MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for 1,4-Dioxane (CAS No. 123-91-1)

FROM: Cathy Simon, Toxics Unit, Air Quality Division

DATE: January 29, 2014

SUBJECT: Updated Screening Levels for 1,4-Dioxane

The screening levels for 1,4-dioxane have been updated. The changes include two new initial threshold screening levels (ITSLs) based on two different averaging times, and a revised initial risk screening level (IRSL) and secondary risk screening level (SRSL). The updated screening levels are as follows:

ITSL (1-hour averaging time) = 7,200 µg/m^3
ITSL (annual averaging time) = 100 µg/m^3
IRSL (annual averaging time) = 0.2 µg/m^3
SRSL (annual averaging time) = 2 µg/m^3

The background information, relevant data, and bases for the updated screening levels are summarized below.

Background

The chemical, 1,4-dioxane is a cyclic diether, and is a colorless liquid with a vapor pressure of 40 mm Hg at 25ºC (EPA, 2013a). The chemical formula for 1,4-dioxane is $C_4H_8O_2$ and the chemical structure is shown below in Figure 1:

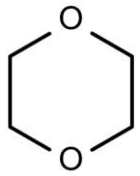

Figure 1. Chemical Structure of 1,4-Dioxane

In August, 2010, the Air Quality Division (AQD) of the Michigan Department of Environmental Quality (MDEQ) revised the screening levels for 1,4-dioxane that were in existence at that time (MDEQ, 2010). The screening levels established in 2010 included the following:

ITSL (24-hour averaging time) = 100 µg/m^3
IRSL (annual averaging time) = 0.04 µg/m^3
SRSL (annual averaging time) = 0.4 µg/m^3

The above ITSL of 100 µg/m^3 (24-hour averaging time) was derived from an oral reference dose of 30 µg/kg-day, established by the U.S. Environmental Protection Agency (EPA). The ITSL was derived pursuant to Rule 232(1)(b) of the Michigan Air Pollution Control Rules. The above IRSL (0.04 µg/m^3) and SRSL (0.4 µg/m^3) were derived from oral cancer slope factors, also established by the U.S. EPA.

In September 2013, the U.S EPA updated the Integrated Risk Information System (IRIS) for 1,4-dioxane. This update included a new inhalation reference concentration (RfC) and a new inhalation unit risk (IUR) value for 1,4-dioxane (EPA, 2013b). In light of the new information in IRIS, the screening levels for 1,4-dioxane were reviewed for possible revision. As part of the evaluation, complete literature reviews were not done, instead the focus was on the updated IRIS information and relevant summary documents prepared by appropriate governmental or scientific agencies.

Update of the ITSL

The new inhalation RfC for 1,4-dioxane listed in IRIS in September 2013 is 30 µg/m^3. In support of the new inhalation RfC and IUR value in IRIS, the U.S. EPA also published an updated review of the scientific literature detailing the toxicological effects of 1,4-dioxane in the document, *Toxicological Review of 1,4-Dioxane (with Inhalation Update)* (EPA, 2013a). This document, along with the Agency for Toxics Substance and Disease Registry's (ATSDR) *Toxicological Profile for 1,4-Dioxane* (ATSDR, 2012), provide the most complete up to date review of the scientific literature dealing with the toxicological effects of 1,4-dioxane.

Data in humans evaluating the effects of exposure to 1,4-dioxane are limited, and considered inadequate for derivation of an inhalation RfC. Several studies in laboratory animals, by both oral and inhalation routes of exposure, have evaluated the toxicological effects of exposure to 1,4-dioxane. Both routes of exposure have been shown to result in adverse effects to various organ systems, including the liver, kidney, and nasal cavities. The U.S. EPA identified four principal animal studies in support of development of an inhalation RfC, including two subchronic inhalation studies (Farley et al, 1934; Kasai et al, 2008) and two chronic inhalation studies (Torkelson et al, 1974; Kasai et al, 2009).

In the subchronic inhalation study by Farley et al (1934), rats, mice, guinea pigs, and rabbits (3-6/species/group) were exposed to 1000, 2000, 5000, or 10,000 ppm of 1,4-dioxane for about 16 hours per week until death or up to 12 weeks. From this study, the U.S. EPA identified a LOAEL of 1000 ppm for liver and kidney degeneration in rats, mice, rabbits, and guinea pigs. The U.S. EPA also found that this study was not adequate to characterize the inhalation risks of 1,4-dioxane due to the lack of control animals, as well as no data reported for low-dose exposure (EPA, 2013a).

In the subchronic inhalation study by Kasai (2008), groups of 10 male and female F344/DuCrj rats were exposed to 0, 100, 400, 800, 1600, 3200, and 6400 ppm of 1,4-dioxane for 6 hours/ day, 5 days/week, for 13 weeks. All rats in the highest dose group died by the end of the first week of exposure, due to renal failure and diagnosed as necrosis of the renal tubules. Adverse histological effects were found in the liver, kidney, and respiratory tract of animals exposed to lower doses. These effects included "nuclear enlargement of the nasal respiratory, nasal olfactory, tracheal, and bronchial epithelium; vacuolic change in the olfactory and bronchial epithelium; atrophy of the nasal epithelium; hydropic change in the proximal tubules of the kidney; and single-cell necrosis and centrilobular swelling in the liver" (EPA, 2013a, p. 56). The most sensitive lesion identified by the authors was nuclear enlargement in the nasal respiratory

epithelium, which was significantly increased at 100 ppm in both male and female rats. This value was also considered a LOAEL by the study authors. The U.S. EPA did not consider nuclear enlargement as an adverse effect, stating that this effect "may be found in any cell type responding to microenvironmental stress or undergoing proliferation" (EPA, 2013a, p56). The U.S. EPA did, however, note that some studies have indicated that nuclear enlargement may also be identified as an early change in response to exposure to a carcinogenic agent. Overall, the U.S. EPA felt that the uncertainty of the meaning of this effect precluded its consideration as an adverse effect.

In the chronic inhalation study by Torkelson et al (1974), groups of 288 male and female Wistar rats were exposed to 111 ppm of 1,4-dioxane vapor for 7 hours/day, 5 days/week for 2 years. The U.S. EPA identified a free standing NOAEL from this study. Because this study only provided a free standing NOAEL, the U.S EPA found it inadequate to use to characterize the inhalation risks of 1,4-dioxane (EPA, 2013a).

In the chronic inhalation study by Kasai et al (2009), groups of 50 male F344/DuCrj rats were exposed to 0, 50, 250, and 1250 ppm of 1,4-dioxane vapor for 6 hours/day, 5 days/week, for 2 years. No female rats were included in this study. The authors justified this decision based on the results of a drinking water study (Yamazaki, et al 1994) in which exposure to 1,4-dioxane induced mesotheliomas only in male rats, but not females.

The results of Kasai et al (2009) showed that exposure to 1,4-dioxane produced both carcinogenic and non-carcinogenic effects in the treated rats. Body weight was significantly decreased in the 1250 ppm dose group, and relative lung and liver weight was significantly increased in this dose group. Various hematological and clinical chemistry effects were also observed in the 1250 ppm dose group including decreased hemoglobin, decreased MCV, decreased MCH, increased AST, increased ALT, increased ALP, increased γ-GTP, and decreased urinary pH.

Histological effects were observed in the liver, kidney, and nasal cavities of the exposed rats in the Kasai et al study (2009). The nasal cavity was the most sensitive tissue to the effects of 1,4-dioxane, with pre-neoplastic and non-neoplastic lesions that were significantly increased at all exposure levels. These effects included nuclear enlargement of the respiratory epithelium, as well as nuclear enlargement, metaplasia and atrophy of the olfactory epithelium. Additional lesions of the nasal cavity seen at the two highest dose levels (250 ppm and 1250 ppm) included squamous cell metaplasia of the nasal respiratory epithelium, inflammation of the nasal olfactory epithelium, and hydropic change and sclerosis of the lamina propria. Pre- and non-neoplastic lesions that were significantly increased in the kidney included nuclear enlargement in the proximal tubule at the two highest doses, and hydropic changes of the proximal tubule only at the highest dose. Significantly increased pre- and non-neoplastic lesions in the liver were only observed at the highest dose level. These included centrilobular nuclear enlargement and necrosis, acidophilic cell foci, basophilic cell foci, and spongiosis hepatis. Kasai et al (2009) also found significantly increased incidences of tumors in various organ systems. These results are discussed in more detail below in the section on cancer risk assessment.

The Kasai et al (2009) chronic inhalation study was selected by the U.S. EPA as the principal study to use in derivation of the inhalation RfC. Incidences of non-neoplastic lesions that were significantly increased were considered as candidates for the critical effect, excluding nuclear enlargement which EPA does not consider to be adverse as discussed above. Table 1 provides a summary of those non-neoplastic lesions evaluated for derivation of the inhalation RfC.

Table 1. Incidence of non-neoplastic lesions in rats from Kasai et al (2009) evaluated for derivation of the inhalation RfC (EPA, 2013a)

Tissue	Endpoint	Concentration (ppm)			
		0	50	250	1250
Liver	Centrilobular necrosis	1/50	3/50	6/50	12/50[a]
Nasal	Squamous cell metaplasia; respiratory epithelium	0/50	0/50	7/50[b]	44/50[a]
	Squamous cell hyperplasia; respiratory epithelium	0/50	0/50	1/50	10/50[a]
	Respiratory metaplasia; olfactory epithelium	11/50	34/50[a]	49/50[a]	48/50[a]
	Atrophy; olfactory epithelium	0/50	40/50[a]	47/50[a]	48/50[a]
	Hydropic change; lamina propria	0/50	2/50	36/50[a]	49/50[a]
	Sclerosis; lamina propria	0/50	0/50	22/50[a]	40/50[a]
[a] $p \leq 0.01$ [b] $p \leq 0.05$					

Benchmark dose (BMD) modeling was used to analyze the candidate endpoints identified in Table 1. A benchmark response (BMR) of 10% extra risk was selected as the response level to use in derivation of the inhalation RfC. The 95% lower confidence limit on the dose associated with this response level ($BMDL_{10}$) was used as the point of departure (POD) for derivation of the inhalation RfC. Due to a lack of model fit or substantial model uncertainty, the U.S. EPA concluded that the BMD modeling results were inadequate for the endpoints of atrophy and respiratory metaplasia of the olfactory epithelium, as well as sclerosis of the lamina propria. For these endpoints, a NOAEL/LOAEL approach was used to determine potential PODs.

After modeling, each $BMDL_{10}$ or NOAEL/LOAEL was duration adjusted and converted to units of mg/m^3 to arrive at the adjusted point of departure (POD_{ADJ}). After analyzing this information, the U.S. EPA selected respiratory metaplasia and atrophy of the olfactory epithelium as the most sensitive endpoints, and co-critical effects to use in derivation of the inhalation RfC. The POD_{ADJ} for both of these endpoints was 32.2 mg/m^3 and was derived from a LOAEL of 50 ppm as follows:

$$POD_{ADJ}(mg/m^3) = 50\ ppm \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} \times \frac{3.6\ mg/m^3}{1\ ppm} = 32.2\ mg/m^3$$

To convert the POD_{ADJ} based on data in rats to a human equivalent concentration (HEC), the U.S. EPA applied a dosimetric adjustment factor (DAF), consistent with the *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (EPA, 1994). Because 1,4-dioxane is water soluble, causes systemic and portal-of-entry effects, is absorbed and distributed throughout the body, and uncertainty exists regarding whether the nasal effects are due to portal-of-entry or systemic delivery, the U.S. EPA concluded that

1,4-dioxane should be treated as a systemic acting gas for purposes of determining the DAF. The calculated DAF based on the ratio of the animal to human blood:air partition coefficient was 1.12. Consistent with the U.S EPA RfC Methodology (1994), when the calculated DAF is greater than one, a default value of one is used as the final DAF. The POD_{HEC} was then determined as follows:

$POD_{HEC} = POD_{ADJ}$ x DAF

POD_{HEC} = 32.2 mg/m^3 x 1.0 = 32.2 mg/m^3

The POD_{HEC} was then divided by a total uncertainty factor (UF) of 1000 to arrive at the inhalation RfC of 0.0322 mg/m^3, which is equivalent to 0.03 mg/m^3 when rounded to one significant figure. The total UF of 1000 was composed of an UF of 3 for animal to human extrapolation (UF_A = 3), an UF of 10 for variation in sensitivity within human populations (UF_H = 10), an UF of 10 for extrapolation from a LOAEL to NOAEL (UF_L = 10), and an UF of 3 for database deficiencies (UF_D = 3).

Rule 232(1)(a) of the Michigan Air Pollution Control Rules specifies than when an inhalation RfC is available, the ITSL equals the RfC. Inhalation RfCs that include a database uncertainty factor are examined on a case-by-case basis to determine the appropriateness of including this uncertainty factor in derivation of the ITSL. The U.S. EPA's rationale for including the database uncertainty factor was the lack of a multigeneration reproductive toxicity study. It is the position of MDEQ-AQD that the lack of a multigeneration reproductive toxicity study by itself is not adequate justification for application of a data base uncertainty factor. Therefore, the UF_D = 3 used in derivation of the inhalation RfC is removed for derivation of the ITSL. The resulting total uncertainty factor applied to the POD_{HEC} is 300 (UF_A = 3; UF_H = 10; UF_L = 10), and the ITSL is derived as follows:

$$ITSL = \frac{POD_{HEC}}{UF_A \; x \; UF_H \; x \; UF_L}$$

$$ITSL = \frac{32.2 \; mg/m^3}{3 \; x \; 10 \; x \; 10} = 0.107 \; mg/m^3 \cong 0.1 \; mg/m^3$$

The above value of 0.107 mg/m^3 is equivalent to 0.1 mg/m^3 or 100 µg/m^3 when rounded to one significant figure. Therefore, the ITSL is 100 µg/m^3 based on an annual averaging time, and derived pursuant to Rule 229(2)(b) of the Michigan Air Pollution Control Rules. Annual averaging time was selected for this ITSL because the critical effect was observed after chronic exposure and a short term ITSL protective of acute effects was derived as described below.

A search for available health benchmark values protective of acute effects from exposure to 1,4-dioxane, revealed two governmental organizations that had established such values applicable to protecting the health of the general public, and that also included adequate scientific documentation and a peer review process. The ATSDR has established an acute inhalation minimal risk level (MRL) of 2 ppm for 1,4-dioxane (ATSDR, 2012). The California EPA (Cal/EPA) has established an acute inhalation reference exposure level (REL) of 3,000 µg/m^3 (one hour exposure) for 1,4-dioxane (Cal/EPA, 2008). These two values were evaluated for use as a potential acute based ITSL for 1,4-dioxane.

The Cal/EPA acute inhalation REL was derived from a study by Young et al (1977) in which four healthy male adult volunteers were exposed to 50 ppm (180 mg/m^3) 1,4-dioxane vapor for 6 hours. All four subjects experienced eye irritation, and two out of four reported olfactory fatigue after 4 and 5 hours. No effects were observed on the following tests taken 24 hours and 2 weeks post exposure: electrocardiogram, respiratory function, blood chemistry, hematological measurements, and urinary analyses. The 50 ppm exposure concentration was identified as a LOAEL by Cal/EPA. The LOAEL of 50 ppm was divided by a total uncertainty factor of 60 (UF_H = 10; UF_L = 6) to get an acute REL of 0.8 ppm, equivalent to 3 mg/m^3 or 3,000 µg/m^3 (Cal/EPA, 2008). The Cal/EPA did not apply any time adjustment to the LOAEL in the derivation of the acute REL, because the volunteers complained of eye irritation throughout the exposure.

The ATSDR utilized a study by Ernstgard et al (2006) to derive the acute inhalation MRL. In this study, six male and six female volunteers were exposed to 0 or 20 ppm of 1,4-dioxane vapor for 2 hours, on two separate occasions. Evaluated endpoints included the following: self-rated symptoms of discomfort to the eyes, nose, and throat, breathing difficulty, solvent smell, headache, fatigue, nausea, dizziness, and feeling of intoxication; respiratory function as assessed by spirometry; nasal swelling; eye blinking as monitored by electromyography; and blood levels of two inflammatory markers, high sensitivity C reactive protein and interleukin 6. No effects on any measured endpoints were observed, except for the perception of smell of 1,4-dioxane, which increased significantly after 3, 60, and 118 minutes of exposure. The ATSDR identified 20 ppm as a NOAEL from this study. This NOAEL was divided by a total uncertainty factor of 10 to account for human variability, resulting in an acute MRL of 2 ppm, equivalent to 7.2 mg/m^3 or 7,200 µg/m^3. The ATSDR acute MRLs generally are derived for exposure periods of 1 – 14 days. In deriving the acute inhalation MRL for 1,4-dioxane, the ATSDR found that no adjustment to 24-hour exposure was necessary "because the first effects observed, as shown by Young et al (1977), are local irritation effects that are not time-dependent" (ATSDR, 2012, p. A-3).

The study by Ernstgard et al (2006), which was used to derive the ATSDR acute inhalation MRL, was also selected to use for derivation of an acute based ITSL for 1,4-dioxane. This study was selected over the Young et al (1977) study used by Cal/EPA, because Ernstgard et al (2006) used a lower dose level, resulting in identification of a NOAEL vs. only a LOAEL from Young et al (1977). In addition, Ernstgard et al (2006) included more subjects and also included both sexes, compared to the study by Young et al (1977). Lastly, the study by Young et al (1977) was primarily designed to evaluate the pharmacokinetics of 1,4-dioxane, and results relating to the effects of 1,4-dioxane were limited to a couple of narrative sentences without specific data. In contrast, the Ernstgard et al (2006) study was specifically designed to evaluate the acute effects of 1,4-dioxane, and provided supporting data and statistical analyses. A total uncertainty factor of 10 to account for human variability (same as for the ATSDR acute MRL) was used to derive the acute ITSL as follows:

Acute ITSL = NOAEL/10

Acute ITSL = 20 ppm/10 = 2 ppm $\cong$ 7,200 µg/m^3

A one-hour averaging time is applied to the acute ITSL, given that the exposure time of the Ernstgard et al (2006) study was limited to two hours, local irritant effects are considered to be not time dependent, and one-hour averaging times are standard for many acute based ITSLs. Therefore, pursuant to Rule 229(2)(b) of the Michigan Air Pollution Control Rules, the acute based ITSL is 7,200 µg/m^3 (1-hour averaging time).

Cancer Risk Assessment

The U.S. EPA has reviewed and evaluated the data related to the carcinogenic potential of 1,4-dioxane, and under its *Guidelines for Carcinogenic Assessment* (EPA, 2005), found that 1,4-dioxane is likely to be carcinogenic to humans by all routes of exposure (EPA, 2013a). This conclusion is based upon the finding that 1,4-dioxane causes cancer in laboratory animals by both the oral and inhalation routes of exposure. Three studies in which 1,4-dioxane was administered in the drinking water (two with rats and mice; one rats only) showed that exposure to 1,4-dioxane resulted in liver tumors in rats and mice, and nasal cavity, peritoneal, and mammary gland tumors in rats only. Two chronic lifetime inhalation exposure animal studies (Torkelson et al, 1974; Kasai et al, 2009) were available that evaluated the carcinogenic potential of 1,4-dioxane. These studies are discussed below.

In the study by Torkelson et al (1974), no treatment related tumors were observed in male and female Wistar rats exposed to 111 ppm of 1,4-dioxane vapor for 7 hours/day, 5 days/week for two years. In the study by Kasai et al (2009), groups of 50 male F344 rats were exposed to 0, 50, 250, or 1250 ppm of 1,4-dioxane vapor for 6 hours/day, 5 days/week for two years. In addition to the increased incidence of pre- and non-neoplastic lesions discussed above in the section on update of the ITSL, exposure to 1,4-dioxane also resulted in significantly increased incidences of tumors in the liver (high dose only), nasal cavity (high dose only), peritoneum (mid and high dose) and subcutis (mid dose only). In addition, a significant dose related trend in tumors was observed in all of these tissues except the subcutis. Although dose specific incidences were not increased for tumors of the kidney, mammary gland, and Zymbal gland, a dose related trend was observed for these tumors. The specific tumor incidence data for the Kasai et al (2009) study are provided below in Table 2.

Table 2: Tumor incidences in male rats exposed by inhalation to 1,4-dioxane (Kasai et al, 2009)

Tissue/Tumor Type	**Concentration of 1,4-dioxane (ppm)**			
	0	**50**	**250**	**250**
Nasal squamous cell carcinoma[c]	0/50	0/50	1/50	6/50[b]
Hepatocellular adenoma[c]	1/50	2/50	3/50	21/50[a]
Hepatocellular carcinoma	0/50	0/50	1/50	2/50
Renal cell carcinoma[c]	0/50	0/50	0/50	4/50
Peritoneal mesothelioma[c]	2/50	4/50	14/50[a]	41/50[a]
Mammary gland fibroadenoma[c]	1/50	2/50	3/50	5/50
Mammary gland adenoma	0/50	0/50	0/50	1/50
Zymbal gland adenoma[c]	0/50	0/50	0/50	4/50
Subcutis fibroma	1/50	4/50	9/50[a]	5/50

[a] $p \leq 0.01$ by Fisher's exact test
[b] $p \leq 0.05$ by Fisher's exact test
[c] Significant dose-related trend by Peto's test

The U.S EPA used the tumor incidence data from the Kasai et al (2009) study to derive an inhalation unit risk value. As part of the cancer risk assessment process, the U.S EPA evaluated various hypothesized mechanisms of action (MOA) for the occurrence of liver and nasal tumors due to 1,4-dioxane exposure. With regards to liver tumors, a hypothesized MOA is that liver tumors occur after sustained proliferation of spontaneously transformed liver cells. The possible key events in this MOA are as follows: "(1) oxidation by CYP2E1 and CYP2B1/2 (i.e.,

detoxification pathway for 1,4-dioxane), (2) saturation of metabolism/clearance leading to accumulation of the parent 1,4-dioxane, (3) liver damage followed by regenerative cell proliferation, or (4) cell proliferation in the absence of cytotoxicity (i.e., mitogenesis), (5) hyperplasia, and (6) tumor formation" (EPA, 2013a, p. 94). The EPA found that this hypothesized MOA is not supported by the data, for various reasons including inadequate data to determine the toxic moiety (parent compound or metabolite), a dose-response relationship linking cytotoxicity and cell proliferation with tumorigenesis cannot be established with available studies, and conflicting data from mouse and rat bioassays suggesting that cytotoxicity may not be a required precursor event for cell proliferation. As with liver tumors, a hypothesized MOA for nasal tumors is sustained proliferation of spontaneously transformed nasal epithelial cells, leading to hyperplasia, and eventually tumor formation. The U.S. EPA evaluated this MOA and also found that it was not supported by the available data. No data were available regarding any hypothesized MOAs for tumors of the kidney, lung, peritoneum, mammary gland, Zymbal gland or subcutis (EPA, 2013a).

When a specific MOA cannot be determined for a carcinogenic compound, the U.S. EPA *Guidelines for Carcinogen Risk Assessment* (EPA, 2005), recommend a linear extrapolation approach. The point of departure for the linear extrapolation is the $BMCL_{10}$, derived from fitting experimental cancer bioassay dose response data to the multistage model. The $BMCL_{10}$ represents the lower 95% confidence limit on the concentration associated with a 10% extra cancer risk. This 10% extra risk is defined as the benchmark response (BMR = 0.1). The inhalation unit risk (IUR), which represents the slope of the linear extrapolation, is then derived as follows:

$IUR = BMR/BMCL_{10}$

The U.S. EPA's benchmark dose software (BMDS) (Version 2.1.1) was used with the incidence data for tumor types occurring with a significantly increased incidence to determine the degree of the multistage model that best fit the data. In addition, a total tumor $BMCL_{10}$ was determined, using the BMDS (version 2.2Beta) MS_Combo program (EPA, 2013a). Experimental concentrations were used for the BMDS modeling, and then each $BMCL_{10}$ was converted to a continuous human equivalent concentration ($BMCL_{HEC}$) by adjusting the duration of exposure and applying a DAF of 1.0 as follows:

$BMCL_{HEC} = BMCL_{10}$ x (6 hours/24 hours) x (5 days/7days) x 1.0

The rationale for the DAF of 1.0 is the same as discussed above for the derivation of the inhalation RfC. Table 3 lists the $BMCL_{HEC}$ and IUR for each tumor type estimated from the modeling results as provided by EPA (2013a).

Table 3. Summary of modeling results using tumor incidence data from Kasai et al (2009)

Tumor Type	$BMCL_{HEC}$ (mg/m^3)	IUR Estimate $(\mu g/m^3)^{-1}$
Nasal cavity squamous cell carcinoma	405.3	2.5×10^{-7}
Hepatocellular adenoma or carcinoma	117.3	8.5×10^{-7}
Renal cell carcinoma	653.7	1.5×10^{-7}
Peritoneal mesothelioma	41.42	2.4×10^{-6}
Mammary gland fibroadenomas	452.5	2.2×10^{-7}
Zymbal gland adenoma	653.7	1.5×10^{-7}
Subcutis fibroma	52.70	1.9×10^{-6}
BMDS MS_Combo Total Tumor Analysis	19.5	5.0×10^{-6}
Table adapted from EPA (2013a)		

The highest IUR listed in Table 3, based on individual tumor type was for peritoneal mesothelioma, with value of 2.4×10^{-6} $(\mu g/m^3)^{-1}$. The IUR based on total tumors was approximately two fold higher with a value of 5.0×10^{-6} $(\mu g/m^3)^{-1}$. The U.S. EPA selected the IUR based on total tumors for the final IUR used to estimate risk from lifetime inhalation exposure to 1,4-dioxane (EPA, 2013a). Using this IUR, an IRSL and SRSL were derived pursuant to Rule 229(1)(c) of the Michigan Air Pollution Control Rules. The resulting IRSL is 0.2 $\mu g/m^3$ and the SRSL is 2 $\mu g/m^3$, with both values based on an annual averaging time.

References

ATSDR. 2012. Toxicological Profile for 1,4-Dioxane. Agency for Toxic Substances and Disease Registry, Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. http://www.atsdr.cdc.gov/toxprofiles/tp187.pdf

Cal/EPA. 2008. Air Toxics Hot Spots Risk Assessment Guidelines. Technical Support Document for the Derivation of Noncancer Reference Exposure Levels. Appendix D.2. Acute, 8-Hour, and Chronic Reference Exposure Summaries. Acute Toxicity Summary – 1,4-Dioxane. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency. Accessed on December 26, 2013. http://oehha.ca.gov/air/hot_spots/2008/AppendixD2_final.pdf#page=80

EPA. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Office of Research and Development, Washington DC. EPA/600/8-90/066F. October 1994.

EPA. 2005. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum, U.S. Environmental Protection Agency, Washington DC. EPA/630/P-03/001F.

EPA. 2013a. Toxicological Review of 1,4-Dioxane (with Inhalation Update) (CAS No. 123-91-1). In Support of Summary Information on the Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency, Washington DC. EPA/635/R-11/003F. September 2013.

EPA. 2013b. Integrated Risk Information System. 1,4-Dioxane (CASRN 123-91-1). Accessed on December 4, 2013. http://www.epa.gov/iris/subst/0326.htm

Ernstgard, L., A. Iregren, B. Sjogren, and G. Johanson. 2006. Acute effects of exposure to vapours of dioxane in humans. Human & Experimental Toxicology 25:723-729.

Fairley A., E. C. Linton and A. H. Ford-Moore (1934). The toxicity to animals of 1:4 dioxan. Journal of Hygiene 34:486-501. http://dx.doi.org/10.1017/S0022172400043266. (Article not reviewed – summary taken from EPA, 2013a).

Kasai, T; Saito, M; Senoh, H; Umeda, Y; Aiso, S; Ohbayashi, H; Nishizawa, T; Nagano, K; Fukushima, S. 2008. Thirteen-week inhalation toxicity of 1,4-dioxane in rats. Inhal Toxicol 20: 961-971. (Article not reviewed – summary taken from EPA, 2013a).

Kasai, Tatsuya, Hirokazu Kano, Yumi Umeda, Toshiaki Sasaki, Naoki Ikawa, Tomoshi Nishizawa, Kasuke Nagano, Heihachiro Arito, Hiroshi Nagashima, and Shoji Fukushima. 2009. Two-year inhalation study of carcinogenicity and chronic toxicity of 1,4-dioxane in male rats. Inhalation Toxicology 21(11):889-897.

MDEQ. 2010. *Memo from Gary Butterfield to 1,4-Dioxane File (CAS # 123-91-1). Subject: Screening Level for 1,4-Dioxane.* August 11, 2010. Michigan Department of Environmental Quality, Air Quality Division.

Torkelson, T. R., B. K. J. Leong, R. J. Kociba, W. A. Richter, P. J. Gehring. 1974. 1,4-Dioxane. II. Results of a 2-year inhalation study in rats. Toxicology and Applied Pharmacology 30: 287-298.

Yamazaki, K; Ohno, H; Asakura, M; Narumi, A; Ohbayashi, H; Fujita, H; Ohnishi, M; Katagiri, T; Senoh, H; Yamanouchi, K; Nakayama, E; Yamamoto, S; Noguchi, T; Nagano, K; Enomoto, M; Sakabe, H. (1994). Two-year toxicological and carcinogenesis studies of 1,4-dioxane in F344 rats and BDF1 mice. In K Sumino; S Sato; NG Shinkokai (Eds.), Proceedings: Second Asia-Pacific Symposium on Environmental and Occupational Health 22-24 July, 1993: Kobe (pp. 193-198). Kobe, Japan: Kobe University School of Medicine, International Center for Medical Research. (Article not reviewed – summary taken from EPA, 2013a).

Young J.D., W.H. Braun, L.W. Rampy. 1977. Pharmacokinetics of 1,4-dioxane in humans. Journal of Toxicology and Environmental Health 3:507-520.

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