Michigan Department of Environmental Quality

Review of a 1,4-Dioxane Presentation by Michael Dourson, Ph.D. on October 8, 2013

Prepared by

The Toxics Steering Group
1,4-Dioxane Subcommittee

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The following abbreviations are used in this report:

CHO	Chinese Hamster Ovary
CYP	Cytochrome P450
MDCH	(Michigan) Department of Community Health
MDEQ	(Michigan) Department of Environmental Quality
MDARD	Michigan Department of Agriculture & Rural Development
DNA	Deoxyribonucleic acid
FAH	Foci of phenotypically Altered Hepatocytes
HCA	Hepatocellular adenoma
HCC	Hepatocellular carcinoma
ILSI	International Life Sciences Institute
IRIS	Integrated Risk Information System
JBRC	Japan Bioassay Research Center
mg/kg/d	milligrams per kilogram per day
MHV	Mouse Hepatitis Virus
MOA	Mode of Action
NCI	National Cancer Institute
NTP	National Toxicology Program
RfD	Reference Dose
RRD	Remediation and Redevelopment Division
SCE	Sister Chromatid Exchange
Subcommittee	Toxics Steering Group 1,4-Dioxane Subcommittee
TERA	Toxicology Excellence for Risk Assessment
TSG	Toxics Steering Group
U.S. EPA	United States Environmental Protection Agency
WOE	Weight-of-Evidence

EXECUTIVE SUMMARY

On behalf of Pall Corporation, Michael Dourson, Ph.D. of Toxicology Excellence for Risk Assessment (TERA), an organization specializing in risk assessment, requested an audience with Michigan Department of Environmental Quality (MDEQ) staff to present and discuss their recent toxicity evaluation of 1,4-dioxane. Specifically, data supporting a proposed mode of action (MOA) for liver tumor formation in laboratory animals exposed to 1,4-dioxane was presented to MDEQ staff on October, 8, 2013. TERA contends that the MOA for liver tumor formation involves hepatic cytotoxicity leading to regenerative hyperplasia, which in turn leads to the promotion of endogenously evoked tumors i.e., a nonmutagenic process. Based on this proposed MOA, a threshold dose was identified that supports a non-linear (i.e., threshold) dose-response risk assessment as opposed to a linear (i.e., nonthreshold) dose response risk assessment typically used for carcinogens.

Chemicals that cause noncancer effects are typically believed to act via a threshold or nonlinear mechanism. The threshold concept is based on the idea that there is a dose of a chemical below which adverse effects are not seen and above which adverse effects do occur. This phenomenon is due to the fact that protective mechanisms are in place up to a certain concentration. At or above this threshold concentration, the cells are no longer able to compensate and adverse effects are exhibited.

Chemicals that cause cancer are typically assumed to act via a nonthreshold or linear mechanism. This assumption is based on the hypothesis that all levels of exposure pose a finite probability, however small, of generating a carcinogenic response. For carcinogens, the U.S. Environmental Protection Agency (U.S. EPA) assumes that a small number of molecular events can evoke changes in a single cell that can lead to uncontrolled cellular proliferation and eventually to a clinical state of disease i.e., cancer.

In response to Pall Corporation's request, the MDEQ convened a subcommittee of the MDEQ's Toxics Steering Group (TSG) to evaluate the merits of TERA's proposal. The TSG 1,4-Dioxane subcommittee reviewed TERA's proposal, the U.S. EPA Integrated Risk Information System (IRIS), 2011 draft toxicological assessment of 1,4-dioxane, and other available scientific information related to identifying a carcinogenic MOA for 1,4-dioxane. In addition, the TSG subcommittee conducted a comparison of TERA's 1,4-dioxane proposal against IRIS's assessment of chloroform, the only chemical identified by the U.S. EPA as a threshold carcinogen, to facilitate the identification of requirements for supporting a threshold MOA. The TSG subcommittee's review and conclusions are summarized in this report.

The TSG subcommittee concludes that the currently available scientific information regarding the carcinogenicity of 1,4-dioxane does not support TERA's hypothesis and are insufficient to deviate from the U.S. EPA's default assumption of linearity for developing a cancer potency factor.

INTRODUCTION

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Chemicals that cause cancer are typically assumed to act via a nonthreshold or linear mechanism. This assumption is based on the hypothesis that all levels of exposure to a carcinogen pose a finite probability, however small, of generating a carcinogenic response. For carcinogens, U.S. EPA assumes that a small number of molecular events can evoke changes in a single cell that can lead to uncontrolled cellular proliferation and eventually to a clinical state of disease i.e., cancer.

In response to Pall Corporation's request, the MDEQ convened a subcommittee of the MDEQ's TSG to evaluate the merits of TERA's proposal. The TSG is comprised of toxicologists from the MDEQ, Michigan Department of Community Health (MDCH) and, the Michigan Department of Agriculture and Rural Development (MDARD). The TSG 1,4-Dioxane subcommittee reviewed TERA's proposal, the U.S. EPA Integrated Risk Information System (IRIS), 2011 draft toxicological assessment of 1,4-dioxane, and other available scientific information related to identifying a carcinogenic MOA for 1,4-dioxane. In addition, the TSG subcommittee conducted a comparison of TERA's 1,4-dioxane proposal against IRIS's assessment of chloroform, the only chemical identified by the U.S. EPA as a threshold carcinogen, to facilitate the identification of requirements for supporting a threshold MOA. The TSG subcommittee's review and conclusions are summarized in the following sections of the report.

EXPANDED DISCUSSION AND ANALYSIS OF TERA PROPOSAL

During the presentation to MDEQ staff on October 8, 2013, Michael Dourson, Ph.D., proposed an MOA for liver tumor formation in mice exposed to 1,4-dioxane. The TSG was tasked by the MDEQ to review the information presented by TERA. The subcommittee members as well as several members of the full TSG along with the MDEQ and RRD management attended the presentation. Responses to TSG toxicologists' comments and questions made during the presentation were submitted to the MDEQ in writing on December 9, 2013, by Dr. Dourson and Jeff Crum, M.S. of Hamp, Matthews, and Associates, a consultant for Pall Corporation.

As background, the 2011 U.S. EPA toxicological review of 1,4-dioxane indicated that "... key events related to the promotion of tumor formation by 1,4-dioxane are not conclusive. Therefore, under the U.S. EPA *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), the U.S. EPA concluded that the

available information does not establish a plausible MOA for 1,4-dioxane, and data are insufficient to establish significant biological support for a nonlinear approach. The U.S. EPA determined that there are no data available to inform the low-dose region of the dose response, and thus, a nonlinear approach was not included." (U.S. EPA, 2011). See the final U.S. EPA toxicological review for the cancer assessment details (U.S. EPA, 2013).

TERA contends that, contrary to the U.S. EPA review of the 1,4-dioxane MOA, the MOA for liver tumor formation by 1,4-dioxane can be elucidated. This MOA involves hepatic cytotoxicity leading to regenerative hyperplasia. Hyperplasia leads to the promotion of endogenously evoked tumors. Based on this MOA, a threshold dose is identified, and a non-linear approach is proposed for dose-response assessment (Dourson, 2013b). The information and data supporting the proposed MOA are also detailed in Dourson et al., 2014. Comments by the subcommittee are presented below:

Weight of Evidence:

The subcommittee finds that the weight of evidence (WOE) supporting TERA's proposed MOA is weak and requires more supporting data for the following reasons.

- TERA's proposal that tumor formation is caused by cytotoxicity is not adequately supported by other studies. In rodents, hepatocarcinomas have been associated with proliferative lesions composed of hyperplastic nodules and foci of phenotypically altered hepatocytes (FAH) (Grisham, 1996). The FAH are commonly accepted as preneoplastic lesions. Preneoplastic lesions are phenotypically altered cell populations that are not neoplastic in nature but could progress to hepatocellular neoplasms (Su, 2003). In rodents, increased FAH is a reliable indicator of hepatocarcinogenicity (Bannasch, 2003). Although FAH is also observed in aged rodent liver (spontaneous), persistent FAH (induced) observed with neoplasms are considered neoplastic. The significant incidence of clear cell and mixed FAH observed in Table 4.8 and 4.9 (U.S. EPA, 2011) for male and female rats in the 1,4-dioxane high dose treatment group and the significant incidence of carcinoma and adenoma observed in the same dose group (Table 4-11) indicate that FAH had progressed to hepatoadenoma (HCA) or hepatocarcinoma (HCC). Data providing the basis for the formation of FAH, whether cytotoxic, mitogenic or genotoxic, may provide insight into the MOA for 1,4-dioxane tumor formation.
- FAH may be one of the preceding events to cancer formation and the occurrence of FAH does not support TERA's MOA proposal. TERA's MOA is partly supported by data from the re-read NCI (NTP) slides which classified FAH under "regenerative hyperplasia" (McConnell, 2013). In contrast to FAH, regenerative hyperplasia is characterized by the presence of one or more nodular lesions that do not have the features of neoplasia and hepatocyte damage in the parenchyma including cytotoxicity, necrosis, atrophy, fibrosis degeneration, and inflammation (Goodman, 1994). In Kano et al. (2009), samples characterized as hyperplasia were reexamined and reclassified into either FAH or HCA according to updated criteria for liver lesions. McConnell (2013) reported high incidence of FAH in male and female rats that received low and high doses of 1,4-dioxane in the NCI study(Table 4). High incidences of adenomas and carcinomas were also observed in both dose groups (Table 5). These data indicate that FAH may be the main event preceding the formation of HCA and HCC in 1,4-dioxane treated rats. The mechanism for FAH formation remains to be elucidated. Since FAH is different from regenerative hyperplasia, the reclassification of FAH to hyperplasia in the McConnell re-read of the NCI study slides may not be appropriate.
- Decreased glycogen reported by McConnell in the 1,4-dioxane-treated rats may be related to the FAH. Acidophilic FAH are reported to contain excess glycogen and are considered

early lesions which reportedly may progress into glycogen-poor basophilic FAH (Goodman, 1994, Su, 2003). This supports the hypothesis that FAH formation may be the event that precedes 1,4-dioxane tumor formation. The use of stop or interim experiments to show the progression of 1,4-dioxane hepatocarcinogenesis would help explain this MOA.

- Although the U.S. EPA considers spongiosis hepatis to be preneoplastic, the evidence is not clear at this time. Spongiosis hepatis is one of the liver lesions identified by the JBRC (1998) in rats exposed to 1,4-dioxane (Table 4-8 and 4-9, U.S. EPA 2012). This lesion was detected in all treated and control male rats while in female rats the lesion was observed only in the high dose group. U.S. EPA describes this lesion as cyst-like and found in the hepatic perisinusoidal or Ito cells. TERA (Dourson, 2013a) noted that the JRBC study described the lesion as "voids in the liver that occurs after a cell degenerates." During the discussion with TERA, MDEQ staff asked whether this lesion contributes to a possible MOA different from the hyperplasia hypothesis. TERA indicated that the "hyperplasia" term used by an earlier Japanese paper (Yamazaki et al, 1994, JBRC 1998) was changed to "foci" in the Kano, 2009 paper. Footnote g of the U.S. EPA (2011) Tables states: "The samples associated with liver hyperplasia for rats and mice in Yamazaki et al. (1994) and JBRC (1998) were re-examined according to updated criteria for liver lesions and were afterwards classified as either HCA or altered hepatocellular foci in Kano et al. (2009)". TERA (2013a) notes that the change in terminology contributed to the difficulty of describing 1,4-dioxane liver lesions consistently. Spongiosis hepatis, also referred to as cystic degeneration, is considered preneoplastic because they are observed together with preneoplastic foci (altered hepatic foci) in the liver or with HCA or HCC, (Bannasch, 2003; Stroebel et al., 1995). However, Karbe and Kerlin (2002) disputed this preneoplastic nature noting that cystic degeneration may be a result of the cellular repair process or a secondary change. The JBRC (1998) study showed the occurrence of spongiosis hepatis in rats in association with preneoplastic clear and mixed-cell foci but the lesion also occurred in livers without tumors; these lesions were not seen in the livers of 1,-4 dioxane treated mice. In Kasai (2009), the incidence of spongiosis hepatis in male rats exposed to 1,4-dioxane vapor by whole-body inhalation for 2 years showed a significant increase in the high dose group but this lesion also appeared in the control group.
- Only information related to the MOA for liver tumor formation was presented i.e., nothing related to the MOA for the other tumor types observed in 1,4-dioxane-treated animals was discussed. In addition, based on his conclusion that 1,4-dioxane did not cause tumors via a mutagenic MOA, Dr. Dourson concluded that an RfD could be derived from the cancer data. The derivation of the RfD is presented in Dourson et al., 2014.
- While some of the data presented is supportive of TERA's proposed MOA for 1,4-dioxane liver tumor formation, the NTP/NCI slide re-read for female mice is not supportive of TERA's MOA and remains unexplained (McConnell, 2013). In other studies, data for female rats or mice were either insufficient to support TERA's MOA or conflicting information was reported. In the two year drinking water study (Kano et al., 2009), a significant increased incidence of HCA and HCC was observed at the lowest dose of 66 mg/kg (Table 5). Information was presented for preneoplastic altered foci in rats, but not for mice. Based on the findings in Kano et al. (2009), a determination of preneoplastic lesions (e.g., cytotoxicity, inflammation or altered cell foci) in female mice at the low dose level cannot be made to support TERA's proposed MOA of cytotoxicity and inflammation as a precursor to tumor formation. TERA presented the Kano et al. (2008) 13-week study results to show that preneoplastic lesions were occurring prior to tumor formation. However, at 13 weeks, the lowest two doses (i.e., 170 and 387 mg/kg/day) had only one animal in each group with slight centrilobular inflammation, but necrosis was not observed (Table 4-2).

Tumor Formation Pathway:

For the Dourson-proposed pathway to be supported, cytotoxicity needs to precede tumor formation for all exposed animals. The measure of cytotoxicity used in the re-read of the NCI male and female mouse liver slides was necrosis. Inflammation was also noted during the slide re-read, but inflammation can be caused by many cellular events and may even cause cytotoxicity. Necrosis preceded liver tumor formation in both male mice and female mice. However, low dose female mice had similar levels of necrosis and inflammation as the female control mice and some female mice with tumors had no evidence of necrosis. The low dose group developed liver tumors, while the control mice did not. The female control group had no tumors, 14/45 females in the low dose group had tumors, and 29/37 females had tumors in the high dose group (Dourson et al., 2013b, Table 4). This indicates that necrosis may not have been a step in the process to tumor formation for 1,4-dioxane.

- A potential explanation for the necrosis and inflammation in female control mice was provided in TERA's December 9, 2013 "Response to MDEQ Questions on 1,4-Dioxane." (Dourson 2013a). The response to Question 2, addressing the high percentage of necrosis and inflammation in female control mice, stated that mice at NCI facilities may have had mouse hepatitis virus (MHV). As a result, female mice may have been more susceptible to the infection, resulting in increased necrosis and inflammation in the female control mice. It was also noted that this infection does not result in hypertrophy or tumors. This presents several issues of concern regarding use of slide re-reads to support MOA determination. If the MHV was present and causing cytotoxicity, these effects may incorrectly be attributed to 1,4-dioxane exposure. Alternately, as animals infected with the MHV may have altered hepatic activity along with reduction of liver regeneration (Charles River 2009; University of Illinois, 2014), the full effects from 1,4-dioxane exposure could have been masked. It is not possible to separate out these effects and reduces the usefulness of the slide re-reads for MOA determination.
- The numbers of individual mice with hypertrophy, necrosis, inflammation, and/or foci were recorded in the response to Question 1, addressing whether animals with liver tumors also had these effects. While mice with and without tumors were separated in the table, the incidences of hypertrophy, necrosis, inflammation, and foci were grouped and counted together. Necrosis is the only one of these four histological descriptions that would be a result of cytotoxicity. Although they may also be related to cytotoxicity, inflammation, hypertrophy, and foci may also be precursors to neoplasms that are not related to an MOA based on cytotoxicity. If necrosis and inflammation could have been due to the MHV, the number of mice with those effects is of limited usefulness. The number of mice with or without tumors and hypertrophy should also have been separately listed in the table, as that effect may have been solely from the 1,4-dioxane exposure. In the response, it was stated that the predominant noncancer effect was hypertrophy. The regenerative cell hyperplasia MOA cannot be solely supported by hypertrophy, although it was the predominant effect and not connected with the potential MHV infection.

Use of Published and Unpublished Data:

Published, peer-reviewed data, when available, are typically preferred over unpublished data. Currently, the U.S. EPA uses Kociba et al., 1974 for derivation of the chronic oral RfD for non-cancer effects whereas TERA proposes to use the unpublished laboratory reports of Kociba et al., 1971 to derive an RfD protective for carcinogenicity.

Comparison of US EPA Chloroform and 1,4-Dioxane Assessments and MOA:

To date, the only substance that the U.S. EPA has determined to be carcinogenic via a threshold (i.e., nonlinear) MOA is chloroform (U.S. EPA, 2001). For the purpose of determining if the information

regarding 1,4-dioxane's MOA is adequate to conclude non-linearity, the Subcommittee compared the IRIS information and conclusions for chloroform and 1,4-dioxane. See Table below:

COMPARISON OF MAJOR CONCLUSIONS IN THE IRIS ASSESSMENT OF CHLOROFORM AND 1,4-DIOXANE:

Chloroform (U.S. EPA, 2001):	1,4-Dioxane (U.S. EPA, 2013):
1. Neoplasia (liver tumors were the only ones found) is preceded by cytotoxicity that leads to sustained and repeated regenerative hyperplasia.	1. MOA data are available only for liver and nasal tumors. Available data do not support any specific MOA. Multiple tumor types were noted in multiple species/strains.
2. Epidemiological data are not available.	2. Epidemiological data are not available.
3. Genotoxicity data are negative. All positive results can be explained away by confounding factors, or they occur at extremely high doses.	3. There are numerous negative mutagenicity assay results. However, 1,4-dioxane was weakly positive for SCE in CHO assay without activation. DNA damage was found in the absence of cytotoxicity.
4. Overall, chloroform is not strongly mutagenic and the predominant MOA is not likely to be genotoxic.	4. Five studies suggest genotoxicity. Overall, 1,4-dioxane is weakly genotoxic.
5. Tumor formation occurred ONLY with cytotoxicity; phosgene is (via CYP2E1 pathway) recognized as a metabolite of interest and a rate-limiting step.	5. Kano, 2008 and the NCI (NTP, 1978) study found liver tumors in the absence of cytotoxicity. Multiple Cytochrome P450 (CYPs) associated with multiple tissue types are induced following exposure. Reactive metabolite(s) are unknown.
6. There were NO cases of tumorigenic response without cell regeneration.	6. Cytotoxicity may not be a required precursor event. Cell proliferation is noted but it's not clear if it's due to cytotoxicity or mitogenesis.
7. Chloroform received a negative score in the ILSI method for DNA reactivity.	7. Not mentioned in the IRIS assessment.
8. Chloroform was negative in the p53 knockout mouse assay.	8. Not mentioned in the IRIS assessment.
9. Chloroform is not a promoter.	9. 1,4-Dioxane is a promoter.
10. Chloroform is not an initiator.	10. 1,4-Dioxane is not an initiator in the three initiation/promotion studies summarized in the Tox Review.
11. Chloroform is not a co-carcinogen.	11. Not mentioned in the IRIS assessment.
12. 85 references for carcinogenicity section.	12. 22 references for carcinogenicity section.

The following is the U.S. EPA's specific conclusion regarding the carcinogenicity of chloroform (U.S. EPA 2001): "Under the Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996a; U.S. EPA, 1999), chloroform is likely to be carcinogenic to humans by all routes of exposure under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues (U.S. EPA, 1998c,d). Chloroform is not likely to be carcinogenic to humans by any route of exposure under exposure conditions that do not cause cytotoxicity and cell regeneration. This weight-of-evidence conclusion is based on: 1) observations in animals exposed by both oral and inhalation pathways which indicate that sustained or repeated cytotoxicity with secondary regenerative hyperplasia precedes, and is probably required for, hepatic and renal neoplasia; 2) there are no epidemiological data specific to chloroform and, at most, equivocal epidemiological data related to drinking water exposures that cannot necessarily be negative, although there are some scattered positive results that generally have

limitations such as excessively high dose or with confounding factors. Thus, the weight-of-evidence of the genotoxicity data on chloroform supports a conclusion that chloroform is not strongly mutagenic, and the genotoxicity is not likely to be the predominant mode of action underlying the carcinogenic potential of chloroform. Although no cancer data exist for exposures via the dermal pathway, the weight-of-evidence conclusion is considered to be applicable to this pathway as well, because chloroform absorbed through the skin and into the blood is expected to be metabolized and to cause toxicity in much the same way as chloroform absorbed by other exposure routes."

Conversely, the U.S. EPA's specific conclusion regarding the carcinogenicity of 1,4-dioxane reads (U.S. EPA, 2013): "A MOA hypothesis involving sustained proliferation of spontaneously transformed liver cells has some support from data indicating that 1,4-dioxane acts as a tumor promoter in mouse skin and rat liver bioassays (Lundberg et al., 1987; King et al., 1973). Dose-response and temporal data support the occurrence of cell proliferation and hyperplasia prior to the development of liver tumors (JBRC, 1998b; Kociba et al., 1974) in the rat model. However, the dose-response relationship for induction of hepatic cell proliferation has not been characterized, and it is unknown if it would reflect the dose-response relationship for liver tumors in the 2-year rat and mouse studies. Conflicting data from rat and mouse bioassays (JBRC, 1998b; Kociba et al., 1974) suggest that cytotoxicity may not be a required precursor event for 1,4-dioxane-induced cell proliferation. Liver tumors were observed in female rats and female mice in the absence of lesions indicative of cytotoxicity (Kano et al., 2009; JBRC, 1998b; NCI, 1978). Thus, data regarding a plausible dose response and temporal progression from cytotoxicity and cell proliferation to eventual liver tumor formation are not available. The MOA by which 1,4-dioxane produces liver, nasal, peritoneal (mesotheliomas), and mammary gland tumors is not conclusive, and the available data do not support any hypothesized carcinogenic MOA for 1,4-dioxane."

Additionally, the following considerations of the IRIS toxicity assessment for 1,4-dioxane should be noted:

- The IRIS assessment has undergone two external peer reviews.
- The role of cytotoxicity as a required precursor of neoplasia is supported by only one study.
- In the majority of studies, the dose-response does not support cytotoxicity as a necessary precursor of neoplasia.
- The Japanese studies provided no interim sacrifice data.
- The dose-response curve for the female mice tumors is very, very steep, and there are no data to inform the low-dose region.
- All of the tumor types induced by 1,4-dioxane are relevant to humans and there is no sufficient support for any one MOA.

The most compelling argument for retaining the U.S. EPA default assumption of linearity for 1,4-dioxane is the presence of multiple tumor types in rodent models, all of which are relevant to humans. TERA hypothesized an MOA for the liver tumors alone. In comparison, the only site of tumorigenesis following exposure to chloroform was the liver. Additionally, genotoxicity data allow for the conclusion that chloroform is not likely to be genotoxic, while 1,4-dioxane is considered weakly genotoxic.

Conclusion:

Based on the 1,4-dioxane assessment considerations as noted in this report, the subcommittee concludes that the data regarding the carcinogenicity of 1,4-dioxane are not sufficient to deviate from the U.S. EPA's default assumption of linearity, as described in the Cancer Guidelines (U.S. EPA, 2005).

TERA'S RESPONSE TO MDEQ QUESTIONS DURING THE OCTOBER, 2013 PRESENTATION

The questions posed by TSG toxicologists during the presentation and the responses provided by TERA in their December 9, 2013 written response, (Dourson, 2013a), are addressed throughout this document. This submittal will be made available upon request.

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