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November 18, 2012

VIA HAND AND ELECTRONIC DELIVERY TO OEHHA

Thomas Mack, Ph.D., M.D., Chairperson, and Committee Members
Carcinogen Identification Committee

RE: Comments of BASF Corporation in Opposition to Listing of Diisononyl Phthalate as a Carcinogen Under Proposition 65

Dear Dr. Mack and Committee Members:

We are submitting the attached Comments of BASF Corporation in Opposition to Listing of Diisononyl Phthalate as a Carcinogen Under California's Proposition 65, prepared by our client to assist the Committee in its evaluation of whether the a group of chemicals referred to collectively as Diisononyl Phthalate (or "DINP") should be designated (or "listed") as a chemical "known to the State to cause cancer" for purposes of the Safe Drinking Water and Toxic Enforcement Act of 1986 ("Proposition 65").

According to an announcement posted by OEHHA, these chemicals will be considered by the Committee at its public meeting on December 5, 2013. We have requested that this letter and the attached BASF Comments be distributed to you along with other documents that OEHHA may provide. We also identify below some critical points the Committee should consider, demonstrating that DINP should not be listed.

1. REFERRAL OF DINP TO THE CIC DOES NOT INDICATE THAT DINP SHOULD BE LISTED

DINP has been referred to this Committee so that you may ***evaluate*** the scientific data and determine ***whether*** the chemical should be listed under Proposition 65. While this may be understood, we feel it is worth mentioning because this is only the second meeting of the Committee for several of its newer members, and it may appear from the nature of this process and some of the documents referred to the Committee that the expected outcome of this proceeding is to list the chemical. In fact, the summary and descriptions of the studies summarized in the document entitled "Evidence on the Carcinogenicity of Diisononyl Phthalate (DINP)" (referred to herein as the "Hazard Identification Document" or "HID"), which OEHHA has provided you, inappropriately imply that OEHHA and or certain researchers believe that DINP should be designated as a carcinogen.

That conclusion, if the Committee were to reach it, would be wrong. But in case the summary of data in the HID creates the impression that listing should be a foregone conclusion, we

call to your attention the following portions of the frequently-overlooked Preface to this Document (at page i), which state as follows:

> ". . . OEHHA selected diisononyl phthalate as a chemical for ***consideration for listing*** by the CIC."
>
> * * * *
>
> "OEHHA developed this document on the ***possible carcinogenicity*** of diisononyl phthalate to assist the CIC in its deliberations on ***whether or not the chemical should be listed*** under Proposition 65."
>
> * * * *
>
> "On December 5, 2013, the CIC is scheduled to deliberate on the [possible] carcinogenicity of DINP and determine ***whether*** the chemical has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer."[1]

2. *Listing a Chemical Requires a Determination by the Committee That the Substance Is "Clearly Shown" by the "Weight-of-Evidence" to Cause Cancer*

It is the role of the Committee, in its collective judgment, to determine ***whether*** DINP should be designated as a carcinogen. That judgment is not a subjective one, however. Rather, it requires an objective determination, in accordance with strict criteria established under Proposition 65 (the statute), its implementing regulations and a further set of guidance criteria established by the Committee itself in 2001.

The Statute. For purposes of this proceeding, a "chemical is known to the state to cause cancer . . . if in the opinion of the state's qualified experts [*i.e.,* the Committee] it has been ***clearly shown*** through ***scientifically valid testing*** according to ***generally accepted scientific principles*** to cause cancer . . . ." California Health & Safety Code § 25249.8(b). (Emphasis added.)[2] (This

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[1] "Evidence on the Carcinogenicity of Diisononyl Phthalate (DINP)," Preface at (i). (Emphasis added).

[2] We have omitted from this quotation portions of the statute that relate to chemicals considered for listing because they are "known to the state to cause ***reproductive toxicity***" or to chemicals that may be listed because an "authoritative body" such as the United States Environmental Protection Agency ("EPA") or Food & Drug Administration ("FDA") have designated them as carcinogens (or reproductive toxicants), or to chemicals that a state or federal agency has formally required to be labeled as causing cancer or as reproductive toxicants. Because it is the role of the Committee members in this proceeding to determine in their judgment whether DINP is "known to cause cancer," those provisions of the statute are not directly relevant to the proceeding here. In this context, however, it is relevant for the Committee to consider that a number of expert bodies, including the Consumer Product Safety Commission, the European Union via its pre-REACH existing chemicals risk assessment process, the European Chemicals Agency, the Australian government, and the Risk Sciences Institute of the International Life Sciences Institute have conducted extensive reviews of the toxicology data on DINP, and none of these bodies have reached a conclusion that DINP should be classified or regulated as a carcinogen. Although none of these agencies is "authoritative" for purposes of Proposition 65, each is certainly competent in assessing carcinogenicity data. A decision by the Committee to list DINP would be inconsistent with the actions of these), as discussed further herein.

standard is incorporated in the passage quoted from the Preface of the OEHHA document, referred to above.)

This determination thus will require the Committee to evaluate all of the data presented to it, to cull from the body of evidence any data that are not "scientifically valid . . . according to generally accepted scientific principles," and to refrain from considering any such "invalid" data in support of listing. This is particularly important in reviewing the HID. In our view, for reasons discussed in the attached BASF Comments, some of the studies summarized in the HID and presented as "evidence of carcinogenicity" would not support such a conclusion.

The Regulations. The duties of this Committee in making its determination are set forth in Proposition 65 implementing regulations, which also have the force of law. In pertinent part, these regulations provide that the CIC may "render an opinion . . . whether [DINP has] been ***clearly shown***, through ***scientifically valid testing*** according to generally accepted principles, to cause cancer."[3]

The ***CIC Criteria Document.*** In addition, the regulations provide the Committee with authority to "[r]eview or propose standards and procedures for determining reproductive toxicity of chemicals."[4] The Committee exercised that authority in March 2001, publishing a document entitled "Guidance Criteria for Identifying Chemicals for Listing as 'Known to the State to Cause Cancer.'"

This document, referred to herein as the "CIC Criteria Document," is five pages long. Accordingly, we have included it as an attachment to this letter, and we address below only the most critical passages.

The CIC Criteria Document provides that:

> The "criteria included herein ***shall be utilized*** by the [CIC] to identify those chemicals which are to be recommended for listing as known to the State to cause cancer."[5]
>
> * * *
>
> "In evaluating the sufficiency of available data, a ***"weight of evidence" approach shall be used*** to evaluate the body of information for a given chemical."[6]

There are no human (epidemiological) studies regarding carcinogenic effects of DINP, so the determination whether it should be designated a carcinogen must be based solely on animal studies. The CIC Criteria Document specifies in this circumstance that a chemical may be listed on the basis of animal data if "it causes invasive cancer in animals . . . ***unless the mechanism of action has been shown not to be relevant to humans . . . .***"[7]

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3 22 Cal. Code Regs. § 25305(b)(2) (emphasis added).

4 22 Cal. Code Regs. § 25305(a)(4).

5 CIC Criteria Document, "General Principles," at Section I.A.

6 *Id.* at Section I.C.

7 *Id.* at Section I.D.

In Section II.B.,[8] the CIC Criteria Document indicates that the key question in evaluating animal data is whether the "weight of the evidence" shows a "causal relationship" between the "cancer outcome" and "the exposure" to the chemical tested.[9]

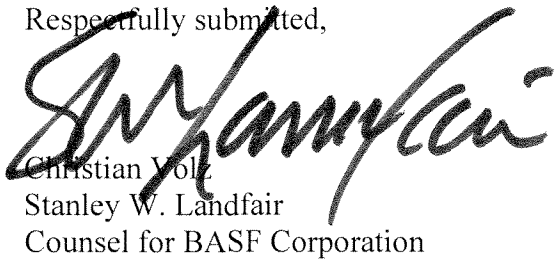
3. *THE WEIGHT OF THE EVIDENCE INDICATES THAT DINP SHOULD NOT BE LISTED*

In the attached BASF Comments, our client demonstrates various reasons why the summaries of the animal data in the are both exaggerated and misleading. To summarize, the HID lists and describes numerous animal studies and indicates that they are persuasive evidence that DINP causes cancer in multiple organs in multiple species, implying that these studies are compelling evidence that DINP would cause the same tumors in humans. A close evaluation of these data, however, and of the reviews of those studies conducted by other expert bodies, shows that all of the tumors that DINP is thought to have caused in rodents (1) are irrelevant to humans; (2) were not detected even in the rodent studies consistently or in numbers that would constitute evidence of carcinogenic effects; and/or (3) for other reasons are not persuasive evidence that exposure to DINP would produce the same effects in humans.

CONCLUSION

For all of the reasons articulated in the attached BASF Comments and those stated above, DINP should not be listed as "known to cause cancer" for purposes of Proposition 65. We look forward to discussing this with you in person at the upcoming December 5 public meeting.

Respectfully submitted,



Christian Volz
Stanley W. Landfair
Counsel for BASF Corporation

Attachments: (1) Comments of BASF Corporation in Opposition to Listing of Diisononyl Phthalate as a Carcinogen Under California's Proposition 65
(2) Guidance Criteria for Identifying Chemicals for Listing as "Known to the State to Cause Cancer"

cc: George Alexeeff, Ph.D., Director, OEHHA
Carol Monahan-Cummings, Chief Counsel, OEHHA

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8 Section II of the Criteria Document is mis-numbered in the original as Section "2."

9 *Id.* at Section II.B.

ATTACHMENT 1

BASF

The Chemical Company

November 18, 2013

Ms. Cynthia Oshita
Office of Environmental
Health Hazard Assessment
Post Office Box 4010, MS-19B
Sacramento, California 95812-4010

RE: COMMENTS OF BASF IN OPPOSITION TO PROPOSED LISTING OF DIISONONYL PHTHALATE AS A CARCINOGEN UNDER CALIFORNIA'S PROPOSITION 65

Dear Ms. Oshita,

These comments are submitted on behalf of BASF Corporation ("BASF") in opposition to the proposed listing of diisononyl phthalate ("DINP") as a carcinogen under California's Proposition 65, and in response to the "Hazard Identification Document" ("HID") entitled "Evidence on the Carcinogenicity of Diisononyl Phthalate (DINP)" prepared by the Reproductive and Cancer Hazard Assessment Branch, Office of Environmental Health Hazard Assessment ("OEHHA"), dated October 2013.

As explained below, the HID presents an exaggerated and misleading assessment of the available animal data on DINP. Both in its executive summary and again in its conclusion, the HID lists animal studies that the HID indicates are persuasive evidence that DINP causes cancer in multiple organs in multiple species, implying that these studies are compelling evidence that DINP would cause the same tumors in humans. A careful review of the animal studies in question, however, and of the reviews of those studies by other expert bodies, discloses that all of the tumors that DINP allegedly caused in rodents are (1) irrelevant to humans; (2) were not detected even in the rodent studies consistently or in numbers that are evidence of carcinogenic effects; and/or (3) are otherwise not persuasive evidence that the same effects would be produced by human exposures to DINP. BASF therefore submits that the Carcinogen Identification Committee ("CIC") should conclude that the weight of all available scientific evidence does not support a conclusion that DINP has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer in humans.

DISCUSSION

The HID suggests that available animal data show evidence that DINP causes cancer in multiple organs in rats, or mice, or both, including: testicular tumors (testicular interstitial cell carcinomas); pancreatic tumors (pancreatic islet cell carcinomas); uterine tumors (endometrial adenocarcinomas); mononuclear cell leukemia; kidney tumors (renal tubular cell carcinomas, renal transitional cell carcinomas); and liver tumors (hepatocellular carcinomas). We will address the evidence for each of these alleged animal tumors in turn.

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Testicular tumors

The HID states that the incidence of testicular interstitial cell carcinomas was increased in one animal study in male SD rats (Bio/dynamics 1986, as reviewed by CPSC, 2001). The HID concedes that "the increase did not reach statistical significance," but asserts that "these tumors are considered uncommon in untreated male SD rats." HID at p. 65. The implication is that this study should be considered to add to the "weight of evidence" that DINP causes cancer despite the lack of a statistically significant increase in the incidence of testicular tumors.

There are multiple reasons to reject that suggestion. First, the rate at which the tumors were detected in the Bio/dynamics study (11.67%) was within the range of its incidence in historical controls (1.4 to 13.3%, McMartin, 1992), and thus its appearance in the study cannot fairly be described as "rare" or suggestive of an effect of DINP. Second, the substance used in the Bio/dynamics study is not currently manufactured and was never commercialized, which raises questions about the relevance of the studies to current commercial forms of DINP. Finally, DINP has not been shown to have adverse effects on the testes. While the studies cited by OEHHA report a minimal effect on the developing male reproductive tract, testicular dysgenesis as evidenced by cryptorchidism or testicular histopathology has not been shown following exposure to DINP. The adult testis of rats has not been shown to be a target organ (CPSC, CHAP, 2001); nor is there any evidence of testicular effects in non-human primates (Hall et al., 1999; Pugh et al., 2000). Therefore, testicular tumors are exceedingly unlikely to be attributable to DINP exposures.

Pancreatic Tumors

The HID states that the incidence of pancreatic islet cell carcinomas was increased in one study in male SD rats (Bio/dynamics, 1986 as reviewed by CPSC, 2001), and in one study in female B6C3F1 mice (Moore, 1998b as reviewed by CPSC, 2001). Again, the HID concedes that in both studies, "the increase did not reach statistical significance," but also again, asserts that "these tumors are considered rare in untreated male SD rats [and untreated female B6C3F1 mice]." HID at pp. 64-5. The implication is that these "rare" tumors should also be considered to add to the weight of evidence that DINP causes cancer in humans.

This suggestion also is clearly unpersuasive. First, as with the testicular tumors discussed above, the incidence of pancreatic cell tumors in both the SD rats and the B6C3F1 mice was within the range of historical controls. The SD rat incidence in the Bio/dynamics study was 4/70 in the high dose group (5.7%). Historical control incidence data for this type of tumor in male SD rats is from 2.9 to 13.8% (McMartin, 1992), and from 1.6 to 25.7% (Charles River Laboratories, 2004). The B6C3F1 mouse incidence in the Moore 1998 study was 2/70 (2.8%) in the high dose group. Historical control incidence data for this tumor in B6C3F1 mice is from 0 to 4% (stated on Table 13, NTP, 2005). Second, this pancreatic tumor was ***not*** observed at elevated levels in the female SD rats in the 1986 Bio/dynamics study or in the male B6C3F1 mice in the Moore 1998b study, and was ***not*** observed in male or female F344 rats in the robust Lington study or the Moore 1998a study. Third, as noted above, the Bio/dynamics study used a formulation of DINP which is not currently manufactured, which raises questions about the relevance of any effects observed in that study for current commercial forms of DINP. Finally, the mode of action for pancreatic islet cell tumors is likely endocrine-related; for example, animals exposed to sodium chlorate (NTP, 2005) developed thyroid gland tumors in rats (with a concomitant decrease in thyroid hormones) and pancreatic islet cell tumors in female mice. Thus, both tumor types may be related to interference with the metabolic homeostasis regulated by the thyroid gland and hormones. There is no such

thyroid-associated effect with DINP. For all these reasons, the non-significant increase in pancreatic islet cell tumors reported in the Bio/dynamics study is not persuasive evidence that DINP causes such tumors in rodents, much less in humans.

Uterine Tumors

The HID states that an increased incidence of uterine tumors (endometrial adenocarcinomas) was observed in female rats in the same 1986 Bio/dynamics study. The HID again concedes that "the increase did not reach statistical significance," but again, claims that these tumors are rare in untreated female SD rats. HID at 65. The implication again is that these "rare" tumors should be considered to add to the weight of scientific evidence that DINP causes cancer in humans.

This suggestion is unpersuasive for essentially all the same reasons stated above. First, the rate at which such tumors were detected (2/69 in the high-dose group) is within the range of historical controls (0.77-5.3%, Charles River Laboratories, 2004; 0-14%, McMartin, 1992), so its appearance in this study cannot fairly be described as "rare." Second, the Bio/dynamics study used a formulation of DINP that is not currently manufactured, which raises questions about the relevance of any effects reported in this study for current commercial forms of DINP. Third, this uterine tumor was ***not*** observed in F344 female rats in the robust Moore (Moore, 1998a, as reviewed by CPSC, 2001) and Lington (Lington et al., 1997) studies. Finally, uterine tumors are endocrine-related, typically associated with activation of the estrogen receptor (Yoshida et al, 2012; Kakehashi et al, 2012). DINP does not interact with the estrogen receptor or act as an estrogen-mimic in whole animals (NTP CERHR Expert Panel Report, 2001 published as Kavlock et al, 2002). Therefore, using this tumor as evidence of carcinogenicity is without scientific merit.

In summary, non-statistically significant increases in testicular, pancreatic and uterine tumors, reported almost exclusively in a single study, within the range of historical controls, using a suspect formulation of DINP, and not observed in the same test animals in other, at least equally robust studies are entirely unpersuasive evidence that DINP causes such tumors even in rodents. They add nothing at all to the weight of scientific evidence that DINP might cause those tumors or any other form of cancer in humans.

Mononuclear Cell Leukemia

The HID states that mononuclear cell leukemia was significantly increased in both male and female F344 rats in three studies (Moore, 1998a as reported by CPSC, 2001,(twice), and Lington et al., 1997). HID at 64. OEHHA makes no reference in the "summary of effects" at page 64 of the HID to the fact that there are questions about the relevance of this particular form of tumor for humans, although OEHHA does note elsewhere that in 2001 "a majority of the CPSC CHAP considered the increased mononuclear cell leukemia observed in DINP-exposed male and female rats to be of questionable significance due to high and variable background and possible strain specificity." HID at 62. That concession, while accurate, understates the extent of expert skepticism regarding the relevance of this tumor to humans. Mononuclear cell leukemia is a rare form of tumor uniquely associated with one particular strain of rat (the F344 rat, for which MCL is actually the most common cause of death in untreated rats); is "an unclassified leukemia with no known human counterpart" (IARC, 1990); and is widely regarded by authoritative bodies as being of very questionable relevance to humans. The expert or authoritative bodies that have expressed

doubts about the relevance of MCL tumors in F344 rats as predictive of any cancer effect in humans include USEPA, NTP, NIH, IARC, and CPSC CHAP (CPSC, 2001, p. 122).

OEHHA appears to rely on a USEPA risk assessment on tetrachloroethylene (EPA, 2012) to support the proposition the MCL tumors are potentially relevant to humans (HID at 34), but the data are unpersuasive. How can increased incidence of MCL in high-dose F344 rats be relevant when MCL tumors are also observed at high rates in F344 controls, and no MCL tumors are observed in SD rats treated at similar high doses? The lack of concordance between strains of rats suggests that a direct action of DINP on bone marrow (or spleen) is unlikely. A more plausible explanation is that DINP, like other peroxisome proliferators, exacerbates a lesion uniquely prevalent in F344 rats via cell proliferation. The same effect is not observed in SD rats because MCL is not a high-background lesion in this strain. A similar mode of action has been debated for chronic progressive nephropathy (Travlos et al., 2011; Hard et al., 2012; Hard et al., 2013). According to Thomas et al. (2007), the MCL lesion is very susceptible to cell proliferators or inhibited by substances that inhibit cell proliferation; therefore, it follows that substances that initiate cell proliferation would lead to a greater incidence of MCL. DINP, like many peroxisome proliferators, has been demonstrated to enhance cell proliferation. Thus, an increase in MCL in rodents *with a predisposition to that lesion* is to be expected. A lack of concordance in other species and other strains of the same species would also be expected with this scenario.

As for relevance to humans, that issue is addressed further below: if a substance does not promote cell proliferation in human cells, non-human primates, or humans, tumors that are incidental to cell proliferation would not be expected to be relevant for humans.

Kidney Tumors

The HID states that renal tubular cell carcinoma was significantly increased in male F344 rats in one study (Moore, 1998a as reviewed by CPSC, 2001), and that renal tubular cell carcinoma and renal transitional cell carcinoma incidence was increased in male F344 rats in two other studies (Moore, 1998a as reviewed by CPSC, 2001; Lington et al., 1997). HID at p. 64. The HID concedes that the increases of tubular and transitional cell tumors in these two studies "did not reach statistical significance," but asserts that "these tumors are rare in untreated male F344 rats." HID at p. 64. OEHHA does not mention the issue of mode of action and relevance to humans in the summary, but does discuss the subject at pages 60-62 of the HID. OEHHA on the one hand acknowledges that CPSC CHAP (2001) concluded that the renal cell tumors observed in male F344 rats were "caused by the a2u-globulin mechanism of action, and therefore rat-specific." HID at p. 62. Yet OEHHA also asserts that the criteria established by IARC to determine whether a particular male rat kidney tumor is the result of the a2u-globulin mechanism of action have not been satisfied in the case of DINP. HID at 60-62. That is, OEHHA argues that CPSC CHAP were wrong in their conclusion on this issue.

BASF concurs in the detailed comments submitted by Exxon Mobil on the subject of these kidney tumors and the a2u-globulin mechanism of action. As Exxon Mobil's comments demonstrate, the data on DINP do in fact meet the criteria established by both IARC and EPA to confirm the presence of the a2u-globulin mechanism of action. Therefore, the evidence is clear that the kidney tumors in the F344 rats are not relevant to humans.

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Liver Tumors

The HID states that the incidence of liver tumors (hepatocellular carcinomas and adenomas) was significantly increased in male and female F344 rats, female SD rats, and male and female B6C3F1 mice in four different studies. The studies in question, and the issue of the mechanism of action producing these tumors and their potential relevance to humans, are discussed in the HID at pages 11-23, 34-37.

The data clearly establish that DINP causes liver cancer in rats and mice. DINP is clearly not mutagenic or genotoxic (HID, p 31, 48; NTP CERHR Expert Panel Report, 2001 published as Kavlock et al, 2002; EC Risk Assessment Report, 2003; EPA, 2005), so these effects observed in rodents reflect a non-genotoxic mechanism of action by which multiple organs in rodents, at least, can be affected. The question is, how relevant are these data to humans? While previous assessments of rodent liver tumors were considered to be not relevant to humans (IARC, 1995; IARC, 2000; CPSC 2001, Klaunig et al, 2003), some in the regulatory community have suggested that recent data reported by Ito et al (2007) demonstrating that PPARα may not be the only mode of tumorigenic action is cause to consider these tumors to be relevant for humans (Guyton et al, 2009). However, the scientific community does not agree and supports the continued interpretation of these tumors as not relevant for humans (Corton et al, 2013). Regardless of the precise mechanism of action (PPAR-alpha, CAR or other nuclear receptor), liver tumors have not been observed in humans or in non-human primates and are unlikely to occur in the absence of cell proliferation. Organ enlargement, specifically liver enlargement, is a hallmark of cell proliferation and can be used to assess potential longer-term effects (Cohen & Grasso, 1981; Cohen, 2010).

Several investigators have evaluated the responses of non-rodent species to DEHP, DINP and other peroxisome proliferators. Examples of studies using human hepatocytes exposed to peroxisome proliferators such as hypolipidemic drugs, DEHP and DINP include: (1) Hasmall et al., (1999 and 2000), found no effects on human hepatocytes exposed to 50 uM nafenopin, 250-700 uM monoethylhexyl phthalate (MEHP), or 250-700 uM DINP; (2) Shaw et al. (2002) replicated the Hasmall study using monoisononyl phthalate (MINP), the monoester of DINP, and also found no effect; and (3) Goll et al.(1999) conducted studies on the effect of DEHP, clofibrate, ciprofibrate, bezafibrate, and nafenopin on replication of human hepatocytes in culture; none induced DNA synthesis in human hepatocytes.

In vivo animal studies of non-human primates have also been reported. Reddy et al. (1984) reported that rhesus monkeys and cynomolgus monkeys given large doses of ciprofibrate had significantly increased liver weight relative to untreated animals. The investigators measured liver-to-body weight ratios, which were significantly increased in the treated animals relative to the control group. Hoivik and coworkers (2004) reported that cynomolgus monkeys treated with 150 or 400 mg/kg/day ciprofibrate for two weeks, but not 3 or 30 mg/kg/day, had significantly higher liver-to-body weight ratios relative to controls, a finding consistent with Reddy et al. (1984). However, Hoivik et al. (2004) also reported that there was no increase in Ki-67 immunostaining in these hepatocytes, a sensitive marker for cell proliferation, and only cellular hypertrophy rather than hyperplasia in the liver. Treatment with 250, 500, or 2500 mg/kg/day fenofibrate was without effect on liver weight or Ki-67 immunostaining. These data helped clarify the previous work by Reddy et al., 1984 and supported the hypothesis that cell proliferation was not the primary contributor to the observed liver weight increase. Cariello et al., 2005 conducted gene array analyses on the liver samples from the study described by Hoivik et al. Using a variety of gene markers, there was no

evidence of upregulation of genes associated with cell proliferation, thus, providing additional evidence that ciprofibrate did not induce increased liver weight via cell proliferation.

Pugh et al., 2000 treated cynomolgus monkeys for two weeks with 250 mg/kg/day of ciprofibrate or 500 mg/kg/day DEHP or DINP. Relative liver weight was unchanged – probably reflecting the dose of ciprofibrate used. Hall et al., 1999 reported similar results with DINP (i.e., no effect on liver weight) in marmosets at 100, 500, and 2500 mg/kg/day. Rhodes et al., 1986 reported on treatment of marmosets with 1000 mg/kg DEHP. Animals were treated with 1000 mg/kg/day DEHP for two weeks. Liver-to-body weight ratios were not elevated in treated animals compared with the control group. Kurata et al., 1998 also reported no increase in liver-to-body weight ratio in marmosets treated with 100, 500, or 2500 mg/kg/day DEHP for 13 weeks. Kurata also reported that 250 mg/kg/day clofibrate had no effect on relative liver weight. Tomonari et al., 2006 treated marmoset monkeys from weaning to adulthood (65 weeks) with 100, 500, or 2500 mg/kg/day DEHP; no increase in relative liver weight was observed in treated animals. Treatment of marmosets for an even longer period of time (roughly half their life span) was without effect. Graham et al., 1994 reported no change in liver weight in marmosets treated with 2, 10, or 20 mg/kg ciprofibrate daily for three years. Thus, the evidence demonstrates that treatment of Old World or New World primates with DEHP, DINP, or any peroxisome proliferator is without effect on indicators of cell proliferation. Furthermore, no effects have been observed in humans. Gariot et al., 1987 reported no effect of daily doses of fenofibrate on hepatomegaly in patients with hyperlipoproteinemia. Thus, the likelihood of DINP or any other peroxisome proliferator having an effect on the liver or any other organ impacted by cell proliferation such as pancreas or MCL (LGL) that would lead to cancer is very low, i.e., none have demonstrated the precursor event of tissue enlargement.

CONCLUSION

DINP has been the subject of extensive reviews by a number of expert bodies including the Consumer Product Safety Commission, the European Union via its pre-REACH existing chemicals risk assessment process, the European Chemicals Agency, the Australian government, and the Risk Sciences Institute of the International Life Sciences Institute. None of these expert bodies have reached a conclusion that DINP should be classified or regulated as a carcinogen. For the reasons set forth above, the Carcinogen Identification Committee should reach the same conclusion: the weight of all available scientific evidence does not clearly show that DINP causes cancer in humans.

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ATTACHMENT 2

GUIDANCE CRITERIA FOR IDENTIFYING CHEMICALS FOR LISTING AS "KNOWN TO THE STATE TO CAUSE CANCER"

1. General Principles

   A. The criteria included herein shall be utilized by the Office of Environmental Health Hazard Assessment Science Advisory Board Carcinogen Identification Committee (CIC) to identify those chemicals which are to be recommended for listing as known to the State to cause cancer. This listing is for purposes of fulfilling the mandate of the Safe Drinking Water and Toxic Enforcement Act of 1986 ("Proposition 65").

   B. These criteria are intended to give the CIC maximal flexibility in evaluating all pertinent scientific information in determining whether a chemical is known to the State to cause cancer. They are intended neither to limit the scope of the Committee's consideration of all appropriate cumulated scientific information, nor to limit the use of best scientific judgement available at the time.

   C. In evaluating the sufficiency of available data, a "weight-of evidence" approach shall be used to evaluate the body of information available for any given chemical. The body of evidence shall include all evidence bearing on the issue of carcinogenicity shown through scientifically valid testing according to generally accepted principles.

   D. The Safe Drinking Water and Toxic Enforcement Act of 1986 states that a chemical is known to cause cancer "if in the opinion of the state's qualified experts it has been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer" without further restriction. Thus if the weight of scientific evidence clearly shows that a certain chemical causes invasive cancer in humans, or that it causes invasive cancer in animals (unless the mechanism of action has been shown not to be relevant to humans), the committee will normally identify that chemical for listing.

   E. The application of causation criteria requires scientific judgements which can only be based on experience, not only with the interpretation of epidemiological studies or animal carcinogenicity experiments in general, but with the circumstances of exposure, the physical and demographic setting, the nature of classification, including pertinent clinical and histologic schemata, and the qualifications of the investigator. Thus, few of the criteria are amenable to the use of absolute restrictions of either a quantitative or qualitative nature.

   F. Whether evaluating the evidence for carcinogenicity in animals or humans, CIC members may make judgements utilizing other, more indirect, scientifically valid observations obtained using generally accepted methods and principles. Such information may derive from studies of genetic toxicology or DNA repair using in vitro methods, cultured mammalian cells, or living prokaryotes, lower eukaryotes, plants, or insects, although changes induced in whole mammals must be considered more pertinent. Quantitative variations in mutagenicity or other short term phenomena cannot be presumed to always

parallel quantitative variations in carcinogenicity, since not all carcinogens are mutagens. Taken alone, a negative test can rarely offer strong evidence against carcinogenicity; although well conducted negative studies can provide important contributory evidence. Each of the following categories of knowledge may be pertinent to carcinogen determinations.

Physical and chemical characteristics of the chemical
Absorption, distribution, metabolism, and excretion characteristics of the chemical
Structure-function and structure-activity relationships
Organ-specific and systemic toxicity, whether after short or long latency
Protein binding, and cellular receptors
Formation of DNA-adducts by means of chemical binding
DNA repair processes
Effects upon the methylation status of DNA
Mutagenicity of the chemical and its propensity to cause chromosomal damage
Mutational spectra in observed tumors with known links to environmental chemicals
A capacity to produce benign tumors known to progress to malignancy
A capacity to produce other effects known to be pre-neoplastic

Epidemiological and experimental studies of such surrogate outcomes must be held to the same strict criteria as studies of invasive cancer.

2. Generally accepted principles of scientifically valid studies of carcinogenesis.

   A. Epidemiological studies of carcinogenesis in humans will be interpreted as showing a causal relationship between the exposure and the cancer outcome depending on the weight of evidence.

      i) Interpretation of the evidence is greatly facilitated by the availability of the specific details of pertinent studies. These details would include:
         a) The setting and the nature of the population studied
         b) The study design and the sequence of observations
         c) The operational definitions of exposure and tumor outcome
         d) The means of controlling pertinent bias and confounding
         e) The sample size(s) and the details of the analysis, including statistical testing

      ii) The weight of evidence depends upon the degree to which each of the following propositions can be verified or rejected.
         a) The occurrence of the exposure and the occurrence of the cancer are associated, such that the outcome is shown to appear more frequently among the exposed than among the unexposed.
         b) The observed association cannot be reasonably explained by chance, based on conventional statistical criteria interpreted in the context of the number of comparisons made.
         c) The observed association is unlikely to be due to any link between the exposure and other known or presumed determinants or well-understood predictors of the outcome. The existence of such other known or presumed determinants does not, by itself, provide evidence for or against a finding of

carcinogenicity. This criterion can ordinarily not be fulfilled by observations that link the characteristics of groups rather than those of individuals.

d) The observed association is unlikely to be explained by biased working definitions of the exposure or the cancer, or by biased methods of enumerating either of them.

e) The plausibility of causation is undiminished or is enhanced by the detailed characteristics of the observed association as follows; none of these individual characteristics provides an absolute criterion for or against causality by itself.

1) The strength of any positive association observed. Credibility is enhanced to the degree that the risk ratio rises, especially (arbitrarily), above 1.5.
2) The relationship between the dose and/or the duration of the exposure and the strength of the association. In general, a direct relationship between these two quantities enhances the plausibility of a causal explanation.
3) Causality of the observed association is consistent with what is known of the toxicological and physiologic effects of the exposure, and with the known causation and pathogenesis of the cancer in question.
4) The consistency and brevity of the latent period between exposure and the time of appearance or diagnosis of malignancy.
5) The histological and anatomical description of the tumors occurring after exposure, including their degree of malignancy or malignant potential.
6) The biologic credibility of causation as an explanation for the pattern of time intervals between the period of exposure and the appearance of the cancer. In general, statistical variation around a specific period of latency enhances the plausibility of a causal explanation.
7) The existence of multiple studies, i.e. multiple independent observations of the same relationship, each of which fulfills the above criteria. These are especially compelling if studies differ in respect to study design, population or setting, measurement technology, analytic strategy, time frame, or means of estimating what would be expected under the hypothesis of no association.
8) The absence of any unambiguous observations which are truly inconsistent with the existence of a causal association. To be informative, a negative study must be of such quality that, if positive, it would have added to the weight of evidence. Such results should be based on definitions of exposure and cancer outcome which are valid and at least as sensitive and specific (i.e. have at least as high positive and negative predictive values) as studies in which an association has been (or would

be) observed. The existence of strong and diverse indirect evidences such as are listed under General Principle F above.

B. Studies of carcinogenesis in animals will be interpreted as showing a causal relationship between the exposure and the cancer outcome depending on the weight of evidence deriving from studies employing scientifically valid principles of testing.

i) Interpretation of the evidence from animal studies is greatly facilitated by the availability of the specific details of pertinent studies. These details would include:

a) The clear definition and, if a single substance, the high purity of the agent under test. If pertinent, the means by which it was collected or extracted, stored, and delivered. In the case of mixtures, the detailed characterization and composition of the sample.
b) The route, schedule, and dosage of exposure and the duration of follow-up. How the dose was monitored, especially in the case of inhalation experiments.
c) The magnitude of the test dose relative to the maximum tolerated dose.
d) The species, strain, sex, and age of the experimental animals.
e) The fact and method of animal selection and randomization, if any.
f) The number of animals in the exposed and in the control groups.
g) The duration of follow-up, the proportion of surviving animals at risk, and the criteria by which the experiment is terminated.
h) The histological and anatomical description of the tumors occurring in both exposed and control animals, including the degree of malignancy or malignant potential of the tumors.
i) The timing of the appearance of tumors.
j) The method of analysis, considering any necessary adjustments for differential survival, differential examination, historical as well as concurrent control experience, and the distinction between progressive tumors and non-progressive tumors found at autopsy.

ii) The weight of evidence depends upon the degree to which each of the following propositions can be verified or rejected with respect to malignancies or tumors of malignant potential.

a) Tumors are found to occur in excess after exposure to the agent.
b) Tumors appear more frequently in the exposed animals than in the unexposed comparison group.
c) The observed difference cannot be reasonably explained by chance, based on conventional statistical criteria interpreted in the context of the number of comparisons made.
d) The frequency of the unexpected tumors is related to the dose of the agent.
e) The plausibility of causation is undiminished or is even enhanced by the detailed characteristics of the observed association as follows; none of these individual characteristics provides an absolute criterion of causality by itself.
    1) The higher the ratio of tumors in exposed to tumors in control animals, the more compelling the result, implying that unusual

tumors, occurring in sites rarely affected under ordinary circumstances, are of special interest.

2) The tumors produced are more aggressive than those occurring in the absence of exposure. If benign, the tumors are of a type known to progress to malignancy.
3) Tumors are produced at an especially low dosage of exposure.
4) Tumors occur in unusual variety, or are produced at an unusually young age or after an especially short interval.
5) Tumors have been found to occur in significant excess (in order of increasing significance) in the two genders of a species, in two distinct species, or in two different experiments carried out in two different laboratories under different protocols. The following circumstances may constitute exceptions to this rule:

-- A single study in one species might be considered to provide sufficient evidence of carcinogenicity, if the malignant tumors occurred to an unusual degree with respect to frequency, type, location, age at onset, or low dosage, or in a strain not otherwise prone to such tumors.

-- Evidence of carcinogenicity in animals deriving from a single study or from multiple studies incompletely or inconsistently described might be considered sufficient if heavily supported by the indirect evidences described under General Principle F above.