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Via e-mail to:

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Via first class mail to:

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REQUEST FOR CORRECTION

I. Affected Persons - Petitioners Filing the RFC

This RFC is submitted jointly by the Center for Regulatory Effectiveness ("CRE") and the American Chemistry Council Phthalate Esters Panel. The primary contacts for this RFC in those organizations are –

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ACC Phthalate Esters Panel: Marian K. Stanley, Manager, (703) 741-5623, Marian_Stanley@americanchemistry.com, American Chemistry Council, 1300 Wilson Blvd., Arlington, VA 22209.

II. EPA Information Dissemination Which is the Subject of the RFC

"Technical Review of Diisononyl Phthalate, CAS NO. 028553-12-0, 071549-78-5, 014103-61-8, 068515-48-0, Office of Environmental Information, Environmental Analysis Division, Analytical Support Branch, August 2000", and statements regarding, and conclusions based on, that Technical Review contained in EPA's rulemaking proposal to add such chemicals to the Toxics Release Inventory, 65 Fed. Reg. 53681 *et seq*., Sept. 5, 2000 (docket control number OEI-100004).

III. Introduction

a. Brief summary

Diisononyl phthalate ("DINP"), a category of three esters, is a chemical which imparts flexibility to a multitude of plastic (principally PVC) products for the consumer, construction, and manufacturing sectors. Such products include vinyl flooring and wall covering, vinyl-coated fabrics, gloves, tubing, shoes, sealants, and electrical insulation.[1]

The preliminary DINP Technical Review of August 2000, and the subsequent September 5, 2000 rulemaking proposal to add the DINP category to the Toxics Release Inventory ("TRI"), are now more than three years old, but are still being disseminated as a source of information on DINP. As discussed in detail below, the preliminary Technical Review and NPRM (hereafter referred to together as the "Review") do not meet the Data Quality standards which were issued after their release. The Review contains substantial omissions of data and analysis, including significant new data and pertinent consensus scientific views which have been published since August 2000[2], biased conclusions which are not consistent with the TRI listing requirements, inaccuracies, and reliance on TRI listing guidance which itself cannot meet Data Quality standards.[3]

Because of the substantial revisions which are needed in the Review, it would not be sufficient simply to amend the Review and issue a final regulatory decision. Fairness and appropriate administrative procedure require that a revised/corrected/updated Review be made available for public comment and subjected to external peer review if the Agency intends to proceed further with the listing proposal. The Office of Management and Budget recently proposed to supplement its Data Quality guidelines to require reliable, independent, and transparent peer review

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[1] Although used in a multitude of consumer products, consumer exposure from such products is not an issue for purposes of TRI listing, since the purpose of the TRI is to provide information only on releases from facilities that manufacture, process, or use a listed chemical.

[2] Significant new data and information has also become available since the end of the extended comment period for the Review on Feb. 2, 2001.

[3] CRE submitted comments on EPA's still-pending proposed renewed Information Collection Requests ("ICRs") for the generic TRI reporting forms. The CRE comments raise the issue of failure of the 1994 TRI listing guidance to comply with the new Data Quality standards, and consequently the inability of the proposed TRI information collections, and any new TRI listing decisions – including the proposed DINP listing -- to meet those standards. CRE comments of July 31, 2003 re EPA Docket Control Nos. OEI-2003-0025 and OEI-2003-0026 (item 6 in 0025).

for all "significant regulatory information" that would be disseminated after January 1, 2004.[4] We contend that the DINP Review is "significant regulatory information", and possibly "especially significant regulatory information", within the meaning of the OMB proposal. As we have noted in recent CRE comments on the Information Collection Requests for the generic TRI reporting forms, it is also necessary to revise and clarify the 1994 TRI listing guidance on which the DINP NPRM was based before revising the Review and making a final regulatory decision.[5] We believe that when the deficiencies in the Review and the listing guidance are corrected, the Agency will conclude that it is not appropriate to continue with its proposal to list DINP on the TRI and require TRI reporting. If, however, the Agency decides to amend the Review and still proceed with the proposal, there must be an opportunity for public comment on the new Review, external peer review, and a new NPRM.

b. The statutory and regulatory context for TRI listings

Under the Data Quality legislation and OMB and EPA guidelines, the term "quality" encompasses "objectivity" and "utility". Both "objectivity" and "utility" must be considered in the appropriate context. As stated in the OMB guidelines, "objectivity" in presentation includes "whether the information is presented within a proper context."[6] "Utility" requires consideration of the purpose of the information, which is also a matter of context.

In this case, the context for objectivity and utility is the TRI statute and regulations and their purpose. The purpose of the TRI is to inform communities of those chemicals which, when released from facilities, are reasonably anticipated to pose a significant risk to public health or the environment. The statute contains criteria for listing such chemicals. All of the preliminary findings regarding TRI DINP listing in the Review were made pursuant to EPCRA section 313(d)(2)(B), commonly known as the TRI chronic health effects section. It provides EPA with the authority to list a chemical on the TRI if –

> (B) The chemical is known to cause or can **reasonably be anticipated** to **cause in humans** --
> (i) cancer or teratogenic effects, or
> (ii) serious or irreversible
> . . . .
> (IV) . . . chronic health effects

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[4] The OMB proposed supplemental guidance on peer review was initially issued for comment on August 29, 2003. See http://www.whitehouse.gov/omb/inforeg/infopoltech.html#dq. The proposal was subsequently published in the *Federal Register* with an extended comment deadline of Dec. 15, 2003. 68 *Fed. Reg*. 54023-29, Sept. 15, 2003.

[5] See note 3, *supra*.

[6] 67 *Fed. Reg*. at 8459 3d col., Feb. 22, 2002.

42 U.S.C. § 11023(d)(2)(B) (emphasis added). The emphasized words are important for this RFC, since the quality of the information EPA has proffered in support of its proposed listing determination (in the form of data, analysis, and conclusions) cannot be consider objective (*i.e.*, accurate, complete, reliable, unbiased) and useful unless it meets those statutory criteria. That an effect has been observed in rodents under laboratory conditions does not provide sufficient basis for determining that the same effect can be "reasonably anticipated" to cause those adverse effects "in humans" under real-world conditions when there are data indicating that those observations of potentially adverse effects in laboratory rodents are not relevant to humans, are unlikely to be serious or irreversible, or would require unrealistic (*i.e.*, not reasonably anticipated) exposures and dose levels in humans.

In 1994, in the course of adding multiple chemicals to the TRI, EPA issued guidance on interpreting the above statutory provisions. That 1994 guidance, which is referenced as a basis for the DINP NPRM, states:

> The hazard assessment was conducted in accordance with relevant EPA guidelines for each adverse human health or environmental effect. . . . During this assessment, the number, severity, and significance of the effects induced by the chemical, **the dose level causing the effect**, and the quality and quantity of the available data . . . and confidence level in the existing data base, were all considered. Where a careful review of the scientific data for a particular chemical results in a **high level of confidence** that the chemical causes an adverse effect **at relatively low dose levels**, EPA believes that this evidence is sufficient for listing . . . . EPA also believes that where a review of the scientific data indicates that the chemical **will** cause various adverse effects **at moderate dose levels**, the total weight-of-the-evidence indicates that there is sufficient evidence for listing . . . . EPA believes that both types of chemicals described above exhibit moderately high to high toxicity based on a hazard assessment.

59 Fed. Reg. 61432-33 (emphasis added). The 1994 guidance does not describe how EPA will determine what constitutes "relatively low dose levels" or "moderate dose levels". The terms "relatively low" and "moderate" dose levels indicate that the dose must be considered "low" or "moderate" in relation to something, but the guidance does not indicate in relation to what.

In the same 1994 notice, EPA responded as follows to public comments urging consideration of likely human exposure levels in making listing decisions:

> The statute is silent on the issue of exposure considerations for the section 313 (d) (2) (B) and (C) criteria. The language of section 313 does not prohibit EPA from considering exposure factors when making a finding under either section 313 (d) (2) (B) or . . . (C). . . . .
>
> For listing determinations made pursuant to EPCRA section 313 (d) (2) (B), in instances where the hazard assessment indicates that the value of listing on

> EPCRA section 313 hazard alone is marginal (i.e., a chemical is of **low toxicity and unrealistic exposures would be necessary for it to pose a risk to communities**), EPA may use exposure considerations in its listing decisions.

59 Fed. Reg. at 61442 (emphasis added). EPA cited this portion of the 1994 guidance in the DINP Review, but implied that it did not apply to DINP because of the preliminary toxicity findings described below. 65 Fed. Reg. at 53686 3d col. This guidance statement is puzzling, because if unrealistic exposures would be necessary in order for a chemical to pose a risk to communities, it is difficult to understand why the chemical would not be considered to have low toxicity. "[L]ow toxicity" cannot be determined without consideration of what would constitute realistic/unrealistic exposure levels.

There is a larger inherent contradiction in the 1994 listing guidance: According to the guidance, the level of toxicity ("high", "moderately high", or "low") must be determined in relation to dose levels; however, the guidance also states that likely human exposure levels will not be considered if a chemical is determined to have high or moderately high toxicity. But the dose levels reasonably anticipated "in humans", and supposedly considered in determining toxicity, cannot be determined without determining humans' likely level of exposure.

c. The Review findings regarding a proposed DINP listing

The specific adverse "serious or irreversible" chronic health effects determined by the Review to be appropriate for listing in the TRI are –

1. **Cancer** (liver, kidney, and mononuclear cell leukemia)

2. **Developmental** (possible growth delays during lifetime; skeletal malformations; absence of kidney and ureter development in some fetuses; dilated kidney pelvises possibly leading to progressive kidney damage and impaired kidney function)

3. **Liver** (increased liver weight and liver enzyme activity; chronic liver lesions)

4. **Kidney** (biochemical indicators of chronic toxicity; and progressive, irreversible damage (nephropathy) leading to early mortality)

All of these proposed determinations are predicated on laboratory studies of rats and mice. There is no supporting human (epidemiologic) data, and studies in primates (marmoset and cynomolgus monkeys – the latter of which was not reviewed by EPA) do not indicate any such effects. There is little discussion in the Review whether the findings in rodents are relevant to humans, and no meaningful discussion of the primate (monkey) data showing no adverse effects

even at high doses.[7] As discussed below, each of the above proposed Review determinations fails to satisfy the OMB and/or EPA Data Quality standards.

EPA received extensive public comments on the Review. The public comments contained far more detail, and relied on a far more extensive database, than the EPA Review, and they requested that EPA issue a revised, and more comprehensive, Review to allow for more informed public comment.[8] Three years have now passed and EPA has not issued a revised Review for public comment.

As the public comments also noted, there is no indication that the EPA Review has undergone peer review. Given the importance of DINP, the controversy surrounding phthalates in general, and the many scientific issues raised by the Review and public comments, the Review should undergo external peer review.[9]

d. Applicability of the Data Quality standards to preliminary information

Both the OMB and EPA guidelines state explicitly that the Data Quality standards and procedures apply to preliminary information. (OMB final guidelines of Sept. 24, 2001; EPA final guidelines in sec. 5.3.) The EPA final guidelines state with regard to information products on which the Agency has requested comments but on which it has not yet taken final action:

> In cases where the Agency disseminates a study, analysis, or other information prior to the final Agency action or information product, it is EPA policy to consider requests for correction prior to the final Agency action or information product in those cases where the Agency has determined that an earlier response would not unduly delay issuance of the Agency action or information product and the complainant has shown a reasonable likelihood of suffering actual harm from the Agency's dissemination if the Agency does not resolve the complaint prior to the

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[7] The preliminary Technical Review (at 48-49, 56) and the NPRM (at 53685 1st col.) allude to the "suggestion" that primates are not responsive to peroxisome proliferation, and reference Hall et al. 1999, but do not discuss the other primate studies (Pugh et al. 2000; Rhodes et al. 1986) and absence of observed adverse effects in those studies. The Technical Review even comments in reference to the Hall et al. 1999 study that "[t]hese subchronic studies provide clear evidence that the liver and kidney are a target organ of DINP in rats but not marmosets" (at 49), but does not discuss why this finding is not given weight.

[8] The health effects portion of the Technical Review document was 12 pages with 29 references. Comments submitted by the American Chemistry Council Phthalate Esters Panel were 73 pages (main text only) and contained over 100 more references than the EPA review.

[9] See footnote 4, *supra,* and related text, regarding the recently proposed OMB supplemental Data Quality guidance on peer review.

final Agency action or information product.

Sec. 8.5. EPA's guidelines also contain a commitment to early quality review to ensure that the final information product complies with the Data Quality standards:

> [W]e do not wait until the point of dissemination to consider important quality principles. While the final review of a document before it is published is very important to ensuring a product of high quality, we know that in order to maximize quality, we must start much earlier. When you read an EPA report at your local library or view EPA information on our web site, that information is the result of processes undertaken by EPA and our partners that assured quality along each step of the way.

Sec. 2.2.

In the present situation, the last comment period on the Review ended over two and one half years ago. Numerous allegations of health effects have been made against the class of phthalates in recent years. The information in the DINP Review has contributed to a perception that DINP is also toxic. The Review, and the lack of any corrective action by EPA, have introduced tremendous business uncertainty into the PVC plastics industry sector. Producers and users do not know whether they should be investing in attempting to identify substitutes and new processes and applications at this time, even though they believe DINP has been shown to be safe and non-toxic under any realistic human exposure scenario. Both the letter and the spirit of the Data Quality guidance therefore demand that the Agency apply its current awareness of Data Quality deficiencies in the Review to withdraw the listing proposal or issue a revised Review document for further public comment and peer review.

Finally, the Review is "influential scientific information" under the definitions in the OMB guidelines.[10] As such, it demands application of higher standards of Data Quality, including the requirement for substantial reproducibility.[11]

IV. Specific Data Quality Deficiencies Requiring Correction

The information discussed below includes citation to some studies that were not published at the time of the Review; thus, they clearly could not have been included in those documents when originally published. However, because those studies are so pertinent to the issues relevant for the DINP listing decision, they should be addressed in any revision of the Review.

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[10] "Influential scientific information" is information that is likely to have a clear and substantial impact on important private sector decisions. OMB Feb. 22, 2002 final guidelines, sec. V, 9.

[11] EPA guidelines sec. 6.3; OMB guidelines at 67 *Fed. Reg.* 8455 2d col.

a. Liver cancer evaluation

1. The Agency's preliminary determination that DINP can be reasonably anticipated to cause liver tumors in rats and mice does not consider and give weight to international scientific opinion, reflected in the recent IARC determination regarding the closely related phthalate DEHP, that the mechanism of carcinogenicity detected in rodents – peroxisome proliferation – is not relevant to humans. [IARC 2000; IARC 1995] The preliminary review is therefore not "complete" as required by the guidelines.

2. The Review does not consider the findings of the 1995 ILSI international workshop which determined that peroxisome proliferators are unlikely to induce cancer in humans, except perhaps under extreme exposures. [Cattley et al. 1998] While the ILSI workshop report is included in the references for the Technical Review, it is not discussed and cited anywhere in the body of the Review. The Review is therefore not "complete".

3. While the Review appears to agree that the carcinogenicity seen in the rodent bioassays was due to peroxisome proliferation, if there were any doubt that this was the case recent published data not considered in the Review demonstrate operation of the peroxisome proliferation mechanism under the conditions of the rodent bioassays. [Mellert et al. 2001, 2001a; Kaufmann et al. 2002] Other data also not considered in the review demonstrate the absence of such a mechanism in primates and human cells. [Pugh et al. 2000; Benford et al. 1986; Baker et al. 1996; Hasmall et al. 1999] The Review is therefore not "complete".

4. The Review gives no weight to the high-dose marmoset study [Hall et al., 1999], which found no peroxisome proliferation or carcinogenicity in those primates. Nor does the Review include any discussion of the high-dose study of cynomolgus monkeys, which found no adverse effects. [Pugh et al., 2000] Those primate studies are entitled to greater weight than the rodent studies as more relevant to humans, especially in view of findings of a peroxisome proliferation mechanism operative in rodents but not in primates or humans. The Review is therefore not "complete", and it does not employ a "weight-of-the-evidence" mode of evaluation, as required by the EPA guidelines.

5. The Review does not consider the conclusions of the CPSC Chronic Hazard Advisory Panel in June 2001 that DINP induces liver cancer in rodents through a peroxisome proliferation mechanism and is "believed not readily induced in humans, especially at doses resulting from current use of consumer products". [CPSC 2001 at 122] The Review is therefore not "complete".

6. The Review does not consider data indicating that the different rates of DINP absorption between rodents and humans/primates makes it impossible for humans to receive the doses that produced liver tumors in rats and mice (even if it is assumed that the mechanism of carcinogenicity can be reasonably anticipated to operate in humans). [Rhodes et al. 1986; Astill 1989; Pugh et al. 2000; Anderson et al. 2001] This Data Quality defect is discussed

in more detail in section *f*, below.

7. The preliminary review is not "objective" and "unbiased" because it substitutes a policy-driven "default assumption" to determine that the peroxisome proliferation-induced rodent carcinogenicity "might" be relevant to humans, and therefore the Agency is justified in a "belief" that, because, according to the Review, unspecified questions remain regarding peroxisome proliferation, DINP can be "reasonably anticipated" to cause cancer in humans. Tech. Rev. at 8, 56. Information must be "unbiased" under both the OMB and EPA guidelines. This aspect of the review is not in accord with that requirement, and is also not in accord with the requirement that influential scientific information be assessed according to the "weight-of-the-evidence". EPA guidelines sec. 6.4. It is also not in accord with the TRI statutory requirement that human health effects be "reasonably anticipated". On this point, therefore, the Review is neither unbiased nor accurate.

b. Kidney cancer evaluation

1. The Review concludes that DINP could also be reasonably anticipated to cause kidney cancer in humans. This conclusion was based on a study which found kidney tumors in male rats. However, studies of female rats and male and female mice did not show this. The tumors found in male rats were of a type associated with an $alpha_{2u}$-globulin process. The Review contains no discussion of the scientific consensus that such tumors are not relevant to human carcinogenicity. EPA guidance in place since 1991 discounts the relevance to humans of male rat kidney tumors associated with an $alpha_{2u}$-globulin process. [EPA 1991] There is no reference to this guidance in the Review or NPRM. An IARC 1999 Consensus Report reached the same conclusion, and it also is not discussed either in the Review or NPRM. [IARC 1999] The Review and NPRM also fail to note that the CPSC CHAP concluded that the kidney tumors occurred through a rodent-specific mechanism that is unlikely to have relevance to human risk. [CPSC 2001] On the other hand, the publication cited by EPA in support of its speculation that the kidney tumors might not have been due solely to the $alpha_{2u}$-globulin mechanism (Ref. 8, Lington et al. 1997) does not in fact support that position. As a result, the EPA information on this point violates the Data Quality guidance in not being "objective", because it is not "complete", "accurate", and "unbiased".

c. Mononuclear cell leukemia ("MNCL")

1. The Review and NPRM finds that DINP increases the incidence of this type of cancer in male and female rats, but not mice. The NPRM notes that this is a common cancer in F-344 rats, but then proceeds to comment that because there is uncertainty about its mechanism and biological relevance for humans, it "cannot be discounted". At 53685 2d col. Converting some alleged uncertainty into "reasonable anticipation" clearly reflects bias in the review, in violation of the "objectivity" requirements of the Data Quality guidelines and the TRI listing requirement that the human health effects be "reasonably anticipated".

2. The CPSC CHAP concluded that MNCL was likely to be strain-specific to F-344 rats, with

great variance in the rates of spontaneous occurrence in controls, and therefore was "of questionable relevance to humans." [CPSC 2001 at 122] Overall, the CHAP found that DINP is not plausibly associated with a significant increase in cancer risk in humans. [CPSC 2001] The CHAP findings were not included in the Review, and therefore it is not "complete" and "objective", as required by the Data Quality guidelines.

d. Developmental Toxicity

1. The Review's speculation that reduced body weight "may" (rather than is "reasonably anticipated" to) cause lifetime developmental delays is contrary to the data in the cited Waterman study. The data showed the effects were transient, with the previously underweight pups returning to weights almost the same as those of controls in adulthood, and that they experienced no reduction in health. This was true even though their mothers were exposed to DINP at levels that induced maternal toxicity. The CPSC CHAP did not, as the NPRM suggests, find that this weight reduction was a "serious effect" of a non-transitory nature (at 53684 2d col.); rather, the CHAP's final report in 2001 stated only that the two-generation study "**suggests** an adverse effect on weight gain in pups **during the perinatal and pre-weaning period of life**." (CPSC 2001 at 54, emphasis added.) There was no reference by the CHAP to this being a "serious effect"or of lifetime significance. The NPRM conclusion that this effect "may" result in "serious" lifetime adverse health effects, and that such lifetime effects are therefore "reasonably anticipated", is therefore both inaccurate and biased, contrary to the Data Quality standards.

2. The Review concludes that DINP can be reasonably expected to cause developmental toxicity because the Agency has a "concern" that the extra cervical ribs observed in some rat litters "may" interfere with normal nerve function and blood flow. This opinion was based on the observation that the extra cervical ribs occurred at doses of 500 mg/kg/day in the absence of or with minimal maternal toxicity. This is inaccurate. The study cited by EPA, Waterman et al. 1999, did not purport to show extra cervical ribs at the 500 mg/kg/day dose, but only at a dose of 1,000 mg/kg/day where the mothers began to show signs of toxicity. The EPA evaluations also do not include the findings of the CPSC CHAP, which concluded that any developmental risk to humans from DINP is "extremely low or non-existent". As discussed below, the internal dose which gave rise to concerns regarding developmental effects in rats is apparently millions of times higher than could occur in humans and is probably not achievable in humans due to pharmacokinetic differences from rats. EPA did not evaluate what exposures and internal doses could be reasonably anticipated to occur in humans as a result of releases from industrial facilities. As a result, the Review and NPRM evaluations are inaccurate and incomplete, and the substitution of a "concern" that such skeletal variations "might" be serious in place of the requirement that they be "reasonably anticipated" to be serious indicates bias and non-objectivity. Finally, the failure to discuss whether a 1,000 mg/kg/day dose can be "reasonably anticipated" to occur in humans, or, rather, is unrealistically high, renders the Agency's preliminary assessment incomplete and inaccurate.

3. Increased incidence of dilated pelvises and the absence of ureter and kidney development in 3 fetuses were noted in the developmental studies at maternally toxic doses of 1,000 mg/kg/day. The Review does not disclose that there is no clear dividing line between normal and pathological variation in the size of the renal pelvis, and that any enlargement is normally a transient condition that disappears postnatally and does not affect renal function. The Review also does not discuss whether any such signs of abnormal kidney development disappeared postnatally. Such post-natal confirmation is required by the Agency's 1991 guidance. [EPA 1991a] In addition, it appears that such findings in the Waterman et al. study were distorted by a 0.0% occurrence in controls, which was a substantial deviation from the normal historical control level of occurrence. The conclusion in the NPRM that these findings "might" lead to progressive kidney damage and impaired function and "therefore are considered to be serious" is therefore based on an incomplete appraisal and is a distortion of the requirement for a finding of "reasonably anticipated" adverse effects and indicates bias. Additionally, as with the issue of extra cervical ribs, the failure to discuss whether a 1,000 mg/kg/day dose can be "reasonably anticipated" to occur in humans near TRI facilities, or, rather, is unrealistically high, renders the Agency's preliminary assessment incomplete and inaccurate.

e. Liver and Kidney Toxicity

1. The Review concludes that the data showed chronic liver and kidney effects in rats and mice at doses ranging from 152 mg/kg/day to 1,888 mg/kg/day. However, such effects were not seen in the primate studies of marmosets and cynomolgus monkeys at doses up to 2,500 mg/kg/day. The Review does not discuss the significance of the different findings in rodent and primate studies. The Review notes, correctly, that "subchronic studies provide clear evidence that the liver and kidney are a target organ for DINP in rats but not marmosets." Technical Review at 49. However, the Review does not then discuss the significance of that finding for the relevance to humans of the liver and kidney toxicity in rats and mice. Additionally, the Review does not discuss the primate study in cynomolgus monkeys (Pugh et al. 2000), which produced similar findings. Since primates are ordinarily considered a better model than rodents for anticipating effects in humans, this is a serious omission, rendering the Review "incomplete" and "biased" under the Data Quality guidelines. Moreover, the Review fails to discuss the pharmacokinetic data on differences with regard to DINP between primates, humans, and rodents, which show that rodents are more sensitive than humans and that the high internal doses needed to produce chronic liver and kidney effects in rodents cannot be achieved in humans. Recent human volunteer pharmacokinetic data show that humans absorb much less phthalates than rodents. [Anderson et al., 2001] Consideration of these differences is necessary for determining whether humans would have to (or could) absorb enough DINP to allow for a reasonable anticipation that the liver and kidney effects observed in rodents would occur in humans. The Review is therefore not "complete", contrary to the Data Quality standards.

f. Conclusions Regarding Overall "High" to "Moderately High" Toxicity

1. The Review states that EPA has preliminarily determined "that the observed liver, kidney, and developmental toxicity occur **at relatively low doses**, and **thus** the Agency believes DINP to have moderately high to high chronic toxicity for each of these effects." 65 *Fed. Reg*. at 53686 3d col. (emphasis added). The NPRM also states that the Agency did not consider human exposure levels in reaching this preliminary conclusion. The Review does not provide any explanation whatsoever of what criteria, if any, were applied in determining that the doses at which allegedly adverse effects were seen in laboratory animals are "relatively low"; nor does it explain in relation to what they were considered "relatively low". The NPRM references the 1994 listing guidance in connection with this preliminary determination , but it does not explain why it did not apply that portion of the 1994 guidance which states that exposure may be considered if it appears that "unrealistic exposures would be necessary for it to pose a risk to communities."[12] These NPRM conclusions are thus not "substantially reproducible", as required for influential scientific information by both the OMB and EPA Data Quality guidelines. They also are not "clear" and "informative" as required by the guidelines. Finally, they cannot be considered "objective", since, without any stated criteria, there is no way for a disinterested third party to determine whether they would reach the same conclusions based on the evidence.

2. The lowest dose at which a potentially adverse effect was seen in laboratory studies of rodents, as reported in the Review, was 152 mg/kg/day for MNCL. Doses for other observed effects ranged from 307 up to 1,888 mg/kg/day. There is no discussion of, or reference to, the absence of observed adverse effects in the two primate studies (marmosets and cynomolgus monkeys, Hall et al. 1999 and Pugh et al. 2000, respectively) at doses up to 2,500 mg/kg/day.

3. Although there is no discussion whatever in the Review of "reasonably anticipated" human exposures and internal doses, there is pertinent data available. The very recent NTP-CERHR monograph on potential reproductive and developmental effects of DINP concluded that "general population exposures to DINP are expected to be lower than . . . 3-30 µg/kg bw/day." [NTP 2003 at II-30] The report does not estimate how much lower. David (David RM, 2000) used NIEHS data and the human data in Anderson et al. 2000 to estimate a human general population internal dose of 1.08 µg/kg bw/day at the 95th percentile. Thus, it appears that even at the lowest dose at which effects were even arguably observed in rodents (152 mg/kg/day), such rodent doses were on the order of over 100,000 times higher than could be reasonably anticipated in humans. If the no effect level in the two primate studies of 2,500 mg/kg/day is considered, likely human internal doses would be approximately 2.5 million times lower than the primate no effect level. The failure of the

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[12] The Summary section of the NPRM does not even state the lowest doses at which toxicity was observed in rodents or primates.

Review to consider the likelihood that human exposures and internal doses would have to be unrealistically high to produce any of the (questionable) adverse effects seen in rodents, and the failure to consider human dose in determining that the toxicity data indicated toxicity at "relatively low" doses, makes the Review fatally incomplete, inaccurate, unreliable and lacking in utility, in violation of the Data Quality standards.

V. Relief Requested

1. EPA should withdraw the current Review.

2. If EPA intends to proceed with the listing proposal, it should first revise the Review to bring it into compliance with the Data Quality standards by --

   -- including and discussing the data not considered and evaluated which is specified above, particularly the primate studies, and exposure/dose and pharmacokinetic data, and evaluation of their implications for humans as opposed to laboratory animals;

   -- making all determinations in accordance with the statutory standard of "reasonably anticipated" to cause adverse health effects "in humans" (as opposed to "might"); and

   -- removing bias due to use of policy-driven default assumptions.

   Any amended Review should be subject to a new opportunity for public comment.

3. If EPA decides to produce a new and Data Quality-compliant Review, it should subject the new Review document to external peer review to ensure its accuracy, completeness, and objectivity, and to ensure that it complies with new OMB Data Quality guidance on peer review.

4. EPA should undertake a new rulemaking to clarify its 1994 TRI listing guidance with regard to how a "relatively low" or "moderate" dose is determined before issuing, or deciding whether to issue, either a new Review or any further rulemaking action on DINP.

5. If EPA still proposes, after the above actions, to continue to propose TRI listing of DINP, it should issue a new NPRM based on the revised Review.

VI. Petitioners as Affected Persons

EPA is continuing to disseminate the DINP Review with all of its deficiencies, and activist

groups and others continue to refer to it as a basis for promoting termination of use of DINP.[13]

The Center for Regulatory Effectiveness is dedicated to improving the federal regulatory process and regulatory decisions. One of its two paramount goals is "[t]o ensure that information which federal agencies disseminate to the public is of the highest quality".[14] Pursuant to this mission, CRE has been a prominent proponent of the Data Quality Act from the time of the Act's drafting through its implementation by OMB and other agencies, including EPA. CRE has commented extensively on OMB's and EPA's proposed Data Quality Guidelines. CRE carefully monitors Data Quality issues for the public and federal agencies on its website, www.TheCRE.com, and has previously commented on the proposed TRI listing of DINP and Data Quality issues in the EPA guidance for listing of substances such as DINP in the TRI. Non-compliance by federal agencies with the Data Quality legislation and guidelines, as in this instance, affects CRE's ability to carry out its mission.

As concerns have been raised about the potential toxicity of other phthalates, greater reliance has been placed on DINP for use in such products because of its apparent lack of toxicity to humans at any level near to which communities might realistically be exposed by TRI releases. Listing of DINP would stigmatize this widely-used plasticizer, and, because of its wide consumer applications, manufacturers, processors, and users would be under immediate pressure to find a substitute. The subject Review is already creating that pressure and introducing substantial business uncertainty into the chemicals, plastics, and consumer products sectors. Companies manufacturing, processing, and using DINP are running out of plasticizer options and must soon consider whether to invest in trying to develop alternative substances, processes, and specifications. Any such decision would entail substantial costs and disruptions. Members of the ACC Phthalate Esters Panel are substantially affected in this manner at this time by the continuing dissemination of the deficient Review.[15]

Respectfully submitted,

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[13] See, *e.g.*, "The Sixth Basic Food Group" by Mindfully.org (www.mindfully.org/Plastic/6th- Basic-Food-Group.htm). The section on DINP states that "EPA . . . preliminarily determined . . . that there is sufficient evidence that chemicals in the DINP category can reasonably be anticipated to cause cancer or other serious or irreversible chronic liver, kidney, or developmental toxicity in humans", and links to a copy of the EPA Sept. 7, 2000 press release regarding the DINP NPRM for TRI listing. (The EPA press release is still disseminated on the web by the Agency.)

[14] See www.thecre.com.

[15] Members of the Panel include BASF Corporation, Eastman Chemical Company, ExxonMobil Chemical Company, Ferro Corporation, PolyOne Corporation, Sunoco Inc. (R&M), and Teknor Apex Company.

Jim J. Tozzi
Member, CRE Advisory Board

cc: OMB/OIRA

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