Toxicity and Risk Assessment
1,4-Dioxane

Question 1: How could I be exposed to 1,4-dioxane?

The major exposure pathway related to environmental releases of 1,4-dioxane (Chemical Abstracts Service [CAS] Registry Number #123-91-1) is ingestion of contaminated drinking water (HC 2018, ATSDR 2012). If you eat food items cooked in contaminated water, you may experience additional exposure.

There are various exposure pathways related to environmental releases that are minor in comparison to ingestion of drinking water:

- Incidental ingestion of impacted soil is possible, but due to 1,4-dioxane's chemical and physical characteristics and its short-term presence in soil, this route of exposure is minor. The *Environmental Fate, Transport, and Investigation Strategies* fact sheet provides more information regarding the behavior of 1,4-dioxane.

- In most cases, dermal (skin) contact and inhalation are minor exposure pathways because most intake is from water ingestion (HC 2018, USEPA 2018). Dermal exposure may occur if impacted soil comes into contact with the skin (ATSDR 2012, HC 2018); however, this exposure pathway is generally assumed to be insignificant due to 1,4-dioxane's short-term presence in soil. ITRC will present additional information on this topic in the forthcoming 1,4-dioxane guidance document.

- Exposure to 1,4-dioxane from eating potentially contaminated food is a minor exposure pathway for two reasons: (1) 1,4-dioxane impurity in food additives is likely to be very low and (2) 1,4-dioxane is no longer used as an inert ingredient in pesticides. Although studies in Japan and the Philippines found 1,4-dioxane in foods, Health Canada noted that exposures in Canada will likely be low due to differences in dietary intakes and study limitations; for details, refer to the Health Canada (HC 2018) and ATSDR (ATSDR 2012) assessments.

Consumer products, including cosmetics, may contain 1,4-dioxane. 1,4-Dioxane may be present as an impurity or as a residual of compounds used to manufacture the consumer product (see the *History of Use and Potential Sources* fact sheet). Therefore, consumer products may be a source of exposure to 1,4-dioxane. Environment Canada (EC 2010) assessed and established exposure estimates for various consumer products.

Question 2: How can exposure to 1,4-dioxane affect human health?

Health effects from environmental exposure to 1,4-dioxane are based on several factors, including the following:

- the amount of 1,4-dioxane present at the point of contact (that is, exposure as measured by a concentration, such as the concentration in drinking water)
- the length of time of contact (exposure duration)
- how often exposure took place (exposure frequency)

In laboratory animals, it has been shown that drinking water ingestion and inhalation of 1,4-dioxane essentially
Toxicity and Risk Assessment: 1,4-Dioxane continued

produce the same type and extent of toxicological effects.
If someone is exposed to very high levels of 1,4-dioxane for short periods of time (less than one year), the liver, kidney, mucus membranes of the nasal passages, and central nervous system may be affected (ATSDR 2012, USEPA 2013). However, exposure to lower levels, such as those typically found in contaminated drinking water, over longer periods (greater than one year, and up to a lifetime) can potentially lead to more severe effects, including specific types of cancer, as shown in laboratory cancer studies in mice and rats (ATSDR 2012, USEPA 2013, HC 2018). However, there are currently no human studies that show a direct link between exposure to 1,4-dioxane and cancer (HC 2018, ATSDR 2012, USEPA 2013, ECB 2002, NICNAS 1998). Based on findings from animal cancer studies, the International Agency for Research on Cancer (IARC 1999) classifies 1,4-dioxane as “possibly carcinogenic to humans” (IARC 1999). The Agency for Toxic Substances and Disease Registry also considers 1,4-dioxane to be “possibly carcinogenic to humans” (ATSDR 2012), whereas the U.S. Environmental Protection Agency (USEPA) classifies it as “likely to be carcinogenic to humans” (USEPA 2013).

It’s useful to place the risk of these health effects into perspective based on measurements of 1,4-dioxane concentration. For example, in general, the ingested maximum amount (dosage) that could occur from drinking 1,4-dioxane-contaminated water in the United States (based on multiple 1,4-dioxane drinking water measurements) is one thousand times less than the amounts (in terms of milligrams of 1,4-dioxane per kilogram of body weight per day) needed to cause liver, kidney, nasal passage, and cancer effects in laboratory animals (CWB 2019, NYS 2019). Typical drinking water exposures are much lower than the high dosages found in occupational settings that have caused death and neurological effects in the past. In the event that someone is exposed to 1,4-dioxane-contaminated drinking water, regulatory values and expertise should be consulted to better understand the potential adverse effects on the individual.

Question 3: What screening levels are available for protection of human health?

Regulatory standards and screening levels are risk-based exposure levels that are protective of cancer and noncancer health effects for the exposed populations (including sensitive groups). Federal and some state agencies have established water, soil, and air standards (promulgated) or risk-based screening levels for 1,4-dioxane (see the Regulatory Framework fact sheet). The derivation of these standards and screening levels for noncancer effects includes toxicity values that incorporate safety factors. Safety factors account for uncertainties, such as extrapolation from animal studies to humans, population variability, and data gaps. Periodic short-term exposure to impacted drinking water or soil above health-based screening levels is generally not a health concern; however, further investigation by an environmental professional may be warranted. ITRC will present additional information on this topic in the forthcoming 1,4-dioxane guidance document.

Question 4: Why are there different health-based standards or guidelines?

As with many contaminants of emerging concern, evaluation of 1,4-dioxane may vary by agency health standards or guidelines (refer to the Regulatory Framework fact sheet). 1,4-Dioxane health standards or guidelines vary by orders of magnitude between regulatory, state, and federal agencies. This is due to the use of different risk-calculation approaches (for example, using a linear or nonlinear low-dose extrapolation for cancer-risk assessment) and the use of different input parameters (such as exposure factors and/or target risks). Important considerations for risk calculations include the selection of key toxicology studies in test animals, identification of effect levels relevant to humans, dose-response assessment, selection of uncertainty factors, exposure pathways (that is, oral, dermal, or inhalation), human exposure assumptions (such as drinking water intake rate, exposure frequency, duration of exposure to affected water, and body weight), and regulatory target risk levels. Differences in the evaluation of each of these variables result
in different health standards or guidelines, which may complicate risk management and communication efforts. More details about factors influencing health-based values between agencies will be presented in the forthcoming 1,4-dioxane guidance document.

**Question 5: Can I find out if I have been exposed to 1,4-dioxane?**

Analysis of potential primary exposure sources (such as drinking water) is the most informative and direct means for assessing if you have been exposed to 1,4-dioxane via the environment. You can have your drinking water tested by certified commercial analytical laboratories. If there is 1,4-dioxane in your drinking water, you likely have been exposed.

In the body, 1,4-dioxane is rapidly changed to β-hydroxyethoxyacetic acid (HEAA) and quickly eliminated in urine (ATSDR 2012). There are methods to measure 1,4-dioxane and HEAA in urine, but various challenges are associated with biomedical testing in humans, including the fact that these methods are not standard commercialized medical tests. This particular urine analysis is not available at the doctor’s office because it requires specialized measurement equipment (ATSDR 2012), and standard procedures for collecting and preserving samples are not yet available. Furthermore, medical test results would not indicate when, where, or how exposure occurred (ATSDR 2012). They also would not predict the potential for nor the types of health effects that could be developed. In addition, HEAA in urine could reflect exposure to other chemicals, such as diethylene glycol (ATSDR 2012, Schep et al. 2009).

**Question 6: Does 1,4-dioxane affect environmental health?**

The impact of 1,4-dioxane on environmental health is generally low. The aquatic toxicity of 1,4-dioxane has been estimated at 201 milligrams per liter (mg/L) for algae to 666 mg/L for fish based on the USEPA’s Ecological Structure Activity Relationships (ECOSAR) estimation program (USEPA 2019). In the United States, only Michigan has a chronic water quality value, set at 22 mg/L (MEGLE 2019). In Europe, the European Chemicals Bureau (ECB 2002) has proposed a multitrophic Predicted No Effect Concentration (PNEC) of 57.5 mg/L based on the limited toxicological data (ECB 2002). These screening values generally exceed observed environmental concentrations by a wide margin, and ecological risk is not expected in most natural environments.

The (ECB 2002) has estimated toxicity threshold estimates for sediment and soil based on equilibrium partitioning (EqP), with PNECs of 43 milligrams per kilogram (mg/kg) in sediment and 14 mg/kg in soil. Generally low observed environmental concentrations of 1,4-dioxane, combined with low absorption potential in soil and sediment, suggest that these media are not relevant for ecological risk. Because 1,4-dioxane does not bioaccumulate, the potential for long-term effects on birds and mammals is low (EC 2010) and of limited further ecological or wildlife concern (ECB 2002).

**Question 7: How can I reduce exposure to 1,4-dioxane?**

If 1,4-dioxane has been detected in your drinking water or municipal water source, using another water source, such as bottled or treated water (see the Remediation and Treatment Technologies fact sheet), will reduce your exposure. Although dermal contact and inhalation are possible sources of exposure, they are minor in nature when compared to exposure from water ingestion.
Toxicity and Risk Assessment: 1,4-Dioxane continued

References
The references cited in this fact sheet, and the other ITRC 1,4-Dioxane fact sheets, are included in one combined list that is available on the ITRC web site.

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