From: <laura.n.winks@exxonmobil.com>
To: <coshita@oehha.ca.gov>
Date: 5/5/2009 2:50 PM
Subject: ExxonMobil Chemical submission to OEHHA: Prioritization Comments Part I
Attachments: ExxonMobil DINP submission Part I.pdf

Dear Ms. Oshita:

This is the first of three emails containing comments from ExxonMobil Chemical regarding the prioritization of chemicals to be considered at the
May 29 meeting of the Carcinogen Identification Committee. These comments pertain specifically to diisononyl phthalate (DINP).

The content of the three emails is as follows:

1st email: This first email has attached Part I of ExxonMobil's comments, which is a summary of the pertinent data.

2nd email: The second email has attached Part II of our comments and its attachments, which provide greater detail on the scientific data.

3rd email: The third email has attached a copy of Klaunig et al. (2003), which is a review of the peroxisome proliferation mechanism, based on data for DINP and other chemicals. Other expert body reviews of the DINP data (CPSC CHAP, EU Risk Assessment, NTP CERHR) have been provided to the CIC by OEHHA and/or are readily available on the Internet. Because Klaunig et al.(2003) is not readily available on the Internet and is not cited by OEHHA, we are providing a copy. It is 6 MB -- if not received please let us know and we will break it down.

ExxonMobil would be pleased upon request to provide a copy of any other study cited in our comments.

If the CIC or OEHHA have any questions or need additional information, please contact me or any of the following scientists:

Ammie Bachman, Ph.D., ammie.n.bachman@exxonmobil.com, (908) 730-2082
Bob Barter, Ph.D., robert.a.barter@exxonmobil.com, (908) 730-2153
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Thank you.
(See attached file: ExxonMobil DINP submission Part I.pdf)
Regards,
Laura N. Winks
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COMMENTS ON PRIORITIZATION OF DIISONONYL PHTHALATE (DINP)
Prioritization: Chemicals For Consulation By The Carcinogen Identification Committee

May 5, 2009

Sent via email (coshita@oehha.ca.gov) to:

Cynthia Oshita
Office of Environmental Health Hazard Assessment
Proposition 65 Implementation
P.O. Box 4010 1001 I Street, 19th floor
Sacramento, California 95812-4010

TO THE CARCINOGEN IDENTIFICATION COMMITTEE (CIC):

ExxonMobil Chemical is submitting these comments in response to notification by the California Office of Environmental Health Hazard Assessment (OEHHA) of 38 chemicals for consultation by the Carcinogen Identification Committee (CIC) at its meeting on May 29, 2009. These comments pertain specifically to diisononyl phthalate (DINP), which is one of the 38 chemicals listed for possible preparation of hazard identification materials by OEHHA. ExxonMobil Chemical is a producer of DINP.

DINP was screened from OEHHA's candidate data base because there is more than one rodent bioassay available for it. Liver tumors were observed in rats and mice, kidney tumors in male rats, and mononuclear cell lymphoma (MNCL) in the Fischer 344 rats. These rodent cancer findings have been the subject of detailed reviews by several independent expert bodies, none of which have concluded that the animal findings are indicative of a likely human cancer risk.

The purpose of these comments is to provide the CIC with relevant scientific information to support the CIC's evaluation of DINP, and specifically the CIC's recommendation to OEHHA concerning the level of priority that should be assigned to DINP for future consideration as a candidate chemical for listing under Proposition 65. Part One of the comments presents a summary of the relevant data for DINP, including mechanistic research and studies in primates. Part Two (contained in a separate pdf) presents the relevant information in much greater detail.

For the reasons stated in these comments, ExxonMobil believes that DINP should be ranked as "no priority" or, at the most, "low priority" for purposes of preparing future hazard identification materials. As is evident from the comments, there is an extraordinary wealth of information pertaining to DINP. If OEHHA staff or members of the CIC have questions, or if we can provide further information – including copies of studies cited herein, please contact Laura Winks, laura.n.winks@exxonmobil.com, (281) 870-6439, or any of the scientists listed below.

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We appreciate the opportunity to present this information.

PART ONE
SUMMARY OF PERTINENT DINP DATA

DINP was screened from OEHHA's candidate data base because there is more than one rodent bioassay available for it. Liver tumors were observed in both rats and mice, kidney tumors in male rats, and mononuclear cell lymphoma (MNCL) in the Fischer 344 rats (Moore, 1998a, 1998b; Lington *et al.*, 1997). However, there is a strong body of evidence that the mechanisms for these lesions in rodents are not applicable to humans and therefore they are not relevant for human risk assessment – a finding that has been made by several expert reviewing bodies. Key points include:

- There are no studies in humans showing a cancer risk from DINP.
- DINP is not genotoxic.
- Studies in primates given high doses of DINP and in human and primate cell cultures show no evidence of a potential cancer response.
- In-depth expert body reviews have determined that DINP is unlikely to pose a human cancer risk
- Worst-case human exposures to DINP are far below levels that could cause cancer, even if the animal data were assumed to be relevant for human risk assessment.

These factors all add up to the conclusion that DINP is extremely unlikely to pose a cancer risk to California residents. Accordingly, DINP should be ranked as "no priority" or, at the most, "low priority" for purposes of preparing future hazard identification materials.

The following provides a summary of the data for each of these points. More detailed information is provided as Part II of these comments.

Human Studies

There are no epidemiology studies on the carcinogenic potential of DINP. However, there are studies in non-human primates and in human and primate cell cultures which support the conclusion that tumors observed in rodent studies of DINP are unlikely to occur in humans. These studies are discussed further below.

Genotoxicity Studies

DINP has been evaluated in multiple *in vivo* and *in vitro* genotoxicity/mutagenicity assays and has been negative in all of them. The robust set of genotoxicity tests includes salmonella tests (Ames tests), tests in mouse lymphoma and mouse micronucleus, *in vitro*

cytogenetics, unscheduled DNA synthesis in rat hepatocytes, cytogenetics in rat bone marrow, and the cell transformation assays in Balb/3T3 mice.

The clear conclusion is that DINP is not genotoxic.

Primate Studies

Typically, animal data on a chemical is limited to studies in rats and mice. For DINP, however, there is also an unusually large amount of primate data – data from species that obviously are much more closely related to humans than are rodents – as well as some *in vitro* data for humans.

There have been two studies of DINP in non-human primates. In one, cygnomolgus monkeys were treated with DINP for 14 days at levels up to 500 mg/kg/day (Pugh *et al.*, 2000). In the other, marmosets were treated with levels up to a 2500 mg/kg/day for 90 days (Hall *et al.*, 1999). (For a 160 pound human, this dose would be about six ounces per day.)

In both of these primate studies, there was no evidence of treatment-related effects, including no changes in liver or kidney weights and no treatment-related changes in histopathology, even at the very high levels of treatment.

These studies were subchronic, versus the chronic bioassays in rodents. However, the lack of adverse effects in the primate studies even at very high doses is in contrast to the progression of pathology in rodents. For example, liver and kidney weights were increased in a 28-day study of rats (BIBRA, 1986). 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 strongly indicate that primates are not adversely affected by DINP in the manner of rodents.

As discussed below, liver tumors in rodents treated with DINP are due to the peroxisome proliferation mechanism. There was no evidence of peroxisome proliferation in either human hepatocytes (Baker *et al.*, 1996; Hasmall *et al.*, 1999; Kamendulis *et al.*, 2002) or other primate hepatocytes tested under *in vitro* conditions (Benford *et al.*, 1986; Kamendulis *et al.*, 2002). Thus studies from several laboratories using hepatocytes from different individuals or different species of primates have demonstrated that a peroxisome proliferator response is not elicited by DINP in humans and other primates.

Thus, primate studies and *in vitro* human and primate tests show no evidence of potential carcinogenicity, even under conditions that unquestionably would in rodents provoke responses that are part of the progression to cancer in those species.

Expert Body Reviews

DINP has not been listed as a carcinogen, nor even to date considered for listing, by the International Agency for Research on Cancer (IARC) or the National Toxicology Program (NTP).[1] DINP has been the subject of several in-depth reviews of its carcinogenic potential by eminent expert review bodies, including:

- The Consumer Product Safety Commission (CPSC) Chronic Hazard Advisory Panel on Diisononyl Phthalate (CHAP) in 2000 and 2001;[2]
- A workgroup of the Risk Science Institute of the International Life Sciences Institute (ILSI) in 2003;[3] and
- The European Union (EU) over a several-year period, culminating in a risk assessment report in 2003.[4]

Each has concluded that DINP is unlikely to pose a cancer risk to humans. In each case, this has been based on the foregoing points (no epidemiology data; lack of genotoxicity; primate data) plus a finding that the three types of cancer lesions in rodents (liver tumors, kidney tumors and mononuclear cell lymphoma) occur by mechanisms not relevant for human risk assessment. Specific conclusions with respect to each liver type are discussed below.

ExxonMobil notes that the U.S. Environmental Protection Agency (EPA) *has not* made a final determination regarding the carcinogenicity of DINP. OEHHA has provided a 2000 Federal Register notice in which EPA proposes to list DINP under Section 313 of the Emergency Planning and Community Right-to-Know Act (EPCRA), in part based on the animal cancer data. However, after receipt of comments, EPA published a revised notice on June 14, 2005, in which it reserved judgment on the potential for DINP to cause cancer in humans.[5] EPA accepted further comments and to date has not issued a final decision.

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1 In 2008, the Natural Resources Defense Council nominated DINP for IARC consideration; IARC has not yet indicated whether it will do so.

2 OEHHA has provided a copy of the CHAP report (CPSC, 2001). It is also available at http://www.cpsc.gov/LIBRARY/FOIA/Foia01/os/dinp.pdf

3 An overview of the ILSI workshop (Cohen *et al.*, 2003) is available at http://rsi.ilsi.org/NR/rdonlyres/4CF3FB16-D1F9-4F44-962F-B1553B4A07EF/0/Cohen.pdf. The report of the PPARα subgroup (Klaunig *et al.*, 2003) is being provided with these comments.

4 The full EU Risk Assessment (ECB, 2003a) is available at http://ecb.jrc.it/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/REPORT/dinpreport046.pdf and a Risk Assessment summary (ECB, 2003b) at http://ecb.jrc.ec.europa.eu/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/SUMMARY/dinpsum046.pdf

5 This notice (Fed Reg, 2005) is available at http://edocket.access.gpo.gov/2005/pdf/05-11664.pdf.

Liver Tumors

There is a robust body of data indicating that the liver tumors observed in DINP rodent studies are due to the peroxisome proliferation (or PPARα) mode of action and are not relevant to humans. The progression of liver effects caused by peroxisome proliferators, leading up to and including tumors, has been well characterized, and there is a strong scientific consensus that such effects are not relevant for human risk assessment (*e.g.*, IARC, 1995; Cattley *et al.*, 1998; Klaunig *et al.* 2003). Liver effects observed in the DINP rodent studies are consistent with the peroxisome proliferation mode of action. In contrast, no such effects have been seen in primate studies, even at DINP doses of 2500 mg/kg/day (Hall *et al.*, 1999; Pugh *et al.*, 2000).

The CPSC CHAP concluded "that DINP causes liver cancer in rodents by a PPARα-mediated mechanism, that is pronounced in rodents and believed not readily induced in humans, especially at doses resulting from current use of consumer products" (CPSC, 2001, p. 122). Subsequently, the CPSC staff, based on the CHAP and on the ILSI workshop (see below), have "concluded that DINP, which is a peroxisome proliferator, is not likely to present a cancer risk in humans" (CPSC, 2003).

The ILSI workgroup reviewed the relationship of peroxisome proliferation and liver tumors in rodents. The results of that workshop are presented in a paper titled "PPAR*α* Agonist-Induced Rodent Tumors: Modes of Action and Human Relevance" (Klaunig *et al.*, 2003). DINP is one of the examples of a peroxisome proliferator discussed in the document. The workshop concluded:

> In summary, the weight of evidence overall currently suggests that the rodent [mode of action] for liver tumors is not likely to occur in humans, taking kinetic and dynamic factors into account. This conclusion is based upon evaluation of the existing body of evidence and would apply to the consequences of exposure to *known* examples of PPAR*α* agonists.

(Klaunig *et al.*, 2003, p. 693.) DINP is a known example of a PPARα agonist that was part of the basis for the workshop conclusions. Therefore, the conclusion of the ILSI workshop is that the liver tumors that occur in rodents treated with DINP are not likely to occur in humans.

The EU in its risk assessment of DINP stated:

> The current literature suggests that only rats and mice are responsive to the carcinogenic effects of peroxisome proliferator, while dogs, non-human primates and humans are essentially non-responsive or refractory. In this way, it should be noted that in monkey, following oral administration of DINP for 14 days or 13 weeks there was no evidence of peroxisome proliferation. This indicates that monkeys and subsequently probably humans are far less sensitive than rodents to peroxisome proliferation and its relative liver effects. It should be noted that recently IARC gave a

> ruling on the carcinogenicity of DEHP and concluded that the mechanism (peroxisome proliferation and PPARα activation) by which DEHP increased the incidence of liver tumours in rodents was not relevant to humans.

(ECB, 2003a, p. 243). The EU did not identify carcinogenicity as a critical endpoint (ECB, 2003a, 2003b) and has not classified DINP as a carcinogen (EC, 2000). In the risk assessment summary document, the EU stated that, on the basis of the peroxisome proliferation evidence, "there is no concern for a potential carcinogenic effect in humans." (ECB, 2003b, p. 14)

Ito *et al*. (2007) have proposed an alternative mechanism for induction of liver tumors by another phthalate (DEHP) that is independent of PPARα activation, but this mechanism is not well-substantiated. The hypothesis, based on studies using mice without functional PPARα, suggests increased production of reactive oxygen species as a result of increased oxidative stress in mouse hepatocytes due to DEHP exposure. The applicability of the Ito *et al.*, 2007 results is limited in that a number of reports have indicated that PPARα null mice are more vulnerable to tumorigenesis, even in the absence of any chemical exposure, due to fundamental mechanistic differences from mice with normal PPARα (Mandard *et al*., 2004; Kostadinova *et al*., 2005; Balkwill and Couseens, 2005; Pikarsky *et al*., 2004; Takashima *et al*., 2008). As spontaneous tumors are known to occur in the PPARα null mice at 24 months, the utility of this mouse model to understand alternative mechanisms of tumorigenesis that are independent of PPARα is problematic and can not currently be used to assess relevance to humans. Importantly, with respect to DINP, literature searches reveal no reports that DINP induces production of reactive oxygen species in livers of rodents, humans or non-humans primates, or in cultured liver cells from these species.

Thus, there is a strong scientific consensus that liver tumors in rodents treated with DINP are due to peroxisome proliferation and are not relevant to humans.

Kidney Tumors

IARC and the EPA have each established criteria for a finding that rat kidney tumors are due to the $alpha_{2u}$-globulin mechanism and therefore are not relevant for human risk assessment. DINP meets these criteria. Therefore, reviewing bodies have found that kidney tumors seen in male rats treated with DINP are not relevant for human risk assessment.

The CPSC CHAP report states:

> Male rat specificity in tumor response, lack of genotoxicity, histopathology findings of cytotoxicity and regeneration, α2μ-globulin accumulation**,** and demonstrated cell proliferation strongly support the criteria for demonstrating α2μ-globulin mechanism (IARC, 1998). Therefore, the renal tumors in male rats at the high dose of DINP are assumed to be rat specific and are not used to predict human cancer risk. (CPSC, 2001, p. 91)

The EU risk assessment states: "Pertaining to kidney tumours, the species and sex-specific alpha 2u globulin mechanism likely responsible for kidney tumours seen in male rats is not regarded as relevant to humans." (ECB, 2003a, p. 223; ECB, 2003b, p. 14)

Thus, there is a strong scientific consensus that kidney tumors in male rats treated with DINP are due to the alpha2u-globulin mechanism and are not relevant to humans

Mononuclear Cell Leukemia (MNCL)

Mononuclear cell leukemia (MNCL) was observed in the two DINP chronic studies conducted in Fisher 344 rats (Lington *et al.*, 1997; Moore *et al.*, 1998a), but not in the bioassay conducted in mice (Moore *et al.*, 1998b). MNCL is a spontaneous lesion that occurs with high and variable frequency in Fisher 344 rats. A number of authoritative bodies, including EPA, NTP, and the National Institutes of Health (NIH), and a recently published academic review (Thomas *et al*., 2007) have questioned the relevance of MNCL data for human risk assessment purposes and have suggested that a weight of evidence approach be taken when statistically identified increases in MNCL are observed. This position has also been taken in expert body reviews of DINP.

The CPSC CHAP concluded: "The findings of mononuclear cell leukemia and renal tubular carcinoma in the rodent bioassay for DINP are of questionable relevance to humans" (CPSC, 2001, p. 122).

The EU Risk Assessment states:

> Regarding MNCL, a clear increase incidence is observed in the two studies conducted with Fisher rats (outside the historical range of spontaneous leukemia), along with shortening of the onset of MNCL. However, MNCL is a common neoplasm in the Fischer 344 rats and the increased incidence after chronic exposure to some substances is likely a strain specific effect with little relevance for humans. Of interest, the IARC categorised MNCL as "an unclassified leukemia with no known human counterpart" and substances which increase MNCL frequency as "not classifiable as to carcinogenicity in humans" (IARC, 1990).

(ECB, 2003a, p. 225).

Thus, there is a strong scientific consensus that mononuclear cell leukemia observed in fisher F344 rats treated with DINP is not relevant to humans.

Testicular Dysgenesis Syndrome (TDS)

In the compilation of studies on DINP, under the heading "Mechanisms", OEHHA lists "Testicular dysgenesis syndrome." The term testicular dysgenesis syndrome (TDS) was coined in 2001 by Skakkebaek *et al.* (2001), who hypothesized that cases of abnormal spermatogenesis,

cryptorchidism (undescended testicles), penile malformations such as hypospadias, and incidences of testicular cancer observed in humans all have a common etiology. Sharpe (2003) proposed that suppression of fetal androgen production and/or increased estrogen exposure might underlie occurrence of this syndrome with respect to certain phthalates.

Data for DINP are inconsistent with respect to anti-androgenic effects in young male rats. Two studies, which used an unrealistically high dose of DINP administered by gavage, resulted in a questionably significant increase in malformation of the male reproductive tract (Gray *et al.*, 2000) or decreased testosterone in male rats (Borch *et al.*, 2004). In contrast, no anti-androgenic effects were observed in male offspring of pregnant rats exposed to higher levels of DINP in the diet (Masutomi, *et al.*, 2003). Additionally, more definitive rat studies (2-generation reproduction and developmental studies) indicate that DINP does not induce cryptorchidism, hypospadias or low sperm counts.

Therefore, the weight of data indicates that DINP does not cause TDS.

Human Exposures to DINP

ExxonMobil is aware that Proposition 65 listing is based on hazard, not risk. However, for purposes of setting priorities, we believe it is appropriate to uses and exposure, and the practical significance of a Proposition 65 listing decision. We believe these factors add to the conclusion that DINP should be a low priority for review.

Since 1999, the CDC has been analyzing samples of urine from the U.S. population for phthalate metabolites. CDC has reported its biomonitoring findings in reports issued in 2001, 2003 and 2005. The 2003 report includes the data from the 2001 report, and provides results for samples from 2541 persons (CDC, 2003). The 2005 report provides data for an additional 2772 persons (CDC, 2005). The DINP exposure corresponding to the urinary metabolite concentration can be calculated using the method of David (2000).

The latest CDC data provide little evidence of any measurable exposure to DINP. Specifically, for the results reported in 2005, no DINP metabolite was detected in the overall population even at the 95th percentile, nor in subgroups divided by age (CDC data were reported by percentiles and the data for DINP was "ND" for all percentiles). DINP was detected only at the 95th percentile for Mexican Americans and Non-Hispanic Blacks in the 2005 report, corresponding to an exposure of 0.67 µg/kg/day for Mexican Americans and less for Non-Hispanic Blacks.

In 2003, no DINP metabolite was detected at the 50th or 75th percentile levels, showing that 75 percent of the population has no measurable exposure from all potential sources.

Conversion of the 2003 report 95th percentile yields a DINP exposure of 0.88 µg/kg/day. The 95th percentile value for children corresponds to a DINP exposure of 0.67 µg/kg/day.[6]

The lowest DINP dose that has been associated with tumor induction is 336 mg/kg/day in female mice, with effects in other species and sexes occurring at levels ranging from approximately 700 to 900 mg/kg/day (Moore *et al.*, 1998a; b). This is more than 336,000 times greater that the highest 95th percentile exposures to this non-genotoxic substance, taken from the 2003 report. As already described, the evidence is that humans are far less sensitive than mice to effects to DINP.

Thus, it is not plausible that exposures of Californians to DINP would contribute to cancer incidence.

Conclusion

ExxonMobil respectfully submits that he foregoing demonstrates that DINP is highly unlikely to cause cancer in humans and should not be listed as a carcinogen. Thus, DINP should be ranked "no priority" or, at the most, "low priority" for development of a hazard identification document.

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NOTE: ExxonMobil would be pleased upon request to provide a copy of any of these studies.

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