

**Chemical Management Plan
Batch 7 Challenge Substances
Submission on
Final Screening Assessments and
Risk Management Proposals**



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INUIT TAPIRIIT KANATAMI

May 3, 2010

Ottawa, Canada

INUIT TAPIIRIT KANATAMI (ITK) Submission - Batch 7 Challenge Substances

May 3, 2010
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Re: Submission on findings of Final Screening Assessments and where applicable, proposed Risk Management Strategy Documents, for four Batch 7 substances (*Canada Gazette* Part I, Part I, Vol. 144 No. 10, March 6, 2010), namely;

1. Oxirane, (butoxymethyl)- (*n*-butyl glycidyl ether) CAS No. 2426-08-6, 1
2. 2-Butanone, oxime (butanone oxime) CAS No. 96-29-7
3. 1,4-Dioxane CAS No. 123-91-1
4. 2-Cyclohexen-1-one, 3,5,5-trimethyl- (Isophorone) CAS No. 78-59-1.

A. Introductory Remarks

The Inuit Tapiriit Kanatami (ITK) is an active participant in the Chemical Management Program (CMP), including the Stakeholder Advisory Council, the CMP Civil Society Capacity Building Project, and the Challenge Program, for which ITK has made several submissions on a select number of substances in the various batches to date.

ITK is mainly concerned about the harm these substances might cause to Inuit people and their environment and the overall chemical burden to which Inuit are exposed over the long-term. While the comments submitted by ITK cover a broad range of issues on these chemicals, they are also channelled through an “Inuit lens” which examines the chemical’s potential for long-range transport that may affect Inuit people; its inclusion in commonly-used products and food; its use in industrial processes, in particular, resource extraction activities; and the disposal of material containing these chemicals.

As in its previous submissions, ITK stresses the need for the assessments to take a precautionary approach in formulating their conclusions, and incorporate pollution prevention and consideration for vulnerable populations as essential components of the screening assessments and risk management. In addition, the potential impact of cumulative and long-term exposure to need to be accounted for in evaluating the decision as to potential toxicity of a substance.

ITK has consistently stated that any substance that is a known or suspected carcinogen, genotoxin, mutagen, or reproductive and/or developmental toxin be designated toxic under the *Canadian Environmental Protection Act* (CEPA 1999), and that risk management strategies be adopted to restrict and/or ban the use and importation of this substance or products containing it.

As more batches are being released, few substances are being proposed or concluded toxic under CEPA 1999, while SNAc (Significant New Activity) provisions under the Act has become more common. This trend is demonstrated by the decisions made for batch 7 substances as a whole. By concluding that substances deemed “high priority” under the Challenge Program do not meet

the criteria for toxicity under the Act, no risk management strategy is required. Likewise, by applying SNAc provisions, any action is forestalled indefinitely, until or only if new uses for the chemical meet the threshold to trigger assessments under the Act (sections 81(3) and 83), prior its re-introduction to Canada.

This is not a means of reducing the overall toxic burden to which Inuit may be exposed. ITK strongly recommends prohibiting the use and hence re-introduction of such chemicals under the existing regulations as the most effective and precautionary measure to take.

B. Overview of Final Assessments for Batch 7

Three out of the fourteen substances have met the criteria for toxicity under the *Canadian Environmental Protection Act 1999* (CEPA 1999). One of these substances, butanone oxime, is of particular interest to ITK as it has been identified as having potential for long-range transport.

Of the remaining eleven substances not found toxic under CEPA 1999, the government has proposed applying Significant New Activity (SNAc) provisions to nine substances (pigments and dyes), five of which are concluded to be persistent, bioaccumulative and inherently toxic (PBiT). This is a slight change from the draft assessment findings on these substances, where only the five PBiT substances were proposed to be subject to SNAc provisions. The rationale for this proposal is that these substances are presently not in commerce in Canada and not entering the environment, but could potentially pose harm if they re-enter commerce in Canada.

Many of these pigments and dyes are found in numerous commonly-used products in the household (paints, etc.). Even though some of these substances may no longer be in commerce, they are likely still in products being used or in products that have been disposed of in some manner, such as incineration. It is also likely that these products are used in communities, and possibly isolated northern communities, where social factors could result in the use of products that are no longer on the market in urban communities in Canada.

As to the remaining two substances in batch 7, 1-4 dioxane and isophorone, they have not been found toxic and no further action on these substances is being taken. Both these substances are categorized as Category 3 carcinogens by the European Union (i.e., substances which cause concern for humans, owing to possible carcinogenic effects) and similarly by other agencies.

C. Comments on Specific Substances

For this submission, ITK is commenting on specific elements of the final screening assessments and risk management proposals for two substances found toxic, Oxirane (*n*-butyl glycidyl ether) and 2-Butanone, oxime (butanone oxime).

In addition, as ITK is duly concerned that two substances with possible carcinogenic effects (1-4 Dioxane and Isophorone) are not found CEPA-toxic, fairly detailed comments are provided on these substances, in anticipation that the government will re-consider its conclusions.

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

a. Overview - Screening Assessment and Conclusions¹

In the categorization process, oxirane (*n*-Butyl glycidyl ether) was identified as presenting an intermediate potential for exposure of individuals in Canada. It has been classified by other agencies on the basis of its carcinogenicity and genotoxicity and designated a high priority substance and as a result, placed under the Challenge Program.

The final screening assessment concluded that on the basis of its carcinogenicity for which there may be a probability of harm at any level of exposure, oxirane meets the criteria for toxicity under the *Canadian Environmental Protection Act* (CEPA 1999), section 64 (c). It has also been proposed for addition to the List of Toxic Substances in Schedule 1, CEPA 1999.

b. Manufacturing and Uses

Based on submitted data, oxirane was not manufactured above the reporting threshold in 2006, but imported amounts were in the order of 10,000 - 100,000 kg. 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. It has not been identified as an *intentional* ingredient in consumer products (e.g., cosmetics, pharmaceuticals, natural health products, or food packaging). According to the Canadian Paints and Coatings Association, all coating applications of oxirane are industrial.

c. Releases and Exposure

Oxirane 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.

Oxirane 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.

There was no information on waste disposal nor was there any environmental monitoring data.

Exposure to oxirane by the general population is expected to be low. While it is generally assumed to be no longer present in cured resin products, it is reportedly present as an impurity in a material preservative used in latex and oleo-resinous paints, though exposures are thought to be low given its reactivity. (One wood finish product identified as having higher levels of the preservative than interior paints, is apparently being reformulated).

Occupational exposures or exposures to vulnerable populations were not investigated.

¹ Final Screening Assessment Report for Oxirane (*n*-butyl glycidyl ether), March 2010
http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7_2426-08-6_rm_en.pdf

d. Health Effects

Carcinogenicity and mutagenicity: Oxirane is classified by the European Commission (EC) as Category 3 for carcinogenicity and as Category 3 for mutagenicity. Due to the lack of long term data, the EC's carcinogenicity classification was based on both the weight of evidence from the genotoxicity data for oxirane 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. Analogs were used in the Health Canada assessment to support the body of evidence on its carcinogenicity.

Genotoxicity: Oxirane has induced chromosomal aberrations and micronucleus formation in *in vivo* assays, lethal mutations in mice, and reverse mutations in *in vitro* assays. In addition, data showing oxirane analogs to increase tumours in multiple organs of rodents via various exposure routes strongly suggests that it would induce tumours by direct interaction with genetic material.

Non-neoplastic effects: These effects include skin irritation and sensitization, conjunctivitis, severe ocular damage, erythema, liver and respiratory effects, testicular atrophy, decreased pregnancy rates, increased foetal death rates, and reduced reproductive capacity. Oxirane and/or its analogs have induced these effects 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 non-neoplastic effects or reproductive/developmental toxicity have been identified.

e. Proposed Risk Management Approach

The proposed human health objective for oxirane (*n*-butyl glycidyl ether) is to minimize human exposure to the greatest extent practicable. As exposures of Canadians were considered low under the current use conditions, the risk management objective is to prevent increases in exposure.

In order to achieve the objective and to work towards achieving the human health objective, the risk management being considered is "the requirement for notification of the federal government regarding any potential changes in the use pattern for oxirane (*n*-butyl glycidyl ether) so that the potential for exposure to the Canadian population does not substantially increase."²

ITK has significant and serious concerns about the adequacy of the proposed risk management approach. No rationale is given for this proposed risk management, which makes it very difficult for ITK to comment specifically on.

ITK expects that the risk management of substances found toxic would be directed to reducing exposure, including exposure to vulnerable populations, especially to any substance, such as oxirane, a non-threshold carcinogen and a mutagen.

Given the acknowledged uncertainties in exposure, health effects, and concentrations of oxirane in Canadian environmental media and consumer products ITK would have anticipated a strategy to address these uncertainties.

² Proposed Risk Management Approach for oxirane (*n*-Butyl Glycidyl ether,) p. 10
http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7_2426-08-6_rm_en.pdf

In that vein, ITK is providing recommendations for consideration in order to develop a more meaningful risk management strategy for this substance.

f. Recommendations

1. Research and monitoring studies need to be conducted to support assumptions made in the Screening Assessment.
2. Concentrations within Canadian environmental media and specific consumer products (e.g. cosmetics, pharmaceuticals) need to be established. Otherwise, the risk management will not address population exposure to this substance via all relevant sources.
3. The risk management focus needs to address the volume already in commerce and its potential presence as an impurity in various products.
4. Exposure to and effects on vulnerable population groups (occupational exposure, children, aboriginal populations) need to be addressed.
5. Studies (long-term) specifically pertaining non-neoplastic effects to assess reproductive or developmental toxicity need to be identified and carried out.
6. Experimental data regarding its carcinogenicity should be acquired. Although the analog data is considered strong and sufficient, and the genotoxicity data is extremely strong, empirical data would strengthen the case for oxirane being of concern to Canadians.
7. There is no public reporting of releases of oxirane to the environment. Releases to water or land were not disclosed. In the interests of public transparency, this substance and any other substance found toxic should be listed on the NPRI at an appropriate reporting threshold.
8. As there is no data on waste disposal of oxirane through facility and product disposal, efforts are required to track this waste and the disposal mechanism. This is likely another source of exposure.
9. Possible substitution by safer alternatives needs to be examined.

g. Conclusion

Limiting the risk management to a requirement for notification of any potential changes in the use pattern is a bare minimum and considered inadequate.

Given the characterization of this substance as carcinogenic and mutagenic, with no threshold, and uncertainties in exposure estimates, ITK suggests that a precautionary approach would be taken to the risk management for this substance, and that consideration is given to reduce exposure to vulnerable populations.

Case 2: 2-Butanone, oxime (butanone oxime) CAS No. 96-29-7

a. Overview –Screening Assessment and Conclusions³

Under categorization, butanone oxide was identified as posing the greatest potential for exposure of individuals in Canada. It has been classified by other agencies on the basis of its carcinogenicity and thereby designated a high priority substance under the Challenge Program. While it met the ecological categorization criteria for persistence, it did not meet the criteria for

³ Screening Assessment for butanone oxime, March, 2010
http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7_96-29-7_en.pdf

bioaccumulation potential or inherent toxicity to aquatic organisms.

On the basis of the potential inadequacy of the margins between estimated exposures to butanone oxime and critical effect levels, the assessors conclude that butanone oxime meets the criterion for toxicity to human health under section 64(c) of CEPA 1999. It has been proposed for addition to the List of Toxic Substances, Schedule 1, CEPA 1999.

While butanone oxime meets the criteria for persistence in air, but not in any other media, the assessors concluded that it does not meet the bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations*, 2000.⁴

ITK is particularly interested in the impacts that butanone oxime may have in Inuit communities due to its potential for long-range transport. In addition to commenting on the risk management approach proposed for butanone oxime, ITK is briefly reiterating aspects of the screening assessment that are a concern to Inuit.

b. Manufacturing and Uses

Butanone oxime is considered a high production volume chemical (HPV) by the Organization for Economic Co-operation and Development (OECD), the US EPA and the European Commission (EC). Worldwide production is estimated at between 10 000 and 20 000 tonnes per year.

In 2006, based on a reporting threshold of 100 kg, butanone oxime was not manufactured by any company in Canada. Imported amounts into Canada () were approximately 500 000 kg and the amounts used were nearly 120 000 kg.. Both import and use amounts are very considerable for the Canadian market.

Its presence in the environment results directly from human activity. Uses in numerous products and processes include; formulation of alkyd paints, varnishes, stains and coatings for both industrial and consumer use, in a number of pesticide products (for example, wood preservatives and antifouling marine paints), as well as in some adhesives, silicone sealants, printing inks and artist paints, and as a corrosion inhibitor in industrial boilers and water treatment systems and serves as a blocking agent in the manufacturing process of urethane polymers.⁵

While butanone oxime is found in some printing inks used in the manufacture of food packaging materials, the assessors indicate that there is no direct contact of butanone oxime with food.

The use of butanone oxime in cosmetics is prohibited in Denmark and in the United Kingdom. In Canada, no current use in cosmetics has been notified, but it is subject to the *Pest Control Products Act* and is categorized as a List 2 Formulant.⁶

c. Releases

The high volume of butanone oxime imported into Canada, together with its diversity of use in a variety of consumer products, indicate potential for widespread release into the Canadian environment. However, there is very little data on the release and fate of butanone oxime in

⁴ *Canadian Environmental Protection Act: Persistence and Bioaccumulation Regulations*, P.C. 2000-348, 23 March 2000, SOR/2000-107. <http://www.gazette.gc.ca/archives/p2/2000/2000-03-29/html/sor-dors107-eng.html>

⁵ Screening Assessment for butanone oxime - p.5,6

⁶ Risk Management Proposal for butanone oxime March 2010 p.9. List 2 designation elevates the priority for reassessment within the PMRA (published on June 28, 2007).

http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7_96-29-7_rm_en.pdf

environmental media in Canada or elsewhere.

While there were no reports of any significant industrial releases of butanone oxime in 2006, the Canadian Chemical Producers' Association reported the release of 356 kg to the environment in 2007.⁷ The National Pollutant Release Inventory (NPRI) does not require reporting of releases of butanone oxime.

d. Persistence and Bioaccumulation

Based on the empirical and modelled data, butanone oxime meets the persistence criterion in air (half-life in air ≥ 2 days), but not for water, soil or sediment as set out in the *Persistence and Bioaccumulation Regulations*. Experimental data “suggest” a low potential to bioaccumulate.

e. Long-Range Transport Potential (LRTP)

Based on modelled data, butanone oxime is expected to have a moderate long-range transport potential, that is, the maximum distance travelled by 63% of butanone oxime is 1376 km. The potential for long-range transport has been further supported by OECD modelled data which suggested an even further travel distance of 3581 kilometres.⁸

f. Ecotoxicity

The toxicity data indicate that butanone oxime has a moderate potential to be toxic to algae and a low potential for most other aquatic organisms. If released to water, butanone oxime is expected to remain mainly within water. Considering the low hydrolysis rate of butanone oxime, the assessment indicates that hydrolysis products are not expected to pose a threat to the ecosystem.

At the same time, the assessment concludes that butanone oxime is unlikely to be causing ecological harm in Canada, while noting “this conclusion was reached despite the conservative assumptions that were made in response to uncertainties encountered in the assessment.”⁹

g. Human Health Concerns

Carcinogenicity was considered in the health effects assessment for butanone oxime, as it had been classified as a Category 3 carcinogen (*causes concern for humans owing to possible carcinogenic effects*) by the European Commission (EC). The EC suggests that butanone oxime may cause cancer in male rats and mice via metabolism to a carcinogenic agent, but have not indicated whether carcinogenicity was due to threshold mechanisms.

Although the mode of induction of tumours is not fully elucidated, the assessment views that tumours observed are not considered to have resulted from direct interaction with genetic material, indicating that butanone oxime is not likely to be genotoxic. While the majority of assays (including oral and inhalation assays) have suggested it is not mutagenic, other assays have suggested otherwise.

In addition to its carcinogenic effects, butanone oxime has been shown to cause dose-related increases in liver hypertrophy and necrosis in rodents via inhalation, and olfactory epithelium degeneration in the nasal passageway. It has also been shown to cause effects in the spleen, blood, and testes at differing doses.

⁷ Screening Assessment for butanone oxime p.6

⁸ Ibid p.8,9 Travel distances of >2000 km represent high LRTP, 700–2000 km is moderate and <700 km is low.

⁹ Ibid p.10-13

Animal studies show that butanone oxime is rapidly absorbed from the gastrointestinal tract, undergoes widespread uptake, distributes over the entire body, is extensively metabolized and does not accumulate in tissues. Excretion of butanone oxime and its metabolites occurs in the urine and bile or as volatiles in expired air.¹⁰

While exposure of the “general population” to butanone oxime is considered to be most likely from the use of consumer products, mainly alkyd paint products, uncertainty is associated with the use of non-Canadian-specific default assumptions in the modelled consumer product exposure scenarios.

h. Summary of Issues – Screening Assessment

Manufacture and Use:

The difference between the amount imported (500 000 kg) and used (120 000 kg) in one year is substantial. The different thresholds under Section 71 CEPA 1999 for reporting import amounts (100 kg) versus use (1 000 kg), may be a contributing factor but this cannot be assumed.

Releases:

Overall, the amounts of butanone oxime released to air, water, and land, or the amounts disposed of from industrial process, or consumer products use are virtually unknown.

No environmental monitoring data was available. Furthermore, butanone oxime is not reported to the NPRI and there are no other mandatory reporting requirements that would determine releases to the environment or disposal amounts. Yet the assessment suggests that the total industrial releases of butanone oxime are low, and that the most significant releases of butanone oxime are expected to take place at the consumer use stage. Without any solid information and data about releases, such expectations are unfounded.

Long-range transport:

Butanone oxime persists in air and there are strong indications that it could travel well beyond 1000 km to nearly 4000 km. This is of particular concern to ITK. However, there is no indication that the impact of long-range transport will be explored as to the likelihood of travelling to the far north and the impact of its deposition in Inuit communities.

Persistence:

The report notes that uncertainties exist regarding the conclusion for persistence in water, soil and sediment. Very limited empirical data was available to estimate approximate half-lives in these media and some models were contradictory. Despite that, the assessors conclude that “the weight of evidence, considering both the empirical and modelled data, indicates that this substance does not meet the persistence criteria for water, soil or sediment.”¹¹

Ecotoxicity:

The report notes that exposures near point sources are expected to be highest in the aquatic compartment, and aquatic organisms are expected to be among the most sensitive to this substance. However, no toxicity data were found for the organisms in the soil or sediment compartments. Furthermore, the significance of soil and sediments as important media of exposure is not well addressed by the effects data available.

¹⁰ Ibid pp. 15-19

¹¹ Ibid p.13

ITK finds the information on ecotoxicity deficient and questions how any conclusions can be drawn based on the above somewhat contradictory statements above, for example.

Human Health:

The screening assessment, as noted by the assessors, does not include a full analysis of the mode of induction of effects, including cancer. Only limited information is available concerning the potential toxicity of butanone oxime following oral and dermal exposure. Other significant gaps and deficiencies identified include:

- Lack of reproductive and developmental toxicity studies based on inhalation exposure;
- Lack of chronic toxicity/carcinogenicity studies based on oral exposure;
- Limited *in vivo* genotoxicity data and a lack of dermal studies for several endpoints except for acute exposures;
- No clinical human toxicity or epidemiological studies were identified.
- There are inherent uncertainties in the interpretation of intraspecies and interspecies variation.
- Modeling was only conducted for only six products and cumulative exposures were not taken into account.
- The assessors indicate that there is no direct contact of butanone oxime with food, despite it being found in some printing inks used in the manufacture of food packaging materials. No evidence is available to support this supposition.

These gaps and uncertainties are very limiting to interpreting the biological significance of the effects of exposure to butanone oxime from environmental media and food in Canada. As a result, the margins of exposure, at least for the so-called general population, are not protective.

Thresholds for Exposure:

There is an assumption that a threshold exists for observing carcinogenic effects from exposure to butanone oxime. ITK strongly recommends that in light of the lack of the gaps and uncertainties, a precautionary approach be taken, and a “non-threshold” approach be adopted.

Populations – General and Vulnerable:

Typically, assessments have looked at the exposure and intake of the “general populations”, including infants and children. But as stated in the assessment, “due to the lack of empirical data on concentrations in several media, estimates of daily intake for the “general population” were not derived.”¹²

There is absolutely no mention, let alone consideration, for the range of vulnerable populations that are potentially exposed to this substance. This includes children, pregnant women, First Nations, Métis and Inuit peoples and disadvantaged, isolated communities. As well, no attention is paid to occupational exposures.

i Proposed Risk Management Approach

The proposed human health objective for butanone oxime is to minimize human exposure to the extent practicable. The risk management being considered for butanone oxime is to restrict the concentration of butanone oxime in indoor alkyd paints available to consumers.

In addition, the federal government has assessed butanone oxime in the event that it were to enter the environment as a result of an environmental emergency and has concluded that the substance

¹² Ibid p.19

meets one of the criteria set out in section 200 of CEPA 1999. Therefore, the government intends to propose adding butanone oxime to the *Environmental Emergency Regulations* with a threshold of 6800 kg.¹³

ITK finds this proposed strategy highly inadequate in that it addresses only the “general population”, considers only one type of a consumer product, and does not even consider examining the impact of long-range transport. Certainly the numerous data gaps and deficiencies that have been detailed in its submission need to be acknowledged and addressed to ensure that risk management actions are effective in protecting human health for all populations.

While the risk management strategy mentions children’s exposure, this was in context to asking industry if any products containing this substance were intended for use by children. But the report states that “given the information received, it is proposed that no risk management actions to specifically protect children are required for this substance at this time.”¹⁴

Regarding substitution and alternatives, the risk management document only mentions research undertaken by the Danish Environmental Protection Agency to investigate the possibilities for substituting butanone oxime in air-drying coatings. This research work concluded that “although further work is required, success in substituting butanone oxime seems rather limited. Acetone oxime, though promising as an alternative, has a dubious health profile. Vitamin E needs to be investigated further, since it presents the best health profile of all the investigated compounds. Amino/amido compounds use might be limited due to their genotoxic potential.”¹⁵

j. Recommendations on Risk Management Approach

ITK strongly recommends that the risk management strategy address outstanding issues, including;

- Vulnerable populations, including children, workers, etc., who are potentially exposed through the use and manufacture of products containing butanone oxime;
- The ensuing impacts of long-range transport, on receiving communities, particularly northern communities;
- The impact of the disposal of products containing butanone oxime and potential releases from disposal methods, whether through incineration, leaching or in other wastestreams;
- The potential for contamination of food through food packaging materials containing butanone oxime;
- A re-examination of the ecotoxicity effects of butanone oxime, due to the lack of appropriate data, including the findings on bioaccumulation;
- Reporting and monitoring environmental releases through an appropriate public reporting system (e.g., NPRI) at an appropriate threshold; and.
- Addressing noted gaps, such as;
 - i. Concentrations within Canadian environmental media, specific consumer products, and food should be established. Furthermore the “significance of soil and sediments as important media of exposure is not well addressed by the effects data available”.

¹³ Proposed Risk Management Approach for 2-Butanone, oxime March 2010, p.11
http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7_96-29-7_rm_en.pdf

¹⁴ Ibid p.11

¹⁵ Ibid p.10

- ii. There is an inherent lack of transparency in information on amounts of butanone oxime imported and used, and released to the environment. For example,
 - The amounts imported annually and used should be examined to fill in any inconsistencies.
 - Releases of butanone oxime to all environmental should be reported (via the NPRI) at an appropriate threshold.
 - Releases and disposal of butanone oxime (e.g., that through facility disposal and product disposal) should be examined and subject to further research since there is no data available on it. That no significant releases were reported, aside from industry data, is of concern given its persistence and air and toxicity to humans.
- iii. More experimental data regarding its carcinogenicity should be acquired for chronic exposures beyond inhalation.
- iv. Data gaps pertaining to reproductive and developmental toxicity via inhalation, *in vivo* genotoxicity, and non-carcinogenic effects via dermal exposures should be filled.
- v. Attention needs to be paid to determining vulnerable population exposures given the processing and use of this chemical.
- vi. The assumption that there is no exposure through food must be tested, since this substance is found in some printing inks used in the manufacture of food packaging materials.
- vii. Efforts should be made to seek potential substitution with safer alternatives.

Case 3: 1,4-Dioxane CAS No. 123-91-1

a. Overview

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.

It has been classified as a Group 2B carcinogen by the International Agency for Research on Cancer (IARC) (possibly carcinogenic to humans); a Category 3 carcinogen by the EC (possible carcinogenic effects); a Group B2 (Probably Carcinogenic to Humans) by the US EPA; and is “reasonably anticipated to be a human carcinogen” by the US National Toxicology Program (NTP).

The final screening assessment concluded that 1,4-dioxane does not meet any of the criteria in section 64 of CEPA 1999.¹⁶

It is ITK’s view that this conclusion is erroneous, and that the assessment has not taken a precautionary approach, considering its noted health effects and several uncertainties that have been cited throughout the assessment document.

The following sections review many of the issues previously raised in ITK’s submission on the draft screening assessment of 1,4-dioxane, along with additional observations.

¹⁶ Refer to Screening Assessment 1,4-Dioxane CAS RN 123-91-1 March 2010, Synopsis http://www.ec.gc.ca/substances/ese/eng/challenge/batch7/batch7_123-91-1_en.pdf

b. Manufacture & Use

1,4-Dioxane has a broad and diverse range of uses in products and processes. Historically, it was used predominantly as a stabilizer for 1,1,1-trichloroethane. This function has been phased out due to controls placed on 1,1,1-trichloroethane use under the Montreal Protocol.

Currently, 1,4-dioxane is used extensively as a solvent for pharmaceutical processing and research and development, as a reagent for laboratory use in Canada, and a carrier solvent in the manufacture of veterinary drugs and natural health products. 1,4-Dioxane is also a component of industrial agents 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 (e.g., 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 an impurity in 168 pest control products that have both food and/or non-food uses; solvents used in making food packaging materials; polysorbates and polyethylene glycol. It may be found as an impurity in ethoxylated food additives and processing aids.¹⁷

No natural source of 1,4-dioxane have been identified. However, limited data indicate that it is a natural constituent in some food items. It is not known whether this occurrence results from natural production or contamination.

In Canada, 10 000 -100 000 kg was manufactured, 10 000 - 100 000 kg was imported, and a similar amount was used in 2006.

1,4-Dioxane is listed on the Cosmetic Ingredient “Hotlist”, in which its intentional use as an ingredient in cosmetics is prohibited, but its presence as an impurity is not listed.

c. Releases to the Environment

Information submitted by industry under the Section 71 notice of CEPA 1999 indicate that in 2006, 10 000 - 100 000 kg of 1,4-dioxane was released, the majority to water and air, into the environment. According to the National Pollutant Release Inventory (NPRI), 13 800 kg was released to air, 6 500 kg to water, and none reported to land for 2006.

Information obtained under Section 71 reveal that 100 - 1000 kg was transferred to hazardous waste facilities and less than 100 kg was transferred to non-hazardous waste facilities.

In the US, 56 000 kg was released to air, 22 000 kg to water and 64 000 kg were released by underground injection in 2006.¹⁸ Even though the assessment notes that the use in the U.S. is more widespread, the emissions to air and water in Canada are more than one-quarter of the reported US figures, which, considering the difference in population, indicates a relatively wide use in Canada.

- The disparity between releases of 1,4-dioxane via underground injection in the US and the lack of reported land releases in Canada requires explanation.
- Use patterns in other countries should be compared with that in the US and Canada.

¹⁷ *ibid* p.4 – 6

¹⁸ *Ibid* p.6

- Limitations from thresholds and criteria for industries required to report 1,4-dioxane to the NPRI may result in an incomplete picture of releases of adequately.

d. Persistence and Bioaccumulation

1,4-Dioxane is not considered persistent in air, but is persistent in water, soil, and sediment. It is considered to have low potential for long-range transport, given the maximum distance travelled by 63% of the substance is 95 km. The assessors indicate that it is unlikely to bioaccumulate or harm aquatic organisms at low concentrations.¹⁹ Consequently, 1,4-dioxane was found to meet the criteria for persistence (in water, soil and sediment), but not for bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations*.

- The conclusion regarding bioaccumulation needs to be re-examined as it relies only on very limited aquatic information.

e. Human Exposure

The principal routes of exposure to 1,4-dioxane for the general population are expected to be from the general environment, food, and the use of consumer products. Drinking water is considered to be the major exposure source, for the “general population”, while indoor air was the second largest. Other than a municipal water treatment plant in the Great Lakes region, no other Canadian water testing was identified.

An exposure estimate via food most generally (using Japanese data suggesting 1,4-dioxane in several food groups) was not included because of potential differences in 1,4-dioxane water content between Canada and Japan, differing food additive provisions, etc. However, the maximum exposure via food additives using Canadian information was calculated for children 1 - 4 years.²⁰

- Inhalation and dermal exposure via consumer products was acknowledged, but only exposure estimates for female adults (weighing 69 kg) and 0- to 6-month-old child exposures were presented.
- A very low number of products that were examined, even though it is known that 25% of all women use at least 15 products daily (many of which may contain 1,4-dioxane).²¹ Given that these personal care products are used over a lifetime, cumulative and long-term exposure to 1,4-dioxane from such products and other types of products and uses need consideration, even if difficult to ascertain.
- Personal care products containing 1,4-dioxane includes baby shampoos, skin moisturizers, body wash and lotions. ITK questions how or why such a substance is used and found in products for babies.²²
- Efforts should be made to determine whether the occurrence of 1,4-dioxane in food results from natural production or contamination by ethoxylated food additives and pesticides.
- There was no consideration for exposures via other consumer products (e.g., detergents) and breast milk, even though there were indications of its presence.

¹⁹ Ibid p.9

²⁰ Ibid p.12-14 For children, 0.335 µg/kg-bw per day

²¹ Environmental Working Group. www.cosmeticsdatabase.com/research/whythismatters.php September 15, 2009.

²² Screening Assessment .14, Table 7a, p. 16 Table 7c

- Vulnerable populations (including worker exposure), beyond children within the “general population” are not addressed. The term “general population” excludes many from various backgrounds who may not be necessarily considered “vulnerable”.
- There is no testing of 1,4-dioxane in drinking water in Canada.

f. Health Concerns

The carcinogen classifications for 1,4-Dioxane are based on “hepatocellular adenomas and carcinomas in mice, tumours 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”. 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 rates of 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 tumorigenesis (that is, formation or production of tumours) following oral exposure.

- Data and conclusions of other agencies suggest it is not a likely a mutagen, although potential modes of action have not been fully elucidated.
- 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. But there are limitations to studies on these effects.
- The assessors concluded that there is a threshold for carcinogenicity, although their reasoning for this is not clear, particularly in light of the noted uncertainty in the mechanism of tumorigenesis”.

g. Uncertainties in Evaluation of Risk to Human Health

- Estimation of intake from food sources, as Canadian monitoring data on the levels of 1,4-dioxane in foods were unavailable.
- The presence or concentrations of the substance in consumer products available in Canada was not determined due to limited information.
- The mechanism of 1, 4-dioxane-induced tumorigenesis and the human relevance of 1, 4-dioxane carcinogenicity are not understood.
- Lack of sufficient data to preclude the distribution of 1,4-dioxane to the nasal tissue by systemic circulation via oral exposure.
- Critical exposure levels associated with non-neoplastic effects via inhalation or dermal exposure to 1,4-dioxane is not known.
- Reproductive toxicity data associated with 1,4-dioxane exposure is not known, as there is no multigenerational study available.

h. Recommendations

- i. Given its carcinogenicity, “uncertainty regarding the mechanism of 1,4-dioxane-induced tumorigenesis”, a precautionary approach is justified and 1,4-dioxane should be designated “toxic” under CEPA, 1999.
- ii. Consumer product exposures (e.g., via cosmetics, food) should be investigated.
- iii. 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.
- iv. Concentrations in water, drinking water, and soil from various Canadian locations should be established.
- v. The full life cycle of products containing 1,4-dioxane, including waste disposal, should be taken into consideration
- vi. Intake estimates need to include levels found in breast milk.
- vii. Reporting releases of 1,4-dioxane to the NPRI should be reviewed to examine the threshold for reporting.
- viii. Long-term inhalation, dermal absorption, and oral studies for carcinogenicity and its non-cancer effects are particularly needed to ensure that all risks are addressed and managed appropriately. The dermal data set specifically needs strengthening.
- ix. Studies should be conducted on possible reproductive and developmental effects of 1,4-dioxane.
- x. Exposures to vulnerable populations need to be addressed. This includes infants and children, pregnant women, communities with cultural differences via food update, First Nations, Métis, and Inuit peoples and occupational exposure.

i. Conclusion

Given the weaknesses in the estimates for exposure levels the uncertainties in the evaluation of risk to human health in the screening assessment, and other noted uncertainties, it is very disappointing that a more precautionary approach has not been taken to this substance to date.

1,4-dioxane 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. ITK strongly urges the government to re-consider the conclusions of the assessment for 1,4-dioxane.

Case 4: 2-Cyclohexen-1-one, 3,5,5-trimethyl-(Isophorone) CAS RN 78-59-1

a. Overview

Isophorone was identified as a high priority for action under the Ministerial Challenge as it was classified by the other agencies as a possible carcinogen. Since isophorone did not meet the ecological criteria for persistence, bioaccumulation potential or inherent toxicity to aquatic organisms under categorization, the screening assessment focussed on risks to human health.

The screening assessment has concluded that based on available information, isophorone is not toxic under the criteria set out in CEPA 1999, nor does it meet the criteria for persistence or bioaccumulation.²³

²³ Screening Assessment Report on Isophorone, March 2010 p.3

ITK challenges these 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 of isophorone to the environment.

The following comments review specific aspects of the screening assessment that draw attention to ITK's concerns as to the conclusion of the screening assessment.

b. Major Uses and Sources

Globally isophorone 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, and in the production of certain chemicals. Although considered an industrial chemical, isophorone, a clear liquid that smells like peppermint, occurs naturally, for example, in cranberries, saffron and in several types of European honey.²⁴

According to information obtained from the Section 71 Notice under CEPA 1999, no isophorone was manufactured in Canada in 2006 (above the 100 kg reporting threshold). Import quantities ranged between 10 000 – 100 000 kg. 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.²⁵ No indication is given 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 was to be discontinued as of December 31, 2009. Its use in cosmetics is prohibited.²⁶

Based on section 71 surveys, isophorone may be present in food packaging, specifically as a processing aid in the manufacture of some linings or coatings for beverage cans, metal spice tins or other food packaging. A probable daily intake estimate for the spice tins application was considered not necessary as significant migration to dry foods was not expected.

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.²⁷

c. 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 it is unknown if such uses reflect the Canadian situation.²⁸ For example ITK is questioning;

- How widely is isophorone used in food packaging and linings or in flavourings?

²⁴ Ibid p.8; also <http://www.atsdr.cdc.gov/tfacts138.html>

²⁵ Ibid p.8

²⁶ Ibid p.7

²⁷ Ibid p.17

²⁸ Ibid p.17

- 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 populations 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. It may be already be in natural health products that are not licensed.

Despite these unknown factors, the assessors considered that the contribution from the intake of isophorone from food and beverages to be negligible.

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

d. Disposal

Issues related to disposal, particularly of food-related products have not 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.

e. Releases

Isophorone is released to the air from inks, paints, and other products containing it. It is also released to the environment from 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, in 2006, approximately 1,000 - 10,000 kg of isophorone was released into the atmosphere and 587 kg was transferred to hazardous waste facilities. 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.

f. Persistence and Bioaccumulation

Once released into the environment, isophorone will be found mainly in air and water. Since it disappears in air rapidly (half-life < 5 hours), it is not persistent in air. In their examination of modelled data on persistence in water, the assessors commented on conflicting results from models regarding biodegradation. However, the assessment concluded that isophorone is not persistent in water, soil or sediment. Furthermore, according to models used, isophorone was considered to have a low potential to bioaccumulate.²⁹ Consequently, the assessment concluded 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 and the potential to bioaccumulate. Even if a substance does not meet the specific criteria in the regulations, it cannot necessarily be inferred that it does not persist in some media or have potential to bioaccumulate to some extent.

g. 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 which showed damage to some leaves a few hours after application of isophorone.³⁰

There is very limited historical monitoring data for the concentration of isophorone in Canadian water bodies, and no recent monitoring data. But given the current uses of isophorone, the report indicated that releases to water could also occur.³¹

The assessors noted that “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.”³²

Given the high importation volumes of isophorone in Canada, along with its many uses, there is potential for widespread release into the Canadian environment. However, the assessors concluded that isophorone was unlikely to cause ecological harm in Canada, even while noting uncertainties due to the lack of empirical data for environmental concentrations in Canada.

Given the lack of information and a high degree of uncertainty, ITK cannot support the conclusion that this substance is necessarily unlikely to cause ecological harm.

h. Human Exposure

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, occupational exposure through inhalation and dermal contact is likely.

²⁹ Ibid p.11,12

³⁰ Ibid p.13

³¹ Ibid p.14

³² Ibid p. 15

In Canada, drinking water and soil have not been identified as a potential source of exposure.³³ 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 isophorone by vulnerable populations (except for children as part of the general population).
- Occupational exposure is only slightly referred to, but in light of the many industrial uses, is clearly a concern.

i. Health Effects

The effects reported by people in the printing industry who have been exposed to isophorone through inhalation include irritation of the skin, eyes, nose, and throat, dizziness and fatigue. The European Commission (EC) has classified it 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, reportedly due to the accumulation of α 2u-globulin, a mechanism not relevant to humans.³⁴

Isophorone is classified by 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 people.³⁵ 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, the assessment considered that the tumours observed did not result from direct interaction with DNA, which means that isophorone is not likely to be genotoxic. As a result, the assessors used a threshold approach to assess risk to human health.³⁶

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 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.

It is for this reason that ITK questions whether or not the MOEs are sufficiently protective given severe limitations and serious gaps in the information. For example,

³³ <http://www.atsdr.cdc.gov/tfacts138.html>; also http://www.oehha.ca.gov/air/chronic_rels/pdf/isophorone.pdf

³⁴ Screening Assessment Isophorone p.22

³⁵ http://www.oehha.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.”

³⁶ Ibid p.22

- There are no studies on whether isophorone causes cancer in people.
- A threshold approach to the effects of isophorone, based on the likelihood that it is not genotoxic, is questionable, given the overall uncertainties of its mode of action.
- Long-term effects of exposure are not addressed.
- 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.
- It is not clear whether isophorone would cause any developmental or neurological effects.

k. Recommendations

Given its carcinogenicity and concern that activities in which the levels of isophorone are not known, ITK recommends a re-evaluation of the conclusion of the screening assessment. ITK further recommends that efforts are made to conduct studies and fill current data gaps including:

- a. Studies using multiple doses and multiple, human-relevant species that address long-term oral exposure, and further elucidating the toxicokinetics and metabolism of isophorone and its metabolites in multiple species;
- b. Determining the extent to which isophorone is used in food packaging or flavouring;
- c. A study of potential effects of use and exposure on vulnerable populations, including occupational exposure;
- d. Establishing requirements for monitoring and mandatory reporting data of releases of isophorone to the environment;
- e. Instituting 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.

j. Conclusion

Given the diversity of use of this substance and that it is considered by some agencies to be a possible carcinogen, the potential hazards it presents, and the uncertainties and gaps noted, a precautionary approach is called for. Isophorone should be declared toxic under CEPA 1999, at the very least for its effect on human health, and a risk management strategy developed to fill in Gaps as noted above, and minimize releases.

By not finding isophorone toxic under CEPA 1999, its use continues without control, and so do the potential risks and hazards associated with it.