Summary of Public Comments Received on the Government of Canada's Draft Screening Assessment Report on Methyloxirane
(CAS RN 75-56-9)

Comments on the draft screening level assessment report on Methyloxirane, a substance included in Batch 1 of substances to be addressed as part of the Chemical Management Plan Challenge under the Canadian Environmental Protection Act 1999 (CEPA 1999), were provided by Dow Chemical Canada Inc., BASF Canada, Reach for Unbleached, Lyondell and the Canadian Council of Grocery Distributors during the 60 day public comment period that took place from January 19, 2008 to March 19, 2008. A summary of the comments that relate specifically to the draft assessment on methyloxirane, along with responses, is presented in the table below. Comments related to subsequent risk management of the substance are addressed separately.

Comment	Response
One commenter indicated that additional information concerning mode of action analyses for induction of effects would be provided to the government. The commenter has requested a meeting with government officials to present this information.	Health Canada officials would be pleased to meet with the commenter to discuss recent work. However, this information was not provided prior to the cut-off date for consideration of information.
A concern was expressed about lack of detail in the documentation regarding the nature of the peer review undertaken.	Information concerning the nature of the external peer review of the sections relevant to assessment of risk to human health will be included in the revised draft.
A commenter indicated that it was felt that a principal source of information on levels of methyloxirane in consumer products cited in the draft assessment report (i.e., Sack et al. 1992) was inappropriate and recommended that this source be more critically examined. Similarly, another commenter questioned the products selected for derivation of estimates of exposure in the draft assessment. Sack TM, Steele DH, Hammerstrom K, Remmers J. 1992. A survey of household products for volatile organic compounds. Atmos Environ 26A(6):1063-1070.	The source of information in question was more critically examined, as recommended. As a result, estimates of exposure from use of consumer products have been modified to beso that the estimates are based on principally on other sources of information. Scenarios for vinyl upholstery cleaner and spot remover have been deleted as examination of these additional sources of information did not support the presence of methyloxirane in these products.
A concern was expressed that using the detection limit from an indoor air study with 2 data points would be questionable or an over-estimate.	In the absence of air monitoring data, the detection limit of methyloxirane from the same study for both indoor and outdoor air was used in the upper bounding estimates of exposure. Because of this uncertainty, ChemCan modelling based on the release threshold was also used to estimate concentrations, and the results support the upper bounding estimate.
The opinion was expressed that ventilation should be considered in derivation of estimates of exposure from consumer products.	The estimates of exposure from consumer products have been refined using a different methodology that incorporates ventilation (Consexpo).
The opinion was put forward that Health Canada did not fully consider the negative *in vivo* genotoxicity of methyloxirane administered by certain routes of	In the screening assessment document, Health Canada tabulated all of the genotoxicity data – both positive and negative. Additionally, some of the negative *in vivo* studies

exposure in the overall assessment of genotoxicity, nor was there mention of these route of exposure in the discussion of genotoxicity in the document. It was also suggested that, although the European Union classified methyloxirane as a Category 2 mutagen, the wording of the recommendation indicates that it was not a clear-cut case, despite the long list of *in vitro* positive genotoxicity results on methyloxirane. It was further suggested that Health Canada did not consider the publication by Albertini and Sweeney (2007) in its evaluation of genotoxicity. Albertini RJ, Sweeney LM. 2007. Propylene Oxide: Genotoxicity Profile of a Rodent Nasal Carcinogen. Crit Rev Toxicol 37:489-520.	were mentioned in the text. This description has been expanded. The Challenge screening assessment of the genotoxicity of methyloxirane was based principally on the conclusions of the European Union, which took into consideration all of the available negative *in vivo* genotoxicity data for methyloxirane. Subsequent to the date of the meeting of Specialised Experts in the European Union, no additional negative data for genotoxicity have become available; however, positive *in vivo* results for DNA lesions and adducts have added to the database for methyoxirane. The debate by the European Union Specialised Experts evaluating the genotoxicity of methyloxirane was centred on weight of evidence for mutagenicity of germ cells. However, the experts were in agreement that there was clear evidence for mutagenicity of methyloxirane in somatic cells *in vitro* and *in vivo*. (ECBI/49/99 – Add. 1 Rev. 17.12.1999) The publication by Albertini and Sweeney (2007) examine the mechanism of action of methyloxirane's genotoxicity. In this article, it was concluded that methyloxirane's DNA-reactive genotoxicity may be necessary but not sufficient for carcinogenicity and therefore did not discount the potential role of genetic damage in the development of tumours. This possibility is already reflected in the screening assessment.
The request was made that No-Observed-Effect Levels (NOELs) for all studies, doses/concentrations for *in vivo* genotoxicity studies, and Klimisch ratings for all studies be provided in the document.	The information in the report is a brief summary of the critical database for the substance which formed the basis for the conclusion in the screening assessment and therefore not an exhaustive presentation of all information.
The opinion was expressed that the data on methyloxirane support a non-linear, threshold mode of action. Further references pertaining to data supporting this mode of action were provided (Albertini and Sweeney, 2007; poster abstract by Pottenger et al. 2008).	As stated in the screening assessment, it is recognized that methyloxirane has induced non-cancer effects and tumour formation in the same "portal of entry" tissues, and there may be a potential linkage between these effects. However, in the absence of a fully elucidated mode of action analysis, it cannot be precluded that tumours observed in experimental animals resulted from direct interaction with genetic material.
The opinion was expressed that the proposed conclusions with respect to human health (i.e. that methyloxirane be considered toxic under paragraph 64*c* of CEPA 1999) were not supported by the data and a conclusion based on precaution was not warranted in this case.	When the critical effect for a substance is considered not to have threshold of exposure for induction of effects, it is assumed that there is a probability of harm to human health at any level of exposure. Therefore, the proposed conclusion was that methyloxirane "may be entering the environment in a quantity of concentration or under conditions that constitute or may constitute a danger in Canada to human life or health." The application of a precautionary approach is required by CEPA 1999.
The comment was made that, even with very conservative consumer product exposure	As a mode of action involving a threshold level of exposure for induction of tumours has not been fully elucidated for

assumptions, this exposure is within the same range as the No Observed Adverse Effect Level (NOAEL) value for cancer effects and NOAEL for the non-cancer effects, but is of much shorter duration.	methyloxirane, Health Canada does not consider it appropriate to determine a NOAEL for cancer from a bioassay for comparison with a metric of exposure. Additionally, if No-Observed-Effect-Levels for non-cancer effects are within the ”same range” as exposure levels, the margin between these levels and those to which humans may be exposed may not be adequate to account for the uncertainties in the database.
A comment was made that this draft screening assessment report demonstrates the need for a mechanism to review risk assessments on a periodic basis and/or when new information becomes available.	New information can be evaluated by the government at any time and a request for the reassessment of any substance can be submitted to the government. The priority for the reassessment of a substance will be examined in relation to other activities and commitments.
An opinion was expressed that perhaps methyloxirane should no longer be labelled a greatest potential for exposure (GPE) substance.	The determination of “greatest potential for exposure” for this substance refers to the results from the prioritization process for existing chemicals (categorization) which the Government of Canada completed in 2006. This determination was based on information collected during the compilation of the Domestic Substances List in the mid-1980s.
It was requested that the sentence regarding the use of methyloxirane as a fumigant be modified to reflect the low quantities applied to a limited number of food products.	Methyloxirane is not a registered pesticide in Canada and its application as fumigant is not practised in Canada, as indicated in the screening assessment.
The opinions from a follow-up letter to the editor from Albertini (2002) regarding the Czene et al. (2002) pilot study examining DNA and hemoglobin adducts in worker populations were not included. Czene K, Osterman-Golkar S, Yun X, Li G, Zhao F, Perez HL, Li M, Natarajan AT, Segerback D. 2002. Analysis of DNA and hemoglobin adducts and sister chromatid exchanges in a human population occupationally exposed to propylene oxide: a pilot study. Cancer Epidemiol Biomarkers Prev 11(3):315-8.	The commentary from Albertini (2002) regarding the Czene et al. (2002) study was not cited in the screening assessment as the Czene study was a small-scale pilot study yielding preliminary results. The text regarding this study has been modified.
The opinion was expressed that, by defaulting to the European Union’s Risk Assessment Report published in 2002, Health Canada has not considered data and that Health Canada should review the last 10 years of published research related to mode of action of methyloxirane.	An updated literature search was performed and relevant data were incorporated into the screening assessment. In the absence of a fully elucidated mode of action, it cannot be precluded that tumours observed in experimental animals resulted from direct interaction with genetic material.
With regards to non-cancer effects, it was suggested that, to reduce the emphasis on NO(A)EL values (which are highly dependent on dose-spacing) benchmark dose (BMD) analysis on nasal lesions be conducted.	In light of the small magnitude of the margins of exposure between effect levels and estimates of exposure from use of consumer products, additional analyses of this type would have little impact on the conclusions in the screening assessment.
A concern was raised that the critical chronic non-cancer effect associated with chronic exposure to methyloxirane that was chosen for calculation of a margin of exposure (MOE)- ”nest-like infolds” in nasal respiratory epithelium of rats at 71 mg/m^3)	Using the more conservative level for non-cancer effects, the margin of exposure for environmental exposures is large. For exposure to methyloxirane through use of some consumer products, the screening assessment report stated that calculation of an MOE using the lowest effect level for

-was not statistically significant. Significance is not reached until higher exposure levels (237 mg/m^3), and the lower effect level should therefore not be utilized to calculate a margin of exposure.	short-term repeated exposure (i.e., 362 mg/m^3) may be more appropriate in light of the infrequent use patterns for such products and therefore an MOE was also calculated on that basis.
The opinion was expressed that going from a screening assessment to a risk management decision caused concern and that there is a need to review the assumptions and approach taken in the hazard and exposure assessment more closely, especially since there are "significant uncertainties" in the existing exposure data.	The government saw the need for action for high priority substances identified in the Challenge. The government also indicated that the absence of information would not preclude it from moving forward with risk management activities for these Challenge substances. However, the development of risk management measures may take into account further information, such as socioeconomic considerations and further characterization of risk.
A commenter stated that exposure to chemical mixtures should be taken into consideration in the screening assessment report and that evaluation and management of isolated chemicals is inadequate to address real risks of exposure.	For most classes of substances, including oxiranes, the available data are insufficient to conduct a cumulative risk assessment.
The comment was received that, in the absence of actual data and with evidence of high residue levels of methyloxirane in foods produced in countries which are exporting to Canada, it is insufficient to exclude the possibility of human exposure from food.	No human exposure is expected as a result of the allowed use as a food additive, since the requirements of the *Food and Drug Regulations* preclude human exposure to methyloxirane in finished foods.
It was commented that anti-seize lubricants for automotive use are the only use indicated in the Household Products Database maintained by the U.S. National Institutes of Health (NIH). None of the other products cited in Sack et al (1992) publication is listed by NIH.	Other uses, including use in paint stripper and spray paint, have been identified in submissions from companies in response to the section 71 notice under CEPA 1999or from other sources in the open literature.
It was stated that the default scenarios for consumer product exposures included in the 1986 U.S. Environmental Protection Agency Exposure scenario publication are outdated and should not be used.	The estimates of exposure from consumer products were recalculated using the Consexpo model and the exposure scenarios and default values included in this model.

Summary of Public Comments Received on the Government of Canada's Risk Management Scope Document for Batch one substance methyloxirane [CAS 75-56-9] on the *Domestic Substances List*

The table below presents a summary of the comments received during the 60-day public comment period that took place from January 19, 2008 to March 19, 2008. Comments summarized below were received by one or more of the stakeholders listed.

Comments on this publication were provided by:

1. Dow Chemical Canada Inc.
2. Canadian Council of Grocery Distributors
3. Reach for Unbleached
4. Canadian Environmental Law Association

Comment	Response
The government is urged to develop a CEPA Guideline for consumer products identifying conditions for which consumer products are not allowed.	The government plans to develop tools to minimize releases of methyloxirane from consumer products.
An instrument to ensure exposure to methyloxirane in consumer products is not expanded into new applications at concentrations that create unacceptable risk should be accomplished through a regulation, CEPA Guideline (above), other acts or a Significant New Activity (SNAc) restriction	The risk management actions being considered for methyloxirane include regulations, instrument(s) and/or tools(s)to minimize release of methyoxirane from consumer products, which would limit both new and existing uses in consumer products.
No regulatory instrument for industry is required. Designate CEPA *Environmental Emergency Regulations* as the CEPA (facility) instrument for methyloxirane	Methyloxirane releases from facilities are currently subject to the *Environmental Emergency Regulations.* Nonetheless the possible requirement for other regulations, instrument(s) and/or tools(s) for industry as it relates to methyloxirane will be considered in the risk management process.
Include in the risk management scope that methyloxirane is not inherently toxic (as outlined in the draft screening assessment)	While the screening assessment concludes that methyloxirane is not inherently toxic to aquatic organisms, it also concludes that it meets the criteria in paragraph 64 (c) of CEPA 1999, that is, it constitutes or may constitute a danger in Canada to human life or health. The risk management scope and approach documents and the Canada Gazette notice indicate that the Ministers of Environment and of Health propose to recommend to Her Excellency the Governor in Council that methyloxirane be added to Schedule 1 to the Act .
The risk management approach should consider the exposure of humans through consumer products.	The risk management regulations, instrument(s) and/or tools(s) being considered for methyloxirane involves minimization of its release from consumer products.
The risk management approach should consider the exposure of humans through food. The presence of methyloxirane on food products such as nuts should not be permitted in any level.	Methyloxirane is subject to the *Food and Drug Regulations*. With respect to its use as a food additive, when combined with water in the food production process, methyloxirane breaks down into non-toxic substances precluding its presence in finished foods. In

Comment	Response
It was recommended that for food applications, the current regulatory limits outlined in section B15.002(1) of the Food and Drug Regulations (i.e. maximum residue level of 0.1ppm) should prevail	addition, issues pertaining to imported fumigated nuts and fruits fall under the regulatory area of Pesticides Management Regulatory Agency (PMRA) and the Canadian Food Inspection Agency (CFIA). There is currently no maximum residue limit (MRL) in Canada, but imported food should not contain more than 0.1 ppm, as per section B15.002(1) of the Food and Drug Regulations.
The risk management approach should also examine the potential for release and exposure during recycling of paper products and disposal of paper recycling sludge.	At this time, no information has been received relating to the use of methyloxirane in paper production.
An appropriate management response should include the elimination of this substance over time. This goal may be reached through the development of a pollution prevention strategy that outlines timelines and targets to prohibit its use, manufacture, import, sale, and disposal, particularly as it pertains to consumer products (i.e., upholstery cleaners). Additional work to determine the level of exposure to these substances from indoor air and dust is required. As a follow-up, the management response should ensure that products containing these substances are prohibited for future use.	The focus for risk management of methyloxirane considers these areas mentioned, in addition to other areas, with the goal of minimization or elimination of its presence in consumer products. However, information obtained subsequent to the release of the draft screening assessment and the risk management scope indicated that methyloxirane is not used in upholstery cleaners in Canada.
The government should commit to prohibit the use of methyloxirane in cosmetic products. This can be achieved by requiring a process to investigate safer alternatives, assess their toxicity, and promote their use in place of methyloxirane.	Methyloxirane, as a monomer, is being recommended for addition to the Cosmetics Ingredient Hotlist, which will prohibit its deliberate use in cosmetics.