

**Submission re:**

Draft Screening Assessments and Risk Management Scope Documents for Batch 7 of the  
Chemicals Challenge

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## Introduction

This submission concerns three Batch 7 substances in the Challenge Program of the Chemicals Management Plan: **Oxirane, (butoxymethyl)- (*n*-butyl glycidyl ether) CAS No. 2426-08-6, 1,4-Dioxane CAS No. 123-91-1 and 2-Cyclohexen-1-one, 3,5,5-trimethyl- (Isophorone) CAS RN 78-59-1**. In this submission concerns will be raised about the quality of the data presented in the screening assessments for these three substances, the lack of precaution in drawing conclusions based on this data, the risk management scope for *n*-butyl glycidyl ether and the failure to find 1,4-dioxane and isophorone toxic according to CEPA 1999. Accordingly, it will be recommended that the risk management scope for *n*-butyl glycidyl ether be broadened and that 1,4-dioxane and isophorone be designated as toxic according to the criteria set out in section 64 of CEPA 1999. It will be recommended further that efforts be made to improve the data bases for risk assessment for all three substances, and that the precautionary approach be used under current uncertainties in the evaluation of risk and in the determination of the risk management scope.

### 1. Oxirane, (butoxymethyl)- (*n*-butyl glycidyl ether) CAS No. 2426-08-6

#### a. Draft Screening Assessment<sup>1</sup>

*n*-Butyl glycidyl ether was identified in the categorization process as a high priority for screening assessment because it was considered to present an intermediate potential for exposure to individuals in Canada and has been classified by other agencies on the basis of carcinogenicity and genotoxicity. It did not meet the criteria for persistence, bioaccumulation or inherent toxicity to aquatic organisms, so the focus of the assessment relates to human health aspects.

Submitted data show that *n*-butyl glycidyl ether was not manufactured above the reporting threshold in 2006, but 10,000 - 100,000 kg were imported. In Canada, it is used in the manufacture of resins (used for coatings, adhesives, binders, sealants, fillers and resins) and it may be imported as an impurity in paint. No consumer products (e.g., cosmetics, pharmaceuticals, natural health products, or food packaging) containing it as an intentional ingredient were identified. The Canadian Paints and Coatings Association has indicated that all coating applications of *n*-butyl glycidyl ether are, to their knowledge, industrial.

According to the assessment, *n*-butyl glycidyl ether may be released into the environment through emissions from industrial facilities producing, handling, storing imported material, or using epoxy-based resins, coatings and adhesives. Submitted data indicates 100 - 1000 kg were released to air in 2006, but releases to water or land were not disclosed. Possible waste-disposal methods were not discussed and there was no environmental monitoring data.

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<sup>1</sup>[*n*-Butyl glycidyl ether Assessment] Environment Canada; Health Canada, *Draft Screening Assessment for the Challenge Oxirane, (butoxymethyl)- (*n*-butyl glycidyl ether) Chemical Abstracts Service Registry Number 2426-08-6*. September 2009. [http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7\\_2426-08-6\\_en.pdf](http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7_2426-08-6_en.pdf)

*n*-Butyl glycidyl ether will reside primarily in the environmental compartment (air, water, or soil) to which it is released. It is considered to be neither persistent in any environmental medium, based on empirical and modelled data, nor bioaccumulative, based on modelled data. It may pose low to moderate toxicity to aquatic organisms at low concentrations according to modelled data.

General population exposure to *n*-butyl glycidyl ether is expected to be low. Using modelled concentrations in air, water, soil and sediment, the upper estimates of intake for the general population was  $<10^{-3}$   $\mu\text{g}/\text{kg}$  bw/day. IARC stated that it is generally assumed to be no longer present in cured resin products. However, it is reportedly present as an impurity in a material preservative used in latex and oleo-resinous paints and modelled estimates suggest a mean airborne and dermal event concentration of  $6 \text{ mg}/\text{m}^3$  and  $0.02 \text{ mg}/\text{kg}$ , respectively, though exposures may be lower given its reactivity. One wood finish product was identified as having higher levels of the preservative than interior paints, but it is apparently being reformulated. Occupational exposures were not investigated. No particular attention was paid to vulnerable populations.

With respect to health effects, *n*-butyl glycidyl ether is classified by the EC as Category 3 for carcinogenicity and as Category 3 for mutagenicity. Due to the lack of long term data for *n*-butyl glycidyl ether, the EC's carcinogenicity classification was based on both the weight of evidence from the genotoxicity data for *n*-butyl glycidyl ether and the carcinogenicity data from the structural analog allyl glycidyl ether. The mutagenicity classification was based principally on positive results from *in vivo* micronucleus assays. Four analogs (allyl glycidyl ether, glycidol, phenyl glycidyl ether and bisphenol-A-diglycidyl ether) were used in the Health Canada assessment to "better support the body of evidence with respect to carcinogenicity". The approach used was stated as being consistent with the general principles of various jurisdictions and authorities (analogs based on a glycidyl (ether) functional group (the most important criteria to assess carcinogenicity), structural similarities, properties, availability of carcinogenicity data, and identification as an analog to *n*-butyl glycidyl ether by various regulatory agencies).

In terms of genotoxicity, *n*-butyl glycidyl ether induced chromosomal aberrations and micronucleus formation in *in vivo* assays, lethal mutations in mice, and reverse mutations in *in vitro* assays. Some assays have shown negative results. However, there is also "convincing evidence of the genotoxicity of allyl glycidyl ether and glycidol".

This substance and/or its analogs has also induced non-neoplastic effects (e.g., skin irritation and sensitization, conjunctivitis, severe ocular damage, erythema, liver and respiratory effects, testicular atrophy, decreased pregnancy rates, increased foetal death rates, reduced reproductive capacity) in experimental animals. Allergic reactions in humans have been investigated in several studies, predominantly occupationally, with response rates lower than in animals. No long term studies pertaining to this or reproductive/developmental toxicity, have been identified.

Data showing *n*-butyl glycidyl ether analogs to increase tumours in multiple organs of rodents via various exposure routes, as well as the genotoxicity evidence strongly suggests that “*n*-butyl glycidyl ether would induce tumours via a mode of action involving direct interaction with genetic material”. A “sufficient to be protective” margin of exposure of 8 orders of magnitude was calculated for non-cancer effects. No other margins of exposure were calculated despite possible other exposure routes and non-cancer effects even though some have been observed via dermal exposure.

The *Risk Management Scope*<sup>2</sup> for *n*-butyl glycidyl ether proposes that it be added to the List of Toxic Substances. The risk management scope document further suggests that risk management will be focused on “a requirement for notification of the federal government regarding any potential changes in the use-pattern for *n*-butyl glycidyl ether so that the potential for exposure to the Canadian population does not substantially increase.”

## b. Concerns

There are a significant number of serious concerns about adequacy of the screening risk assessment and the risk management scope document for *n*-butyl glycidyl ether.

1. The major concern is with the risk management scope, which is limited to “a requirement for notification of the federal government regarding any potential changes in use pattern for *n*-butyl glycidyl ether so that the potential for exposure to the Canadian population does not substantially increase” [*n*-Butyl glycidyl ether RM Scope, 6]. Risk management of all substances found toxic should involve this requirement, and also the requirement to report significant increases in quantities used, but there should also be steps taken to reduce exposure, including exposure to vulnerable populations, to any substance found to be carcinogenic and mutagenic.
2. No justification is provided for the scope being proposed for risk management of *n*-butyl glycidyl ether. It is very difficult to respond to an inadequate risk management scope for which no justification is provided except by disagreeing with it. Scoping is a very important aspect of the development of risk management regulations, and special care must be taken to ensure that the scope is broad enough to manage risks adequately, especially given the uncertainties in exposure and health effects assessment.
3. According to the *Screening Risk Assessment* for *n*-butyl glycidyl ether, “where relevant, research and monitoring will support verification of assumptions used during the screening assessment” [*n*-Butyl glycidyl

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<sup>2</sup> [n-Butyl glycidyl ether RM Scope] Environment Canada; Health Canada, *Risk Management Scope for Oxirane, (butoxymethyl)- (n-Butyl glycidyl ether) Chemical Abstracts Service Registry Number (CAS RN): 2426-08-6*. September, 2009. [http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7\\_2426-08-6\\_rm\\_en.pdf](http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7_2426-08-6_rm_en.pdf)

4. There are uncertainties concerning concentrations of *n*-butyl glycidyl ether in Canadian environmental media and consumer products. Lack of published data does not imply that the substance is not present. Given this uncertainty, there is great uncertainty in human exposure potential.
5. No attempt is made to consider exposure to and effects on vulnerable populations.
6. No studies specifically designed to assess reproductive or developmental toxicity were identified.

### **c. Recommendations**

1. In light of its potential carcinogenicity, genotoxicity and various non-cancer effects at relatively low margins of exposure, *n*-butyl glycidyl ether should be designated as toxic under CEPA 1999 and added to the List of Toxic Substances in Schedule 1.
2. Concentrations within Canadian environmental media and specific consumer products (e.g. cosmetics, pharmaceuticals) should be established. There is concern that lack of knowledge of the consumer products in which it may be an impurity could result in risk management that will not address population exposure to this substance via all relevant sources.
3. Releases and disposal of *n*-butyl glycidyl ether through facility disposal and product disposal should be subject to further research since there is no data available on it. Relying on industry reported releases to air alone and modeling to derive exposure estimates is of concern.
4. Experimental data regarding the carcinogenicity of *n*-butyl glycidyl ether should be acquired. Although the analog data is considered strong and sufficient, which is supported by other jurisdictions' reliance on it, and the genotoxicity data is extremely strong, empirical data would help to further strengthen the case for *n*-butyl glycidyl ether being of concern to Canadians.
5. Attention needs to be paid to determining vulnerable population exposures (e.g., occupational groups), particularly given the processing and use of this chemical.
6. Work needs to be done to determine possible developmental or reproductive effects.
7. The risk management focus needs to be expanded to address the volume already in commerce and its potential presence as an impurity in various products.

#### **d. Conclusion**

Given the characterization of this substance as carcinogenic and mutagenic, and uncertainties in exposure estimates in the screening assessment, it is very disappointing that a more precautionary approach was not taken to the risk management scope for this substance. It should be broadened to include exposure reduction, especially for vulnerable populations.

### **2. 1,4-Dioxane CAS No. 123-91-1**

#### **a. Draft Screening Assessment<sup>3</sup>**

1,4-Dioxane was identified in the categorization process as a high priority for screening assessment because it was considered to pose the greatest potential for exposure of individuals in Canada and is classified by other agencies on the basis of carcinogenicity. Although 1,4-dioxane met the ecological categorization criterion for persistence, it did not meet the criteria for bioaccumulation potential or inherent toxicity to aquatic organisms. Therefore, the screening assessment focuses mainly on information relevant to human health risks.

1,4 Dioxane may be present in some foods, either naturally or as a contaminant. Anthropogenic emissions may occur when the substance is being produced or processed. Another main source in Canada is as a byproduct in ethoxylation reactions during the formation of polymers used in a variety of industrial and consumer applications (1,4-Dioxane Assessment, 5). In 2006, between 10,000 and 100,000 kg were manufactured in Canada, between 10,000 and 100,000 kg were imported into Canada, and between 10,000 and 100,000 kg were used in Canada.

1,4-Dioxane is used extensively as a solvent for pharmaceutical processing and research and development and as a reagent for laboratory use. It is used as a carrier solvent in the manufacture of pharmaceuticals, veterinary drugs and natural health products. It is also a component of industrial agents that are used as corrosion inhibitors, antioxidants and heavy equipment degreasers.

Residual 1,4-dioxane is formed during the production of ethoxylated substances used in a variety of applications, such as cosmetics, detergents, food packaging, agricultural products and industrial processes. In Canada, ethoxylated substances containing 1,4-dioxane as a by-product are produced and used as surfactants, emulsifiers, wetting agents and foaming agents in various industries. It is also found as a formulant impurity in 168 pest control products that have both food and non-food uses. It may be found as an impurity in certain food additives or

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<sup>3</sup> [1,4-Dioxane Assessment] Environment Canada; Health Canada, *Draft Screening Assessment for the Challenge 1,4-Dioxane Chemical Abstracts Service Registry Number 123-91-1*. September 2009. [http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7\\_123-91-1\\_en.pdf](http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7_123-91-1_en.pdf)

processing aids. Although it is on Canada's Cosmetics "Hotlist," and thus cannot be used as an ingredient in cosmetics, it may be present as an impurity.

According to information submitted by industry under section 71 of CEPA 1999, between 10,000 and 100,000 kg of 1,4-dioxane were released into the environment in 2006, the majority of which were to water or air. 100-1,000 kg were transferred to hazardous waste facilities and less than 100 kg were transferred to non-hazardous waste facilities. Information reported under NPRI indicated that 13,000 kg were released to air and 6,500 kg were released to water in 2006.

1,4-Dioxane will reside primarily in the compartment (air, water, soil) to which it is released. It is not considered persistent in air, but is in water, soil and sediment, and is considered to have a low potential for long range transport. It is unlikely to bioaccumulate or to harm aquatic organisms at low concentrations.

With respect to human exposure, "The general population is expected to be exposed to 1,4-dioxane from environmental media (ambient air, indoor air and drinking water), from food and during the use of consumer products (personal care and household products) containing this substance" [1,4-Dioxane Assessment, Synopsis, 2]. "Drinking water represented the predominant contribution to the total estimated daily intake for all age groups" [1,4-Dioxane Assessment, 12]. The evidence presented with respect to each of these sources is summarized below:

- Canadian sources were used in estimating the intake from both ambient and indoor air.
- Soil studies are limited.
- Data relating to drinking water is limited to a single study of a municipal water treatment facility in the Great Lakes region.
- No studies pertaining to 1,4-dioxane in food in Canada were found. Japanese studies were considered not relevant to the Canadian situation.
- Estimates were made with respect to the presence of 1,4-dioxane in foods containing food additives or processing aids that might contain the substance as an impurity. Further, it is expected that residual levels of 1,4-dioxane in foods will be low due to its volatility.
- There are several studies showing the presence of 1,4-dioxane in a variety of personal health care products in varying concentrations. The concentration in hair dye has been estimated, as no studies have been conducted.
- Women's exposure from personal care products was estimated based on exposure to five products, with the assumptions of 69 kg body weight and 10% available for dermal exposure, 90% for inhalation. Exposure of children 0-6 months was estimated based on exposure to three products.

- Exposure from dishwashing liquid, detergents and other household products was estimated for dishwashing liquid only, using a body weight assumption of 75 kg.
- No estimates were made for exposure via cosmetics, although 1,4-dioxane “may be present as a manufacturing impurity” [1,4-Dioxane Assessment, 6].

With respect to health effects assessment, carcinogen classifications by various international agencies are based on “observed hepatocellular adenomas and carcinomas in mice, tumors of the nasal cavity, liver subcutaneous tissues, mammary gland and peritoneal mesotheliomas in rats and tumours of the liver and gallbladder in guinea pigs orally exposed to 1,4-dioxane” [1,4-Dioxane Assessment, 17]. Some of these effects were observed when exposed via drinking water at a very low concentration.

The only available chronic inhalation study did not evidence carcinogenicity or other adverse effects. Dermal exposure did not induce tumours in mice unless another chemical was administered prior to application (then tumours in lung, kidney, spleen and liver were observed). Danish Cancer Registry data showed significantly higher than expected incidence ratios for liver tumours in male workers exposed to 1,4-dioxane and other chemicals in occupational settings “and an increase in liver cancer incidence of 50% was identified in one workplace where only 1,4-dioxane was used”. Its critical effect is considered to be tumorigenesis following oral exposure.

Other systemic effects (e.g., central nervous, respiratory and blood systems and stomach) via oral, dermal and inhalation have also been seen. Reproductive and immunological effects were also observed in mice.

Using the upper-bounding daily intake from general environmental exposure, the level at which no tumours or any adverse effects were observed (NOAEL) and the LOAEL for non-cancer effects, MOEs were 7000 - 84 000. Using the same NOAEL and LOAEL, as well as upper-bounding intake from consumer products by the dermal and inhalation routes, MOEs were 8000 - 13 300. A dermal LOAEL was not used.

Data and conclusions of other agencies suggest that 1,4-dioxane is not likely a mutagen. However, although “all tests for mutagenicity were negative,” significantly higher chromosomal aberrations were seen in workers exposed to various mutagens, including 1,4-dioxane. It was also “positive in assays ... for effects on deoxyribonucleic acid (DNA),” typically at “higher doses or following prolonged exposure and often in the presence of cytotoxicity.”

The draft screening assessment concludes that “1,4-dioxane is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends.” It further concludes that “1,4-dioxane is not entering the environment in a quantity or concentration or under conditions that

constitute or may constitute a danger in Canada to human life or health,” based on the adequacy of the margins of exposure (1,4-Dioxane Assessment, 24). Consequently, it is proposed that 1,4-dioxane does not meet any of the CEPA 1999 criteria for toxicity. Accordingly, no risk management scope document was developed.

#### **b. Concerns**

1. The assessors concluded that there is a threshold for carcinogenicity, although their logic is not clear. The logic may be that this threshold exists because 1,4-dioxane promotes tumors at doses where its oxidation to its metabolites becomes saturated. However, the assessors later stated that “there is uncertainty in the mechanism of tumorigenesis.” This lack of clarity suggests that more work should be done to determine whether the substance is a “threshold” carcinogen.
2. There is a concern that so little is known about exposure to 1,4-dioxane, including exposure from food, breast milk, drinking water, personal care products, household products other than liquid dishwashing soap, and cosmetics.
3. There is concern that the lower limit margins of exposure for environmental and consumer product exposure and levels at which no tumors or adverse effects are observed are relatively small.
4. Given (1) - (3) above, there is great concern that the conclusion of the screening assessment, i.e., “on the basis of the adequacy of the margins between conservative estimates of exposure to 1,4-dioxane and critical effect levels, it is proposed that 1,4-dioxane is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human health or life,” [1,4-Dioxane Assessment, 24] is not sufficiently precautionary.
5. There is a concern that little special attention was paid to vulnerable populations.
6. There is a concern that the full life cycle of products containing 1,4-dioxane, including waste disposal, was not considered.

#### **c. Recommendations**

1. Given its carcinogenicity, “uncertainty regarding the mechanism of 1,4-dioxane-induced tumorigenesis” and relatively small lower-limit margins of exposure between environmental and consumer product exposure and levels at which no tumors or adverse effects are observed, 1,4-dioxane should be designated as “toxic” under CEPA 1999 and added to the List of Toxic Substances in Schedule 1.
2. Given that “data on dose-response and temporal progression with which to characterize and/or identify the key events in the processes of 1,4-dioxane-induced tumour formation of different types ... are insufficient, inconsistent or not available,” [1,4-Dioxane Assessment, 23] a precautionary approach is justifiable.

3. Given the use of multiple personal care products containing 1,4-dioxane as an impurity by a large number of Canadians, especially women and children, exposure estimates should be reconsidered, as they are likely underestimated.
4. Exposure from cosmetics should be investigated.
5. Exposure from household products beyond liquid dish detergent should be investigated.
6. Greater attention needs to be paid to vulnerable population exposure.
7. Concentrations in water, drinking water and soil from various locations in Canada need to be established.
8. Studies should be conducted on possible reproductive and developmental effects of 1,4-dioxane.
9. Exposure from food should be investigated.
10. The full life cycle of products containing 1,4-dioxane, including waste disposal, should be taken into consideration.
11. Risk management should consider safer ways of producing personal health care and household products and cosmetics without creating 1,4-dioxane as an impurity. 1,4-dioxane simply should not be present in products designed for babies and children.

#### **d. Conclusion**

Given the weaknesses in the estimates for exposure levels and the uncertainties in the evaluation of risk to human health in the screening assessment, it is very disappointing that a more precautionary approach was not taken to this substance. The substance should be declared toxic under CEPA 1999 and efforts should be made to lower exposure via personal care products (especially those designed for children), household products and cosmetics. This principle holds for any substance characterized for carcinogenicity by international bodies, especially those for which the reasoning concerning threshold effects is unclear,

### **3. 2-Cyclohexen-1-one, 3,5,5-trimethyl- (Isophorone) CAS RN 78-59-1**

#### **Overview<sup>4</sup>**

Isophorone was identified as a high priority for action under the Ministerial Challenge as it was classified by the European Commission and the US Environmental Protection Agency as a possible carcinogen. Since the work done under categorization indicated that isophorone did not meet the ecological criteria for persistence, bioaccumulation potential or inherent toxicity to aquatic organisms, the draft screening assessment is mainly focussed on risks to human health.

The draft screening assessment proposed that based on available information, isophorone does not meet any of the criteria set out in section 64 of CEPA 1999, that is, it is not entering the environment in a quantity or concentration or under conditions that constitute

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<sup>4</sup> [Isophorone Assessment] Health Canada; Environment Canada, *Draft Screening Assessment for the Challenge 2-Cyclohexen-1-one, 3,5,5-trimethyl- (Isophorone) Chemical Abstracts Service Registry Number 78-59-1*. September 2009. [http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7\\_78-59-1\\_en.pdf](http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7_78-59-1_en.pdf)

or may constitute a danger in Canada to human life or health, or the environment [Isophorone Assessment, 3]. Further to that, the assessors found that isophorone does not meet the criteria for persistence or bioaccumulation as set out in the *Persistence and Bioaccumulation Regulations*.

Our organizations challenge the proposed conclusions, especially in light of so much uncertainty cited throughout the assessment document, the lack of empirical data, and particularly any current data. Furthermore, other than information from a Section 71 Notice under CEPA 1999 for the year 2006, there is no monitoring or reporting of releases to the environment.

Given the diversity of use of this substance from its various industrial applications as a solvent to its use in pesticides, food flavouring and packaging, and given that it is considered by some agencies to be a possible carcinogen, the potential hazards it presents, coupled with the uncertainties and gaps noted, should result in the assessors applying a precautionary approach and designating isophorone toxic under CEPA 1999. That would lead to developing measures to “manage” the risks posed by this substance. If they do not do so, its use will continue without control, and so will the potential risks and hazards associated with it.

The following comments review specific aspects of the draft screening assessment that draw attention to out general concerns.

### **Major Uses and Sources**

Isophorone is a clear liquid that smells like peppermint. Globally it is used extensively as a solvent in some printing inks, paints, lacquers, finishes, vinyl resins, copolymers, in adhesives for plastics, polyvinyl chloride and polystyrene materials, metal coatings, and pesticides. It is also used as an intermediate in the production of certain chemicals. Although it is considered an industrial chemical, isophorone has been found to occur naturally, for example, in cranberries, saffron and in several types of European honey.<sup>5</sup>

According to information obtained from the Section 71 Notice under CPA 1999, for the year 2006, no isophorone was manufactured in Canada (above the 100 kg reporting threshold). Import quantities ranged between 10,000 and 100,000 kg. According to Statistics Canada, global imports have been in the vicinity of 20,000 kg in the past few years, the exception being the year 2000 when over 80,000 kg was imported [Isophorone Assessment, 8]. The assessment report gave no indication as to how much isophorone was used in that same year.

In Canada, isophorone is permitted as a non-medicinal ingredient for use as a flavour enhancer in licensed natural health products; however, it is not found in current licensed natural health products. It is also used as a formulant in one registered pesticide in Canada, but this use will be discontinued as of December 31, 2009. Its use in cosmetics is prohibited [Isophorone Assessment, 7].

Based on information in section 71 surveys, isophorone may be present in food packaging. Specifically, isophorone may be used as a processing aid in the manufacture of some linings or coatings for beverage cans, metal spice tins or other food packaging. A

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<sup>5</sup> Isophorone Assessment, p. 8; see also <http://www.atsdr.cdc.gov/tfacts138.html>

probable daily intake estimate for the spice tins application was considered not necessary due to the fact that significant migration to dry foods is not expected.

As the assessment report indicates, the extent to which the exposure assessment in this report captures the presence of isophorone as a result of its use as a flavour in foods sold in Canada, if such use exists, is not known. Most of the data on the levels of isophorone in foods were taken from a Japanese study, and the source of the isophorone in the foods in that study was not conclusive [Isophorone Assessment, 17].

### **Consumer Products**

The *Food and Drug Regulations* do not include any provisions to control the addition of flavours, including isophorone, to foods. “Usual” uses for isophorone as a food flavour ranging from 0.50 to 16.80 parts per million (ppm) have been reported by the US Flavor and Extract Manufacturers’ Association (FEMA) in 1994, but as the assessment indicates, it is unknown if such uses reflect the Canadian situation [Isophorone Assessment, 17].

Despite these unknown factors, the assessors consider that the contribution of this source to total intake of isophorone is negligible. Assumptions as to the intake of isophorone from food and beverages have been made without any supporting information. For example:

- How widely is isophorone used in food packaging and linings or in flavourings?
- How much isophorone used for these purposes is imported into Canada? Are these food items accounted for by the imported amounts indicated under Section 71 or are they in addition to these amounts?
- What population groups are more likely to be exposed through using the food and drinks from containers made with isophorone or flavoured with it (e.g., vulnerable populations, including children, differing cultural backgrounds, populations with a relatively high use of flavoured and/or packaged foods)?
- While isophorone may not be found in current licensed natural health products, its use in these products is permitted. In other words, it could potentially be introduced into such products without any prohibition. Also, it may be already be in natural health products that are not licensed.

We are concerned about the lack of regulation that could lead to its use in natural food products and also very concerned about limitations to the *Food and Drug Regulations Act* that result in no control over the addition of flavourings in food, and particularly for cases such as isophorone, a possible carcinogen.

### **Disposal**

Other than some indication of release from industrial sites, disposal, particularly of food-related products, has not been considered. It is unlikely that the various types of packaging (tins, cans or other) containing isophorone are disposed of in any consistent or safe manner. Interestingly, transfers to hazardous waste facilities were reported by

industry. This raises the question as to whether all the packaging material containing isophorone should be sent to hazardous waste facilities.

### **Releases**

Isophorone is released to the air from inks, paints, and other products containing it. Since it has many different applications, releases to the environment may originate from a wide variety of industrial sources including iron and steel manufacturers, coal-fired power plants, manufacturers of photographic equipment and supplies, automobile tire plants, and printing operations.

Isophorone may also be present in water from industrial releases. In water, it can be broken down by bacteria over a period of several days to about a month. In soil, it may be broken down by bacteria, filter to groundwater, or evaporate to the air.

In Canada, under information submitted for the year 2006, approximately 1,000 to 10,000 kg of isophorone were released into the atmosphere and 587 kg were transferred to hazardous waste facilities in 2006.

No releases to land or water or transfers to non-hazardous waste facilities were identified in the submitted information. It is not listed on the NPRI or US Toxics Release Inventory Program.

The lack of mandatory reporting or monitoring of releases of isophorone to the environment results in an absence of information that is vital to drawing and meaningful conclusions as to exposure from releases.

### **Persistence and Bioaccumulation**

Once released into the environment, isophorone will be found mainly in air and water. Isophorone disappears in air rapidly (half-life < 5 hours) and is therefore not persistent in air. In their examination of modelled data regarding persistence in water, the assessors commented on conflicting results from models regarding biodegradation in water. However, the assessment concluded that isophorone is not persistent in water, and using a relationship between water and sediment, also not persistent in soil or sediment. Furthermore, based on the models used to determine bioaccumulation factors, isophorone indicated a low potential to bioaccumulate [Isophorone Assessment, 11-12], consequently, the assessment has determined that isophorone does not meet the criteria for persistence or bioaccumulation under the *Persistence and Bioaccumulation Regulations*.

The vacuum of experimental data, coupled with conflicting results and provisions under the regulations as to what constitutes persistence, may give an erroneous interpretation of persistence in water, soil and sediment, and the potential to bioaccumulate. Even if a substance does not meet the specific boundary criteria set out in the aforementioned regulations, it cannot necessarily be inferred that it does not persist in some media or bioaccumulate to some extent.

### **Ecotoxicity**

Empirical data suggests isophorone has a low to moderate potential for toxicity to aquatic organisms. Modelled data has concurred with this observation. There was no toxicity data

for terrestrial organisms, aside from four crops (cotton, soybean, corn and wheat) which showed damage to some leaves a few hours after application of isophorone. After 56 hours all plants showed evidence of recovery [Isophorone Assessment, 13].

While there is very limited historical monitoring data for the concentration of isophorone in Canadian water bodies, there appears to be no recent monitoring data. Yet the report indicated that given the current uses of isophorone, releases to water could also occur [Isophorone Assessment, 14].

The assessors note that “regarding ecotoxicity, the significance of soil as a potentially important medium of exposure is not well addressed by the effects data available, but exposure in this medium is not expected to be significant” [Isophorone Assessment, 15]. One source of uncertainty is the lack of empirical data for environmental concentrations in Canada.

Furthermore, the report refers to high importation volumes of isophorone into Canada and large use volumes of the substance, which together would indicate the potential for widespread release into the Canadian environment. However, the assessors find it unlikely for isophorone to cause ecological harm in Canada.

These confusing and somewhat contradictory statements exemplify an all-too-common situation encountered in this assessment (and others as well). Where there is clearly lack of information and a high degree of uncertainty on which to base a conclusion, nevertheless, a conclusion is drawn that dismisses the likelihood that the substance could cause ecological harm.

### **Human Exposure**

According to the assessment report, while the major use of isophorone is industrial, the principal source of exposure of the general population is thought to be through food and beverages. However, because of its use in so many industrial processes, exposure through inhalation and dermal contact, particularly in workplaces using isophorone, is likely.

In Canada, drinking water and soil have not been identified as a potential source of exposure.<sup>6</sup> Neither outdoor nor indoor air is reported to be a likely source of exposure in Canada since it has a rapid biodegradation half-life in the atmosphere.

- Exposure estimates for consumer products (e.g., food) were not calculated.
- No consideration is given to exposure of vulnerable populations to isophorone (except for children as part of the general population).
- Occupational exposure is only slightly referred to, but in light of the many industrial uses, it is clearly a concern.

### **Health Effects**

The effects of isophorone reported by people who have been exposed are irritation of the skin, eyes, nose, and throat, and dizziness and fatigue. These effects have occurred in workers who breathed vapours of isophorone and other chemicals in the printing industry

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<sup>6</sup> <http://www.atsdr.cdc.gov/tfacts138.html>; also [http://www.oehha.ca.gov/air/chronic\\_rels/pdf/isophorone.pdf](http://www.oehha.ca.gov/air/chronic_rels/pdf/isophorone.pdf)

and are dependent on concentration levels. For example, throat, eye, and nasal irritation were reported at higher acute concentrations. Internationally, isophorone has been classified by the EC as irritant of the eye and respiratory system.

Short-term exposure of animals to high levels of isophorone has caused inactivity and coma. Some animal studies suggest that isophorone may cause birth defects and slower growth in the offspring of rats and mice that breathed the vapours during pregnancy. These studies found some harmful health effects in adult female animals. However, the screening assessment indicated that isophorone is not considered to be a developmental or reproductive toxicant.

When rats and mice were given high doses of isophorone in food or water for a long time, the male rats developed kidney disease. This was reportedly due to the accumulation of  $\alpha$ 2u-globulin, a mechanism not relevant to people [Isophorone Assessment, 22].

Isophorone is classified by the European Commission (EC) and the US Environmental Protection Agency (EPA) as a *possible human carcinogen* (Category C carcinogen), based on adequate evidence in animals and inadequate evidence in humans.<sup>7</sup> In male rats, exposure to isophorone by ingestion caused an increase in tumours of the kidney, liver, and lymph and reproductive glands. There was no increase in tumours in female rats or mice.

Although the mode of induction of tumours is not fully elucidated, as indicated in the assessment, the tumours observed are not considered to have resulted from direct interaction with DNA and that isophorone may exert its toxic effects through a mechanism other than direct interaction with DNA and is not likely to be genotoxic, a conclusion also of other agencies. As a result, the assessors used a threshold approach to assess risk to human health [Isophorone Assessment, 22].

The lowest-observed-effect-level (LOEL) reported for oral exposures was 250 mg/kg-bw per day, “based on non-neoplastic effects observed after chronic exposure (nephropathy in female rats; liver necrosis, hepatocytomegaly in male mice); whereas the potentially chemical-related increase in tumour incidence was observed only at higher doses.”

Other non-neoplastic effects include reduced body weight gain in male rats, increased mortality in female mice, sluggishness and lethargy in rats, and staggering in mice.

While the assessment found that the Margins of Exposure (MOE) to be adequately protective of human health due to repeat exposure, the determination of MOEs was limited. No other MOEs were calculated, as the assessors assumed that consumer product exposure was likely negligible.

Clearly, there are many uncertainties regarding how isophorone acts to induce its toxic effects. Also there are severe limitations and serious gaps in the information that would help in providing a more informed assessment of this substance and what would represent a protective MOE.

- There are no studies on whether isophorone causes cancer in people.

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<sup>7</sup> [http://www.ohha.ca.gov/air/chronic\\_rels/pdf/isophorone.pdf](http://www.ohha.ca.gov/air/chronic_rels/pdf/isophorone.pdf) Category 3:EC “Substances which cause concern for man owing to possible carcinogenic effects but in respect to which the available information is not adequate for making a satisfactory assessment.”

- There is no clear explanation as to taking a threshold approach to the effects of isophorone.
- Long-term effects of exposure are not addressed or even understood.
- Vulnerable populations have not been addressed.
- The potential impact of consumer product exposure (isophorone in food packaging and its use as a flavouring additive) has not been taken into account.
- Other health effects, particularly related to occupational exposure (e.g., carcinogenic effects following chronic low dose exposure), need to be considered.
- There is some confusion as to whether there are any developmental or neurological effects from exposure to isophorone.

### **Summary Comments and Recommendations**

Given its carcinogenicity and concern about products in which the levels of isophorone are not known, the assessment needs to re-evaluate its proposed finding that isophorone does not meet the criteria for toxicity under section 64 CEPA 1999.

Within this re-evaluation assessment, attempts should be made to fill current data gaps if possible and include:

- a. Studies using multiple doses and multiple, human-relevant species that address long-term oral exposure
- b. Studies further elucidating the toxicokinetics and metabolism of isophorone and its metabolites in multiple species
- c. The extent to which isophorone is used in food packaging or flavouring is not known and needs to be determined.

Other recommendations:

- a. Monitoring and mandatory reporting data of releases are required.
- b. Effects on vulnerable populations and workplace exposure should be examined.
- c. Revisions to the *Food and Drug Act* regarding the permitted use of isophorone in food packaging and flavouring and in natural food products. Such use should be prohibited.

### **Conclusion**

In light of the uncertainties and gaps in information and its categorization as a possible carcinogen by international agencies, isophorone should be declared toxic. This would require developing a strategy to “manage” this substance. Otherwise, it is virtually “dropped” from any consideration.