2-BUTOXYETHANOL

No comments were provided on the **environmental sections** of the CEPA PSL Assessment Report on 2-butoxyethanol.

Comments on the **health-related sections** of the CEPA PSL Assessment Report on 2-butoxyethanol were provided by E. Berry (Vice President, Canadian Manufacturers of Chemical Specialties Association), R.J. Kiefer (Director of Scientific and International Affairs, Canadian Manufacturers of Chemical Specialties Association) and C.M Price (CHEMSTAR, on behalf of the American Chemistry Council's Ethylene Glycol Ethers Panel). Many of the comments received from these reviewers were identical.

To ensure transparency and defensibility in the timeframe mandated for completion of the assessments under CEPA, early submission of relevant data is encouraged and a cut-off date for their consideration specified. This ensures their appropriate consideration in the context of the complete identified database and full assessment through the several stages of internal and external review. Data submitted following the cut-off date are considered primarily in the context of establishing priorities for updating assessments in the strategic options/risk management phase or subsequently conducting full reassessments.

Comment	Response
The conclusions presented in the CEPA PSL assessment report regarding the risk to health associated with exposure to 2-butoxyethanol through use of certain consumer products are different from those of other national and international agencies.	Prior to and during the preparation of the CEPA health assessment, staff of Health Canada reviewed formally (in international programs) and consulted informally, colleagues in other countries who had or were reviewing 2-BE. However, the CEPA health assessment includes data that were not available at the time of completion of several of these other assessments (e.g., the 2 year bioassay conducted by the National Toxicology Program; additional data relevant to estimation of exposure in a national context). In addition, the results of the CEPA assessment are not inconsistent with the conclusions of other agencies, but rather, address a different mandate, for which process for review and finalization also varies. In none of the other reviews, for example, was general population exposure considered in a national context. For Priority Substances, exposure from all media in the general environment (including indoor air) is considered as a basis for control of the most important sources of human exposure. There are also several stages of external review of CEPA assessments, prior to finalization.

Comment	Response
Undue reliance is placed in the Assessment Report on the multimedia study conducted by Conor et al. It was suggested that there are substantial data on concentrations of 2-butoxyethanol and exposure during use that indicate that non-occupational human exposures would not exceed 0.01 mg/m^3.	There are few data on the concentrations of 2-butoxyethanol in indoor air, the principal medium of exposure of the general population and none adequate to serve as the basis for quantitative characterization of levels in the residential environment. The limitations of the Conor et al. study and resulting uncertainties in quantitative results were and are delineated in both the draft and final Assessment Report. Based on these limitations, reliance on these data as a basis for characterization of exposure is limited to the qualitative observation that concentrations in residential indoor air are greater than those in outdoor air and to characterization of indoor air as the principal medium of exposure of the general population not exposed through consumer products. Though the reviewer makes reference to Asubstantial data that indicate that non-occupational human exposures would not exceed 0.01 mg/m^3, descriptions of most studies highlighted for comparison in the comments are either inadequate for critical review or the methodology in these investigations is inadequate as a basis for quantitative characterization. In only one of these investigations for which both the number of samples and reporting were limited, were levels in the residential environment determined; these were similar to those measured by Conor et al. The extent of reliance permitted by the description or methodology in identified studies is reflected in the revised Assessment Report.
Presentation of data on levels of 2-butoxyethanol in indoor air in other countries is misleading, as only the range is presented in the assessment report.	Additional detail on the nature of reporting for and limitations and results of these studies has been presented in the revised Assessment Report.
The units for the studies by Norback et al. (1995, 1996) were incorrect.	Units were corrected. The error likely occurred as a result of conversion in word processing.
Several comments related to the estimates of exposure to 2-butoxyethanol through use of consumer products containing the	The estimates of exposure to 2-butoxyethanol from consumer products have been revised, based on additional consideration of relevant data. For example, estimates of exposure to 2-butoxyethanol in personal

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substance. (See more specific comments of this nature below).	care products have been deleted. Additional specific comments have been addressed below.
It was suggested that the composition of the consumer products tested by Cao (1999) for Health Canada is unlikely to be similar to those currently marketed in Canada for consumer use.	The consumer products tested by Cao (1999) were those not intended for institutional, commercial or workplace use purchased from retail outlets in Ottawa during 1998 and 1999. The measured concentrations of 2-butoxyethanol in these products were consistent with information provided in the comments. Additional information concerning the presence of 2-butoxyethanol in consumer products has and is being gathered as part of the risk management phase.
The quantity of product used in the cell in the emissions testing by Cao (1999) was excessive and not related to the use of the product.	The purpose of these investigations was to determine the rate of emission of 2-butoxyethanol from products under similar conditions; the mass of the product within the cell would not affect initial emission rates.
Product use scenarios for the estimates of exposure to 2-butoxyethanol via consumer products are not realistic. For example, removal of cleaning products from the surface after application was not incorporated into the derivations.	These product use scenarios are standardized, with the source indicated in the Assessment Report. Although some products are wiped from the surface following application, 2-butoxyethanol would continue to be released from the cloth or paper towel with which it was removed, and thus continue to contribute to indoor air levels. As well, these estimates do not take into account additional exposure to 2-butoxyethanol from overspray during application of some products, which could contribute to overall exposure.
Estimates of exposure to 2-butoxyethanol through dermal contact with products containing the substance should incorporate available permeability constants.	The estimates of exposure from consumer products have been revised with permeability constants being incorporated for products, which are aqueous-based solutions.
Exposure models used in the assessment predict concentrations, which are above the saturation vapour concentration.	These preliminary bounding estimates were intended to predict the maximum possible concentration in air resulting from instantaneous evaporation of the 2-butoxyethanol contained in the relatively large quantity assumed per application in a standardized product use scenario. However, the commenter is

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	correct, and the estimates of exposure in the Assessment Report have been further refined, with these predictions being deleted.
The comment was made that the weight of evidence for 2-butoxyethanol suggests that it is not genotoxic; while the Assessment Report indicates that the results of in vitro studies were mixed.	The results of identified in vitro studies were mixed, as positive results were obtained in some studies. As stated in the Assessment Report, these data suggest that 2-butoxyethanol may be very weakly genotoxic in vitro. As noted also, the majority of the relevant studies did not incorporate metabolic activation, a limitation in view of the principal toxic effects of this compound (i.e., haematological effects) likely being due to a metabolite rather than the parent compound.
It was indicated that reference to observations of effects on blood in humans is unjustified, particularly the study by Haufroid et al (1997).	Such effects were observed in several case studies of incidental exposure; as indicated in the Assessment Report, the changes observed in the study by Haufroid et al (1997) were slight, but statistically significant. In addition, these studies contribute only minimally to the weight of evidence for an association between exposure to 2-butoxyethanol and haematological effects.
It was suggested that a tumorigenic concentration not be derived on the basis of the incidence hepatocellular carcinomas in the chronic bioassay in male mice, as the NTP did not consider these tumours to be related to exposure to 2-butoxyethanol.	In the final version of the NTP study report, it was concluded that these tumours might have been exposure-related. This conclusion was revised from that presented in the earlier draft of the report on the basis of comments received during the Technical Reports Review Subcommittee.
Speculations regarding mode of action for various effects should be deleted.	Assessment of weight of evidence for potential modes of action is a critically important component of PSL assessments. Text has been modified to indicate the lack of information on mode of induction of these tumours.
No data are available which suggest that renal clearance of metabolites is related to greater sensitivity of female mice to the induction of forestomach lesions, nor are there	Text deleted from the assessment report.

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data showing that well studied aldehydes cause similar lesions.	
New toxicity studies concerning the mode of induction of liver hemangiosarcomas and toxicokinetics in mice exposed to 2-butoxyethanol were submitted.	As stated above, a cut-off date for identification of relevant data is necessary to complete the assessment within the legislated deadline and to maintain the integrity of the peer review. However, based on preliminary scoping of these studies, they would not impact upon the conclusions of the health assessment.
Available PBPK models should be used in derivation of the Tolerable Concentration.	Available PBPK models were utilized in the derivation of the Tolerable Concentration to the extent justified on the basis of the number of untested assumptions, which contribute to their uncertainty. Description thereof has been expanded in the revised assessment. (As indicated in the Assessment Report, on this basis, use of the models for interspecies adjustment is justified primarily on the basis of their mathematical validation; they add little additional value to scaling of basic kinetic parameters). The AUC in animals was predicted on the basis of the PBPK model of Lee et al. (1998), since AUCs in the critical study were reported for the post-exposure period, only. Similarly, direct adjustment of the AUC for working versus resting conditions for humans was compared with output of the PBPK model for humans of Corley et al. (1997).
Lesions of the forestomach should not be used to develop a Tolerable Concentration because humans do not have a forestomach and the route of exposure of the mice in the critical bioassay was likely via preening of the substance adsorbed to the fur. In addition, The US EPA (the only other regulatory agency who published an evaluation subsequent to the publication of the results of the 2 year bioassay by the NTP) did not consider these lesions in the derivation of a reference dose or	The relevance of these effects to humans observed in multiple studies in mice cannot be dismissed on this basis. The reviewer provided no supportive evidence that these were related to preening of the substance absorbed to the fur. Indeed, submitted information appears to provide evidence to the contrary. The additional research by Green and Bennett indicates that the forestomach and glandular stomach of mice exposed to radiolabelled 2-butoxyethanol via inhalation or intravenous injection contained similar amounts of label, suggesting that the substance or its metabolites are delivered to these organs via the circulation, rather than solely by preening. The US EPA has not documented explicit rationale for not considering these lesions, which occurred at all exposure levels in female mice as critical in the

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concentration.	development of a reference dose or concentration. Therefore, it is not possible to comment on this aspect of the EPA assessment.
The haematological endpoint for derivation of a tolerable concentration should have been mean cell volume.	The reviewers provided no rationale for selection of the suggested endpoint nor is this consistent with endpoints selected by others, cited in reviewer's comments. In the CEPA assessment, benchmark concentrations were developed for several haematological endpoints. The tolerable concentration was based on the most sensitive endpoint as well as that for which available data were available for comparison of species differences in toxicokinetics and dynamics (which formed the basis for the compound-specific adjustment factors used in lieu of the more conservative default values).
Benchmark concentrations should not be derived for Kupffer cell pigmentation, as this effect is secondary to haemolysis.	Benchmark concentrations were derived for this endpoint primarily for comparison with those for primary haematological endpoints to determine if it might be a more sensitive indicator of haemolytic damage. Since the TC for haematological effects is based on increased mean cell haemoglobin, this BMC has no impact on the outcome of the assessment.
The hybrid model should not be used to model continuous endpoints such as haematological parameters since it introduces an arbitrary decision and invalid assumptions.	Use of the hybrid model is preferred since its definition of the BMC is more consistent with the definition for discrete data (a 5% increase in excess risk). Fixing an adverse response based on a percentile of the control distribution is no more arbitrary than using a percent change in mean response, as is done using conventional methods. The assumption of normality is believed to be reasonable and the advantages gained by using the hybrid model outweigh the additional uncertainty introduced by this assumption.
In the derivation of benchmark concentrations for forestomach hyperplasia, the incidence of lesions of all severities should not have been combined. A severity grade of 1 should not be included as an adverse effect. Incidence of the	BMCs calculated based on the assumption that only severity grades 2 to 4 constituted an effect (with animals with grade 1 lesions being combined with controls) are within a factor of 3 of the BMCs presented in the assessment. This information was and continues to be delineated in Section 3.3.5, namely Uncertainties and Degree of Confidence in the Human Health Risk

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individual severity scores for the more severe levels (2-4) should instead be used.	Characterization.
In the derivation of a BMC based on the incidence of epithelial hyperplasia in the forestomach of female mice, a probit model should have been used, as it provides a better fit to this data.	For consistency across Priority Substances, BMCs are based on the multistage model provided that statistical and visual fit to the data are adequate, as is the case for the relevant data on 2-BE.
The compound-specific adjustment factor should have been based on interspecies differences in peak levels of the metabolite, butoxyacetic acid (BAA), rather than the "area under the curve value' for this metabolite.	A rationale for use of peak levels was not provided with exception of reference to Corley et al. (1994), which indicated that either could be used as dose surrogate. As indicated in the Assessment Report, area under the curve has been selected since available data indicate that duration of exposure may be an important determinant of 2-BE induced health effects; moreover, in the absence of compelling data to inform the relevant choice, use of AUC is conservative.
For characterization of risk, a Tolerable Concentration derived on the basis of health effects observed in a chronic study should not be compared to short-term exposure levels as arise from use of consumer products.	This uncertainty was, and continues to be addressed in Section 3.3.5, namely Uncertainties and Degree of Confidence in the Human Health Risk Characterization. For the reasons indicated therein, exposure of a proportion of the population is expected to be greater than estimated. In addition, haematological effects similar to those observed following chronic exposure have also been observed in experimental animals following acute, short- and long-term exposure.
The conclusions of the assessment seem to be based upon an application of the "precautionary principle", although this would be inconsistent with the statutory mandate.	As outlined in the "Approach to Human Health Risk Assessment for Priority Substances", the degree of conservatism in assessments of Priority Substances is a function primarily of the extent of data available, with health-protective defaults being adopted in the absence of relevant experimental data. For the assessment of 2-BE, the contention is inconsistent, for example, with the incorporation in the Tolerable Concentration for haematological effects of an adjustment factor which is considerably less than default, based on the adequate data available as a basis for quantitation of interspecies

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	variation in toxicokinetics and toxicodynamics. Limitations of the available data, which impact on degree of conservatism, are delineated in the Section entitled “Uncertainties and Degree of Confidence in the Human Health Risk Characterization”.
It was suggested that a peer review panel be convened to review the CEPA assessment.	The draft CEPA health assessment was externally reviewed by several experts in various fields, as described in the Introduction to the Assessment Report.