Summary of Public Comments Received on Ethylbenzene (CAS RN 100-41-4) Draft Screening Assessment

Comments on the draft screening assessment for ethylbenzene to be addressed as part of the Chemicals Management Plan were submitted by Assembly of First Nations, Canadian Network for Human Health and Environment, Canadian Paint and Coatings Association, Canadian Vehicle Manufacturers' Association, Imperial Oil, and Styrene Information & Research Center.

A summary of comments and responses is included below, organized by topic:

TOPIC	COMMENT	RESPONSE
Communication	Provide parents and pregnant women with advice and measures to reduce ethylbenzene exposure from cars, attached garages, in-home photocopiers, printers, caulking and on reducing exposure through ingestion.	Emissions of ethylbenzene from vehicle interiors, attached garages, electronics, and consumer products were considered in the Screening Assessment and were found to have adequate margins of exposure. Information can also be found in the Public Summary on Ethylbenzene: http://www.chemicalsubstanceschimiques.gc.ca/fact-fait/glance-bref/ethylbenzene-eng.php Health Canada provides information on chemicals found in gasoline and other fuels that can enter the home through vehicle exhaust or vapours from stored fuel coming from attached garages or traffic: http://www.healthycanadians.gc.ca/healthy-living-vie-saine/environment-environnement/home-maison/interactive-interactif-eng.php
Consultations	The government should consult industry if further risk assessment of ethylbenzene used in industrial settings is planned.	Comment noted.
Methodology	Commenter supports using the 95th percentile ambient air concentration that is used in the assessment to characterize risk for ethylbenzene.	Comment noted.
	Toxicokinetic analysis of ethylbenzene in rat and human blood (Tardif et al. 1997) suggests that blood levels have reached a plateau four hours after inhalation of 200 ppm or less, suggesting that home consumer exposure scenarios are unlikely to result in significant impacts to human health.	Limitations in the Tardif et al. (1997) study preclude citing it as a meaningful blood concentration comparison. In particular results of this study are based on a small sample size (only 4 volunteers exposed to ethylbenzene for 7 hours with no background information provided), and no control subjects. Also, the Tardif et al. (1997) study method did not provide a blood collection description, time of blood sampling, and a description of how ethylbenzene levels in blood were measured. Numerical data were also missing (in graph only) and the rat sample size was small - with only two dose levels analyzed.
	The data in Tardif et al. (1997) can be extrapolated to blood concentrations associated with consumer product exposures. Using an internal systemic dose margin of exposure comparison can reduce uncertainty due to differences in rat and human physiology – for subjects exposed to ethylbenzene through inhalation.	
	There should be further health effects testing on less complex organisms.	Studies show that bioconcentration factors for ethylbenzene are low, and accumulation is not expected as it does not persist in water, soil or sediment. Available information indicates ethylbenzene is unlikely to cause adverse effects in aquatic or terrestrial ecosystems.
	There is support for using toxicity data from mammalian studies to assess potential impacts of ethylbenzene on wildlife. Using a Lowest Observed Effects Concentration of 75 ppm based on the percentage of female rats that die after being exposed to the substance for 104 weeks. A predicted environmental concentration of 4.4 µg/m^3 is also appropriate.	Comment noted for the use of the Predicted Environmental Concentration (PEC) of 4.4 µg/m^3.
Information Gathering	Since the study conducted by Midorikawa et al. (2004) provided key evidence for ethylbenzene genotoxicity, its limitations should be briefly noted in the screening assessment.	The final screening assessment is updated.
	It should be noted that the Voluntary Children's Chemical Evaluation Program (2007) was subjected to a peer-review.	The final screening assessment is updated to include information from the suggested references.

	Suggested references related to cytochrome P450 (CYP) CYP2F2-mediated mouse lung tumours mode of action were provided.	
	It should be noted that ethylbenzene was specifically identified with the chronic progressive nephropathy (CPN)-mediated mode of action for rat kidney tumours. Suggested references were provided.	
	A study by Mellert et al. (2007) should be cited where findings show no evidence of ethylbenzene-induced tumors in male or female reproductive organs of rats orally dosed at 750 mg/kg/day for 90 days.	
	A genotoxicity review (Henderson et al. 2007. A review of the genotoxicity of ethylbenzene. Mut Res 635:81-89) was suggested for citation in the screening assessment.	
Information and Data Needs	Additional information is needed on the relationship between constant low level exposure of fetuses to ethylbenzene and health effects (i.e. endocrine disruption and neurotoxicity studies). Specifically, levels measured in umbilical cord blood and the link between ethylbenzene-induced neurotoxicity and attention deficit and hyperkinetic disorder (ADHD) in children. It is noted that exposure to ethylbenzene at 350 ppm affects an area of the brain (mesostriatal dopamine deficit in the striatum). A reference was provided where this area of the brain was found to be hypofunctional in children with ADHD (Lou et al. 1989. Striatal dysfunction and attention deficit and hyperkinetic disorder. Arch Neurol 46-52).	Effects on the endocrine glands (thyroid hyperplasia) were examined in a study cited in the screening assessment (Chan et al. 1998; NTP 1990) and effects were observed at high dose levels only, and following prolonged exposure periods. Two references cited in the screening assessment show no evidence of neurotoxicity at a 500 ppm exposure level and show that exposure levels at or exceeding 750 ppm for rabbits resulted in dopamine depletion in striatal and tubero-infundibular areas of the brain (Romanelli et al. 1986; Mutti et al. 1988); these concentrations far exceed the inhalation critical effect levels (75-300 ppm) used in the risk characterization of the ethylbenzene screening assessment. Data on ethylbenzene in umbilical cord blood was not identified and there is no available information to associate ethylbenzene exposure with Attention deficit hyperactivity disorder (ADHD). The suggested reference (Lou et al. 1989) is not related to ethylbenzene.
	A sentence in the genotoxicity section was unclear.	The genotoxicity section in the final screening assessment is updated.
	The potential lack of qualitative and/or quantitative relevance of animal tumor findings to humans should be clearly noted. The summary sentence in the “mode of action for carcinogenicity” section should include kidney.	This section has been updated in the final screening assessment.
	Further research is needed on the source for ethylbenzene in foods.	Noted. However, food is not identified as a major source of exposure.
	The lack of developmental neurotoxicity effects in rats based on Faber et al. (2007) and Li et al. (2010) should be cited in the paragraph beginning “Other nervous system effects” on p56.	This section has been updated in the final screening assessment.
	Cited immunotoxicity references on p58 should include Li et al. (2010).	The final screening assessment is updated to include the information from the suggested reference.

	Scientific research on microplastics in fresh water ecosystems in Canada is lacking and there is not enough scientific research being done (on microplastics in fresh water ecosystems) in Canada to provide a strong local reference.	The ethylbenzene risk analysis is based on knowledge of site specific releases - including releases to surface water and groundwater. Ethylbenzene is not known to be a component of microplastics - it is used as feedstock for styrene production which is then used to manufacture various types of polymers such as polystyrene. Therefore, there is no evidence of releases of ethylbenzene from the breakdown of plastics or microplastics.
	Is the breakdown of microplastics in the environment and resulting increased levels in freshwater ecosystems being studied? In particular what is being done to study bio-accumulation of microplastics in the environment and identification of methods for their removal?	
	There appears to be a data gap for health effects linked to exposure due to leaching or migration from food packaging.	The estimate of exposure from food presented in the assessment accounts for the potential migration of ethylbenzene from food packaging since this estimate is based on the United States Food and Drug Administration Total Diet Study which includes packaged and unpackaged food. Conservative assumptions were used to determine margins of exposure. Comparison of the oral intake estimate from environmental media including food, with the critical chronic oral NOAEL, results in margins of exposure that are considered to adequately account for uncertainties in the health effects and exposure databases.
	The mouse lymphoma study conducted by Seidel et al. (2006), and described in the main body of text should be included in Appendix 9.	Appendix H (formerly Appendix 9 in the draft) in the final screening assessment is updated to include the information from the suggested reference.
	Include more information on health effects of ethylbenzene due to oral routes of exposure as this substance is found in food.	A chronic oral carcinogenicity study and a number of repeated-dose toxicity studies on experimental animals that were fed specified amounts of ethylbenzene were referenced in the screening assessment. Comparison of the oral intake estimate from environmental media including food with the highest subchronic oral NOAEL result in margins of exposure that are considered adequate to account for uncertainties in the health effects and exposure databases.

	To make important economic development decisions on which industries and extractive technologies to support, First Nations must be able to know the full extent of any environmental or health risk posed by the application or activity of EB (i.e. application as a hydraulic fracturing fluid). Occupational exposure is also a consideration in this regard.	Exposure and risk to the environment and human health from ethylbenzene when used in hydraulic fracturing fluids were not considered- specifically in the screening assessment; however, the available information indicates that levels of ethylbenzene in the environment are below levels of concern. Activities are taking place in Canada and internationally to identify substances used in hydraulic fracturing or contained in hydraulic fracturing wastewater, and to characterize releases of, and exposure of the environment to, these substances. As information evolves, future activities may be considered by Environment Canada or Health Canada. Of note, daily intakes of ethylbenzene for the Canadian general population from environmental media, including drinking water, were estimated in the Screening Assessment. The margins of exposure from these sources of exposure were found to be adequate. With respect to occupational exposure, this assessment investigates potential risks to the environment and/or to human health associated with exposures in the general environment. Hazards related to chemicals used in the workplace should be classified accordingly under the Workplace Hazardous Materials Information System (WHMIS). A conclusion under CEPA on the substances in the Chemicals Management Plan is not relevant to, nor does it preclude, an assessment against the hazard criteria for the WHMIS that are specified in the *Controlled Products Regulations* for products intended for workplace use. Canadians who may be exposed to ethylbenzene in the workplace should consult with their employer and occupational health and safety representative about safe handling practices, applicable laws and requirements under the WHMIS.
	Not enough information is provided on amount of ethylbenzene used in hydraulic fracturing and its presence in drinking water from fracking.	
	Additional information on ecosystem impacts affecting human health related to drinking water, ground water affected by hydrofracking, soils and bioaccumulation, polystyrene food packaging and child ingestion via mouthing. A precautionary risk management approach should be employed.	
Risk management	Include recommendations on how to address data gaps in risk management plans.	In the Risk Management Scope published in the *Canada Gazette* (February 8, 2014) the Government of Canada solicited input into the data gaps of greatest relevance with regards to the exposures of concern to Canadians, notably varnishes, stains, lacquers and concrete sealers. Recent industry surveys and targeted sampling of certain products of concern were undertaken in 2013- 2014 by Health Canada. The results indicated that the products identified in the draft screening assessment report have been and/or continue to be reformulated or removed from the market. The *Volatile Organic Compound (VOC) Concentration Limits for Architectural Coatings Regulations* (published on September 30, 2009 in *Canada Gazette*, Part II) appear to have contributed to these market changes.

	Homes and buildings in disrepair in First Nation communities may release increased levels of ethylbenzene. Proposed risk management should consider reducing exposures for First Nations living on reserve.	Attached garages, smoking, building materials and electronic products are identified as potential sources of ethylbenzene in indoor air and are considered in the Screening Assessment Report; emissions as a result of buildings in disrepair were not specifically identified. The estimated exposure to ethylbenzene from indoor air was considered to be conservative. Health Canada's First Nations and Inuit Health publication on Indoor Air provides specific information on indoor air contaminants (including tobacco smoke and chemical products) and provides tips for maintaining good indoor air quality and minimizing health risks (http://www.hc-sc.gc.ca/fniah-spnia/promotion/public-publique/home-maison/fn-pn/air-eng.php).
Human Exposure	When present in the atmosphere, ethylbenzene may accumulate in food. It may also accumulate in food from soils treated with biosolid /sewage sludge.	Ethylbenzene is more likely found in the atmosphere or in water. There is no indication that ethylbenzene has been detected in biosolids/sewage sludge.
	Ethylbenzene could potentially be released from mouth guards and appliances that contain this substance.	No information on migration of ethylbenzene from mouth guards was identified; exposure for children mouthing plastic objects that may contain residual levels of ethylbenzene was estimated and no risk was found to be associated with this potential source of exposure.
	Exposures in the home to accumulated ethylbenzene from photocopiers and printers should be addressed.	In Levoic et al. (1998) the photocopiers studied were for office use - to be operated in ventilated rooms. Residential photocopy machine emissions are accounted for in the Canadian indoor air monitoring data for assessing exposure from environmental media.
	Information was provided on ethylbenzene in certain paint and coating products (restricted to industrial/professional use). The few remaining consumer products that contain ethylbenzene may be reformulated.	Comment noted.
	It was agreed that the selection of indoor air concentrations used in the assessment and the use of the established Canadian Drinking Water Quality Guideline as an upper-bound estimate of daily exposure to ethylbenzene are appropriate.	Note that a new *Canadian Drinking Water Guideline* for ethylbenzene has been published since the comment period on the draft screening assessment has ended. The screening assessment has been updated accordingly.
	Aerosol paint products should not be included in the assessment as most are used outdoors and do not contain ethylbenzene in excess of existing prescribed limits and those of new regulations in the United States,	Margins of exposure for aerosol paint were found to be adequate.
Human health effects assessment	Ethylbenzene was detected in blood in 90% of the people surveyed. What are the known cumulative effects of multiple and chronic exposures on human development?	For developmental effects, the margins of exposure were considered adequate. A comparison of blood biomonitoring data from the National Health and Nutrition Examination Survey (NHANES) with chronic critical effect levels that were converted into human steady-state venous blood concentrations also resulted in adequate margins of exposure.

	Since ototoxicity is identified as a critical health effect, the assessment should note that the endpoints identifying the NOAEC of 300 ppm in Cappaert et al. (2000) were based on effects to both auditory thresholds and loss of outer hair cells (OTC) observed at 400 ppm, while the LOAEC of 200 ppm reported in Gagnaire et al. (2007) was conservatively based on a loss in OTC only (auditory thresholds were altered at 400 ppm). The likely human relevance of ethylbenzene-induced ototoxicity can be further strengthened by comparing to similar ototoxicity effects induced by styrene, a close structural analogue of ethylbenzene.	Detailed information from Cappaert et al. (2000) and Gagnaire et al. (2007) was described in Appendix H of the screening assessment. The specific effects on auditory thresholds and loss of outer hair cells were noted in the text of the screening assessment. Information on styrene was not added to the screening assessment since available information specific to ethylbenzene was considered sufficient. A summary of a recent epidemiological study, which monitored workers who had relatively specific exposure to ethylbenzene, was added to the screening assessment (Zhang et al. 2013).
	Conclusions in the draft screening assessment were supported, namely: The potential mode of action for carcinogenicity as related to human cancer risks; ototoxicity representing the most appropriate and likely human relevant endpoint for characterizing potential short term exposure risks; the uncertainty of the relevance of ethylbenzene-induced tumours on rats and mice in humans and existing mode of action and toxicokinetic data establish low qualitative and/or quantitative relevance to humans.	Comment noted.
Ecological risk characterization	The risk quotient analyses calculations appear to be for major exposure events and consider cumulative impacts. In table 13 (page 26) of the screening assessment, the risk quotient for ground water is greater than 1. It is stated as 3.5. Therefore, the possibility of adverse ecological effects may exist.	Ethylbenzene rapidly breaks down in both the aerobic and anaerobic environment and exposure normally occurs in areas close to release points – limiting routes of exposure as reflected in characterization of “worst-case” scenarios for air, water, sediment, and soil. The exception was for ground water; however, this was based on 25 year old data where a very conservative assessment factor was used. Even when conservative scenarios and assumptions were applied there was no evidence of cumulative exposure.
Human health risk characterization	The toxicological significance of the developmental LOEC of 100 ppm based on increased incidence of extra ribs in rats exposed during gestation (Hardin et al. 1981) was questionable, as the same effect was not observed in other studies where animals were exposed during pre-gestation and gestation periods.	The LOEC of 100 ppm is the lowest inhalation LOEC identified from the available developmental toxicity studies as described in Appendix H. This is a LOEC, not a LOAEC; hence, the screening assessment did not consider the effect at this level as adverse. As described in the screening assessment, collective evidence suggested minor developmental effects were observed at high dose levels and following prolonged exposure periods.
	Charest-Tardif et al. (2006) concluded that toxicokinetic saturation was likely present in mice at exposure concentrations above 500 ppm, but blood Cmax and AUC data in this study indicate that saturation may be present in the 75 and 200 ppm exposure range. Regardless, these data nonetheless suggest that ethylbenzene tumor data observed in mice only at 750 ppm in the NTP bioassay have limited if any relevance to human risk given the large margins of exposure to human general population and consumer exposures identified in the draft (Slikker et al. 2004; Carmichael et al. 2006).	Comment noted.

	Adjust the critical no observed adverse effect level (NOAEL) to a human equivalent concentration using physiologically-based pharmacokinetic (PBPK) models to consider differences in duration and frequency of experimental exposure and human exposure scenario, species differences in respiratory minute volume and pulmonary surface area, and species differences in air/blood partition coefficient.	The adjustment and/ or modelling methods used by different agencies are diverse and vary in complexity (US EPA 1991; California EPA-OEHHA 2007; ATSDR 2010). Other PBPK model adjustments to benchmark data appeared to have limited influence on assessment outcomes (California EPA-OEHHA 2007). Overall, it is considered that additional adjustment of the critical effect levels obtained from animals to a human equivalent concentration may generate other uncertainties.
Uses and releases	Other uses of ethylbenzene from pest control products, to cosmetic products to products that contain styrene should be included in the Risk Management Scope.	Use of ethylbenzene in pest control products is not included in the Screening Assessment Report as these uses are considered by the Pest Management Regulatory Agency under the *Pest Control Products Act*. Ethylbenzene exposures from cosmetics were included in the screening assessment report and were not identified as a concern.
Conclusion	The proposed conclusion that ethylbenzene in mixed xylene solvents presents a potential health risk is not supported by the Priority Substances List Assessment Report for Xylenes (Environment Canada and Health Canada. 1993) that this substance does not present a health risk.	With respect to human health, the conclusions proposed in the draft screening assessment were based on consumer products information which has since been revised based on further investigation into consumer products on the market currently. The final screening assessment no longer includes a quantitative estimate of inhalation exposure to ethylbenzene containing concrete floor sealer, since those types of products were found to be for outdoor use only. The collective information on products containing ethylbenzene also indicates that caulking type products currently on the market contain a maximum of 2% ethylbenzene; this maximum concentration was used in estimating exposure from caulking application in the final screening assessment and was found to be associated with an adequate margin of exposure. Photocopy machine emissions are accounted for in the Canadian indoor air monitoring data for assessing exposure from environmental media. Overall it was determined that margins of exposure from use of consumer products are considered adequate to account for uncertainties in the health effects and exposure databases.
	Based on internal systemic dose margin of exposure comparison, the proposed conclusion that ethylbenzene enters the environment at concentrations constituting a danger to human health should be reconsidered.	
	A decision to list ethylbenzene in Schedule 1 of the *Canadian Environmental Protection Act, 1999* (CEPA) would be supported. There should also be restrictions on levels of ethylbenzene in copier ink and caulking materials.	

	The conclusion that environmental species exposure to ethylbenzene in air, surface water, sediment, and soil ‘probably do not exceed concentrations associated with effects’ is appropriate given the low risk quotient values obtained from most exposure scenarios.	