. David Eastmond was the CIC member responsible for summarizing the data on DINP and making a recommendation for its priority category. His initial recommendation was that DINP be placed in the "high" category, based largely on concerns about human exposure to DINP.¹ After public comments, his final recommendation was to put DINP at the lower end of the high priority category, which was the recommendation the CIC accepted pending confirmation that exposures are low.²

The information provided herein demonstrates that exposures to DINP are indeed very low for all subpopulations, including children. For this reason, and the reasons presented in its May 5, 2009 comments to OEHHA, ExxonMobil continues to believe that DINP should be considered a low priority for development of Hazard Identification material.

Over the past decade, several biomonitoring studies have been conducted on human populations. The studies analyze concentrations of DINP metabolites in spot samples of urine. Methods for converting these metabolite concentrations to the corresponding DINP exposures have been published, and the resulting DINP exposures indicated by the data are very low – far below the conservative acceptable daily intake (ADI) developed by the Consumer Product Safety Commission (CPSC). This is true for children and all other subpopulations for which data have been presented.

<u>Part I</u> of the following explains the process for converting biomonitoring data, consisting of analyses of urinary concentrations of DINP metabolites, to the corresponding DINP exposures. We note the three differing values that studies have used for the molar fraction of the monoester metabolite (MINP). Two values are extrapolated from data on other phthalates of similar molecular weight. One of the values and the molar fraction values for the oxidative metabolites are based on a study of a single dose administered to a single volunteer. Results from a study conducted on 20 adult volunteers will be available with the next several months; those results will provide greater certainty regarding the correct molar fractions.

<u>Part II</u> provides a summary of biomonitoring studies on DINP conducted by the Centers for Disease Control and Prevention (CDC), which involved analyses of the monoester, MINP.

Part III discusses recent biomonitoring studies that analyzed the oxidative metabolites of DINP. Both parts include tables that provide the DINP exposures calculated from the biomonitoring data. As shown, whether based on the monoester or the oxidative metabolites, the exposures to DINP are all well below the conservative ADI.³

¹ CIC May 29, 2009 Meeting Transcript [hereinafter "Transcript"], p. 22.

² Transcript at 97 and 159; OEHHA (2009).

³ The derivation of the ADI is explained in the Appendix to this document.

<u>Part IV</u> discusses the issue of children's exposures to DINP. The available data indicate that these exposures are very low.

<u>Part V</u> addresses concerns raised at the CIC meeting regarding other subpopulations and the degree of DINP exposure. The available biomonitoring data indicate that there is very little difference in DINP exposures between various subpopulations. The exposures as measured by biomonitoring data are less than exposures that had been previously estimated on the basis of environmental media data. The biomonitoring captures all sources of DINP exposure by giving the aggregate exposure, and that exposure, whether based on the monoester or on oxidative metabolites, is very low.

Overall, the biomonitoring and exposure data for DINP paint a reassuring picture – that exposures to DINP are very low. These data support a prioritization of DINP for development of Hazard Identification materials in the low category.

I. CONVERSION OF BIOMONITORING DATA TO HUMAN EXPOSURES

To date, the majority of biomonitoring for DINP has consisted of analysis of human urine spot samples for metabolites of DINP. Initial efforts measured levels of the monoisononyl phthalate (MINP), the first metabolite of DINP, which is formed by cleaving one of the two alkyl chains from the benzenedicarboxylic acid moiety. More recently, analysis has included other secondary metabolites formed by oxidation of MINP. The results are reported as micrograms of metabolite per liter of urine (μ g/L) and, in some cases, as micrograms of metabolite per gram of creatinine (μ g/g). Creatinine adjustment is used to correct for variations in urinary dilution of spot samples (*e.g.*, Shealy et al., 1997).

To have meaning for risk assessment, the urinary concentration of the metabolite must be converted to the level of DINP exposure, in micrograms per kilogram of body weight per day $(\mu g/kg/day)$ that was required to provide the observed urinary concentration. This then enables comparison of the exposure indicated by the biomonitoring to acceptable dose values derived from animal toxicology testing.

David (2000) and Kohn et al. (2000) have provided a formula for converting urinary creatinine-adjusted concentrations of phthalate metabolites to the associated DINP exposure, which can be represented thus:

DINP exposure $(\mu g/kg/day) = UE (\mu g/g) \times C mg/kg/day) \times MWd$ F x 1000 mg/g x MWm

where:

UE = urinary concentration of the metabolite per gram of urinary creatinine; C = daily urinary creatinine clearance normalized by body weight; F = the ratio of moles monoester excreted per moles diester ingested; MWd = the molecular weight of the diester; and MWm = the molecular weight of the metabolite.

For <u>creatinine clearance (C)</u>, David (2000) used a value of 20 mg/kg/day for adults, taken from Tietz (1986). That source also provides creatinine clearance rates of 11 mg/kg/day for children and 9.8 mg/kg/day for infants. Kohn et al. (2000) used values of 23 mg/kg/day for men and 18 mg/kg/day for females, taken from Harper et al. (1977).

David (2000) used a molar ratio (F) based on Anderson et al. (2000). That group had administered known doses of phthalates to three human volunteers and measured the amounts of monoesters then excreted in the urine. Anderson et al. did not include DINP in the study, so David used the reported value for DIDP of 0.18.⁴ Koch et al. (2000) took their molar ratio value from a study by Peck and Albro (1982), which provides detailed data for a single individual that received DEHP intravenously. Again, DINP was not part of the study; therefore, Koch et al. used the DEHP molar fraction for DINP, giving a value of 0.11. More recently, Koch and Angerer (2007) administered a single dose of deuterium-labeled DINP to a single volunteer and measured urinary concentrations of metabolites with hydroxy, oxo and carboxy functional groups (OH-MINP, oxo-MINP, and carboxy-MINP, respectively). This yielded molar ratios of approximately 0.20 for OH-MINP, 0.11 for carboxy-MINP, 0.11 for oxo-MINP and 0.022 for the monoester, MINP.⁵ A study sponsored by the European Council of Plasticizers and Intermediates recently has measured the conversion and excretion of DINP metabolites in 20 adult human volunteers following ingestion of known amounts of DINP. The report for this study is anticipated later this year; ExxonMobil will forward the study results to OEHHA when they are available and those results will provide greater certainty regarding the correct molar fractions.

The <u>molecular weight</u> of DINP (MWd) is 419 that of MINP (MWm) is 293. OH-MINP has a molecular weight of 308, oxo-MINP 307, and carboxy-MINP 322.

If creatinine-adjusted values are not available, Wittassek et al. (2007) provide the following equation:

DINP exposure $(\mu g/kg/day) = MUE \text{ (moles/L) } x \text{ UV (L) } x \text{ MWd}$ F x BW (kg)

where MWd and F have the same meanings as above and:

MUE = the urinary concentration of the metabolite, converted to moles per liter; UV = the volume of urine excreted in 24 hours; and BW = individual body weight.

⁴ At the time, this study appeared only in abstract form. The full study report was subsequently published as Anderson et al. (2001), but did not include the results for DIDP.

⁵ Wittassek et al. (2007) report the excretion fraction, based on Koch and Angerer (2007), to be 19% for OH-MINP and 10% for oxo-MINP.

Wittassek et al. (2007) had <u>urinary volume (UV)</u> and <u>body weight (BW)</u> values for each individual in their study of adults, but did not report those data. However, on average the adult 24-hour urinary volume is about 1.6 liters⁶ and the standard adult body weight used in toxicology is 70 kg.

II. CDC MINP BIOMONITORING

The CDC has published a series of three reports that include the results of urinary metabolite levels for several phthalate esters, including DINP. CDC uses urine samples collected across the United States as part of the National Health and Nutrition Examination Survey (NHANES). The samples from the first three reports were analyzed for the MINP metabolite and the results are reported both as micrograms per liter (μ g/L) and micrograms per gram of creatinine (μ g/g).

The first CDC results for phthalates were released in a journal article that reported the results of phthalate monoester analyses for NHANES samples collected from 289 adults (weighted toward minority groups) during 1988-1994 (Blount et al., 2000). David (2000) and Kohn et al. (2000) were published in the same issue as Blount et al. and provided values for DINP exposures derived from the Blount et al. data.

In 2001, the CDC published its first National Report on Human Exposure to Environmental Chemicals ("Exposure Report") (CDC 2001). It provided results from a population of 1029 individuals sampled in the 1999 NHANES survey. CDC published a second Exposure Report in 2003 (CDC 2003). That provided the results of analyses from the 2001 report population combined with the results from an additional population of 1512 individuals sampled in the 2000 NHANES survey, for a total sample size of 2541. The reported results were broken out by age, gender and race. In 2005, CDC published its third Exposure Report (CDC 2005). It reports the values in the second National Report, and separately provides values from a population of 2721 individuals sampled in the 2001 and 2002 NHANES surveys. In all cases, the sampling was designed to be representative of the U.S. population. A fourth report is expected to be released by the CDC in the last quarter of 2009.

Table 1 provides results from the various CDC reports and the calculated DINP exposures indicated by those results, using the methodologies of David (2000) and Koch et al. (2000). Several points are evident from the table:

- For all years of sampling and all demographic groups, the median value was less than the level of detection (LOD). The LOD was very low 1 μg/L for Blount et al. (2000) and 0.8 μg/L for the CDC exposure reports, indicating median DINP exposures are minimal.
- The indicated exposures are well below the conservative ADI derived for DINP. Regardless of the year of sampling, the demographic breakdown, or the molar fraction used for the calculations, the highest 95th percentile value is 9.1 micrograms per kilogram

⁶ See Diem and Lentner (1970); Medline Plus (2007); Mayo Clinic Staff (2008).

per day (μ g/kg/day). This is over 12-fold below the ADI of 120 μ g/kg/day, which itself is 100-fold below the calculated benchmark dose, which in turn is 7-fold below the highest NOAEL below the lowest LOAEL in rodents (see Appendix).

- The data suggest that exposures in the U.S. have been decreasing over time. For example, the 95th percentile value of MINP for the total population, in µg/g creatinine, has gone from 6.8 in Blount et al. (samples from 1988-1994) to 4.29 in the CDC second Exposure Report (samples from 1999-2000), to less than the LOD in the third Exposure Report (samples from 2000-2001).⁷ This pattern is consistent for all demographic groups.
- While there are slight differences in the 95th percentile values of MINP between ethnic groups, the differences are reduced and sometimes reversed by consideration of the creatinine-adjusted values versus the raw urinary concentrations. For example, in the second Exposure Report, the 95th percentile urinary concentration of MINP in non-Hispanic Blacks was nearly twice as great as that in non-Hispanic Whites. However, with creatinine adjustment, the value for the Whites was slightly higher than the Blacks. In all cases, the differences are so slight that, within the likely margins of error, they are essentially identical.

III. OXIDATIVE METABOLITE BIOMONITORING

The hydrolytic monoester of DINP, monoisononyl phthalate (MINP), has been used as a single biomarker for human exposure assessment. However, the detection of MINP can be low due to the fact that MINP can be further metabolized to form oxidative metabolites before being excreted in the urine (Silva et al., 2006). For example, in a report published by Koch and Angerer (2007), a single bolus dose of deuterium-labeled DINP (1.27 mg/kg-bw) was administered to a single individual with multiple urine samples taken during a 48 hour period for quantification of metabolite formation and excretion. Within 48 h, 43.6% of the applied dose was recovered in urine primarily as oxidative metabolites: 20.2% as OH-MINP, 10.7% as carboxy-MINP, 10.6% as oxo-MINP and 2.2% as MINP. Oxidative metabolites of DINP were first theorized to exist in rats, (McKee *et al.*, 2002) but were not identified in humans until 2006 (Silva *et al.*, 2006).

The DINP-related values reported in Blount et al. (2000) and the three CDC Exposure Reports were concentrations of the monoester metabolite, MINP. More recently, researchers in the CDC laboratories and researchers in Germany have analyzed urine samples for oxidative metabolites of DINP as they have been identified. Silva et al. (2006) of the CDC analyzed samples collected in 2005 from 129 adult volunteers in the U.S. Koch et al. (2007) analyzed samples from 25 individuals, 12 females and 13 males, in Southern Germany with ages ranging between 6 and 73 years. Wittassek et al. (2007) performed a retrospective study on samples in the German Environmental Specimen Bank for Human Tissues that were collected from 634

⁷ CDC did not report a 95th percentile value in its first Exposure Report; the 90th percentile in that report was $3.8 \ \mu g/g$.

subjects; primarily students age 20-29, 326 males and 308 females. The metabolite concentrations calculated in these studies are presented in Table 2.

Based on the metabolite concentrations calculated in these studies, we have calculated the corresponding DINP exposure using the equations described in Part I above for Table 2. In general, the calculated DINP exposure based on a given oxidative metabolite are in agreement between studies and well below the ADI. Some variability is noted between the studies and is likely the result of several factors. For example, the molar fractions (conversion factors) are based on data from a single volunteer administered a single dose of labeled DINP (Koch and Angerer, 2007). Additionally, differences in geographic location, sample population demographics, random statistical fluctuations, variation inherent in the collection of spot samples of urine from many individuals, and the exacting preparation and analytical techniques required for detection of low part per billion concentrations when measuring metabolite concentrations all contribute to the observed variability.

Based on the measured DINP oxidative metabolites, the calculated exposures to DINP (Table 2) in all cases, even the 95th percentile, are very low and well below the conservative ADI of 120 μ g/kg/day, which is itself over 1000-fold below a level in which minor effects were seen in rats.⁸

Additionally, while the above mentioned studies have sufficient sensitivity to detect DINP exposure in a larger fraction of the population based on oxidative metabolite levels, because the levels of DINP exposure calculated from the oxidative metabolites are on the same order as those derived from the CDC monoester analyses (*See* Table 3) and well below the conservative ADI it can be seen that DINP exposure from all types metabolites are very low.

IV. CHILDREN'S EXPOSURES

At the May 29 CIC meeting, Dr. Eastmond indicated concern about exposure of children to DINP, and he appeared to suggest that if children's exposures are low he would recommend lowering DINP's priority category.⁹ The data reported to date indicate that children's exposures are indeed very low.

Biomonitoring data for children are more limited than for adult populations, but the data that are available indicate very low exposures to DINP. The CDC biomonitoring has included children from 6 years of age up, and has broken out the biomonitoring data by age group. As shown in Table 1, in the second Exposure Report the calculated 95th percentile DINP exposures for children ages 6-11 years are slightly less than those of the total population, and are far below

⁸ See the Appendix for an explanation of the derivation of the ADI. The CPSC Chronic Hazard Advisory Panel on DINP (CHAP) derived and used that ADI for its assessment of risk to children, based on the most sensitive endpoint (considering both cancer and non-cancer data) (CHAP, 2001, pp. 122-123).

⁹ Transcript at 94.

the conservative ADI value, which is itself over 1000-fold below a level in which minor effects were seen in rats (*see* Appendix). In the third Exposure Report, children's exposures were below the level of detection even at the 95th percentile.

Brock et al. (2002) analyzed phthalate monoesters in urine samples from 19 infants, aged 11.8 to 16.5 months. Mono-isononyl phthalate (MINP) was not detected in any of the samples.

In addition to biomonitoring data, a number of fairly detailed studies have been performed to estimate potential child exposure from mouthing of toys (RIVM, 1998; CPSC 2002; Sugita et al., 2003). In general, as additional mouthing data have been collected over time, the ability to focus on toy-specific mouthing events has led to reduced estimates of exposure for child mouthing of plastic toys. In comparing exposure estimates across studies, it is thus important to consider which mouthing events (i.e., toys, fingers, clothing, etc.) were included in the mouthing time estimate.

In 2001, the Chronic Hazard Advisory Panel (CHAP) developed an estimate of a plausible upper bound on the extent of potential DINP exposure from children's toys. CHAP indicated a number of areas of uncertainty in the exposure estimate which could be addressed to develop a more definitive estimate. Following the CHAP 2001 assessment, a number of these areas of uncertainty have been addressed. Specifically, the subsequent CPSC 2002 analysis includes consideration of data developed on the portion of toys that contain DINP, additional migration data specific to toy products, and a new observational study that included better categorization of mouthing activities by item mouthed.

The 2002 CPSC document indicated: "The staff concluded that oral exposure to DINP from mouthing of soft plastic toys, teethers and rattles is not likely to present a health hazard to children. Since children mouth other children's products less than they do toys, teethers and rattles and since dermal exposure is expected to be minimal, staff does not believe that other children's products are likely to present a health hazard to children." In support of this statement, CPSC cited exposure estimates determined by CPSC staff based upon the new mouthing observation study and the new toy-specific migration data (see Tables 4 and 5). CPSC indicates that these estimates include a number of conservative hypothetical analyses.

The observational study used to develop these exposure estimates represents the largest mouthing study to date with the greatest level of categorization. The survey included 169 children ages 3-36 months. Trained observers watched each child for 12- twenty minute periods over 2 days. Items mouthed were placed into one of 13 categories. Most importantly, this study included soft plastic toys as a specific category. This study found that the largest single non-pacifier category was anatomy (fingers, hands, skin). Soft plastic toys represented only a small part of mouthing time. CPSC (2002) also presented a comparison of results from this study with other mouthing studies for the category of non-pacifier mouthing time (indicated to be the smallest category that was the same for all 3 studies examined) (see Table 6). This comparison shows that on an equal category basis, the CPSC mouthing time observations were similar to or greater than those of other studies.

The newer studies enabled CPSC to address the CHAP (2001) comments: "Based upon the results of the CPSC observation study which was not complete when the CHAP met, CPSC staff believes it is very unlikely that children will mouth soft plastic toys for more than 75 minutes per day." Further, the results of the new observational study indicate a mean mouthing time for soft plastic toys of 1.3 minutes/day for the 3-12 month age group and 1.9 minutes/day for the 12 -24 month age group (the group with the highest mouthing time) (see Table 5; Kiss 2002, Greene 2002a). Even the hypothetical cases included in Table 5, which were intentionally conservative, result in low exposure estimates. For example, utilizing mouthing times for all toys, teethers and rattlers and assuming that 100% of these products contained DINP, estimated exposures were well below levels of concern for all age groups.

In summary, both child-specific biomonitoring data and child-specific exposure estimates for mouthing of toys indicate that children's potential exposure to DINP is well below acceptable daily intake levels. Even the 95th percentile values of the hypothetical mouthing scenarios of the CPSC analysis, designed to provide estimates greater than expected exposures, were well below the ADI. Together, this information consistently supports that child-specific exposures are low.

V. OTHER SUBPOPULATIONS AND DEGREE OF EXPOSURE

Comments at the May 29 CIC meeting raised some DINP exposure concerns which were not warranted. At the meeting, Dr. Eastmond stated:

[T]he woman from UCSF mentioned that by looking at other metabolites, there's actually widespread exposure in a sub-population, and they're not sure how this is occurring. . . . I guess the real thing for me comes down to the children's exposure, and are there sub-populations that are exposed at fairly high levels?¹⁰

The statements to which Dr. Eastmond was referring were as follows:

And in that study [Silva et al., 2006], which is not listed in your recent studies, they found a subset of the population, which was essentially adult men, when they looked for a different metabolite than they looked for before, it was an oxidative metabolite. They looked for three different ones and they found them in over 97 percent of the people in that study. These were exposures from sources that we don't understand, but we know that there is widespread exposure to this chemical.¹¹

¹⁰ Transcript pp. 93-94.

¹¹ Transcript p. 85

These statements, however, are inaccurate or misleading. The Silva study was not on a subset of the population, and the results of biomonitoring, regardless of metabolite used, show that the aggregate exposures to DINP are very low. We discuss these points below.

A. Subpopulations

The Silva et al. (2006) study was not conducted solely on men. Rather, the authors characterize the study population as "a demographically diverse group of 129 U.S. adults of both sexes." The Silva results were reported for the total group – they were not broken out by gender.

The one study that provides a comparison of male and female DINP exposures is the second CDC Exposure Report. As can be seen from Table 1, the 95th percentile values for men and women were approximately equal.¹² In the third Exposure Report, concentrations for both men and women, even at the 95th percentile, were less than the level of detection.

Children's exposures are discussed in Part IV, above. The only other subpopulation data available to date, besides age and gender, are data for different ethnic groups. As shown in Table 1, 95th percentile DINP exposures of Mexican-Americans and non-Hispanic Blacks were slightly less than those of non-Hispanic whites in the second Exposure Report (samples from 1999-2000). In the third Exposure Report, there were small DINP exposures detectible at the 95th percentile for Mexican-Americans and non-Hispanic Blacks, whereas the 95th percentile DINP exposure for non-Hispanic whites was less than the level of detection (samples from 2001-2002). The fourth CDC Exposure Report will provide further data for evaluation of ethnic exposure differences. In any event, the exposures for each group are very small – well below the conservative ADI value.

B. Degree of Exposure

As discussed in Part III, recent studies have shown that a larger fraction of ingested DINP is excreted as oxidative metabolites than as monoester, making the oxidative metabolites a more sensitive marker for calculating exposure. Accordingly, whereas MINP concentrations are below the level of detection in the supermajority of samples, researchers have now been able to quantify DINP oxidative metabolite concentrations in samples for over 95% of their study populations.

The analytical methods which have enabled the quantification of DINP exposures at lower levels do not indicate that exposures are higher or more significant than previously thought. Instead, it is an indication there is increased sensitivity of the assay quantification system and still validates that overall exposure is low. Prior to publication of the biomonitoring studies, exposure estimates based on environmental sampling predicted low levels of exposure to

¹² Given the many variables and thus sources of error in the sampling and analyses of metabolites and calculation of DINP exposures from those data, we believe that values that differ by only a few $\mu g/kg/day$ should be regarded as equal.

DINP for the population in general.¹³ With the biomonitoring data, we are able to know what actual total exposures are without resorting to estimates based on environmental media data and assumptions about human interaction with those media. Biomonitoring captures *all* sources of exposure and shows convincingly that the aggregate exposure to DINP for all segments of the population is very low.

CONCLUSION

Prior to 2006, MINP biomonitoring was used for back calculation exposure estimates for DINP. Through advances in analytical techniques and methodology, the identification and use of oxidative metabolites as biomarkers of DINP has increased assay sensitivity and reduced the uncertainty in DINP exposure calculations. Biomonitoring the oxidative metabolites of DINP clearly demonstrate that all-source exposure to DINP is well below the conservative ADI for all demographic groups. Finally, when focusing on children's exposure, both child-specific biomonitoring data and child-specific exposure estimates for mouthing of toys indicate that children's potential exposure to DINP is well below acceptable daily intake levels.

Thus, ExxonMobil believes that these exposure data, in conjunction with the toxicological database summarized in its May 5, 2009 comments to OEHHA, supports that DINP be a low priority for the development of Hazard Identification materials.

¹³ For example, the Center for the Evaluation of Risks to Human Reproduction (CERHR) Expert Panel on phthalates estimated exposures to DINP to be less than 3-30 µg/kg/day (CERHR 2000).

Table 1.
DINP Exposures Calculated from CDC Monoester Biomonitoring Data

Parameter	MINP Concentration		Calculated DINP Exposure (µg/kg/day)*			ADI µg/kg/day	
	μg/L urine	µg/g creatinine	F = 0.18	F = 0.11	F = 0.022		
	T						
		Blount et al. (2000)	0.21	0.00	1.7	120	
Geometric Mean	1.5	1.3	0.21	0.32	1.7	120	
50 th Percentile	<lod< td=""><td><lod< td=""><td>< 0.16</td><td>< 0.26</td><td><1.3</td><td>120</td></lod<></td></lod<>	<lod< td=""><td>< 0.16</td><td>< 0.26</td><td><1.3</td><td>120</td></lod<>	< 0.16	< 0.26	<1.3	120	
95 th Percentile	7.3	6.8	1.08	1.7	9.1	120	
	CDC	Einet Europaune Dar	- o w 4				
coth p (1		First Exposure Rej		-0.0	.1 1	120	
50 th Percentile	<lod< td=""><td><lod< td=""><td>< 0.1</td><td>< 0.2</td><td><1.1</td><td>120</td></lod<></td></lod<>	<lod< td=""><td>< 0.1</td><td>< 0.2</td><td><1.1</td><td>120</td></lod<>	< 0.1	< 0.2	<1.1	120	
90 th Percentile	4.3	3.8	0.60	1.0	5.1	120	
	CDC Se	cond Exposure Rej	oort**				
50 th Percentile – Total	<lod< td=""><td><lod< td=""><td><0.1</td><td>< 0.2</td><td><1.1</td><td>120</td></lod<></td></lod<>	<lod< td=""><td><0.1</td><td>< 0.2</td><td><1.1</td><td>120</td></lod<>	<0.1	< 0.2	<1.1	120	
95 th Percentile – Total	3.50	4.29	0.68	1.11	5.72	120	
95 th Percentile – Women	2.50	4.29	0.61	1.00	5.02	120	
95 th Percentile – Men	4.90	4.24	0.77	1.26	6.30	120	
95 th Percentile – age 6-11 yrs	5.70	6.00	0.52	0.72	3.58	120	
95 th Percentile – Mex-Amer.	1.40	3.51	0.56	0.81	4.68	120	
95 th Percentile – non-Hisp. Black	6.80	4.26	0.68	1.11	5.68	120	
95 th Percentile – non-Hisp. White	3.50	5.00	0.79	1.30	6.67	120	

CDC Third Exposure Report**						
50 th Percentile – Total	<lod< td=""><td><lod< td=""><td>< 0.1</td><td>< 0.2</td><td><1.1</td><td>120</td></lod<></td></lod<>	<lod< td=""><td>< 0.1</td><td>< 0.2</td><td><1.1</td><td>120</td></lod<>	< 0.1	< 0.2	<1.1	120
95 th Percentile – Total	<lod< td=""><td><lod< td=""><td>< 0.1</td><td>< 0.2</td><td><1.1</td><td>120</td></lod<></td></lod<>	<lod< td=""><td>< 0.1</td><td>< 0.2</td><td><1.1</td><td>120</td></lod<>	< 0.1	< 0.2	<1.1	120
95 th Percentile – Women	<lod< td=""><td><lod< td=""><td>< 0.1</td><td>< 0.2</td><td><1.1</td><td>120</td></lod<></td></lod<>	<lod< td=""><td>< 0.1</td><td>< 0.2</td><td><1.1</td><td>120</td></lod<>	< 0.1	< 0.2	<1.1	120
95 th Percentile – Men	<lod< td=""><td><lod< td=""><td>< 0.1</td><td>< 0.2</td><td><1.1</td><td>120</td></lod<></td></lod<>	<lod< td=""><td>< 0.1</td><td>< 0.2</td><td><1.1</td><td>120</td></lod<>	< 0.1	< 0.2	<1.1	120
95 th Percentile – age 6-11 yrs	<lod< td=""><td><lod< td=""><td>< 0.1</td><td>< 0.2</td><td><1.1</td><td>120</td></lod<></td></lod<>	<lod< td=""><td>< 0.1</td><td>< 0.2</td><td><1.1</td><td>120</td></lod<>	< 0.1	< 0.2	<1.1	120
95 th Percentile – Mex-Amer.	1.00	2.31	0.37	0.60	3.08	120
95 th Percentile – non-Hisp. Black	1.00	1.62	0.26	0.42	2.16	120
95 th Percentile – non-Hisp. White	<lod< td=""><td><lod< td=""><td>< 0.1</td><td>< 0.2</td><td><1.1</td><td>120</td></lod<></td></lod<>	<lod< td=""><td>< 0.1</td><td>< 0.2</td><td><1.1</td><td>120</td></lod<>	< 0.1	< 0.2	<1.1	120

Table 1. continued.

NC Not calculated. CDC stated that the proportion of results below limit of detection was too high to provide a valid result.

- LOD Level of detection. For Blount et al. (2000), the LOD was 1 μ g/L (see Koch et al., 2000). For the CDC Exposure reports, the LOD was 0.8 mg/L. Because the LOD was not reported in terms of μ g/g creatinine, for purposes of calculating a corresponding exposure we have assumed the value in μ g/g creatinine is the same as that in μ g/L urine. As can be seen from the table, this is approximately true where values were measured and, at the low levels of detection, this assumption makes only a very slight difference in the result.
- * With respect to the Blount et al. data, we have given the exposure values reported by David (2000) and Koch et al. (2000), as indicated by italicized numbers. In all other cases, the values were calculated for this submission according to the methods given in Part I of these comments, using various values for the molar fraction (F). F = 0.18 is the value used by David (2000), taken from Anderson et al. (2000). F = 0.11 is the value used by Koch et al. (2000), taken from Peck and Albro (1982). F = 0.022 is the value measured by Koch and Angerer (2007), based on data from a single individual. A fourth value for F will be available within the next few months from a study with data for 20 individuals.
- ** The 50^{th} percentile value for each subpopulation was less than the level of detection.

	Table 2.
DINP Exposures Calculated from	Oxidative Metabolite Biomonitoring Data

	Metabolite	Concentration	Calculated DINP Ex	ADI			
Parameter	μg/L urine	µg/g creatinine	based on creatinine	based on urine	µg/kg/day		
		Silva et al., 2	006				
50 th percentile OH-MINP	13.2			1.12	120		
50 th percentile oxo-MINP	8.4			1.4	120		
50 th percentile carboxy-MINP	1.2			0.20	120		
50 th percentile MINP	<lod< td=""><td></td><td></td><td>< 0.05</td><td>120</td></lod<>			< 0.05	120		
95 th percentile OH-MINP	43.7			3.71	120		
95 th percentile oxo-MINP	46.2			7.45	120		
95 th percentile carboxy-MINP	16.6			1.11	120		
95 th percentile MINP	<lod< td=""><td></td><td></td><td>< 0.05</td><td>120</td></lod<>			< 0.05	120		
		Koch et al., 2	007				
50 th percentile OH-MINP	2.5			0.21	120		
50 th percentile oxo-MINP	1.3			0.21	120		
50 th percentile carboxy-MINP	5.0			0.84	120		
Mean OH-MINP	14.9			1.27	120		
Mean oxo-MINP	8.9			1.4	120		
Mean carboxy-MINP	16.4			2.75	120		
Wittassek et al., 2007							
50 th percentile OH-MINP	2.0	1.9	0.14	0.17	120		
50 th percentile oxo-MINP	1.0	1.0	0.14	0.16	120		
95 th percentile OH-MINP	11.9	11.1	0.809	1.01	120		
95 th percentile oxo-MINP	5.6	5.4	0.75	0.90	120		

* Calculated according to the methods explained in Part I of these comments.

Table 3. 95th Percentile Human Exposure to DINP in µg/kg/day Calculated from Metabolite Monitoring

		DINP	ADI
Study	Metabolite	exposure*	µg/kg/day
Blount et al., 2000	MINP	1.1-9.1	120
CDC 2 nd Exposure Report, 2003	MINP	0.7-5.7	120
CDC 3rd Exposure Report, 2005	MINP	<lod< td=""><td>120</td></lod<>	120
Silva et al., 2006	Oxidative Metabolites	<lod-7.5< td=""><td>120</td></lod-7.5<>	120
Wittassek et al., 2007	Oxidative Metabolites	0.1-1.7	120

See Tables 1 and 2.

*

 Basis: Item specific mouthing time – Greene 2002a Migration rates for plastic toys, in vitro data adjusted to expected in vivo rates 					
Age in Months	Exposure in ug/kg/day - Mean (95 th Mouthing Time in				
	percentile) minutes/day –				
	Basic Case – Soft	Mean (95 th			
	Plastic Toys, 42% with	percentile)			
	DINP	100% with DINP			
3-<12	0.07 (0.44)	0.17 (0.94)	1.3 (7.1) N=54		
12-<24	0.08 (0.53)	0.22 (1.11)	1.9 (8.8) N=66		
24-<36	0.03 (0.12)	0.07 (0.27)	0.8 (3.3) N=49		

Table 4.CPSC (2002) Mouthing Study

Additional Information:

• Observers: Trained observers

• Observation Periods: 12- twenty minute periods over 2 days

Total mouthing time is extrapolated to the time the child is awake and not eating.

Migration Rate:

- Used distribution of migration rates for various DINP containing toys, mean =4.1 ug/10 cm²/min, range 1-11; Values of zero added to distribution to approximate 42% market fraction of DINP
- Product specific in vitro migration rates were adjusted to in vivo conditions by sampling from the distribution of the factor M_{human}/M_{lab} . (M_{human} 1.17 ± 0.38 (N=19), M_{lab} 4.18 ± 0.45)

	Soft plastic toys, teethers, and rattlers, 100% with DINP*		All soft plastic items (excluding pacifiers), 100% with DINP		All toys, teethers and rattlers, 100% with DINP	Pacifiers, 1009	% with DINP*
Age in Months	Exposure in ug/kg/day - Mean (95 th percentile)	Mouthing Time in minutes/day – Mean (95 th percentile)	Exposure in ug/kg/day - Mean (95 th percentile)	Mouthing Time in minutes/day – Mean (95 th percentile)	Exposure in ug/kg/day - Mean (95 th percentile)	Exposure in ug/kg/day - Mean (95 th percentile)	Mouthing Time in minutes/day – Mean (95 th percentile)
3-<12	0.45 (2.15)	3.1 (17.4)	0.63 (2.90)	4.4 (17.5)	2.91 (10.71)	4.75 (24.55)	33 (190)
12-<24	0.22 (1.12)	2.0 (9.3)	0.41 (1.69)	3.8 (13.0)	0.84 (3.35)	2.82 (17.44)	27 (201)
24-<36	0.08 (0.33)	1 (2.3)	0.37 (1.70)	4.2 (18.5)	0.28 (1.25)	1.71 (5.41)	19 (51)

Table 5.CPSC (2002) Additional Hypothetical Cases

Mouthing times from Kiss, 2002; Greene, 2002a.

*For these categories, mouthing times were only provided in min/hr, they were converted to min/day as per the equation listed in Babich et al., 2004, using the average age in months for the age group of interest

Table 6.CPSC (2002) Daily average non-pacifier*mouthing times from various studies in minutes per day

Age group (months)	Groot et al 1998 (min/day)	Juberg et al 2000 (min/day)	CPSC (min/day
0-18	32.4	36.0	61.0
19-36	9.3	5.0	39.5

*Smallest category of objects that is the same for all 3 studies

References

Articles marked with an asterisk (*), which provide biomonitoring data, are being separately provided. Any other references also will be provided, upon request.

- Anderson, W., Castle, L., Scotter, M., Massey, R. and Springall, C. (2001). A biomarker approach to measuring human dietary exposure to certain phthalate diesters. Food Additives & Contaminants 18(12):1068-174.
- Anderson, W., Ayesh, R., Castle, L., Scotter, M., Springall, C. A biomarker approach to quantify human dietary exposure to phthalates, risk assessment and communication for food safety [Abstract]. Presented at the First Joint CSL/JIFSAN Symposium on Food Safety & Nutrition, 20-22 June 2000, Central Science Laboratory, Sand Hutton, York, UK.
- *Blount, B., Silva, M., Caudill, S., Needham, L., Pirkle, J., Sampson, E., Lucier, G., Jackson, R., Brock, J. (2000). Levels of seven urinary phthalate metabolites in a human reference population. Environ Health Perspectives 108(10):979-982, available at http://ehpnet1.niehs.nih.gov/docs/2000/108p972-982blount/blount-full.html.
- *Brock, J., Caudill, S., Silva, M., Needham, L., Hilborn, E. (2002). Phthalate monoester levels in the urine of young children. Bulletin of Environmental Contamination and Toxicology 68:309–314 (2002), available at http://www.springerlink.com/content/5mp02v0pnlaxgnt3/fulltext.pdf?page=1.
- *CDC (2001). The national report on human exposure to environmental chemicals. Centers for Disease Control and Prevention, Atlanta, GA.
- *CDC (2003). Second national report on human exposure to environmental chemicals. Centers for Disease Control and Prevention, Atlanta, GA.
- *CDC (2005). Third national report on human exposure to environmental chemicals. Centers for Disease Control and Prevention, Atlanta, GA, available at: <u>http://www.cdc.gov/exposurereport/report.htm</u>.
- CERHR (2000). NTP-CERHR expert panel report on diisononyl phthalate. NTP-CERHR-DINP-00, National Toxicology Program Center for the Evaluation of Risks to Human Reproduction, Research Triangle Park, NC, available at <u>http://cerhr.niehs.nih.gov/chemicals/phthalates/dinp/DINP-final-inprog.PDF</u>.
- CHAP (2001) Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Diisononyl Phthalate (DINP), U.S. Consumer Product Safety Commission Directorate For Health Sciences, Bethesda, MD, available at <u>http://www.cpsc.gov/LIBRARY/FOIA/Foia01/os/dinp.pdf</u>.

- CPSC Consumer Product Safety Commission (2002). Response to petition HP 99-1. Request to ban PVC in toys and other products intended for children five years of age and under. USCPSC.
- *David, R. (2000). Exposure to phthalate esters. Environ Health Perspectives 108:A440, available at <u>http://ehpnet1.niehs.nih.gov/docs/2000/108-10/correspondence.html#exp</u>.
- Diem, K. and Lentner, C. (eds.) (1970). Geigy Scientific Tables, 7th Ed. Distributed by Geigy Pharmaceuticals, Division of CIBA-GEIGY Corp., Ardsley, N.Y.

Greene M (2002a). Mouthing times among young children from observational data. Tab G of CPSC (2002).

Greene M (2002b). Mouthing times and DINP risk for children over three years of age. Tab H of CPSC (2002).

Harper, H., Rodwell, V., Mayes, P. (1977). Review of physiological chemistry. Lange Medical Publications, Los Altos, CA.

Kiss, CT (2002). A mouthing observation study of children under 6 years of age. Tab F of CPSC (2002).

- *Koch, H., Angerer, J. (2007). Di-iso-nonylphthalate (DINP) metabolites in human urine after a single oral dose of deuterium-labeled DINP. Int J Hyg Environ Health. 210(1):9-19.
- *Koch, H., Müller, J., Angerer, J. (2007). Determination of secondary, oxidised di-isononylphthalate (DINP) metabolites in human urine representative for the exposure to commercial DINP plasticizers. J Chromatogr B Analyt Technol Biomed Life Sci. 847(2):114-25.
- *Kohn, M., Parham, F., Masten, S., Portier, C., Shelby, M., Brock, J., Needham, L. (2000). Human exposure estimates for phthalates. Environ Health Perspect 108:A440-A442, available at <u>http://ehpnet1.niehs.nih.gov/docs/2000/108-10/correspondence.html#exp</u>.
- Mayo Clinic Staff (2008). Water: How much should you drink every day? Available at <u>http://www.mayoclinic.com/health/water/nu00283</u>.
- McKee, R., El-Hawari, M., Stoltz, M., Pallas, F., Lington, A. (2002). Absorption, disposition and metabolism of di-isononyl phthalate (DINP) in F-344 rats. *J Appl Toxicol*, 22(5), 293-302.

Medline Plus (2007), Urine 24-hour volume, at <u>http://www.nlm.nih.gov/medlineplus/ency/article/003425.htm</u>.

- Peck, C., Albro, P. (1982). Toxic potential of the plasticizer di(2-ethylhexyl) phthalate in the context of its disposition and metabolism in primates and man. Environ Health Perspect 45:11-17, available at <u>http://ehp.niehs.nih.gov/members/1982/045/45003.PDF</u>.
- OEHHA (2009). Summary of Chemical Prioritizations (Table), in Meeting Synopsis and Slide Presentations Carcinogen Identification Committee Meeting Held on May 29, 2009, posted at <u>http://www.oehha.org/prop65/public_meetings/cic060509.html</u>.
- Shealy, D., Burr, J., Ashley, D., Patterson, D., Camann, D., Bond, A. (1997). Correlation of environmental carbaryl measurements with serum and urinary 1-naphthol measurements in a farmer applicator and his family. Environ Health Perspect 105:510-513, available at http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1469864&blobtype=pdf.
- *Silva, M., Reidy, J., Preau, J., Needham, L., Calafat, A. (2006). Oxidative metabolites of diisononyl phthalate as biomarkers for human exposure assessment. Environ Health Perspect. 114(8): 1158–1161, available at http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1552017&blobtype=pdf.
- RIVM Rijksinsitituut voor Volksgesondheid en Milieu (National Institute of Public Helath and Environment (1998). In Könemann WH (ed), Phthalate Release from Soft PVC Baby Toys. National Institute of Public Health and Environmental Protection (RIVM), Report from the Dutch Consensus Group. RIVM Report 31 3320 002, Bilthoven, The Netherlands.
- Sugita T, Kawamura Y, Tanimura M, Matsuda R, Niino T, Ishibashi T, Hirabahashi N, Matsuki Y, Yamada T, Maitani T. (2003). Estimation of daily oral exposure to phthalates derived from soft polyvinyl chloride baby toys. Shokuhin Eiseigaku Zasshi.;44(2):96-102.
- Tietz, M., ed. (1986). Textbook of clinical chemistry. W.B. Saunders Co., Philadelphia, PA, p. 1821.
- *Wittassek, M., Angerer, J. (2008). Phthalates: metabolism and exposure. Int J Androl. 31(2):131-8.
- *Wittassek, M., Wiesmüller, G., Koch, H., Eckard, R., Dobler, L., Müller, J., Angerer, J., Schlüter, C. (2007). Internal phthalate exposure over the last two decades--a retrospective human biomonitoring study. Int J Hyg Environ Health. 210(3-4):319-33.

APPENDIX DERIVATION OF THE ACCEPTABLE DAILY INTAKE FOR DINP

In 2000, the Consumer Product Safety Commission (CPSC) convened a Chronic Hazard Advisory Panel (CHAP) on DINP, which reviewed data for carcinogenicity and other toxicological endpoints for DINP. The CHAP determined that exposures to DINP necessary to theoretically trigger cancer in humans were so high as to be implausible, and therefore did not base its risk assessment on cancer.¹ It developed an acceptable daily intake for DINP based on the most sensitive endpoint observed in rodent studies – spongiosis hepatis. This effect was seen in male (but not female) rats at 359 mg/kg/day in Moore (1998) and at 152 mg/kg/day in Lington et al. (1997). The No Observed Effect Levels (NOELs) in these chronic exposure studies were 88 mg/kg/day and 15 mg/kg/day, respectively. (Note: The lowest level at which liver tumors have been observed in rats is 733 mg/kg/day (Moore, 1998)).

CPSC pooled the data from the Lington and Moore studies to derive a Benchmark Dose (BMD_{05}) of 12 mg/kg/day. This value was divided by a safety factor of 100 to give an ADI of 0.12 mg/kg/day (or 120 μ g/kg/day). The ADI is very conservative for several reasons:

- Spongiosis hepatis is a spontaneously occurring lesion of unknown health significance that has been reported only in rats, primarily males, and teleost fish. It has not been linked to any pathological or toxicological process in rats nor is there any evidence that spongiosis hepatis occurs in humans.²
- Although the number of male rats with spongiosis hepatis increased with dose, the severity was judged as minimal to moderate in most cases, and the average frequency did not increase with increasing dose.
- The ADI is conservatively based on a BMD₀₅. The BMD₁₀, which would be a higher value, is typically considered to be an appropriate point of departure for risk assessment.³
- The BMD₀₅ is less than clear NOEL values of 15 mg/kg/day and 88 mg/kg.⁴

¹ CHAP (2001) at cover letter and pp. 3, 5 and 124-125.

² See, e.g., Su et al. (1997) and Su et al. (1998), which contain detailed descriptions of the histopathology of about 200 human livers and include no mention of spongiosis hepatis or similar lesions.

³ See, e.g., EPA (2008).

⁴ In Lington et al. (1997), the next highest dose above 15 mg/kg/day was 152 mg/kg/day. Thus, the combination of the Lington and the Moore studies gives a NOEL of 88 mg/kg/day.

Appendix References

- CHAP (2001) Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Diisononyl Phthalate (DINP), U.S. Consumer Product Safety Commission Directorate For Health Sciences, Bethesda, MD, available at http://www.cpsc.gov/LIBRARY/FOIA/Foia01/os/dinp.pdf.
- EPA (2008). Benchmark Dose Software (BMDS) On-line Tutorial, Part II, available at http://www.epa.gov/ncea/bmds/bmds_training/methodology/intro.htm (page last updated September 30, 2008).
- Lington, A., Bird, M., Plutnick, R., Stubblefield, W., Scala, R. (1997). Chronic toxicity and carcinogenic evaluation of diisononyl phthalate in rats. Fundam Appl Toxicol 36: 79-89.
- Moore, M. (1998). Oncogenicity study in rats with di(isononyl) phthalate including ancillary hepatocellular proliferation and biochemical analyses. Covance Laboratories Incorporated, Vienna, VA 22182. May 13, 1998. Covance 2598-104.
- Su, Q., Benner, A., Hofmann, W.J., Otto, G., Pichlmayr, R., and Bannasch, P. (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.
- Su, Q., Schröder, C., Hofmann, W., Otto, G., Pichlmayr, R., Bannasch, P. (1998). Expression of hepatitis B virus X protein in HBV-infected human livers and hepatocellular carcinomas. Hepatology 27:1109-1120.