May 5, 2009

Via E-Mail

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

Re: Prioritization of DINP by the Carcinogen Identification Committee

Dear Ms. Oshita:

The American Chemistry Council Phthalate Esters Panel (Panel)[1] submits these comments to the Office of Environmental Health Hazard Assessment (OEHHA) regarding the toxicology of diisononyl phthalate (DINP). The Panel understands that these comments will be forwarded to the Carcinogen Identification Committee (CIC) prior to its May 29, 2009, public meeting. Importantly, the CIC will provide OEHHA with advice on the prioritization of DINP, and 37 other chemicals, for possible preparation of hazard identification materials. These materials will be used by the CIC at future meetings to decide which chemical or chemicals to add to the Proposition 65 list of carcinogens.

The Panel is composed of all major manufacturers and some users of DINP and other primary phthalate esters in commerce in the United States. OEHHA's efforts to prioritize DINP thus have a direct and substantial impact on the Panel members. Based on the weight of the scientific evidence, the Panel strongly urges the CIC and OEHHA to assign DINP, "no priority," or, at most, a "low priority."

DINP was identified by OEHHA for consultation by the CIC based on a compilation of relevant studies identified during a preliminary toxicological evaluation. References, including three rodent bioassays, genotoxicity data and mechanistic studies related to tumor induction and Testicular Dysgenesis Syndrome (TDS), were provided to the CIC for its review and consideration.

As set forth in more detail below, and in the comments submitted under separate cover by the ExxonMobil Chemical Company, which the Panel fully endorses and incorporates herein by reference, there is a strong body of evidence that DINP-induced lesions in rodents are not

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[1] The Panel members are: BASF Corporation, Eastman Chemical Company, ExxonMobil Chemical Company, and Ferro Corporation. Teknor Apex Company, a major user of the materials, is an associate member.

relevant to humans – a finding that has been made by several expert reviewing bodies. Studies based on DEHP have suggested alternative mechanisms for tumorigenesis in genetically-altered mice are not relevant to humans. Moreover, exposure to DINP does not result in TDS. In addition, environmental exposures to DINP, as consistently evidenced by biomonitoring data from the Centers for Disease Control and Prevention (CDC), are remarkably low, and far below levels of concern.

I. DINP IS NOT MUTAGENIC OR GENOTOXIC

The conclusion that DINP is not mutagenic or genotoxic is supported by a robust database. DINP was not mutagenic in an Ames assay using 5 strains of *Salmonella typhimurium* and did not induce an increase in chromosomal aberrations in Chinese hamster ovary cells (Zeiger *et al*., 1985; McKee *et al*., 2000). Additionally, it did not cause unscheduled DNA synthesis in rat hepatocytes (Litton Bionetics, 1981). In vivo, DINP was inactive in a micronucleus test in mouse bone marrow (McKee *et al*., 2000) and it did not induce an increase in chromosomal aberrations in rat bone marrow cells (Microbiological Associates, 1981). DINP was inactive in a mouse lymphoma test and in a cell transformation assay in Balb 3T3 cells Barber *et al*., 2000).

II. ANIMAL CANCERS IN RODENTS EXPOSED TO DINP ARE NOT RELEVANT TO HUMANS

DINP at high does produces liver tumors in rats and mice, kidney tumors in male rats, and mononuclear cell leukemia (MNCL) in rats (Lington *et al*., 1997; Moore, 1998a,b; Bio/dynamics, 1986). There is a substantial body of research providing compelling evidence that these tumors in rodents are not relevant for human health assessment.

A. Liver Tumors Observed in Rodents Are Due to Peroxisome Proliferation

There is a robust body of data indicating that the liver tumors observed in DINP rodent studies were due to the peroxisome proliferation (or PPARα) mode of action. 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). All liver effects observed in the DINP rodent studies, with the possible exception of spongiosis hepatis (a spontaneous lesion in rats), were consistent with the peroxisome proliferation mode of action. In contrast, no such effects were seen in the primate studies, even at doses of 2500 mg/kg/day (Hall *et al.*, 1999; Pugh *et al.*, 2000).

Primate data provide the best basis for determining whether chronic effects seen in rodents can reasonably be anticipated to occur in humans. There have been two *in vivo* 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 colossal 2500 mg/kg/day for 90 days (Hall *et al.*, 1999). In both of these primate studies, there was no evidence of treatment-related effects, including liver or kidney weights or treatment-related changes in histopathology, even at the very high levels of treatment. There was no evidence of peroxisome proliferation in non-human primate hepatocytes tested under *in vitro* conditions (Benford *et al.*, 1986; Kamendulis *et al.*, 2002), or in human hepatocytes (Baker *et al.*, 1996; Hasmall *et al.*, 1999; Kamendulis *et al.*, 2002).

Thus, studies from several laboratories using hepatocytes from different individuals or different species of non-human primates have demonstrated that a peroxisome proliferator response is not elicited by DINP in these species. And of particular relevance to the CIC's review of DINP, these studies show no evidence of potential carcinogenicity, even under conditions that unquestionably would elicit tumorigenesis in rodents, including the progression to cancer.

B. Numerous scientific reviews provide further support for the position that the rodent liver tumors have no relevance to humans

A review of peroxisome proliferation by the International Agency for Research on Cancer (IARC) concluded that rats and mice had a much higher propensity for peroxisomal proliferation than other species including humans. Specifically, IARC concluded that "...the mechanism by which DEHP increases the incidence of hepatocellular tumors in rats and mice is not relevant to humans" (IARC, 1995; Cattley *et al*., 1998; Klaunig *et al*., 2003). Although DINP has not yet been evaluated by IARC, the available data are very similar to those for DEHP, so similar conclusions are anticipated.

In 2003, a workgroup of the ILSI Risk Science Institute reviewed the relationship of peroxisome proliferation and liver tumors in rodents. The results of that workshop are presented in a paper titled "PPARα 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 PPARα 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.

Other reviews support the ILSI and IARC conclusions. For example, the Consumer Product Safety Commission (CPSC) Chronic Hazard Advisory Panel on Diisononyl Phthalate

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" (CHAP, 2001, p. 122). Subsequently, the CPSC staff, based on the CHAP and on the ILSI workshop, have "concluded that DINP, which is a peroxisome proliferator, is not likely to present a cancer risk in humans" (CPSC, 2003).

Similarly, the European Union (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, 2003, p. 243, emphasis added). The EU did not identify carcinogenicity as a critical endpoint (ECB, 2003) and has not classified DINP as a carcinogen (EC, 2000).

In the summary of available scientific information on DINP, OEHHA references the U.S. Environmental Protection Agency's (EPA's) 2000 proposal to add DINP to the list of toxic chemicals subject to the reporting requirements under EPCRA section 313. In its original proposal to list DINP, EPA stated that DINP can reasonably be anticipated to cause carcinogenicity, based on liver tumors, kidney tumors and mononuclear cell leukemia (MNCL) observed in rodent studies.[2] In 2005, EPA revised its hazard assessment in response to public comments and subjected the revised assessment to peer review by both EPA experts and external peer reviewers. This revised assessment, however, was not included by OEHHA in the materials provided to the CIC. Importantly, in this revised assessment, EPA reconsidered the evidence of DINP carcinogenicity and stated that "at this time, EPA reserves judgment on whether DINP can reasonably be anticipated to cause cancer in humans."[3]

Recent studies conducted in Japan using PPAR-knockout mice (KO) suggested that liver tumors might occur in KO mice via a PPAR-independent mechanism (Ito *et al*., 2007). However, no such tumors were observed in wild-type mice with an intact PPAR receptor. Therefore, the relevance of these tumors in KO mice to humans and the PPAR mode of action is unclear.

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[2] 65 Fed. Reg.53684-86, (Sept. 5, 2000).

[3] 70 Fed. Reg. 34439-40, (June 14, 2005).

C. Kidney Tumors Observed in Male Rats Are Due to Alpha-2u-Globulin Nephropathy and Are Not Relevant to Humans

The kidney tumors observed in bioassays in male rats were the result of induction of alpha-2μ-globulin. Male rats are known to be susceptible to formation of kidney tumors through a mechanism involving alpha2u-globulin accumulation. Because humans do not produce alpha2u-globulin, such male rat kidney tumors are not relevant for human health assessment. (EPA, 1991; Swenberg and Lehman-McKeeman, 1998).

As acknowledged in EPA's revised hazard assessment on DINP, the CPSC CHAP (2001), and the EU Risk Assessment (ECB, 2003), the data for DINP meet the criteria for the existence of alpha-2u-globulin nephropathy, a male rat-specific mechanism not relevant to humans. In particular, EPA states:

> The data obtained in [DINP] studies were evaluated against published criteria for evaluating male-specific nephropathy and its relevance to human. The results of this evaluation indicate that: (1) all three EPA criteria for existence of the alpha-2u-globulin mode of action have been met; (2) six of the seven International Agency for Research on Cancer (IARC) criteria for existence of the alpha-2u-globulin process have been met; and (3) EPA has not found other information or data to suggest that another mechanism is likely to be involved. **Based on this evaluation, the Agency believes that DINP-induced kidney tumors are associated with a male rat-specific mechanism involving alpha-2u-globulin accumulation in the kidney and that this mechanism is not appropriate for estimating hazard in humans**.[4]

The seventh IARC criterion that EPA asserts has not been met is evidence that DINP binds to alpha-2u-globulin.[5] Binding of DINP to alpha-2u-globulin, however, has been shown by Schoonhoven *et al.*, (2001).

Thus all criteria of both the EPA and IARC criteria for the alpha-2u-globulin mechanism are met by the DINP data. For chemicals that meet the alpha-2u-globulin:

> Male rat renal tubule tumors arising as a result of a process involving α_{2u}-g accumulation do not contribute to the qualitative weight-of-evidence that a chemical poses a human carcinogenic hazard. Such tumors are not included in dose-response extrapolations for the estimation of human carcinogenic risk. (EPA, 1991, p. 85.)

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[4] *Id.* at 68-69 (citations and footnotes deleted, emphasis added).

[5] *Id.* at 69, note 4.

D. Mononuclear Cell Leukemia Observed in Fisher F344 Rats Is Not Relevant to Humans

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). Reviewing this data, 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" (CHAP, 2001, p. 122). Moreover, 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).

(EU, 2003, p. 225).

Other authoritative bodies, including EPA, the National Toxicology Program, the National Institutes of Health, 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 the application of a weight of evidence approach when statistically identified increases in MNCL are observed.

III. RECENTLY PROPOSED PPARA-INDEPENDENT MECHANISMS OF TUMORIGENESIS ARE NOT WELL SUBSTANTIATED

An alternative mechanism for phthalate ester (*i.e.,* DEHP) induced liver tumors has been recently proposed that is independent of PPARα activation (Ito *et al*., 2007). 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, however, is limited in that a number of reports have indicated that PPARα null mice are more vulnerable to tumorigenesis in the absence of any chemical exposure due to fundamental mechanistic differences (Mandard *et al*., 2004; Kostadinova *et al*., 2005; Balkwill and Couseens, 2005; Pikarsky *et al*., 2004; Takashima *et al*., 2008). Spontaneous tumors are known to occur in the PPARα null mice at 24 months. The utility of this mouse model to assess alternative mechanisms of tumorigenesis, therefore, is problematic as is its relevance to humans. Importantly, there are no known reports

on the ability of DINP to induce production of reactive oxygen species in livers of rodents, humans or non-humans primates, or in cultured liver cells from these species.

IV. EXPOSURE TO DINP DOES NOT RESULT IN TESTICULAR DYSGENESIS SYNDROME

The term Testicular Dysgenesis Syndrome (TDS) was introduced in 2001 when it was 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 (Skakkebaek *et al*., 2001). In particular, it has been proposed that suppression of fetal androgen production and/or increased estrogen exposure is the underlying basis of this syndrome (Sharpe, 2003). The available data, however, are inconsistent in demonstrating that DINP produces antiandrogenic 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 antiandrogenic 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 (*i.e.*, 2-generation reproduction and developmental studies) indicate that DINP does not induce cryptorchidism, hypospadias or low sperm counts and therefore do not support attributing TDS to DINP exposure **(**Waterman *et al*., 2000).

V. HUMAN EXPOSURES TO DINP ARE FAR BELOW LEVELS THAT COULD CAUSE CANCER, EVEN IF THE ANIMAL DATA ARE ASSUMED RELEVANT FOR HUMAN RISK ASSESSMENT

Since 1999, the CDC has been analyzing samples of urine from the U.S. population for phthalate metabolites. CDC has reported its biomonitoring findings, representative of the U.S. population, 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).

For the results reported in 2003, no DINP metabolite was detected at the 50th or 75th percentile levels. At the 95th percentile, the creatinine-corrected value for the total population was 4.29 ug/g, which corresponds to a DINP exposure of 0.88 µg/kg/day. The 95th percentile creatinine-corrected value for children, age 6-11, was 6.00, corresponding to a DINP exposure of 0.67 mg/kg/day.

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] DINP was detected 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.

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. It was detected at the 95th percentile for Mexican Americans and Non-Hispanic Blacks, although the levels reported were lower than those reported in 2003. The higher of the two 95th percentile levels was for Mexican Americans – 2.31 ug/g, that converts to an exposure of 0.67 µg/kg/day.

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 95th percentile exposures to this non-genotoxic substance. Even assuming humans were 100 times more sensitive than mice, exposures would still be more than 3360 times lower than a level necessary to produce tumors in mice. The scientific evidence, however, 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, even if the animal data are assumed relevant to human risk assessment.

CONCLUSION

Based on the available data for DINP, it can be concluded that the cancer findings in rodent bioassays are not relevant to humans, proposed alternative mechanisms for tumorigenesis are problematic, and a role for DINP in TDS is not well substantiated. Moreover, it is not plausible that exposures of Californians to DINP would contribute to cancer incidence, even if the animal data are assumed relevant to human risk assessment. The Panel, therefore, urges the CIC and OEHHA to assign DINP a "no priority" or, at most, "low priority." If you have any questions regarding this submission, please contact me at (703) 741-5609 or at Chris_Bryant@americanchemistry.com.

Sincerely,

Chris Bryant

Chris Bryant, Managing Director
Chemical Products and Technology Division

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