

Screening Assessment for the Challenge

***n*-Hexane**

**Chemical Abstracts Service Registry Number
110-54-3**

**Environment Canada
Health Canada**

August 2009

Synopsis

Pursuant to section 74 of the Canadian Environmental Protection Act, 1999 (CEPA 1999), the Ministers of the Environment and of Health have conducted a screening assessment of *n*-hexane, Chemical Abstracts Service Registry Number 110-54-3. This substance was identified in the categorization of the Domestic Substances List as a high priority for action under the Challenge, as it was considered to pose greatest potential for exposure to individuals in Canada and had been classified by the European Commission on the basis of reproductive toxicity. The substance did not meet the ecological categorization criteria for persistence or bioaccumulation potential. Therefore, the focus of this assessment of *n*-hexane relates to human health risks.

n-Hexane is a naturally occurring component of crude oil and natural gas and is present in refined petroleum products such as motor fuels. According to data submitted in CEPA 1999 section 71 responses, over 5 billion kilograms of *n*-hexane were manufactured and 10–100 million kilograms of *n*-hexane were imported into Canada in 2006. Although the section 71 survey did not apply to activities of *n*-hexane in fuel, both reported quantities included activities related to fuel.

The physical and chemical properties of *n*-hexane make this substance ideal for many uses and applications. It is used as a solvent, a formulation component, a chemical intermediate, a processing aid, and a dispersant in various chemical processes. Another major use of *n*-hexane besides its use in petroleum is in food processing as a solvent for extraction of vegetable oils. A wide variety of products known to contain *n*-hexane in Canada include adhesives, sealants, binders, fillers, lubricants, paints and coatings, rubber and rubber cements, brake cleaners, and degreasers.

n-Hexane has been measured in ambient and indoor air in Canada and the major route of exposure to *n*-hexane by the general population of Canada is expected to be inhalation. Exposure from other media (drinking water, soil) and food was estimated to not contribute significantly to total exposures.

Products containing *n*-hexane are used primarily for professional purposes and exposure to *n*-hexane by the general population from these sources is expected to be minimal and infrequent.

The critical effect level for repeated-dose toxicity via inhalation was based not only on nervous system effects in a 24-week rat inhalation study but also on increased number of resorptions in a mouse developmental toxicity study. The margin of exposure between the critical effect level for inhalation and the upper-bounding exposure estimate for *n*-hexane is considered to be adequately protective.

The critical effect level for repeated-dose toxicity via the oral route was based on adverse effects in heart muscle and related parameters in a 30-day rat study. Comparison of the critical effect level for repeated dose effects via the oral route and the upper-bounding

estimate of daily intake of *n*-hexane by the general population in Canada, yields a margin of exposure that is considered to be adequately protective.

Based on the available information on its potential to cause harm to human health and the resulting margins of exposure for repeated-dose effects, it is concluded that *n*-hexane is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

On the basis of ecological hazard and reported releases of *n*-hexane, it is concluded that this substance is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends. *n*-Hexane does not meet the criteria for persistence or bioaccumulation as set out in the Persistence and Bioaccumulation Regulations.

This substance will be included in the upcoming *Domestic Substances List* inventory update initiative. In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment.

Based on the information available, it is concluded that *n*-hexane does not meet any of the criteria set out in section 64 of CEPA 1999.

Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or human health. Based on the results of a screening assessment, the Ministers can propose to take no further action with respect to the substance, to add the substance to the Priority Substances List (PSL) for further assessment, or to recommend that the substance be added to the List of Toxic Substances in Schedule 1 of the Act and, where applicable, the implementation of virtual elimination.

Based on the information obtained through the categorization process, the Ministers identified a number of substances as high priorities for action. These include substances that

- met all of the ecological categorization criteria, including persistence (P), bioaccumulation potential (B) and inherent toxicity to aquatic organisms (iT), and were believed to be in commerce; and/or
- met the categorization criteria for greatest potential for exposure (GPE) or presented an intermediate potential for exposure (IPE), and had been identified as posing a high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

The Ministers therefore published a notice of intent in the *Canada Gazette*, Part I, on December 9, 2006 (Canada 2006), that challenged industry and other interested stakeholders to submit, within specified timelines, specific information that may be used to inform risk assessment, and to develop and benchmark best practices for the risk management and product stewardship of those substances identified as high priorities.

The substance *n*-hexane was identified as a high priority for assessment of human health risk because it was considered to present GPE and had been classified by another agency on the basis of reproductive toxicity.

The Challenge for *n*-hexane was published in the *Canada Gazette* on November 17, 2007 (Canada 2007). A substance profile was released at the same time. The substance profile presented the technical information available prior to December 2005 that formed the basis for categorization of this substance. As a result of the Challenge, submissions of information were received.

Although *n*-hexane was determined to be a high priority for assessment with respect to human health, it did not meet the ecological criteria for potential for persistence or bioaccumulation potential. Therefore, this assessment focuses principally on information relevant to the evaluation of risks to human health.

Under CEPA 1999, screening assessments focus on information critical to determining whether a substance meets the criteria for defining a chemical as toxic as set out in section 64 of the Act, where

- “64. [...] a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that
- (a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
 - (b) constitute or may constitute a danger to the environment on which life depends; or
 - (c) constitute or may constitute a danger in Canada to human life or health.”

Screening assessments examine scientific information and develop conclusions by incorporating a weight of evidence approach and precaution.

This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents, stakeholder research reports and from recent literature searches, up to August 2008. Key studies were critically evaluated; modelling results may have been used to reach conclusions. Evaluation of risk to human health involves consideration of data relevant to estimation of exposure (non-occupational) of the general population, as well as information on health hazards (based principally on the weight of evidence assessments of other agencies that were used for prioritization of the substance). Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The screening assessment does not represent an exhaustive or critical review of all available data. Rather, it presents a summary of the critical information upon which the conclusion is based.

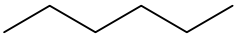
This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. The human health portions of this assessment have undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from scientific experts selected and directed by Toxicology Excellence for Risk Assessment (TERA), including Susan Griffin (US EPA), Donna Vorhees (Science Collaborative – North Shore), and Joan Strawson (TERA). The ecological portions of the assessment have also undergone external written peer review/consultation. Additionally, the draft of this assessment was subject to a 60-day public comment period. Although external comments were taken into consideration, the final content and outcome of the screening risk assessment remain the responsibility of Health Canada and Environment Canada. The critical information and considerations upon which the assessment is based are summarized below.

Substance Identity

n-Hexane is a straight-chain saturated aliphatic hydrocarbon with 6 carbon atoms with the molecular formula of C₆H₁₄. At standard temperature and pressure, it is a colourless flammable liquid with high volatility and gasoline-like odour (IPCS 1991, NIOSH 1994, O'Neil 2001). It is poorly soluble in water but soluble in most organic solvents (IPCS 1991, NIOSH 1977). It can be easily analyzed by gas chromatography coupled with flame ionization detection or mass spectrometry¹ (IPCS 1991).

Basic information on the identity of *n*-hexane is summarized in Table 1.

Table 1. Substance Identity of n-Hexane

Chemical Abstracts Service Registry Number (CAS RN)	110-54-3
Name on Domestic Substances List (DSL)	Hexane
Inventory names²	Hexane (TSCA, EINECS, ENCS, AICS, SWISS, PICCS, ASIA-PAC, NZIoC); <i>n</i> -Hexane (ECL, PICCS)
Other names	Hexyl hydride; NSC 68472; Skellysolve B; UN 1208
Chemical group (DSL Stream)	Discrete organics
Major chemical class or use	Aliphatic hydrocarbon
Major chemical sub-class	Volatile organic compound
Chemical formula	C ₆ H ₁₄
Chemical structure	
SMILES²	CCCCC
Molecular mass	86.18 g/mol

¹ National Chemical Inventories (NCI). 2007: AICS (Australian Inventory of Chemical Substances); ASIA-PAC (Asia-Pacific Substances Lists); ECL (Korean Existing Chemicals List); EINECS (European Inventory of Existing Commercial Chemical Substances); ENCS (Japanese Existing and New Chemical Substances); PICCS (Philippine Inventory of Chemicals and Chemical Substances); TSCA (US EPA Toxic Substances Control Act Inventory); SWISS (Swiss Giftliste 1 and Inventory of Notified New Substances); NZIoC (New Zealand Inventory of Chemicals).

² Simplified Molecular Input Line Entry System

For the purpose of this assessment, the substance is referred to as *n*-hexane (rather than its DSL name “hexane”) throughout this report in order to avoid potential ambiguity associated with the term “hexane” which may commonly refer to both *n*-hexane and

¹ Although IPCS (1991) refers to the analysis as “mass spectroscopy”, the original articles (Tsuruta 1980; DiVincenzo et al 1976) describe it as “mass spectrometry”.

hexanes. While *n*-hexane is a substance of specific molecular structure, hexanes contain *n*-hexane and other hexane isomers, which are branched hydrocarbons of the same molecular formula (C_6H_{14}), namely, 2-methylpentane (isohexane), 3-methylpentane, 2,2-dimethylbutane, and 2,3-dimethylbutane.

In a laboratory or under a research setting, *n*-hexane with high purity (also commonly referred to as analytical grade hexane) is used as a solvent or a reagent, and may contain from 0.5 to 5% of other hexane isomers (Baker and Rickert 1981, IPCS 1991, Sandmeyer 1981). It may also contain other less volatile impurities, such as benzene, which has been detected at a trace level of 0.05% (Baker and Rickert 1981). Technical grade hexane has a lesser purity and consists of approximately 50% *n*-hexane and 50% isohexane and cyclohexane, and contains impurities such as benzene (0.001%) and other aromatics (0.01%) (Verschuere 2001).

Commercial hexane, on the other hand, may refer to a wide range of solvent mixtures that consist of hexane isomers including *n*-hexane and related 6-carbon compounds (such as cyclohexane and methyl cyclopentane), and possibly small quantities of C_5 and C_7 hydrocarbons (Eastman and Mears 2000). Concentration of *n*-hexane in commercial hexane may range anywhere from 20 to 80% (IPCS 1991). Low levels of pentane and heptane isomers, acetone, methyl ethyl ketone, dichloromethane, and trichloroethylene may also be included, as well as other less volatile impurities, up to 0.04 % (IPCS 1991).

While commercial hexane is expected to be most commonly used in industrial or commercial settings, this assessment was conducted specifically on *n*-hexane (CAS RN 110-54-3). In cases where this assessment is to be extended to address hexanes as well as other organic solvents, significant consideration should be given to the specific situation of its use.

Physical and Chemical Properties

Table 2 summarizes key physical and chemical properties of *n*-hexane, which are of importance to this report. All values are experimental unless specified as modelled, such as in cases where experimental values were not available.

Table 2. Physical and Chemical Properties for *n*-Hexane

Property	Value	Reference
Melting point (°C)	-95.3	Lide 1997
	-94.3	Verschuere 2001
Boiling point (°C)	68.7	Lide 1997; Verschuere 2001
Density (kg/m ³)	0.66 @ 25°C	Lide 1997
Vapour pressure (kPa)	20.2 @ 25°C	PhysProp 2007
	20.4 @ 25°C	Daubert 1989

Property	Value	Reference
	16.0 @ 20°C	Verschuereen 2001
	25.3 @ 30°C	
Henry's Law constant (Pa·m³/mol)	1.82×10 ⁵	HENRYWIN 2000
Log K_{ow} (Octanol-water partition coefficient)	3.90	Hansch et al. 1995
Log K_{oc} (Organic carbon-water partition coefficient)	2.17 (modelled)	PCKOCWIN 2000
Water solubility (mg/L)	9.5 @ 25°C	McAuliffe 1966
	9.5 – 13 (distilled water) @ 20°C	Verschuereen 2001
	75.5 (salt water) @ 20°C	
Other solubilities	Very soluble in ethanol, ethyl ether and chloroform	Lide 1997
	Soluble in alcohol, acetone and ether	Lewis 1997
	Miscible with alcohol, chloroform, and ether	O'Neil 2001

Sources

n-Hexane is a highly volatile, naturally occurring component of the paraffin (also referred to as alkane or aliphatic) fraction of crude oil and natural gas. It is a constituent of heating and motor fuels refined from petroleum produced from crude oil and natural gas (ASTDR 1999). *n*-Hexane has been identified as a High Production Volume (HPV) chemical by OECD (OECD 2004) and the United States (US EPA 1990).

According to the responses to the section 71 survey of CEPA 1999 received before May 22, 2009, over five billion kilograms (5 x 10⁹ kg) or 5 million tonnes of *n*-hexane were manufactured in Canada in 2006 (Environment Canada 2007b). The total quantity imported into Canada in the same calendar year was reported to be in the range of 10 – 100 million kilograms (Environment Canada 2007b). This survey did not apply to any person who manufactured, imported, or used hexane in fuel, however, a significant portion of the submissions reported activities related to fuels (Environment Canada 2007b).

According to Statistics Canada, total crude oil and equivalent petroleum products in Canada in 2006 amounted to 104 million cubic meters (104 x 10⁶ m³), out of which 98 million cubic meters (98 x 10⁶ m³) belonged to light and heavy crude oil (Statistics Canada 2006). Crude bitumen and other condensates accounted for the remaining amount. Hexanes have been reported to comprise 1.3 – 10.74% in light and 1.09 – 7.91% in heavy crude oils with mean compositions of 4.87% and 4.11% by volume, respectively (Crude Quality 2009a,b). Applying the maximum hexane composition of 10.74%, the maximum possible quantity of *n*-hexane in crude oil in Canada in 2006 can be estimated to be 10.5 x 10⁶ m³ or approximately 6 900 tonnes.

The net production of petroleum products from refinery production of crude oil and equivalents in 2006 was reported to be $120 \times 10^6 \text{ m}^3$, of which $42 \times 10^6 \text{ m}^3$ is comprised of motor gasoline (Statistic Canada 2006). In Canada, the maximum concentration of *n*-hexane in gasoline is found to be 5% with an average concentration of 2.69% (Personal communication from Risk Management Bureau, Health Canada to Risk Assessment Bureau, Health Canada, dated 2008-10-09; unreferenced). Based on the net production volume of motor gasoline in Canada in 2006 ($42 \times 10^6 \text{ m}^3$), the maximum amount of *n*-hexane in motor gasoline in the specified year can then be estimated to be $2.1 \times 10^6 \text{ m}^3$ or $1.4 \times 10^6 \text{ kg}$.

Commercial hexane is manufactured via two-tower distillation of a suitable hydrocarbon feedstock, which may be straight-run gasoline distilled from crude oil or natural gas liquids. It can also be obtained from the remains of catalytic reformates after the removal of aromatic compounds. *n*-Hexane can be purified from hexane mixtures using molecular sieves (IPCS 1991).

Other minor sources of *n*-hexane have been recognized as biogenic production by fungi in ducts and insulation materials in homes and office buildings (Ahearn et al. 1996), marine phytoplankton (McKay et al. 1996), and terrestrial plants (Rinnan et al. 2005).

Uses

A major global use of *n*-hexane is as a component in fuels and other petroleum products (NLM 2005). Although use of *n*-hexane in fuels was exempted from section 71 data collection under CEPA 1999, a significant portion of the submissions reported activities related to fuels (Environment Canada 2007b). End-use fuels such as motor vehicle gasoline and liquefied petroleum gas formulated with *n*-hexane is not a primary focus of this assessment. It will be addressed separately under the petroleum Sector Stream Approach of the Chemicals Management Plan.

High solubility of *n*-hexane in oil, its low boiling point and narrow boiling point range, and relatively low cost make this substance ideal for many applications besides its use in petroleum products (Eastman and Mears 2000).

Food processing is another major global application of *n*-hexane, where it is used as a solvent for extraction of vegetable oils from various seeds and crops (ATSDR 1999, Mears and Eastman 2005, O'Neil 2001, ICPS 1991). It is also used in the production of defatted products such as defatted soy flour (ATSDR 1999; IPCS 1991) and food grade silicone (Jet-Lube of Canada Ltd. 2007).

In Canada, hexane is listed as a food additive permitted for use as a carrier or extraction solvent (Canada 1978). The permitted maximum residue limits of hexane in food are; 10 parts per million (ppm) in vegetable fats, oils, and oil seed meals, 25 ppm in spice extracts or natural extractives, 2.2% in the solvent used for hop extract, and 1.5 ppm in

pre-isomerized hop extract (Canada 1978). The *Controlled Products Regulations* established under the *Hazardous Products Act* requires *n*-hexane to be disclosed on the Material Safety Data Sheet that must accompany workplace chemicals when it is present at a concentration of 1% or greater as specified on the Ingredient Disclosure List (Canada 1988a,b).

n-Hexane is also used as a defoaming agent and/or a raw material in the manufacturing of polyolefins, elastomers, synthetic rubbers and some pharmaceuticals (Mears and Eastman 2005, NLM 2005, IPCS 1991). In Canada, *n*-hexane has been used as a defoaming agent in the manufacture of coating and adhesives for polyolefin films and polystyrene resins. Solvent residues may be found in the formulations of coating and adhesives used in food packaging at ppm levels. Another food related use of *n*-hexane is as a propellant for aerosols in the formulation of lubricants and cleaners. Lubricants have no direct food contact and cleaners are used then followed by a water rinse after the treatment to remove any residues. Considering its physical and chemical properties and its use under well-ventilated conditions in food plants, none of the uses are expected to cause any indirect exposure to *n*-hexane from food (Personal communication from Food Packaging Materials and Incidental Additives Sections, Health Canada to Risk Assessment Bureau, Health Canada, dated 2008-08-11; unreferenced).

Other uses of *n*-hexane in Canada include as a solvent, a formulation component, a chemical intermediate, a processing aid, and a dispersant in various chemical processing (Environment Canada 2007b). A wide range of its uses lead to a variety of end products including adhesives, sealants, binders, fillers, lubricants, paints and coatings, rubber and rubber cements, break cleaners, and degreasers, all of which are recognized globally (ATSDR 1999, IPCS 1991, Mears and Eastman 2005, NLM 2005). *n*-Hexane is also a common laboratory reagent and solvent (Environment Canada 2007b).

Cosmetic products which were notified to Health Canada to contain *n*-hexane include manicure preparation products (one polish thinner, one resin activator, and one speed cure), one skin moisturizer, and one animal hair styling aerosol product (CNS 2008).

n-Hexane is also found as a component of mineral spirits in 15 insecticide products at a concentration of less than 0.1% (Personal communication from Pest Management Regulatory Agency, Health Canada to Risk Assessment Bureau, Health Canada, dated 2008-09-22; unreferenced).

n-Hexane is widely used in the manufacture of veterinary medicinal ingredients (active ingredients) as well as some veterinary drugs as marketed products. It is not used as a medicinal or non-medicinal ingredient. All marketed products are required to meet international standards for residual solvents to be authorized for sale in Canada and the maximum residual limit for *n*-hexane is 290 ppm (Personal communication from Veterinary Drugs Directorate, Health Canada to Risk Assessment Bureau, Health Canada, dated 2008-08-22; unreferenced).

Releases to the Environment

Information reported under section 71 of CEPA 1999 indicated that the total release of *n*-hexane to the environment in 2006 was 1 000 – 5 000 tonnes (1 – 5 million kilograms), of which the majority was released to the atmospheric compartment at approximately 99.7% of the total quantity of reported releases. Only 0.25% and 0.05% releases were reported to water and to land, respectively (Environment Canada 2007b). The environmental releases reported under the National Pollutant Release Inventory (NPRI) indicated 4 438 tonnes (4.438 million kilograms) of *n*-hexane were released to air, while releases of 0.855 tonnes to water and 1.2 tonnes to land were reported in 2006 (NPRI 2008).

The majority of *n*-hexane release to the environment is considered through the manufacture, use, and disposal of various products associated with the petroleum industry (Bingham et al. 2001). Indeed the summary of top 50 industries' reported emissions under NPRI 2006 indicated that the petroleum sector comprised 68% of the total number of reporting facilities in Canada. In terms of released quantity to air, petroleum and agricultural-food sectors comprised approximately 80% of the total release quantity to air, followed by the rubber and chemical manufacturing sector and the textile sector.

As a component of petroleum products, the release of *n*-hexane to environmental media by the use of heating and motor fuels is expected to contribute to the total ambient air concentration where most of the demand for gasoline involves transportation. While in most cases *n*-hexane in gasoline is consumed during its combustion in engines, gasoline use and handling could result in emissions during refuelling, evaporation during storage, and exhaust releases when there is incomplete combustion of fuels (US EPA 1994).

Environmental Fate

The physical and chemical properties of *n*-hexane summarized in Table 2 indicate its high volatility (boiling point of 68.7°C and vapour pressure of 16.0 – 25.3 kPa) and relatively low adsorptivity to soil or sediment (log K_{oc} of 2.17). The results of the Level III Equilibrium Criterion model are summarized in Table 3, suggesting that *n*-hexane will predominantly reside in air and water, depending on the compartment of release.

Table 3. Results of the Level III Equilibrium Criterion model (EQC 2003)

100% of <i>n</i> -hexane released to:	Percentage of <i>n</i> -hexane partitioning into each compartment			
	Air	Water	Soil	Sediment
Air	100	0	0	0
Water	8.9	89.6	0	1.5
Soil	75.8	0	24.2	0

If released to water, *n*-hexane is not expected to adsorb to suspended solids and sediment based upon the estimated log K_{oc}. Volatilization from water surfaces is expected to be an

important fate process based on the estimated Henry's Law constant and limited water solubility. The solubility of *n*-hexane in water is increased by the presence of methanol (Groves 1988).

If released to soil at depth, *n*-hexane is expected to have a relatively high mobility based on the estimated Koc value of 150. Volatilization from moist soil surfaces is expected to be an important fate process based on the estimated Henry's Law constant (1.82×10^5 Pa·m³/mol) and low water solubility. *n*-Hexane may volatilize from dry soil surfaces as well due to its high vapour pressure. *n*-Hexane will undergo biodegradation in soil and water but volatilization is expected to be the predominant process in the environment (Solano-Serena et al. 2000).

Persistence and Bioaccumulation Potential

Environmental Persistence

Given the information on potential releases of *n*-hexane to the environment and partitioning information described previously, the environmental compartments of concern are air and water. Once released into the environment, *n*-hexane appears to be degraded fairly rapidly in the environment (Tables 4a and 4b).

Table 4a. Empirical data for persistence of n-hexane

Medium	Fate process	Degradation value	Endpoint (units)	Reference
Air	Atmospheric oxidation	1.91	Half-life (days)	Atkinson 1989
Water	Biodegradation	100	Ready Biodegradation (%)	NITE 2002

In the atmosphere, the main degradation pathway of vapour-phase *n*-hexane is by reaction with photochemically-produced hydroxyl radicals. The experimental reaction rate of 5.61×10^{-12} cm³/mol·sec (Atkinson 1989) equates to a half-life of 1.91 days, assuming first order kinetics, a 12 hour day, and the hydroxyl radical concentration of 1.5×10^6 OH radicals/cm³ (Table 4a). Empirical data for biodegradation in water indicated 100% biodegradation over 28 days in a ready-biodegradation test for *n*-hexane (NITE 2002), leading to the half-life of *n*-hexane in water of much less than 182 days.

Despite its relatively short half-life (1.9 days) for photooxidation (Tables 4a and 4b), atmospheric *n*-hexane is one of the least photochemically reactive hydrocarbons (Katagiri and Ohashi 1975). While similar hydrocarbons such as *n*-pentane and methyl pentane undergo photochemical conversion to smog containing peroxyacetyl nitrate and ozone, *n*-hexane is not expected to have a pronounced effect on the physical properties of the atmosphere, to participate in the depletion of the ozone layer, or to alter precipitation patterns (CIIT 1977).

Because few experimental data on the degradation of *n*-hexane are available, a QSAR-based weight-of-evidence approach (Environment Canada 2007a) was applied using the degradation models shown in Table 4b. The modelled data support the conclusions based on empirical data as they predict this substance to degrade relatively fast in air and water.

Table 4b: Modelled data for degradation of *n*-hexane

Fate process	Model and model basis	Model result and prediction	Extrapolated half-life (days)
AIR			
Atmospheric oxidation	AOPWIN 2000	$t_{1/2} = 1.9$ days degrades fast	< 2
Ozone reaction	AOPWIN 2000	n/a ¹	n/a
WATER			
Hydrolysis	HYDROWIN 2000	n/a ¹	n/a
Biodegradation (aerobic)	BIOWIN 2000 ² Sub-model 3: Expert Survey (ultimate biodegradation)	3.31 ³ Ultimate degradation in weeks	< 182 ⁵
Biodegradation (aerobic)	BIOWIN 2000 ² Sub-model 4: Expert Survey (primary biodegradation)	3.99 ³ Primary degradation in days	< 182 ⁵
Biodegradation (aerobic)	BIOWIN 2000 ² Sub-model 5: MITI linear probability	0.65 ⁴ biodegrades rapidly	< 182 ⁵
Biodegradation (aerobic)	BIOWIN 2000 ² Sub-model 6: MITI non-linear probability	0.86 ⁴ biodegrades rapidly	< 182 ⁵
Biodegradation (aerobic)	TOPKAT 2004 Probability	0.98 ⁴ Biodegrades rapidly	< 182 ⁵
Biodegradation (aerobic)	CATABOL 2004-2008 % BOD (biological oxygen demand)	% BOD = 98 biodegrades rapidly	< 182 ⁵

¹ n/a: not available. Model does not provide an estimate for this type of compound.

² Calculated using EPIsuite (2007).

³ Output is a numerical score.

⁴ Output is a probability score.

⁵ Expected half-lives for BIOWIN, TOPKAT and CATABOL models are determined based on Environment Canada (2009a).

The results in Table 4b indicate that all the aerobic degradation models (BIOWIN 3, 4,5,6, TOPKAT and CATABOL) suggest this substance biodegrades rapidly. Moreover, the probability model results are greater than 0.5, the cut-off suggested by Aronson et al. (2006) that identifies substances as having “fast” biodegradation (based on the MITI probability models). The overall conclusion from BIOWIN is “ready biodegradable”, however, this substance may not degrade rapidly under anaerobic conditions.

Other ultimate degradation models, CATABOL and TOPKAT, suggest that *n*-hexane undergoes mineralization in a 28 day time frame with a predicted high probability or high extent of biodegradation. TOPKAT, which simulates the MITI 28 day biodegradation test, produced a probability of 0.98 which is higher than the suggested threshold for non-persistent substances in this model (> 0.7) (TOPKAT 2004). CATABOL predicted 98%

biodegradation based on the OECD 301 ready biodegradation test (%BOD), which has been suggested to indicate “not persistent” (Aronson and Howard 1999) with a half-life in water of < 182 days. Assuming a first order rate kinetics, the calculated half-life from CATABOL is 5 days. *n*-Hexane was considered to be within the model domain of CATABOL, and the estimated reliability was high at 1.0.

Considering the results of the BIOWIN probability models as well as its overall conclusion and the results of the other ultimate degradation models, there is a strong consensus suggesting that the biodegradation half-life in water is < 182 days. This conclusion supports the empirical data while being consistent with its physical and chemical properties of this substance.

Using an extrapolation ratio of 1:1:4 for a water:soil:sediment biodegradation half-life (Boethling et al. 1995), the half-life in soil is also < 182 days and the half-life in sediment is < 365 days. This indicates that *n*-hexane is not expected to be persistent in soil and sediment.

Based on the empirical and modelled data described above (Tables 4a and 4b), *n*-hexane does not meet any of the persistence criteria (half-life in air ≥ 2 days, half-lives in soil and water ≥ 182 days, and half-life in sediment ≥ 365 days) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential for Bioaccumulation

The experimental log K_{ow} value for *n*-hexane suggests that this chemical has a low potential to bioaccumulate in the environment (Table 2). Since no experimental bioaccumulation factor (BAF) or bioconcentration factor (BCF) data for *n*-hexane were available, a predictive approach was applied using available BAF and BCF models as shown in Table 5 below.

Table 5. Fish BAF and BCF predictions for *n*-hexane

Test Organism	Endpoint	Value wet weight (L/kg)	Reference
Fish	BAF	575	Gobas BAF/BCF Middle Trophic Level (Arnot and Gobas 2003) ($k_M = 0$)
		407	
Fish	BCF	302	CPOPs 2008 without mitigating factors ¹
		51.2	CPOPs 2008 with mitigating factors ¹
		201	BCFWIN 2000

¹ Mitigating factors are calculated based on structure and include water solubility, metabolism, maximum cross-sectional diameter of the molecule, and the presence of phenolic or acidic groups.

The modified Gobas BAF middle trophic-level model for fish predicted a BAF of 575 L/kg, without consideration of biotransformation, indicating that *n*-hexane does not have the potential to bioconcentrate nor biomagnify in the environment. The results of BCF

model calculations provide additional evidence supporting the low bioconcentration potential of this substance.

In addition, experimental bioconcentration data were available for two analogous substances, cyclohexane (CAS RN 110-82-7) and octane (CAS RN 540-84-1), through the Japanese National Institute of Technology and Evaluation database (NITE 2002). These substances are reported to have maximum BCF values of 129 and 540, respectively.

Based on the available empirical and kinetic-based modelled values and BCF data for analogous substances, *n*-hexane does not meet the bioaccumulation criterion (BCF or BAF $\geq$ 5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Potential to Cause Ecological Harm

As described previously, *n*-hexane has short half-lives in all environmental compartments. It is also expected to have a low bioaccumulation potential.

A - In the Aquatic Compartment

There is modelled and experimental evidence that *n*-hexane causes harm to aquatic organisms at low to moderate concentrations. These data are summarized in tables 6a and 6b.

A study conducted for the Dutch Government investigated the toxicity of numerous substances that are transported by ship in order to categorize their potential hazard to the environment (TNO 1987). Three species were involved in the testing: *Chaetogammarus marinus*, *Mysidopsis bahia*, and *Daphnia magna*. Test solutions were prepared by adding an amount in excess of the water solubility, stirring for 24 hours and allowing separation for an additional 24 hours. Tests were conducted in closed glass vessels and the test medium was replaced every 24 hours. Concentrations were measured by gas chromatography. Results show borderline high toxicity to the saltwater invertebrate species *C. marinus* and *M. bahia*.

Table 6a. Empirical data for aquatic toxicity of n-hexane

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
<i>Artemia salina</i> ¹	Acute (24 hours)	EC ₅₀ ²	1.51	Foster and Tullis 1985
<i>Chaetogammarus auratus</i> (Goldfish)		LC ₅₀ ³	4	Verschueren 2001
<i>Brachionus calyciflorus</i>			68 ⁴	Snell et al 1991a
<i>Brachionus plicatilis</i> ¹			154 ⁵	Snell et al 1991b
<i>D. magna</i>	Acute (48 hours)	LC ₅₀	2.1	TNO 1987
<i>C. marinus</i> ¹	Acute (96 hours)	LC ₅₀	0.4	
<i>M. bahia</i> ¹			0.4 ⁶	
<i>Pimephales promelas</i>			2.5	Geiger et al. 1990
<i>Tilapia mossambica</i>			113 ⁴	Ghatak et al. 1988
<i>Chironomidae</i>			595 ⁴	Panigrahi and Konar 1989
<i>Cyclops viridis</i>			732.5 ⁴	
<i>Melanoides tuberculata</i>			1900 ⁴	
<i>Branchiura sowerbyi</i>			3286.5 ⁴	Ghatak et al. 1988

¹ Saltwater organism.² EC₅₀ – The concentration of a substance that is estimated to cause some toxic sublethal effect on 50% of the test organisms.³ LC₅₀ – The concentration of a substance that is estimated to be lethal to 50% of the test organisms.⁴ Above the substance's reported water solubility of approximately 10 mg/L in distilled water (Table 2).⁵ Above the substance's reported water solubility of approximately 75 mg/L in salt water (Table 2).⁶ Categorization pivotal iT value.

In addition, from the U.S. EPA ecotoxicology database (ECOTOX 2007) nine studies are available that report median acute aquatic toxicity to fish and invertebrates due to exposures ranging from 1 to 4 days. The range of reported median values is from 1.5 to approximately 3300 mg/L.

A range of aquatic toxicity predictions were also obtained from the various QSAR models considered. Table 6b lists those predictions that were considered reliable and that were used in the QSAR weight-of-evidence approach for aquatic toxicity (Environment Canada 2007a).

Table 6b. Modelled data for aquatic toxicity of *n*-hexane

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
Fish	Acute (96 hours)	LC ₅₀ ¹	5.3	TOPKAT 2004
			1.05 ³	ECOSAR 2004
			1.6	ASTER 1999
			10.6	AIES 2003-2005
			20.4 ⁴	CPOPs 2008
Invertebrate	Acute (48-96 hours)	LC ₅₀	0.08 ³	ECOSAR 2004
			1.28 ³	ECOSAR 2004
		EC ₅₀ ²	208.8 ⁴	TOPKAT 2004
			12.4	CPOPs 2008
	Chronic (16 days)	EC ₅₀	0.15 ³	ECOSAR 2004
Algae	Acute (96 hours)	EC ₅₀	0.89 ³	ECOSAR 2004

¹ LC₅₀ – The concentration of a substance that is estimated to be lethal to 50% of the test organisms.

² EC₅₀ – The concentration of a substance that is estimated to cause some toxic sublethal effect on 50% of the test organisms.

³ Estimates influenced by experimental log K_{ow} used in ECOSAR.

⁴ Estimates may be above the approximate water solubilities for distilled water (10 mg/L) or salt water (75 mg/L)(Table 2).

These results indicate that *n*-hexane is, in general, moderately hazardous to aquatic organisms (i.e., acute LC₅₀ or EC₅₀ values were mostly > 1.0 mg/L and < 100 mg/L), though it potentially could be highly toxic to some taxa (e.g., two acute values were < 1.0 mg/L).

Available empirical data indicate that *n*-hexane could cause harm to sensitive aquatic organisms at relatively low concentrations in water. The modelled results support the empirical data, indicating high to moderate toxicity to aquatic organisms.

B - In Other Environmental Compartments

n-Hexane is not acutely toxic to mammalian species. The 4 hour acute inhalation toxicity to mice has been reported at 48,000 ppm (169,000 mg/m³) (O'Neil 2001). Similarly, the rat oral LD₅₀ has been reported as 28,710 mg/kg (Lewis 1996).

Ecological Exposure Assessment

n-Hexane is naturally produced in the environment, but is also manufactured, imported and used in large volumes in Canada (i.e., millions of kilograms per year). The many activities reported in Canada during the calendar year 1986 for the DSL and the section 71 survey (Environment Canada 2007b) for 2006 show that uses of this substance in Canada are widespread. The NPRI listed more than 300 facilities that reported releases of *n*-hexane to the environment in 2006 (NPRI 2008). Submissions were also received as a result of the section 71 survey of CEPA 1999, which included reported releases to the environment (Environment Canada 2007b).

Given the data submitted under section 71 of CEPA 1999 (Environment Canada 2007b) and the NPRI release data (NPRI 2008), *n*-hexane is expected to be introduced to the environment in Canada mostly through point and disperse atmospheric emissions. Environment Canada's National Air Pollution Surveillance (NAPS) network (NAPS 2000 - 2008) has recorded *n*-hexane concentrations in the atmosphere. In more than 20 000 measurements taken across the country for the years 2000-2008, *n*-hexane concentrations did not exceed $282 \mu\text{g}/\text{m}^3$ (0.08 ppm).

n-Hexane has been detected, but not quantified, in Lake Erie and Lake Ontario (GLWQB 1983) and in drinking water in the United States (Kool et al. 1982). Water samples taken from the Gulf of Mexico contained *n*-hexane at an average concentration of 4.6 ng/L (Sauer et al. 1978). No more recent monitoring data pertaining to the presence of this substance in Canadian surface waters have been identified.

Since a proportion of *n*-hexane may be released to water, a generic scenario was used to estimate a realistic worst case concentration of *n*-hexane resulting from an industrial discharge using Environment Canada's Industrial Generic Exposure Tool – Aquatic (IGETA). A facility located in Montréal, Québec, reported the release of less than 1 tonne to the aquatic environment and accounted for the majority of the reported releases to water. Therefore, the release of 1 tonne of *n*-hexane was assumed, spread over 250 days per year and with approximately 20% removal during sewage treatment. This scenario (involving application of a ten-fold dilution factor to the estimated concentration in sewage treatment plant effluent) provides a conservative predicted environmental concentration (PEC) of 0.0001 mg/L. Details regarding the inputs used to estimate this concentration and the output of the model are described in Environment Canada (2009b).

Characterization of Ecological Risk

The approach taken in this ecological screening assessment was to examine available scientific information and develop conclusions based on a weight-of-evidence approach and precaution as required under CEPA 1999.

A risk quotient (RQ) analysis, integrating potential exposures with potential adverse ecological effects, was performed for aquatic ecosystems. A conservative predicted no-effect concentration (PNEC) was derived by selecting the lowest experimental toxicity value (see Table 6a), and dividing it by a conservative application factor of 100. The use of this application factor is to account for the uncertainties associated with potential differences in species sensitivities and to extrapolate from a laboratory-based measure of acute effects to a predicted chronic no-effect concentration in the field. The PNEC calculated for *n*-hexane was 0.004 mg/L based on tests with the invertebrate species *C. marinus* and *M. bahia*. A conservative scenario of industrial releases to water estimates that the resulting risk quotient (PEC/PNEC) for *n*-hexane is 0.03. In addition, the measured atmospheric concentrations are many orders of magnitude below levels reported to cause acute toxicity in mice via inhalation.

Based on the information available, *n*-hexane is unlikely to be causing ecological harm in Canada.

Uncertainties in Evaluation of Ecological Risk

For *n*-hexane, there were a limited number of experimental data for degradation, and no experimental data for bioaccumulation identified during this evaluation. Estimation of these properties relied primarily on QSARs. While there are uncertainties associated with the use of QSAR models to estimate chemical and biological characteristics, approaches used provided for meaningful interpretation of the information and identification of substances that are priorities for further actions. While there were numerous ecotoxicological studies available for *n*-hexane, the volatility of the substance makes it difficult to produce accurate results. Several of the reported toxicity values were well above the reported water solubility of the substance.

It is also noted that, with regard to ecotoxicity, evaluation primarily focused on the toxicity to organisms in the pelagic aquatic environment. The release and partitioning behaviour of this substance can result in the exposure of organisms living in other media (air, soil). Limited data on potential effects to such organisms have been identified.

Given the large quantity and widespread use of *n*-hexane in commerce, it is likely that releases to the Canadian environment are substantially higher than those derived solely from the NPRI reporting. Some releases of *n*-hexane to water are expected, but the substance is quite volatile. Therefore, conservative assumptions were made when using models to estimate concentrations of *n*-hexane in receiving water bodies. A key uncertainty relates to the lack of empirical data on environmental concentrations in Canada, which was addressed by using a conservative exposure model to calculate a PEC. There is also uncertainty associated with the PNEC used in the risk quotient calculation, because of limited amount of empirical toxicity data available. This was addressed by dividing the critical toxicity value by an assessment factor of 100.

Potential to Cause Harm to Human Health

Exposure Assessment

Environmental Media and Food

Upper-bounding estimates of daily intake of *n*-hexane for all age groups are summarized in Appendix 1a. The estimates ranged from 32 microgram per kilogram body weight ($\mu\text{g}/\text{kg-bw}$) per day for seniors (> 60 years old) to 95 $\mu\text{g}/\text{kg-bw}$ per day for children (6 months to 4 years old).

The maximum concentrations of *n*-hexane reported in ambient and indoor air in Canada were used for the estimation. Indoor air represented the predominant contribution to the total estimated daily intake for all age groups, ranging from 24 to 73 $\mu\text{g}/\text{kg-bw}$ per day,

followed by ambient air ranging from 7 to 21 $\mu\text{g}/\text{kg-bw}$ per day. Together, air is estimated to be the major source of exposure to *n*-hexane by the general population of Canada.

n-Hexane concentration ranges in ambient and indoor air reported in Canada among the selected critical studies are presented in Table 7.

Table 7. Concentrations of *n*-hexane reported in selected Canadian studies in ambient and indoor air ($\mu\text{g}/\text{m}^3$)

Concentration ¹	Ambient Air ² ($\mu\text{g}/\text{m}^3$)	Indoor Air ³ ($\mu\text{g}/\text{m}^3$)
Mean	0.15 – 8.2	1.2 – 8.0
Minimum	0.001 – 1.5	0.3 – 0.385
Maximum	1.35 – 282	26.6 – 138
Lowest Detection Limit	0.0068	0.0068

¹ Lowest detection limit in ambient and indoor air was 0.0068 $\mu\text{g}/\text{m}^3$.

² Selected critical studies in ambient air include: AENV 2004; Gouvernement du Québec 2002; OMEE 2000; Ville de Montréal 2002; Health Canada 2008; NAPS 2000 – 2008; OMOE 2005.

³ Selected critical studies in indoor air include: Bell et al. 1991; Davis and Otson 1996; Fellin et al 1992; Fellin and Otson 1997; Otson and Zhu 1997.

While the highest concentration of *n*-hexane in ambient air reported in Canada between 2000 and 2008 was 282 $\mu\text{g}/\text{m}^3$ at a NAPS station in a residential area in Windsor, Ontario in 2002 (NAPS 2002), the summary of NAPS data indicates that the mean concentration of *n*-hexane falls in the range of 0.15 to 1.5 $\mu\text{g}/\text{m}^3$ s (NAPS 2000 – 2008). The mean concentration of *n*-hexane in other studies also falls in the range of 0.15 – 8.2 $\mu\text{g}/\text{m}^3$ (AENV 2004; Gouvernement du Québec 2002; OMEE 2000; Ville de Montréal 2002; Health Canada 2008; OMOE 2005). Comparison of the highest concentration to the mean concentration range reported among all critical studies clearly shows that the total upper-bounding estimate of daily intake of *n*-hexane based on the maximum reported value of 282 $\mu\text{g}/\text{m}^3$ is a conservative estimate.

Similarly, the highest concentration of *n*-hexane in indoor air in the critical data set (Canadian studies in the 1990s-2000s) was 138 $\mu\text{g}/\text{m}^3$ from a study conducted in Windsor, Ontario in 2006 (Health Canada 2008). This study was performed over a two year period in 2005 and 2006, and the mean concentration of *n*-hexane ranged from 2.3 to 8.0 $\mu\text{g}/\text{m}^3$. In other studies, the mean concentration of *n*-hexane ranged from 1.2 to 8.0 $\mu\text{g}/\text{m}^3$ (Bell et al. 1991; Davis and Otson 1996; Fellin et al 1992; Fellin and Otson 1997; Otson and Zhu 1997). Therefore, the indoor air contribution to the total upper-bounding estimate of daily intake of *n*-hexane based on the maximum reported value of 138 $\mu\text{g}/\text{m}^3$ is also considered as a conservative estimate.

One localized source of *n*-hexane where the general population of Canada would be exposed is at gas stations during filling up of a motor vehicle gas tank. Potential exposure to *n*-hexane vapour from motor gasoline was reported in Canada in 1985-1986 (PACE 1987, 1989). This study was conducted in two phases (summer 1985 and winter 1986) at 50 service stations in five cities across Canada (Halifax, Montreal, Toronto, Calgary, and

Vancouver) to assess exposure of service station attendants (long-term) and self-serve customers (short-term) to gasoline vapours during normal activities. The short-term study was conducted using a personal sampler for 10 – 15 minutes to represent the time during fill-up of a gas tank by a customer. The study was done for regular leaded gasoline, regular unleaded gasoline and super unleaded gasoline. The mean concentration of *n*-hexane among all short-term studies (114 samples in summer; 119 samples in winter) was 16 800 µg/m³ (maximum 185 000 µg/m³) in summer, and 24 700 µg/m³ (maximum 329 000 µg/m³) in winter. Maximum composition of *n*-hexane in each type of gasoline ranged from 6.06 % (super unleaded) to 12.47% (leaded) in summer and from 3.67 (super unleaded) to 7.21% (leaded) in winter. The current level of *n*-hexane in the air at gas station is expected to be lower than the reported values in this study, as the current average composition of *n*-hexane in gasoline (2.69% as stated in the “Sources” section) is lower than the reported composition in mid 1980s (PACE 1987, 1989),

A similar study was conducted more recently in Belgium in 1997 where concentrations of *n*-hexane vapour, during filling up of a gas tank, were measured for 120 samples (CONCAWE 1997). The mean concentration of *n*-hexane vapour measured was 2 250 µg/m³ (maximum 7 300 µg/m³). In this study, the average sampling time was only 1 minute and 38 seconds, which is significantly shorter than the Canadian study in 1985-1986 (PACE 1987, 1989).

Emissions of *n*-hexane at gas stations would contribute to higher localized ambient air concentrations of *n*-hexane at stations across the county. However, the exposure during gasoline fill-ups at gas stations is not considered critical based on the short exposure time and based on the health effects assessment (refer to the following “Health Effects Assessment” section), which indicated that critical nervous system effects were not observed for short-term exposures of *n*-hexane in robust toxicity studies.

No Canadian data were available in water and soil. Concentrations in drinking water and soil were modelled using ChemCAN 6.0 (ChemCAN 2003), based on the release information to air in 2006 reported under NPRI (NPRI 2008). The modelled contribution to the total estimated daily intake values from water and soil for all age groups resulted in negligible levels (less than 1×10^{-7} µg/kg-bw per day) compared to air.

Several non-Canadian studies were identified to report the presence of *n*-hexane in food. It has been reported in extra-virgin olive oil at levels of 19.1 - 95.3 µg/L (Overton and Manura 1995). Maximum mean residue concentrations in peanut oil and sunflower oil have been reported at 0.9 mg/kg and 1.5 mg/kg, respectively (Hautfenne et al. 1987). It has also been detected in headspace analysis of roasted filberts (Kinlin et al. 1972), and chickpea seed (Rembold et al. 1989), as well as in soy protein products (Honing et al. 1979).

As the dataset was poor for food, the estimates from food sources were determined according to the most recent information on residual levels in foods summarized in Appendix 1b. Based on the levels of residual *n*-hexane typically found in refined vegetable oils of 0.8 ppm, the highest daily intake of *n*-hexane from foods is estimated to

be 1.45 µg/kg-bw per day for the 6 - 8 year old age group (Appendix 1b; Personal communication from Chemical Health Hazard Assessment Division, Health Canada to Risk Assessment Bureau, Health Canada, dated 2008-10-15; unreferenced). This estimate indicates that the contribution from food sources at the worst case is 1.95% of the estimated total daily intake. Therefore, this percentage was incorporated to all age groups for a conservative estimate of the total daily intake of *n*-hexane from environmental media and food.

The contribution from food sources is considered an overestimate due to following factors. An *n*-hexane residue level of 0.8 ppm was assumed for the oil component of all processed foods containing vegetable oil as an ingredient. This is the maximum level of *n*-hexane found in commercial grade hexane. However, processed foods that contain vegetable oil are in many instances exposed to processing temperatures that far exceed the boiling point of *n*-hexane (68.7°C). It is therefore expected that *n*-hexane residues in the oil component of processed foods would be further reduced during the cooking process. In addition, all food categories containing vegetable oil as an ingredient were considered including oils extracted without the use of hexane, such as virgin oils and cold-pressed oils, since there was no way of distinguishing them from oils extracted using hexane only (Personal communication from Chemical Health Hazard Assessment Division, Health Canada to Risk Assessment Bureau, Health Canada, dated 2008-09-26; unreferenced).

Confidence in the upper-bounding estimate of exposure to *n*-hexane via environmental media and food is considered to be high as recent Canadian data were available for both ambient and indoor air which represented the predominant source of exposure. No Canadian data were identified in other media (drinking water, soil) and food, however, these media were estimated not to contribute significantly to the total daily intake, which agrees with its physical and chemical properties (high volatility and low water solubility). The total upper-bounding estimate of exposure to *n*-hexane is considered to be a conservative estimate.

Consumer Products

Based on the information submitted under the section 71 survey of CEPA 1999, the major use categories of *n*-hexane in consumer products were identified as adhesives, lubricant, paints, and automotive parts cleaners and degreasers (Environment Canada 2007b). For some of these products including lubricant (< 60%), brake parts cleaner and degreaser (< 100%), automobile parts cleaning products (i.e., tire shine, < 60%), and contact cleaner (< 90%), concentrations of *n*-hexane in the products are relatively high as indicated by the percentages in brackets (Environment Canada 2007b). Many of these products are for automobile care/maintenance products and considered primarily for professional use. Although it may also be used by the general population, these products are considered to be used outdoors and/or infrequently. Under such circumstances, exposure via inhalation during the use of these products is expected to be minimal.

Other products where interior use (i.e., basements, garages) may be expected include construction adhesive, gasket sealant, spray paint, weatherstrip adhesive, weatherstrip

cement, and spray adhesive. Maximum concentrations of *n*-hexane for each type of products according to the submitted and publically available information are summarized in Table 8 together with use conditions based on consumer product exposure model parameters (frequency of use and exposure duration) (RIVM 2006, US EPA 1986).

Table 8. Consumer products containing *n*-hexane and use conditions based on exposure model parameters

Consumer product	Concentration of <i>n</i> -hexane		Use Condition		
	Maximum %	Reference	Frequency of use (/year)	Exposure duration (min)	Reference
Construction Adhesive	30	Childers 2007	2	240	RIVM 2006
Gasket Sealant	25	Permatex Inc. 2007	3	45	
Spray Paint	20	Sherwin-Williams ³	2	20	
Weatherstrip Adhesive ¹	15	Permatex Canada 2004	N/A	N/A	
Spray Adhesive	30	Permatex Canada 2005	12	240	
Weatherstrip Cement ²	8.9	Permatex 2003	7	16	US EPA 1986

¹ No matching exposure scenario available for the product (RIVM 2006, US EPA 1986).

² No matching exposure scenario available from RIVM (RIVM 2006).

³ Personal communication from Sherwin-Williams to Environment Canada, dated 2008-08-27, unreferenced.

The model suggests that the use of these products presented in Table 8 results in exposure duration of 5 to 240 min. Exposure estimates during short-term use of consumer products were not developed for this substance based on the following reasons.

The use of these products is considered primarily for professional use and is expected to be infrequent by the general population. In addition, any potential contribution of consumer products to total exposure of the general population is captured in indoor and ambient air levels, for which empirical data were available from recent Canadian studies. Finally, based on the health effects assessment (refer to the following “Health Effects Assessment” section), critical nervous system effects were not observed for short-term exposures of *n*-hexane in robust toxicity studies.

Similar considerations were taken for a small number of cosmetic products containing *n*-hexane notified to Health Canada (CNS 2008, refer to “Uses” section) and exposure estimates were not derived for these products in this assessment.

Health Effects Assessment

Appendix 2 contains a summary of the available health effects information for *n*-hexane.

The European Commission has classified *n*-hexane as Category 3 (causes concern for human reproduction) Risk phrase R62 (possible risk of impaired fertility) for

reproductive toxicity. This classification was based on effects observed in male rat following inhalation or oral exposure to *n*-hexane or its metabolite 2,5-hexanedione in male reproductive toxicity studies (European Commission 1997, 2004). Effects observed include histological changes in the testes and epididymis as well as changes in sperm parameters, and are described in more detail below.

Male rats were exposed to *n*-hexane at 3524 mg/m³ (1000 ppm) for 61 days. At 2 weeks and 10 months after cessation of exposure, testicular damage was observed in the form of decreased size and weight of testes, atrophy of seminiferous tubules and loss of nerve growth factor-immunoreactive cell population. Total loss of germ cell line occurred in a few animals up to 14 months post-exposure (Nylén et al 1989).

In an inhalation testes morphology study in male rats lasting from 1 day up to 6 weeks, focal degeneration of spermatocytes and mild exfoliation of elongated spermatids were observed at 17622 mg/m³ (5000 ppm) (De Martino et al. 1987). The effects were first observed after 24 hours of treatment. Other effects observed at various time intervals after cessation of exposure included the presence of degenerating germ cells and inflammatory cells in the seminiferous tubules. The severity of the lesions in the seminiferous tubules increased with the duration of exposure, and extended treatment resulted in reduction in diameter and collapse of the tubules, including aplastic tubules. The testes and/or epididymides of all rats were affected after 3 weeks in groups exposed up to 6 weeks.

When administered orally in a 6-month comparative toxicity study in male rats, atrophy of the testicular germinal epithelium was observed at the highest dose of 4000 mg/kg-bw/day (Krasavage et al. 1980). In another oral reproductive study in male rats, there were no treatment-related effects on sperm or reproductive organs at the tested doses of 10000 mg/kg-bw/day for 5 days or 20000 mg/kg-bw for 1 day (Linder et al. 1992).

In an inhalation developmental toxicity study in mice, an increase in resorptions was observed at 705 mg/m³ (200 ppm) and higher (early and late resorptions significantly increased at 705 mg/m³ and late resorptions significantly increased at 17622 mg/m³) (Mast et al. 1988a).

When administered orally to mice in a developmental study, decreased average maternal weight gain was observed at 2200 mg/kg-bw/day and 2170 mg/kg-bw/day, but not at higher doses up to 9900 mg/kg-bw/day. Decreased foetal weight was observed at 7920 mg/kg-bw/day and above. Maternal deaths were observed at 2830 mg/kg-bw/day and above. (Marks et al. 1980). There was no evidence of teratogenicity in both inhalation and oral developmental studies in rats and mice (Bus et al. 1979; Marks et al. 1980; Mast 1987; Mast et al. 1988a; Stoltenburg-Didinger et al. 1990).

No guideline cancer studies were identified using *n*-hexane only. In a subchronic lung morphology study conducted in male rabbits exposed by whole body inhalation for 24 weeks, papillary tumours in terminal bronchioles and alveolar ducts were observed at the only tested concentration of 10573 mg/m³ (3000 ppm) (Lungarella et al. 1984). Multiple

short-term genotoxicity assays have been conducted *in vitro*, most of which were negative. *In vivo* studies for chromosome aberrations tests in bone marrow cells of rats and mice were positive (Hazleton Labs 1992, Shelby and Witt 1995, NTP 1991), whereas those for micronuclei and sister chromatid exchange and dominant lethal assays were all negative (Litton Bionetics 1980, Mast et al. 1988c, NTP 1991, Shelby and Witt 1995).

No chronic animal studies using pure *n*-hexane have been identified. However, neurotoxicity is identified as the most sensitive endpoint based on numerous subchronic animal studies. The lowest-observed-effect-concentration (LOEC) for inhalation exposure was 705 mg/m³ (200 ppm) based on decreased distal latency, motor nerve conduction velocity and mixed nerve conduction velocity (distal and, distal plus proximal combined) in male rats in a 24-week study (12 hrs/day). No clinical signs of neurotoxicity were observed at any concentration (Ono et al. 1982).

In a 16-week study in which male rats were exposed to *n*-hexane by inhalation at higher concentrations, similar effects were observed, including a dose-dependent reduction in motor nerve conduction velocity at 4230 and 10574 mg/m³ (Huang et al. 1989). Paranodal swelling and clinical signs of neuropathy (marked reduction in grip strength, slowness of motion) were also present at these concentrations. The LOEC for this study was 1762 mg/m³ based on a dose-related decrease in the nervous system-specific protein, β -S-100.

Other inhalation studies suggest that when daily exposure was of shorter duration, effects on the nervous system may be less severe, or first appear at higher doses. In a 13-week inhalation study in rats, early stage paranodal swellings of the tibial nerve were evident in 1/5 and 4/5 male rats at 22907 and 35243 mg/m³ (6500 and 10000 ppm) respectively. No clinical signs of neuropathy were observed (Cavender et al. 1984). In a 13-week inhalation study in mice, paranodal swellings of the tibial nerve were observed in both sexes, and decreased locomotor activity was observed in females at 35243 mg/m³ (10000 ppm). Non-neurotoxic effects included a dose-related increase in lesions of the nasal turbinates in males and in females at 35243 mg/m³ (10000 ppm) (NTP 1991).

The lowest-observed-effect-level (LOEL) for exposure via the oral route was 189 mg/kg-bw/day based on adverse effects in heart muscle and related parameters (reduction in ventricular fibrillation threshold, decreased levels of myocardial magnesium and potassium, changes in the ultrastructure of the myocardium) in male rats exposed to 0 or 189 mg/kg/day for 30 days through gavage (Khedun et al. 1996). In a 90-day oral rat study (males only), signs of neurotoxicity (severe hindlimb weakness or paralysis with dragging of at least one hind foot, morphologic changes in nerve tissue), were observed at the highest dose of 4000 mg/kg bw/day (Krasavage et al. 1980).

There are a considerable number of human studies which measured nervous system effects. Three of the more pertinent studies are described in Appendix 2 and summarized below.

Male workers from a tungsten carbide alloys producing factory were evaluated to assess the effects of low levels of *n*-hexane on the peripheral nervous system. They were exposed to an average *n*-hexane concentration of 204 mg/m³ (58 ppm) in the breathing zone over an average period of 6.2 years. However, there was also co-exposure to acetone. Compared to controls, exposed workers showed an increased frequency of headache, dyesthesia in limbs and muscle weakness, decreases in muscle strength, in vibration sensation of the radial processes [as stated in original paper], and in maximal MCV and residual latency of motor nerve conduction in the posterior tibial nerve (Sanagi et al. 1980).

Mutti et al. (1982) observed both clinical and electrophysiological signs of neuropathy in shoe factory workers exposed to a mixture of hydrocarbons, including *n*-hexane over a 9-year period. Based on time-weighted average concentrations for *n*-hexane, sleepiness, dizziness, weakness in limbs, hypoesthesia and paraesthesia were more frequent in all exposed workers. Motor action potential (MAP) was reduced in median, ulnar and peroneal nerves in both mild (243 mg/m³) and high (474 mg/m³) exposure groups, while in the high exposure group, motor nerve conduction velocity (MCV) was decreased in the median and peroneal nerves.

In an offset printing factory, mean background TWA of *n*-hexane was 222 mg/m³ (63 ppm) and mean personal air concentration of *n*-hexane for offset machine workers was 465 mg/m³ (132 ppm). Subjects worked at this facility for an average of 2.6 years (range one month to 12 years), and in the trade for an average of 6.4 years (range one month to 30 years). While other solvents (i.e. toluene) were present in cleaning solutions used by the workers, *n*-hexane was predominant. The exposed workers were divided into three groups according to signs of peripheral neuropathy: healthy workers, subclinical (showing abnormalities in nerve conduction parameters), and symptomatic (showing both clinical and electrophysiological evidence of peripheral neuropathy), and compared to a control group. In healthy workers, sensory action potential (SAP) in nerves was decreased compared to controls. In the subclinical group, SAP, SAP amplitude and MCV were decreased, as well as a mild reduction in MAP amplitude and mild prolongation in mean distal latency (DL). In the symptomatic group, further reduction in SAP, MAP amplitudes and MCV, including an obvious prolongation in mean DL, and clinical signs of peripheral neuropathy were observed (numbness, paraesthesia, and pain and weakness in extremities). This study showed how degradation of electrophysiological parameters was related to clinical signs of neuropathy in humans (Chang et al. 1993).

Humans may recover from *n*-hexane induced neuropathy within 1-3 years after termination of exposure but deterioration of muscle strength and sensory deficits commonly worsen within 2-5 months of the cessation of exposure before slow recovery begins. However, certain neurotoxic effects may persist in cases of very high exposures. The mechanism of continued progression of effects after termination of exposure is not clear (Huang 2008).

Several toxicokinetic studies have been conducted in laboratory animals but only a few in humans. In a 4-hr inhalation study in male volunteers, 22-24% of *n*-hexane was absorbed

across the lungs and the average half-life for *n*-hexane in blood was 1.5-2 hrs (Veulemans et al. 1982). It is principally metabolized in the liver to various metabolites that are then distributed in the blood to various organs and tissues. No oral absorption studies were identified, although a single oral exposure study in human volunteers identified 2,5-hexanedione as the main metabolite in urine (Baelum et al. 1998). In occupational exposure studies where there was exposure to other substances in addition to *n*-hexane, metabolites identified in urine included 2,5-hexanedione, 2,5-dimethylfuran, 2-hexanol, γ -valerolactone, and 4,5-dihydroxy-2-hexanone. The major metabolite of *n*-hexane in laboratory animals is 2-hexanol. No toxicokinetic studies based on dermal exposure were identified (US EPA 2005).

Level of confidence in the toxicity database is moderate to high as there is sufficient information to address the endpoint of concern (neurotoxicity) based on inhalation exposure, including human studies which measured neurotoxicity, and adequate information on acute, short-term, subchronic and genotoxicity endpoints. Animal studies measuring reproductive and developmental endpoints were limited and chronic toxicity data were lacking, although some carcinogenicity data were provided via a 24-wk inhalation study in rabbits.

Although a thorough analysis of the mode of action of *n*-hexane is beyond the scope of this screening assessment, it is recognized that the neurotoxicity observed following *n*-hexane exposure is likely caused by its metabolite 2,5-hexanedione. This γ -diketone appears to have the ability to interact with specific proteins on neurofilaments, via pyrrole formation, which eventually results in neuropathy. Structural analogues, such as *n*-heptane and pentane, do not have the ability to form γ -diketone metabolites (US EPA 2005).

Characterization of Risk to Human Health

Based principally on the classification from the European Commission, an important effect of hexane is impaired fertility. However, the US EPA (2005) and the ATSDR (1999) identified the nervous system as the target organ for *n*-hexane exposures. Neurotoxic effects due to hexane exposure were observed at concentrations lower than those observed for impaired fertility effects.

Several human studies suggested neurotoxic effects at inhalation levels lower than those identified from animal toxicity studies. However, the human epidemiology studies are not as robust as the animal studies because effects from co-exposure to several other substances could not be separated from effects due to *n*-hexane exposure and due to other confounding factors inherent in epidemiology studies. Thus, the critical effect level for repeated-dose toxicity via inhalation is considered to be 705 mg/m³, based on decreases in nerve conduction parameters in a 24-week rat study, and increased number of resorptions in a mouse developmental toxicity study.

The principal source of exposure to hexane is expected to be through inhalation (ambient and indoor air). A comparison between the lowest LOEC for repeated dose toxicity (705

mg/m³) and measured ambient and indoor air concentrations of 282 µg/m³ and 138 µg/m³, respectively, resulted in margins of exposure (MOEs) of approximately 2500 (ambient air) and 5100 (indoor air), which were considered to be adequately protective.

The critical effect level for repeated-dose toxicity via the oral route (189 mg/kg-bw/day) was based on adverse effects in heart muscle and related parameters in a 30-day rat study. Comparison of the critical effect level for repeated dose effects via the oral route and the upper-bounding estimate of daily intake of *n*-hexane by the general population in Canada (95 µg/kg-bw/day) for children (0.5-4 years old), resulted in a margin of exposure (MOE) of approximately 2000, which is considered to be adequately protective.

MOEs were not established for consumer products containing *n*-hexane as the use of these products are considered specialized and/or infrequent by the general population, and critical nervous system effects were not observed for short-term exposures in robust toxicity studies. In addition, many products considered are for outdoor use and exposure via inhalation is expected to be minimal. Finally, the empirical data on *n*-hexane concentration in air from recent Canadian studies account for exposures associated with the use of consumer products.

There was insufficient information to assess the carcinogenicity of *n*-hexane. No chronic studies were available; however, evidence of lung tumours at a high *n*-hexane concentration (10,573 mg/m³) was observed in a 24-wk rabbit study.

Uncertainties in Evaluation of Risk to Human Health

The scope of this screening assessment does not take into consideration a full analysis of the mechanism of action of *n*-hexane, and it does not take into account possible differences between humans and experimental animals in sensitivity to effects induced by this substance or in metabolism of the substance. There is uncertainty surrounding the relevance to humans of the reproductive effects observed in male rats. Lack of chronic studies leads to uncertainty regarding long-term and carcinogenic effects.

Although *n*-hexane is often present in co-occurrence with other substances, the exposure from *n*-hexane through its commercial mixture formulation was not considered in this report.

The level of uncertainty in quantification of population exposure to *n*-hexane in the general environment is low based on the fact that there were sufficient recent Canadian studies that examined the concentration of this substance in the critical environmental media, ambient and indoor air. Although the concentration of *n*-hexane in other environmental media (water and soil) and food were not available, these media were estimated not to play significant roles in exposure estimates for the general population, which is in agreement with its physical and chemical properties.

Conclusion

Based on the information presented in this screening assessment, it is concluded that *n*-hexane is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends. Additionally, *n*-hexane does not meet the criteria for persistence or bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Based upon the potential adequacy of the margins of exposure between conservative estimates of exposure to *n*-hexane via environmental media and critical effect levels for inhalation exposures, it is concluded that hexane be considered as a substance that is not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that hexane does not meet the criteria in paragraphs 64(a), 64(b) or 64(c) of CEPA 1999. Additionally, hexane does not meet the criteria for persistence or bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

References

- [ATSDR] Agency for Toxic Substances and Disease Registry. 1999. Toxicological Profile for *n*-Hexane., U.S. Department of Health and Human Services, Public Health Service. July 1999. Available at <http://www.atsdr.cdc.gov/toxprofiles/tp113.html>
- Ahearn DG, Crow SA, Simmons RB, Price DL, Noble JA, Mishra SK, and Pierson DL. 1996. Fungal colonization of fibreglass insulation in the air distribution system of a multi-story office building: VOC production and possible relationship to a sick building syndrome. *Journal of Industrial Microbiology and Biotechnology*. 16. 280-285.
- [AIES] Artificial Intelligence Expert System. 2003-2005. Version 1.25. Ottawa (ON): Environment Canada. Model developed by Stefan Niculescu. Available from: Environment Canada, Existing Substances Division, New Substances Division, Ottawa, K1A 0H3.
- [AENV] Alberta Environment. 2004. Assessment report on hexane for developing ambient air quality objectives. Prepared by Cantox Environmental Inc. and RWDI West Inc. [cited in CCME 2008].
- [AOPWIN] Atmospheric Oxidation Program for Microsoft Windows [Estimation Model]. 2000. Version 1.91. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm
- Arnot JA, Gobas FAPC. 2003. A generic QSAR for assessing the bioaccumulation potential of organic chemicals in aquatic food webs. *QSAR Comb Sci* 22(3): 337-345.
- Aronson D, Howard PH. 1999. Evaluating potential POP/PBT compounds for environmental persistence. North Syracuse (NY): Syracuse Research Corp., Environmental Science Centre. Report No.: SRC-TR-99-020.
- Aronson D, Boethling B, Howard P, W Stiteler W. 2006. Estimating biodegradation half-lives for use in chemical screening. *Chemosphere* 63: 1953-1960.
- [ASTER] Assessment Tools for the Evaluation of Risk [Internet]. 1999. Duluth (MN): US Environmental Protection Agency, Mid-Continent Ecology Division. Available from: http://www.epa.gov/med/Prods_Pubs/aster.htm Restricted access.
- Atkinson, R. 1989. Kinetics and mechanisms of the gas-phase reactions of the OH radicals with volatile organic compounds. *Journal of Physical and Chemical Reference Data*. Monograph No. 1. Available from [Introduction]: <http://aprc.ucr.edu/VOCINTRO.pdf>
- Baelum J; Molhave L, Hansen SH, Vaeth M. 1998. Metabolic interaction between toluene, trichloroethylene and *n*-hexane in humans. *Scand J Work Environ Health* 24:30-37. [cited in US EPA 2005].
- Baker TS and Rickert DE. 1981. Dose-dependent uptake, distribution and elimination of inhaled *n*-hexane in the Fischer-344 rat. *Toxicology and Applied Pharmacology*. 61. 414-422 [cited in IPCS 1991].
- Barni-Comparini I, Lungarella G, Fonzi L. 1982 Response of lung enzyme activities in rabbits following short term exposure to *n*-hexane: correlation between morphological and biochemical changes. *Agents Actions* 12:737-742.
- [BCFWIN] BioConcentration Factor Program for Microsoft Windows [Estimation Model]. 2000. Version 2.15. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics;

Syracuse (NY): Syracuse Research Corporation. Available from:
www.epa.gov/oppt/exposure/pubs/episuite.htm

Beall C, Delzell E, Rodu B, Sathiakumar N, Lees PS, Breyse PN, Myers S. 2001. Case-control study of intracranial tumors among employees at a petrochemical research facility. *J Occup Environ Med.* 43(12):1103-13.

Bell RW, Chapmen, RE, Kruschel BD, Spencer MJ, Smith KV and Lulis MA. 1991. The 1990 Toronto Personal Exposure Pilot (PEP) Study. ISBN 0-7729-7962-6

Bingham E et al. 2001. *Patty's Toxicology*. 5th ed NY, NY: John Wiley Sons 4th edition [cited in NLM 2005].

Biodynamics Inc. 1978. 26-Week inhalation toxicity study of *n*-hexane in the rat. EPA Document No. FYI-AX-1081-0137; NTIS No. OTS0000137-0.

[BIOWIN] Biodegradation Probability Program for Microsoft Windows [Estimation Model]. 2000. Version 4.02. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from:
www.epa.gov/oppt/exposure/pubs/episuite.htm

Boethling RS, Howard PH, Beauman JA, Larosche ME. 1995. Factors for intermedia extrapolations in biodegradability assessment. *Chemosphere* 30(4):741-752.

Bottenheim JW and Shepherd MF. 1995. C₂ – C₆ hydrocarbon measurements at four rural locations across Canada. *Atmospheric Environment* 29(6) 647-664.

Bus JS, White EL, Tyl RW, Barrow CS 1979. Perinatal toxicity and metabolism of *n*-hexane in Fischer-344 rats after inhalation exposure during gestation. *Toxicol Appl Pharmacol.* 51(2):295-302.

Canada. 1978. *Food and Drug Regulations*, C.R.C., c.870, Part B, Division 16 Food Additives. Available from: http://laws.justice.gc.ca/en/showdoc/cr/C.R.C.-c.870/bo-ga:l_B-gb:l_16/20090602/en#anchorbo-ga:l_B-gb:l_16

Canada. 1988a. Ingredient Disclosure List [Internet]. S.O.R./88-64.[cited September 2008]. Available from: <http://laws.justice.gc.ca/PDF/Regulation/S/SOR-88-64.pdf>

Canada. 1988b. Controlled Products Regulations [Internet]. S.O.R./88-66. Available from: <http://laws.justice.gc.ca/PDF/Regulation/S/SOR-88-66.pdf>

Canada. 1999. *Canadian Environmental Protection Act, 1999 = Loi canadienne sur la protection de l'environnement, 1999*. Statutes of Canada = Statuts du Canada, Chapter 33. Act assented to September 14, 1999. Ottawa: Queen's Printer. Available at Canada Gazette (Part III) 22(3): chapter 33. Available from: <http://canadagazette.gc.ca/partIII/1999/g3-02203.pdf>

Canada. 2000. *Canadian Environmental Protection Act, 1999: Persistence and Bioaccumulation Regulations*, P.C. 2000-348, 23 March, 2000, SOR/2000-107, Canada Gazette, Part II, vol. 134, no. 7, p. 607-612. Available from: <http://canadagazette.gc.ca/partII/2000/20000329/pdf/g2-13407.pdf>

Canada. 2006. Department of the Environment, Department of Health. *Canadian Environment Protection Act 1999*: Notice of intent to develop and implement measures to assess and manage the risks posed by certain substances to the health of Canadians and their environment. Ottawa: Public Works and Government Services Canada. Canada Gazette. Part I, vol. 140, no. 49, p. 4109-4116. Available from: <http://canadagazette.gc.ca/partI/2006/20061209/pdf/g1-14049.pdf>

Canada 2007. Department of the Environment, Department of Health. *Canadian Environmental Protection Act, 1999: Notice of fourth release of technical information relevant to substances identified in the Challenge*. Canada Gazette, Part I, vol. 141, no. 46, p. 3192–3196. Available from: <http://canadagazette.gc.ca/partI/2007/20071117/pdf/g1-14146.pdf>

[CCME] Canadian Council of Ministers of the Environment. 2008. Canadian Soil Quality Guidelines for the Protection of Environmental and Human Health. *n*-Hexane 2008. 10p. Available from: <http://www.ec.gc.ca/ceqg-rcqe>

Carelli V, Franceshini F, Venturi S, Barboni P, Savini G, Barbieri G, Pirro E, La Margia C, Valentino ML, Zanardi F, Violante FS, Mattioli S. 2007. Grand rounds : Could occupational exposure to *n*-hexane and other solvents precipitate visual failure in Leber hereditary optic neuropathy? *Environmental Health Perspectives* 115: 113-115.

[CATABOL] [Computer Model]. 2004–2008. Version 5.10.2. Predicting microbial biodegradation (BOD, CO₂ Production), metabolic pathways and stable biodegradation products. Bourgas (BG): Bourgas Prof. Assen Zlatarov University, Oasis Laboratory of Mathematical Chemistry. Available from: <http://oasis-lmc.org/?section=software&swid=1>

Cavender FL, Casey HW, Salem H; Graham DG, Swenberg JA, Gralla EJ. 1984. A 13-week vapor inhalation study of *n*-hexane in rats with emphasis on neurotoxic effects. *Fundam Appl Toxicol* 4(2 Pt 1):191-201.

Chang CM, Yu CW, Fong KY, Leung SY, Tsin TW, Yu YL, Cheung TF, Chan SY. 1993. *n*-hexane neuropathy in offset printers. *Journal of Neurology, Neurosurgery, and Psychiatry* 56:538-542.

[ChemCAN]. 2003. ChemCAN: level III. fugacity model of regional fate of chemicals. Version 6.00. Peterborough (ON): Canadian Environmental Modelling Centre, Trent University. Available from: <http://www.trentu.ca/academic/aminss/envmodel/models/CC600.html>

[CIIT] Chemical Industry Institute of Toxicology. 1977. *n*-Hexane. CIIT Current Status Reports, No. 1. Research Triangle Park, North Carolina, USA [cited in IPCS 1991].

Childers. 2007. CHIL-STIX® CP-85 Adhesive. Material Safety Data Sheet [Internet]. Specialty Construction Brands, Inc. IL, USA. [cited 2008-08-31] Available from: <http://www.insulationfabricators.com/PDFs/Childers/Childers%20-%20CP-85%20Chil-Stix%20Adhesive%20-%20Data.pdf>

CONCAWE 1997. Exposure profile: gasoline. Prepared for the CONCAWE petroleum products management group by the special task force on petroleum product exposure profiles (STF-14). Brussels.

Crude Quality. 2009a. Crude Quality Data Summaries. Light Crude Quality Project Light Ends Summary (March 2009). Crude Quality Inc. Edmonton, Alberta, Canada. Available from: http://www.crudemonitor.ca/current/light/rpt_lightends.pdf

Crude Quality. 2009b. Crude Quality Data Summaries. Heavy Crude Quality Project Light Ends Summary (March 2009). Crude Quality Inc. Edmonton, Alberta, Canada. Available from: http://www.crudemonitor.ca/current/heavy/rpt_lightends.pdf

[CNS] Cosmetic Notification System [Proprietary database]. 2008. Available to Health Canada, Cosmetics Division.

[CPOPs] Canadian POPs Model. 2008. Gatineau (QC): Environment Canada, Existing Substances Division; Bourgas (BG): Bourgas Prof. Assen Zlatarov University, Laboratory of Mathematical Chemistry. [Model developed based on Mekenyan et al. 2005]. Available upon request. Described in: Mekenyan G,

Dimitrov SD, Pavlov TS, Veith GD. 2005. POPs: a QSAR system for creating PBT profiles of chemicals and their metabolites. *SAR QSAR Environ Res* 16(1–2):103–133.

Daubert TE, Danner RP. Physical and Thermodynamic Properties of Pure Chemicals Data Compilation. Washington, D.C.: Taylor and Francis. 1989 [cited in NLM 2005].

Davis CS, Otson R. 1996. Estimation of emissions of volatile organic compounds (VOCs) from Canadian residences. In: Wang W, Schnoor J, Doi J, editors. *Volatile organic compounds in the environment*. West Conshohocken (PA): American Society for Testing and Materials. p. 55-65.

De Martino C, Malorni W, Amantini MC, Scorza Barcellona P, Frontali N. 1987. Effects of respiratory treatment with *n*-hexane on rat testis morphology. I. A light microscopic study. *Exp Mol Pathol*. 46(2): 199-216.

Eastman AD, Mears DE. 2000. Hydrocarbons C₁ – C₆. In: *Kirk-Othmer Encyclopaedia of Chemical Technology*. John Wiley & Sons, Inc. Available from: <http://www.mrw.interscience.wiley.com/emrw/9780471238966/kirk/article/cceast.a01/current/pdf>

[ECOSAR] Ecological Structural Activity Relationships [Internet]. 2004. Version 0.99h. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: <http://www.epa.gov/oppt/exposure/pubs/episuite.htm>

[ECOTOX] ECOTOXicology Database [Database on the Internet]. 2007. Release 4.0. Washington (DC): US Environmental Protection Agency, Office of Research and Development; US Environmental Protection Agency, National Health and Environmental Effects Research Laboratory's Mid-Continent Ecology Division. [cited 2007 February]. Available from: <http://cfpub.epa.gov/ecotox/>

Environment Canada. 2007a. Guidance for conducting ecological assessments under CEPA, 1999, Science resource technical series, Technical guidance module: QSARs. Reviewed draft working document. Gatineau (QC): Environment Canada, Existing Substances Division.

Environment Canada. 2007b. Data for Batch 4 substances collected under the *Canadian Environmental Protection Act, 1999, Section 71: Notice with respect to Batch 4 Challenge substances*. Canada Gazette, Part I, vol. 141, no. 46, p. 3196–3214. Data compiled by Environment Canada, Existing Substances Program.

Environment Canada. 2008. Volumes of Liquid Fuels Produced / Imported for Sale in Canada Reported to Statistics Canada and Environment Canada for 2006. Available from: http://www.ec.gc.ca/cleanair-airpur/caol/ogeb/fuels/reports/sulphurLiquid2006/p1_eng.cfm#table1_1

Environment Canada. 2009a. Guidance for Conducting Ecological Assessments under CEPA, 1999: Science Resource Technical Series, Technical Guidance Module: Suggested Approach to Determining the Persistence of a Chemical from Biodegradation Data. Reviewed Draft Working Document. Gatineau (QC): Environment Canada, Existing Substances Division. Ottawa, K1A 0H3.

Environment Canada. 2009b. IGETA (Industrial Generic Exposure Tool – Aquatic) Report: CAS RN 110-54-3. Gatineau (QC): Environment Canada, Existing Substances Division.

[EPISuite] Estimation Programs Interface Suite for Microsoft Windows [Estimation Model]. 2007. Version 3.2 Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

[EQC] Equilibrium Criterion Model. 2003. Version 2.02. Peterborough (ON): Trent University, Canadian Environmental Modelling Centre. Available from: <http://www.trentu.ca/academic/aminss/envmodel/models/EQC2.html>

European Commission. 1997. Summary Record Commission Group of Specialised Experts in the fields of Carcinogenicity, Mutagenicity and Reprotoxicity. Meeting at Belgirate, 4-5 June 1997. European Commission Directorate General JRC. Joint Research Centre. Environment Institute. European Chemicals Bureau. ECBI/28/97. http://ecb.jrc.ec.europa.eu/DOCUMENTS/Classification- Labelling/ADOPTED_SUMMARY_RECORDS/2897_sr_SE0697.pdf

European Commission. 2004. *n*-hexane. Commission Directive 2004/73/EC of 29 April 2004. Annex IB. Official Journal of the European Union. 16.6.2004. L216/28. European Commission. 29th ATP. http://ecb.jrc.ec.europa.eu/DOCUMENTS/Classification-Labelling/DIRECTIVE_67-548-EEC/ATPS_OF_DIRECTIVE_67-548-EEC/29TH_ATP_SUBSTANCE_ANNEXES/Annex-1B_EN.doc

Fellin P, Barnett SE, and Tran QA. 1992. Results of a National Pilot Study of Airborne Volatile Organic Compounds in Canadian Residences-Volume 1, CEC J2431, Prepared for Health and Welfare Canada, Tunney's Pasture, Ottawa, Ontario, DSS File: H4078-0-C659, Concord Environmental Corporation, 2 Tippet Road, Downsview, Ontario, M3H 2V2, October, 1992.

Fellin P, Otson R. 1997. Emissions of VOC from residences in the Metropolitan Toronto area. In: Proceedings of the 90th Annual Meeting of Air & Waste Management Association; 1997 June 8-13; Pittsburgh (PA): AWMA.

Foster GD, Tullis RE. 1985. Quantitative Structure-Toxicity Relationships with Osmotically Stressed *Artemia salina* Nauplii. *Environ.Pollut.Ser.A* 38:273-281

Geiger DL, Brooke LT, Call DJ. 1990. Acute Toxicities of Organic Chemicals to Fathead Minnows (*Pimephales promelas*), Volume 5. Ctr.for Lake Superior Environ.Stud., Univ.of Wisconsin-Superior, Superior, WI :332 p.

Ghatak, DB, Hossain MM, Konar SK. 1988. Acute Toxicity of *n*-Heptane and *n*-Hexane on Worm and Fish. *Environ.Ecol.* 6(4):943-947

Gouvernement du Québec. 2002. Critères de qualité de l'air: Fiches synthèses. Ministère de l'Environnement, Direction du suivi de l'état de l'environnement, Service des avis et des expertises [cited in CCME 2008].

[GLWQB] Great Lakes Water Quality Board. 1983. An Inventory of Chemical Substances Identified in the Great Lakes Ecosystem 195p.

Groves FR. 1988. Effect of cosolvents on the solubility of hydrocarbons in water. *Environmental Science and Technology*. 22. 282-286 [cited in IPCS 1991].

Hansch C, Leo A, Hoekman D. 1995. Exploring QSAR: Hydrophobic, Electronic, and Steric Constants. Washington (DC): American Chemical Society. [cited 2007 February] [as cited in HSDB 1983].

[HSDB] Hazardous Substances Data Bank [Database on the Internet]. 1983 - . Bethesda (MD): National Library of Medicine (US). [cited 2007 February]. Available from: <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>

Hautfenne A, Pocklington WD and JP Wolff. 1987. Determination of 'hexane' residues in oils: Results of a collaborative study and the standardised method. *Pure & Applied Chemistry*, 59(11): 1561-1570.

Hazleton Laboratories America, Inc.1979. In Vitro and In Vivo Mutagenicity Studies, Hexane, Final Report Draft.EPA Document No. FYI-OTS-0381-0106, Fiche No. OTS0000106-0 [cited in TSCATS 2008]

Hazelton Laboratories. 1992. Initial submission: in vivo and in vitro mutagenicity studies *n*-hexane (hexane UV) (final report) with attachments and cover letter dated 020592. Submitted under Section 8ECP of TSCA. EPA Document No. 88-920000955; NTIS No. OTS0535721.

Health Canada. 1998. Exposure factors for assessing total daily intake of priority substances by the general population of Canada. Unpublished report. Ottawa (ON): Health Canada, Environmental Health Directorate. Available upon request.

Health Canada. 2008. Windsor Ontario Exposure Assessment Study 2005, 2006: VOC Sampling Data Summary. DRAFT. Fuels and Exposure Assessment Section. Air Health Sciences Division. Healthy Environments and Consumer Safety Branch. February 2008. 85p.

[HENRYWIN] Henry's Law Constant Program for Microsoft Windows [Estimation Model]. 2000. Version 3.10. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Honig DH, Warner KA, Selke E, and Rackis JJ. 1979. Effects of residual solvents and storage on flavour of hexane/ethanol azeotrope extracted soy products. *Journal of Agricultural and Food Chemistry*. 27(6) 1383 - 1389.

Houk V, Schalkowsky S, Claxton L. 1989. Development and validation of the spiral Salmonella assay: an automated approach to bacterial mutagenicity testing. *Mutat Res* 223:49-64.

Howd R, Rebert C, Dickinson J, Pryor GT 1983. Comparison of the rates of development of functional hexane neuropathy in weanling and young adult rats. *Neurobehav Toxicol Teratol* 5:63-68.

Huang C-C. 2008. Polyneuropathy induced by *n*-hexane intoxication in Taiwan. *Acta Neurologica Taiwanica* 17: 3-10.

Huang J, Kato K, Shibata E, Sugimura K, Hisanaga N, Ono Y, Takeuchi Y. 1989 Effects of chronic *n*-hexane exposure on nervous system-specific and muscle-specific proteins. *Arch Toxicol* 63:381-385.

Huang J, Shibata E, Kato K, Asaeda N, Takeuchi Y. 1992. Chronic exposure to *n*-hexane induces changes in nerve-specific marker proteins in the distal peripheral nerve of the rat. *Human & Experimental Toxicology* 11:323-327.

[HYDROWIN] Hydrolysis Rates Program for Microsoft Windows [Estimation Model]. 2000. Version 1.67. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Ikedo M, Koizumi A, Kasahara M, Fujita H. 1986. Combined effects of *n*-hexane and toluene on norepinephrine and dopamine levels in rat brain tissues after long-term exposures. *Bull Environ Contam Toxicol* 36:510-517.

International Labour Office. 1983. *Encyclopedia of Occupational Health and Safety*. Vols. I&II. Geneva, Switzerland: International Labour Office. p.1042 (cited in NLM 2005).

[IPCS] International Programme on Chemical Safety. 1991. *n*-Hexane. Geneva (CH): World health Organization. (Environmental Health Criteria 122). Jointly sponsored by the United Nations Environment Programme, the International Labour Organization, and the World Health Organization. Available from: <http://www.inchem.org/documents/ehc/ehc/ehc122.htm>

[IRDC] International Research and Development Corporation. 1992a. 6-Month continuous inhalation exposures of rats to hexane mixtures - Phase I. EPA Document No.FYI-0892-0901; NTIS No. OTS0000901K6.

[IRDC] International Research and Development Corporation. 1992b. 6-Month continuous inhalation exposures of rats to hexane mixtures - Phase II. EPA Document No. FYI-0892-0901; NTIS No. OTS0000901K5.

Ishidate M, Sofuni T, Yoshikawa K, Hayashi M, Nohmi T, Sawada M, Matsuoka A. 1984. Primary mutagenicity screening of food additives currently used in Japan. *Food Chem Toxicol* 22:623-636.

Issever H, Malat G, Sabuncu HH, Yuksel N. 2002. Impairment of colour vision in patients with *n*-hexane exposure-dependent toxic polyneuropathy. *Occup Med (Lond)*. 52(4):183-6.

Jet-Lube of Canada Ltd. 2007. Food Grade Silicone Aerosol. Material Safety Data Sheet [Internet]. Jet-Lube Canada Ltd. Edmonton, Alberta, Canada. [cited 2008-08-31] Available from: <http://www.jetlubecanada.com/Food%20Gd%20Sil%20msds.pdf>

Kasahara M, Suzuki H, Takeuchi Y, Hara I and Ikeda M. 1987. *n*-Hexane, benzene and other aromatic components in petroleum distillate solvents in Japan. *Industrial Health*. 25. 205-214 (cited in IPCS 1991).

Katagiri Y and Ohashi T. 1975. Photochemical reactions of hydrocarbons in smog chamber. Annual Report of the Kanagawa Prefectural Institute for Environmental Protection. 6. 47 (cited in IPCS 1991).

Khedun, SM; Maharaj, B; Naicker, T. 1996. Hexane cardiotoxicity—an experimental study. *Israel Journal of Medical Sciences* 32:123-128.

Kimura ET, Ebert DM, Dodge PW.1971. Acute toxicity and limits of solvent residue of sixteen organic solvents. *Toxicol Appl Pharmacol* 19:699-704.

Kinlin TE, Muralidhara R, Pittet AO, Sanderson A, Walradt JP. 1972. Volatile components of roasted filberts. *J Agric Food Chem* 20. 1021-1028.

[KOAWIN] Octanol Air Partition Coefficient Program for Microsoft Windows [Estimation Model]. 2004. Version 1.00. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Kool, H.J., C.L. Van Kreijl, and B.C.J. Zoetman BCJ. 1982. Toxicology assessment of organic compounds in drinking water. *CRC Crit Rev Environ Control* 12 (4):307-57.

[KOWWIN] Octanol-Water Partition Coefficient Program for Microsoft Windows [Estimation Model]. 2000. Version 1.67. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Krasavage WJ, O'Donoghue JL, DiVincenzo GD; Terhaar CJ 1980. The relative neurotoxicity of methyl-*n*-butyl ketone, *n*-hexane and their metabolites. *Toxicol Appl Pharmacol* 52:433-441.

Lankas G, Baxter C, Christian R. 1978 Effect of alkane tumor-promoting agents on chemically induced mutagenesis in cultured V79 Chinese hamster cells. *J Toxicol Environ Health* 4:37-42.

Lewis RJ. 1996. Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, p. 1800

- Lewis RJ, Sr (Ed.). 1997. Hawley's Condensed Chemical Dictionary. 13th ed. New York, NY: John Wiley & Sons, Inc. p.574 [cited in NLM 2005].
- Lide, DR, editor. 1997. CRC Handbook of Chemistry and Physics. 78th Edition. CRC Press, Inc. Boca Raton, FL.
- Linder RE, Strader LF, Slott VL, Suarez JD. 1992. Endpoints of spermatotoxicity in the rat after short duration exposures to fourteen reproductive toxicants. *Reprod Toxicol*. 6(6):491-505.
- Litton Bionetics Inc. 1980. Mutagenicity evaluation of *n*-hexane in the mouse dominant lethal assay [final report]. EPA Document No. FYI-AX-1081-0137; NTIS No. OTS0000137-0.
- Lungarella, G; Barni-Comparini, I; Fonzi, L. 1984. Pulmonary changes induced in rabbits by long-term exposure to *n*-hexane. *Arch Toxicol* 55:224-228.
- Lungarella, G; Fonzi, L; Centini, F. 1980. Respiratory tract lesions induced in rabbits by short-term exposure to *n*-hexane. *Res Commun Chem Pathol Pharmacol* 29:129-139.
- Marks TA, Fisher PW, Staples RE. 1980. Influence of *n*-hexane on embryo and fetal development in mice. *Drug Chem Toxicol*. 3(4):393-406.
- Mast, T. 1987. Inhalation developmental toxicology studies: Teratology study of *n*-hexane in rats [final report]. Public Health Service, U.S. Department of Health and Human Services; TER90082. Prepared by the Pacific Northwest Laboratory, Richland, WA, for the National Toxicology Program, National Institute for Environmental Health Services, Research Triangle Park, NC; PNL-6453.
- Mast T, Decker J, Stoney K, Westerberg R, Evanoff. 1988a. Inhalation developmental toxicology studies: Teratology study of *n*-hexane in mice [final report]. Public Health Service, U.S. Department of Health and Human Services; NTP TER90083. Prepared by the Pacific Northwest Laboratory, Richland, WA, for the National Toxicology Program, National Institute for Environmental Health Services, Research Triangle Park, NC; PNL-6590.
- Mast T, Hackett P, Decker J, Westerberg R, Sasser L, McClanahan B, Rommereim R, Evanoff J. 1988b. Inhalation reproductive toxicology studies: sperm morphology study of *n*-hexane in B6C3F1 mice. Prepared by the Pacific Northwest Laboratory Richland, WA, for the National Toxicology Program, National Institute for Environmental Health Services, Research Triangle Park, NC; PNL-6672. Available from: National Technical Information Service, Springfield, VA; NTIS No. DE89000262.
- Mast T, Rommereim R, Evanoff J, Sasser L, Decker J, Stoney K, Weigel R, Westerberg R. 1988c. Inhalation reproductive toxicology studies: male dominant lethal study of *n*-hexane in Swiss (CD-1) mice. Prepared by the Pacific Northwest Laboratory Richland, WA, for the National Toxicology Program, National Institute for Environmental Health Services, Research Triangle Park, NC; PNL-6679. Available from: National Technical Information Service, Springfield, VA; NTIS No. DE89000271.
- Mayer V, Goin C. 1994. Induction of chromosome loss in yeast by combined treatment with neurotoxic hexacarbons and monoketones. *Mutat Res* 341:83-91.
- McAuliffe, C. 1966. Solubility in Water of Paraffin, Cycloparaffin, Olefin, Acetylene, Cyclo-olefin and Aromatic Hydrocarbon. *J Phys Chem* 70:1267-75. [cited 2007 February]. [as cited in HSDB 1983-]
- McCarroll, N; Keech, B; Piper, C. 1981a. A microsuspension adaptation of the *Bacillus subtilis* "rec" assay. *Environ Mutagen* 3:607-616.
- McCarroll, N; Piper, C; Keech, B. 1981b. An *E. coli* microsuspension assay for the detection of DNA damage induced by direct-acting agents and promutagens. *Environ Mutagen* 3:429-444.

McKay WA, Turner MF, Jones BMR et al. 1996. Emission of hydrocarbons from marine phytoplankton – Some results from controlled laboratory experiments. *Atmospheric Environment* 30: 2583-2593. [Cited in ATSDR 1999.]

Mears DE, Eastman AD. 2005. Hydrocarbons. In: Kirk-Othmer Encyclopaedia of Chemical Technology. John Wiley & Sons, Inc. (updated 2007. searched June 18, 2007). Available from: <http://www.mrw.interscience.wiley.com/emrw/9780471238966/kirk/article/survmea.a01/current/pdf>

Mortelmans, K; Haworth, S; Lawlor, T; Speck W; Tainer B; Zeiger E. 1986. Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. *Environ Mutagen* 8(Suppl 7):1-119.

[MPBPWIN] Melting Point Boiling Point Program for Microsoft Windows [Estimation Model]. 2000. Version 1.41. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Mutti A, Cavatorta A, Lommi G, Lotta S, Franchini I. 1982. Neurophysiological effects of long-term exposure to hydrocarbon mixtures. *Arch Toxicol Suppl.* 5:120-4.

[NAPS] National Air Pollutants Surveillance Network. 2000 – 2008. [Prepublication NAPS data on Excel spreadsheet] Environment Canada. Air Monitoring Data.

[NCI] National Chemical Inventories [Database on a CD-ROM]. 2007. Issue 1. Columbus (OH): American Chemical Society. [cited 2008 Feb]. Available from: <http://www.cas.org/products/cd/nci/require.html>

[NIOSH] National Institute for Occupational Safety and Health. 1977. Criteria for a recommended standard: Occupational exposure to alkanes (C5-C8). DHEW (NIOSH) Publication No. 77-151. Cincinnati, Ohio, USA [cited in IPCS 1991].

[NIOSH] National Institute for Occupational Safety and Health. 1994. NIOSH Pocket Guide to Chemical Hazards. DHHS (NIOSH) Publication No. 94-116. Washington, D.C.: U.S. Government Printing Office, June, p.162 [cited in NLM 2005].

[NITE] National Institute of Technology and Evaluation. 2002. Biodegradation and Bioconcentration of the Existing Chemical Substances under the Chemical Substances Control Law. [cited 2007 March]. Available from: http://www.safe.nite.go.jp/data/hazkizon/pk_e_kizon_input_second.home_object

[NLM] National Library of Medicine. 2005. Hazardous Substances Data Bank (HSDB). Available from: <http://www.toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB>.

[NPRI] National Pollutant Release Inventory. 2008. Gatineau (QC): Environment Canada. [last updated 2008-06-09; last reviewed 2008-06-09; cited September 2008]. Available from: http://www.ec.gc.ca/pdb/querysite/query_e.cfm

[NTP] National Toxicology Program. 1991. Toxicity studies of *n*-hexane in B6C3F1 mice (inhalation studies). Public Health Service, U.S. Department of Health and Human Services; TOX-2. Available from: National Institute for Environmental Health Services, Research Triangle Park, NC.

Nylén, P, Ebendal T, Eriksdotter-Nilsson M, Hansson T, Henschen A, Johnson A-C, Kronevi T, Kvist U, Sjöstrand NO, Höglund G, Olson L. 1989. Testicular atrophy and loss of nerve growth factor-immunoreactive germ cell line in rats exposed to *n*-hexane and a protective effect of simultaneous exposure to toluene or xylene. *Arch Toxicol.* 63: 296-307.

O'Neil, M.J. (ed.). 2001. The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. 13th Edition, Whitehouse Station, NJ: Merck and Co., Inc., p. 837

Ono, Y., Y. Takeuchi and N. Hisanaga. 1981. A comparative study on the toxicity of *n*-hexane and its isomers on the peripheral nerve. *Int. Arch. Occup. Environ. Health* 48: 289-294 [cited in U.S. EPA, 2005b].

Ono, Y; Takeuchi, Y; Hisanaga, N; Hisanaga N, Iwata M, Kitoh J, Sugiura Y. 1982. Neurotoxicity of petroleum benzene compared with *n*-hexane. *Int Arch Occup Environ Health* 50:219-229.

[OMEE] Ontario Ministry of Environment and Energy. 2000. Air Quality in Ontario 2000 Report [Internet]. Toronto (ON): the Ministry. Available from: <http://www.ene.gov.on.ca/envision/air/AirQuality/2000report.htm>

[OMOE] Ontario Ministry of Environment. 2005. Ontario Air Standards for *n*-Hexane Standards Development Branch. [cited in CCME 2008].

[OECD]. Organization for Economic Co-ordination and Development. 2004. The 2004 OECD List of High Production Volume Chemicals. Paris, France. <http://www.oecd.org/dataoecd/55/38/33883530.pdf>.

Otson R and Zhu J. 1997. In proceedings of the Air & Waste Management Association's 90th Annual Meeting and Exhibition. Toronto. ON. June 1997. Paper No. 97-TP54.02. [cited in CCME 2008]

Overton SV and Manura JJ. 1995. Analysis of volatile organics in cooking oils by thermal desorption-gas chromatography-mass spectrometry. *Journal of Agricultural and Food Chemistry*, 43: 1314-1320.

[PACE] PACE Gasoline Exposure Study Task Force. 1987. A Study of Exposure to Motor Gasoline Hydrocarbon Vapours at Service Stations (Phase II-Summer Study). PACE Report No. 87-5.

[PACE] PACE Gasoline Exposure Study Task Force. 1989. A Study of Exposure to Motor Gasoline Hydrocarbon Vapours at Service Stations (Phase III-Winter Study). PACE Report No. 89-3.

Panigrahi, A.K., and S.K. Konar. 1989. Acute Toxicity of Some Petroleum Pollutants to Plankton, Fish and Benthic Organism. *Environ.Ecol.* 7(1):44-49

[PCKOCWIN] Organic Carbon Partition Coefficient Program for Microsoft Windows [Estimation Model]. 2000. Version 1.66. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

Pellizzari ED, Hartwell TD, Harris III BSH. 1982. Purgeable organic compounds in mother's milk. *Bulletin of Environmental Contamination and Toxicology*. 28(3):322-328.

Permatex. 2003. Material Safety Data Sheet. [Internet] DCD-19 Weatherstrip cement 2FO. Permatex, Inc. Hartford, CT, USA [cited 2008-08-31] Available from: http://www.permatex.com/documents/msds/01_USA-English/80328.pdf

Permatex Canada. 2004. Material Safety Data Sheet. [Internet] 82 Black Super Weatherstrip Adhesive. 5 Fl.oz. Item No. 81850. Permatex Canada, Inc. Mississauga, ON, Canada. [cited 2008-08-31] Available from: <http://ccinfoweb.ccohs.ca/msds/pdf/permatex/4985703.pdf>

Permatex Canada. 2005. Material Safety Data Sheet. [Internet] PC Heavy Duty Spray Adhesive. 10 PC Heavy Duty Spray Adhesive 311GR AE 10-30% Item No: 30224. Permatex Canada, Inc. Mississauga, ON Canada. Available from: <http://ccinfoweb.ccohs.ca/msds/pdf/permatex/4985425.pdf>

Permatex Canada. 2007. Material Safety Data Sheet (MSDS). 98D High Track Gasket Sealant. Permatex Canada, Inc. Milton, ON, Canada. Equivalent US product MSDS available from: http://www.permatex.com/documents/msds/03_Canada-English/80063_03.pdf

- Perocco P, Bolognesi S, Alberghini W. 1983. Toxic activity of seventeen industrial solvents and halogenated compounds on human lymphocytes cultured in vitro. *Toxicol Lett* 16:69-75.
- [PMRA] Pest Management Regulatory Agency. 2007. Regulatory Note REG 2007-04: PMRA list of formulants [Internet]. Ottawa (ON): Health Canada, Pest Management Regulatory Agency. Available from: <http://www.pmr-arla.gc.ca/english/pdf/reg/reg2007-04-e.pdf>
- [PhysProp] Interactive PhysProp Database [Database on the Internet]. 2007. Syracuse (NY): Syracuse Research Corporation. [cited 2007 February]. Available from: <http://www.syrres.com/esc/physdemo.htm>
- Pryor G, Dickinson J, Howd R, Rebert C. 1983. Neurobehavioral effects of subchronic exposure of weanling rats. *Neurobehav Toxicol Teratol* 5:47-52.
- Raitta C, Seppäläinen AN, Huuskonen MS. 1978. *n*-hexane maculopathy in industrial workers. *Albrecht Von Graefes Arch Klin Exp Ophthalmol* 209:99-110.
- Rembold H, Wallner P, Nitz S, Kollmannsberger H, Drawert F. 1989. Volatile components of chickpea (*Cicer arietinum* L.) seed. *J. Agric. Food Chem.* 37. 659 – 662.
- Rinnan R, Rinnan A, Holopainen T, Holopainen J and Pasanen P. 2005. Emission of non-methane volatile organic compounds (VOCs) from boreal peatland microcosms – effects of ozone exposure. *Atmospheric Environment*, 39: 921-930.
- [RIVM] Rijksinstituut voor Volksgezondheid en Milieu. 2006. Consumer Exposure (ConsExpo) Model [Internet]. Version 4.1. The Netherlands: The National Institute for Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu). Available from: <http://www.rivm.nl/en/healthanddisease/productsafety/ConsExpo.jsp#tcm:13-42840>
- Sahu SC, Lowther DK, Jones SL. 1982. Biochemical response of rat lung to inhaled *n*-hexane. *Toxicol Lett* 12:13-17.
- Sanagi S, Seki Y, Sugimoto K, Hirata M. 1980. Peripheral nervous system functions of workers exposed to *n*-hexane at a low level. *Int Arch Occup Environ Health* 47:69-79. [cited in US EPA 2005].
- Sandmeyer EE. 1981. Aliphatic hydrocarbons. In: Clayton, G.D. & Clayton, F.E., ed. *Patty's industrial hygiene and toxicology*. 3rd ed. New York, Chichester, Brisbane, Toronto. John Wiley and Sons. Vol.2B. pp.3175-3220. [cited in IPCS 1991].
- Sauer TC Jr. 1981. Volatile organic compounds in open and coastal surface waters. *Organic Geochemistry*. *Organic Geochemistry*. 3(3): 99-101 [cited in NLM 2005].
- Sauer, TC, Sackett, WM and Jeffrey, LM. 1978. VLHs in the surface coastal waters of the Gulf of Mexico. *Mar. Chem.* 7, pp. 1–16.
- Seppäläinen AM, Raitta C, Huuskonen MS. 1979. *n*-Hexane-induced changes in visual evoked potentials and electroretinograms of industrial workers. *Electroencephalogr Clin Neurophysiol.* 47(4):492-8.
- Shamsky S, Samimi B. 1987. Organic vapors at underground gasoline tank removal sites. *Applied Industrial Hygiene*. 2:242-5 [cited in NLM 2005].
- Shelby, M, Witt, K. 1995. Comparison of results from mouse bone marrow chromosome aberration and micronucleus tests. *Environ Mol Mutagen* 25:302-313.
- Snell, T.W., B.D. Moffat, C. Janssen, and G. Persoone. 1991a. Acute Toxicity Tests Using Rotifers IV. Effects of Cyst Age, Temperature, and Salinity on the Sensitivity of *Brachionus calyciflorus*. *Ecotoxicol. Environ. Saf.* 21(3):308-317

Snell, T.W., B.D. Moffat, C. Janssen, and G. Persoone. 1991b. Acute Toxicity Tests Using Rotifers. III. Effects of Temperature, Strain, and Exposure Time on the Sensitivity of *Brachionus plicatilis*. *Environ.Toxicol.Water Qual.* 6:63-75

Solano-Serena F et al. 2000 Biodegradability of volatile hydrocarbons of gasoline. *Applied Microbiology and Biotechnology.* 54: 121-25 (cited in NLM 2005)

Statistics Canada. 2006. The Supply and Disposition of Refined petroleum Products in Canada. December 2006. Catalogue no. 45-004-XIE. Available from: <http://www.statcan.gc.ca/cgi-bin/af-fdr.cgi?l=eng&loc=http://www.statcan.gc.ca/pub/45-004-x/45-004-x2006012-eng.pdf&t=The%20Supply%20and%20Disposition%20of%20Refined%20Petroleum%20Products%20in%20Canada>

Stoltenburg-Didinger G, Altenkirch H, Wagner M. 1990. Neurotoxicity of organic solvent mixtures: embryotoxicity and fetotoxicity. *Neurotoxicol Teratol.* 12(6):585-9.

[TNO] Nederlandse organisatie voor Toegepast Natuurwetenschappelijk Onderzoek. 1987. Aquatic Toxicity of Compounds That May Be Carried By Ships (MARPOL 1973, ANNEX II). A Progress Report for 1986. Report number R86/326a. Order Number 16603. Delft, The Netherlands. May 8, 1987.

[TOPKAT] Toxicity Prediction Program [Internet]. 2004. Version 6.2. San Diego (CA): Accelrys Software Inc. Available from: <http://www.accelrys.com/products/topkat/index.html>

[TSCATS] Toxic Substance Control Act Test Submission [database on the internet]. 2008. Syracuse Research Corporation, USA. [cited Oct 2008] Available From: <http://esc.syrres.com/scripts/tscacgi.exe>

Tsuruta H. 1980. Microdetermination of *n*-hexane in biological samples by gas chromatography-mass spectrometry. *Industrial Health* 18: 113-115.

[US EPA] United States Environmental Protection Agency. 1986. Standard scenarios for estimating exposure to chemical substances during use of consumer products, volumes 1 & 2. Washington (DC): prepared for the US EPA, Office of Toxic Substances, Exposure Evaluation Division, by Versar, Inc. Contract no. 68-02-3968.

[US EPA] United States Environmental Protection Agency. 1990. High production volume (HPV) challenge program: the HPV voluntary challenge chemical list. Washington (DC): U.S. Environmental Protection Agency. Available from: <http://www.epa.gov/hpv/pubs/update/hpvchmlt.htm>

[US EPA] United States Environmental Protection Agency. 1994. Automobile Emissions: an Overview. EPA 400-F-92-007. Ann Arbor, MI: U.S. EPA, Office of Mobile Sources, National Vehicle and Fuel Emissions Laboratory (cited in ATSDR 1999).

[US EPA] United States Environmental Protection Agency. 2002. PBT Profiler Methodology [Internet]. Washington (DC): US EPA, Office of Pollution Prevention and Toxics [cited August 2008]. Available from: <http://www.pbtprofiler.net/methodology.asp>

[US EPA] United States Environmental Protection Agency. 2005. Toxicological review of *n*-hexane (CAS No. 110-54-3) in support of summary information on the Integrated Risk Information System (IRIS). EPA/635/R-03/012. 141 pp. plus appendices.

Verschuere K. 2001. Handbook of Environmental Data on Organic Chemicals. Volumes 1-2. 4th ed. John Wiley & Sons. New York, NY. 2001, p. 1269 and p. 1271

Veulemans H, Van Vlem E, Janssens H, Masschelein R, Leplat A. 1982. Experimental human exposure to *n*-hexane. Study of the respiratory uptake and elimination, and of *n*-hexane concentrations in peripheral venous blood. *Int Arch Occup Environ Health* 49:251-263. [cited in US EPA 2005].

Ville de Montréal. 2002. Réseau de surveillance de la qualité de l'air de la Ville de Montréal. Montréal (QC): Ville de Montréal, Direction de l'environnement, Réseau de Surveillance de la Qualité de l'Air. Available from:
http://ville.montreal.qc.ca/pls/portal/docs/page/rsqa_fr/media/documents/rapport_donnees_2002.pdf

[WATERNT] Water Solubility Program [Estimation Model]. 2002. Version 1.00. Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from: www.epa.gov/oppt/exposure/pubs/episuite.htm

[WSKOWWIN] Water Solubility for Organic Compounds Program for Microsoft Windows [Estimation Model]. 2000. Version 1.41 Washington (DC): US Environmental Protection Agency, Office of Pollution Prevention and Toxics; Syracuse (NY): Syracuse Research Corporation. Available from:
www.epa.gov/oppt/exposure/pubs/episuite.htm

Appendix 1a: Upper-bounding estimates of daily intake of n-hexane by the various age groups of the general population in Canada (µg/kg-bw per day)

Route of Exposure	0 - 0.5 years ^{1,2,3}			0.5 - 4 years ⁴	5 - 11 years ⁵	12 - 19 years ⁶	20 - 59 years ⁷	60 + years ⁸
	Breast Milk Fed	Formula Fed	Not Formula Fed					
Ambient Air ⁹	9.86	9.86	9.86	21.1	16.5	9.37	8.05	6.99
Indoor Air ¹⁰	33.9	33.9	33.9	72.5	56.5	32.2	27.6	24.0
Drinking Water ¹¹	N/A *	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Soil ¹²	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Total without Food	43.7	43.7	43.7	93.7	73.0	41.5	35.7	31.0
Estimated Total with Food ¹³	44.6	44.6	44.6	95.5	74.4	42.3	36.4	31.6

* Not applicable

¹ Hexane was detected in 8 out of 12 samples of breast milk but not quantified in the USA (Pellizzari et al. 1982).

No quantified data available for concentrations of hexane in breast milk.

² Assumed to weigh 7.5 kg, to breathe 2.1 m³ of air per day, to drink 0.8 L of water per day (formula-fed) or 0.3 L/day (not formula-fed) and to ingest 30 mg of soil per day (Health Canada 1998).

³ For exclusively formula-fed infants, intake from water is synonymous with intake from food. The concentration of hexane in water used to reconstitute formula was based on modelling. No data on concentrations of hexane in formula were identified for Canada or elsewhere. Approximately 50% of not formula-fed infants are introduced to solid foods by 4 months of age and 90% by 6 months of age (NHW 1990 in Health Canada 1998).

⁴ Assumed to weigh 15.5 kg, to breathe 9.3 m³ of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day (Health Canada 1998).

⁵ Assumed to weigh 31.0 kg, to breathe 14.5 m³ of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day (Health Canada 1998).

⁶ Assumed to weigh 59.4 kg, to breathe 15.8 m³ of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).

⁷ Assumed to weigh 70.9 kg, to breathe 16.2 m³ of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).

⁸ Assumed to weigh 72.0 kg, to breathe 14.3 m³ of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).

⁹ The highest concentration of hexane in ambient air reported, 281.680 µg/m³, at NAPS station (residential area in Windsor, Ontario, 2002), was used to calculate the upper bounding limit of exposure estimate (NAPS 2002). The critical data were selected from a dataset of Canadian studies on hexane concentration in ambient air reported between 1992 and 2008 (AENV 2004; Gouvernement du Québec 2002; OMEE 2000; Ville de Montréal 2002; Health Canada 2008; NAPS 2000 – 2008; OMOE 2005). Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998).

¹⁰ The highest concentration of hexane in indoor air reported, 138.157 µg/m³, in Windsor, Ontario, was used to calculate the upper bounding limit of exposure estimate (Health Canada 2008). The critical data were selected from a dataset of Canadian studies on hexane concentration in ambient air reported between 1991 and 2008 (Bell et al. 1991; Davis and Otson 1996; Fellin et al 1992; Fellin and Otson 1997; Health Canada 2008; Otson and Zhu 1997). Canadians are assumed to spend 21 hours indoors each day (Health Canada 1998).

¹¹ No Canadian specific data on concentration of hexane in drinking water was identified. Modelling using ChemCAN 6.0 (ChemCAN 2003) and selecting Average for Canada region, indicated that the concentration of hexane in water would be approximately 6x10⁻⁴ ng/L, based on 4438 tonnes of hexane released to air reported under NPRI in 2006 (NPRI 2008).

¹² No measured data were identified. Modelling using ChemCAN 6.0 (ChemCAN 2003) and selecting average for Canada region, indicated that the concentration of hexane in soil would be approximately 1.96x10⁻⁴ µg/kg, based on 4438 tonnes of hexane released to air reported under NPRI in 2006 (NPRI 2008).

¹³ Total estimate with food was calculated based on the data obtained from Food directorate (Health Products and Food Branch, Health Canada) in the respective age groups (Appendix 1b). In the two age groups where highest consumption of hexane was estimated, food contributed 1.95% of total intake which was applied to all age groups.

*Appendix 1b: Upper-bounding estimates of daily intake of *n*-hexane from foods based on the level of residual *n*-hexane typically found in refined vegetable oils (0.8 ppm)*

Age group	Percentile	Intakes of vegetable fats and oils from all food sources (g/kg-bw/day) ¹	Daily intake of <i>n</i> -hexane (µg/kg-bw/day)
6-8 yrs	50%	0.73	0.58
	90%	1.58	1.26
	95%	1.81	1.45
19-30 yrs	50%	0.28	0.22
	90%	0.71	0.57
	95%	0.87	0.70

¹ Health Canada and Canadian Heart Health Initiative (CHHI). Vegetable Fats and Oils Intake Figures derived from Federal-Provincial Nutrition Surveys (1990's). Data generated by the Division of Statistics and Epidemiology, Bureau of Biostatistics and Computer Applications, Health Products and Food Branch. Unpublished document; available upon request

Notes:

- Percentage of *n*-hexane in commercial hexanes can range from 20-80% (IPCS 1991). Therefore, daily intake estimates for *n*-hexane are based on 80% of the level of residual hexanes typically found in refined vegetable oils, as indicated by the Institute of Shortening and Edible Oils (1 ppm).
- The age groups listed above are the specific child and adult age groups with the highest consumption of vegetable fats and oils relative to other age groups.
- While hexane is listed in the *Food and Drug Regulation* (FDR) for use in hop extract, the Brewers Association of Canada has indicated that hexane has not been used as an extraction solvent for hops since 2000. It has been replaced mainly by carbon dioxide. In addition, the Association has indicated that all inventories of hop extracts that would have used hexane are likely no longer on the market.
- Hexane is listed in the FDR for use in spice extracts, natural extractives and vegetable oil seed meals. While no consumption data were available for these food ingredients, their contribution to the total diet is considered negligible in comparison to vegetable fats and oils. In addition, the Canadian Spice Association has stated that hexane residues in spice extracts are typically in the 5-15 ppm range and spice extracts themselves are typically found in the final food as consumed in the 0.01-0.05% range. Based on these usage levels, typical hexane residues in the final food would be < 0.0015 ppm, significantly less than the 1 ppm level that may be found in refined vegetable oils.
- The FDR lists several alternate extraction solvents in addition to hexane that may be used in or upon spice extracts, natural extractives and vegetable oil seed meals.

Appendix 2: Summary of health effects information for *n*-hexane

Endpoint	Lowest effect level/Results
Laboratory animals and in vitro	
Acute toxicity	Lowest inhalation LC50 (mice, 4-hr exposure) = 169 168 mg/m³ (48 000 ppm) (O'Neil 2001). Lowest oral LD50 (rat) = 15 840, 29 700 and 28 710 mg/kg-bw in 14-days old young adults and older adults Sprague-Dawley rats, respectively (Kimura et al. 1971). No dermal LD50 was identified.
Short-term repeated-dose toxicity	Lowest inhalation LOEC: 705 mg/m³ (200 ppm) based on decreased body weight gain in male Wistar rats exposed to 0, 705 or 1410 mg/m³ (0, 200 or 400 ppm) continuously for 30 days through inhalation. The effect was also significant at 1410 mg/m³. At 1410 mg/m³ significant increases in norepinephrine levels were observed in the thalamus, dorsal, olfactory and frontal cortex, and cerebellum (Ikeda et al. 1986). Other inhalation LOEC: 1678 mg/m³ (476 ppm) based on increased dose-related pulmonary secretions (both enzymatic and non-enzymatic biochemicals) in male Sprague-Dawley rats exposed to 0, 1678, 4950, 5907 mg/m³ (0, 476, 1149 or 1675 ppm) for 6 hrs/day, 5 days/week for 4 weeks through whole body inhalation (Sahu et al. 1982). Other inhalation studies: Lungarella et al. 1980, Barni-Comparini et al. 1982, Howd et al. 1983. Lowest oral LOEL: 189 mg/kg-bw/day based on statistically significant reduction in ventricular fibrillation threshold, and decreased levels of myocardial magnesium and potassium, and changes in the ultrastructure of the myocardium in male Wistar rats exposed to 0 or 189 mg/kg/day for 30 days through gavage (Khedun et al. 1996). Other oral studies: Ono et al. 1981. No dermal studies were identified.
Subchronic toxicity	Lowest inhalation LOEC: 705 mg/m³ (200 ppm) based on decreased distal latency, motor nerve conduction velocity and mixed nerve conduction velocity (distal and, distal plus proximal combined) in male Wistar rats exposed to 0, 705, 1762 mg/m³ (0, 200 or 500 ppm) <i>n</i>-hexane by whole body inhalation, 12hrs/day for 24 weeks. Degenerations of the myelin sheaths and axons were observed at all doses. Histopathological examination was performed on only one animal per dose-group. No clinical signs of neuropathy were observed at any concentration (Ono et al. 1982). Other inhalation LOEC: Male Wistar rats were exposed to 0, 1762, 4230 or 10574 mg/m³ (0, 500, 1200 or 3000 ppm), 12 hrs/day, 7 days/week for 16 weeks through whole body inhalation. A statistically significant decrease in nervous system-specific protein β-S-100 was observed in all dose-groups. The following effects were observed in both mid- and high-dose groups: reduction in grip strength, slowness of motion, decreased motor nerve conduction velocity, increased incidence of paranodal swelling with demyelination and remyelination of the peripheral nerves.

Endpoint	Lowest effect level/Results
	Body weight gain and motor nerve conduction velocity decreased in a concentration-dependant manner. Histological examination was performed in one animal per dose-group (Huang et al. 1989). Other inhalation studies: Male and female F344 rats were exposed to 0, 10573, 22908, 35243 mg/m³ (0, 3000, 6500 or 10000 ppm) 6 hrs/day, 5 days/week for 13 weeks through whole body inhalation. Early stage of paranodal swellings of the tibial nerve were observed in 1/5 and 4/5 male rats at 6500 and 10000 ppm respectively, and were present in less than 5% of the teased nerves examined. One male showed greatly enlarged axons in the medulla. No clinical signs of neurotoxicity were observed. Other effects included exposure related decrease in body weight gain and decreased brain weight at 10000 ppm in male rats (Cavender et al. 1984). Male and female mice were exposed to 0, 1762, 3524, 14097 or 35243 mg/m³ (0, 500, 1000, 4000 or 100000 ppm) 6 hrs/day, 5 days/week for 13 weeks through whole body inhalation. At 10000 ppm, locomotor activity was decreased in female mice, and paranodal swellings of the tibial nerve was observed in ¾ males and ¾ females. Non-neurotoxic effects included dose-related (except in females at 4000 ppm where effects were reduced) inflammatory, erosive and regenerative lesions of the nasal turbinates. Most males and females were affected at 10000 ppm, but fewer males were affected at lower exposure (NTP 1991). Other inhalation studies: Pryor et al. 1983, Howd et al. 1983, Huang et al. 1992, Biodynamics 1978, IRDC 1992a,b, Lungarella et al.1984. Lowest oral LOEL: 570 mg/kg-bw/day based on decreased body weight gain in male CD (SD) BR rats exposed to 0, 570, 1140 or 4000 mg/kg-bw/day, 5days/week for 90 days (120 days for the high dose group) through gavage. Other effects, observed in the high dose group only, included severe hindlimb weakness or paralysis with dragging of at least one hind foot and morphologic changes in nerve tissue (multifocal axonal swelling, adaxonal myelin infolding and paranodal myelin retraction) (Krasavage et al. 1980). No other adequate oral study has been identified. No dermal studies were identified.
Chronic toxicity	No chronic studies were identified.
Carcinogenicity	New Zealand White rabbits were exposed to 0 or 10573 mg/m³ (0 or 3000 ppm) 8 hrs/day, 5 days/week for 24 weeks by whole body inhalation during a lung morphology study. Irregular foci of cellular proliferation and papillary tumours (but incidences were not reported) in terminal bronchioles and in alveolar ducts were observed at both 1 and 120 days post exposure, and were comparable between the 1-day and the 120-day post exposure groups (Lungarella et al.1984). No other studies identified.
Genotoxicity <i>in vivo</i>	Dominant lethal assay: Negative: CD-1 male mice, (0, 705, 1410 mg/m³ [0,100, 400 ppm] by whole body inhalation 6 hrs/day, 5 days/week for 8 weeks (Litton Bionetics 1980). Negative: male CD-1 mice, (0, 705, 3524, 17622 mg/m³ [0, 200, 1000, 5000 ppm] by whole body inhalation, 20 hrs/day, 5 days (Mast et al.

Endpoint	Lowest effect level/Results
	1988c). Chromosome aberrations: Positive: bone marrow cells, male Sprague-Dawley CD rats, inhalation (0, 529, 1057, 2115 mg/m³ (0, 150, 300, 600 ppm), 6 hrs/day, 5 days). (Hazleton Laboratories America Inc. 1992) Positive: bone marrow cells, male Sprague-Dawley CD albino, inhalation (0, 352, 1410 mg/m³ (0, 100, 400 ppm), 6 hrs/day, 5 days/week for 4 weeks). (Hazleton Laboratories America Inc. 1992) Negative: bone marrow cells, B6C3F1 mice, intraperitoneal (Shelby and Witt 1995) Negative: bone marrow cells, mice, intraperitoneal (500, 1000 or 2000 mg/kg), (NTP 1991) Micronuclei Negative: bone marrow cells, B6C3F1 mice, intraperitoneal (Shelby and Witt 1995) Negative: bone marrow cells, mice, intraperitoneal (500, 1000 or 2000 mg/kg) nonchromatic and polychromatic erythrocytes (NTP 1991) Sister chromatid exchange Negative: bone marrow cells, mice, intraperitoneal (500, 1000 or 2000 mg/kg, NTP 1991)
Genotoxicity <i>in vitro</i>	Mutagenicity: Negative: <i>Salmonella typhimurium</i> TA98, TA1535, TA1537, TA1538 with and without activation (Hazleton Laboratories America Inc. 1979) Positive: <i>Salmonella typhimurium</i> TA100, without activation (Hazleton Laboratories America Inc. 1979) Negative: L5178Y mouse lymphoma cells (TK locus), with and without activation (Hazleton Laboratories America Inc. 1992) Negative: <i>Salmonella typhimurium</i> TA98, TA100, TA1535, TA1537, with and without activation (Mortelmans et al. 1986) Negative: <i>Salmonella typhimurium</i> TA92, TA94, TA98, TA100, TA1535, TA1537, presence or absence of activator not specified (Ishidate et al. 1984) Negative: <i>Salmonella typhimurium</i> TA98, TA100, with and without activation, considered insignificant by authors (Houk et al. 1989) Chromosome aberrations: Negative: Chinese hamster ovary cells, with and without activation (NTP 1991) Borderline positive: <i>Saccharomyces cerevisiae</i> D61.M, without activation, chromosomal loss (Mayer and Goin 1994) Borderline positive: Chinese hamster fibroblasts, without activation, polyploidy (Ishidate et al. 1984) Sister chromatid exchange: Negative: CHO cells, without activation (NTP 1991) Borderline positive: CHO cells, with activation (NTP 1991) DNA damage: Negative: <i>Escherichia coli</i> WP2, WP2urvA, WP67, CM611, WP100, W3110polA+, P3478pol-, with and without activation (McCarroll et al. 1981a)

Endpoint	Lowest effect level/Results
	Negative: <i>Bacillus subtilis</i> H17, M45, with and without activation (McCarroll et al. 1981b) Negative: Chinese hamster cells V79, without activation, induction/promotion (Lankas et al. 1978) Borderline positive: Human lymphocytes, without activation, inhibition of DNA synthesis (Perocco et al. 1983) Negative: Human lymphocytes, with activation, inhibition of DNA synthesis (Perocco et al. 1983)
Developmental toxicity	Lowest inhalation LOEC for developmental toxicity: 705 mg/m³ (200 ppm) based on increased total intrauterine death (early plus late resorptions) in female Swiss CD-1 mice exposed to 0, 705, 3524, 17622 mg/m³ (0, 200, 1000 or 5000 ppm) by whole body inhalation 20 hrs/day on days 6-17 of gestation. At 17622 mg/m³ (5000 ppm), late resorptions were significantly increased and there was a reduction in maternal body weight at day 18 of gestation, a decrease in the gravid uterine weight to extragestational weight gain ratio, and a decrease in total cumulative weight gain for dams, which was believed to be due to the reduction in gravid uterine weight rather than to a decrease in extragestational gain. <i>n</i>-Hexane was not teratogenic (Mast et al. 1988a). Other inhalation studies: Bus et al. 1979; Mast 1987; Stoltenburg-Didinger et al. 1990. Lowest oral LOEL for developmental toxicity: 7920 mg/kg-bw/day based on decreased average foetal weight. Female CD-1 mice were exposed by gavage to 0, 260, 660, 1320 or 2200 mg/kg-bw/day of <i>n</i>-hexane in cottonseed oil in one dose (<i>die</i>), or to 0, 2170, 2830, 7920 or 9900 mg/kg-bw/day of <i>n</i>-hexane in cottonseed oil administered in three doses (<i>tid</i>) on days 6-15 of gestation. Other effects included decreased average maternal weight gain in the 2200 mg/kg-bw/day <i>die</i> group and the 2170 mg/kg-bw/day <i>tid</i>. <i>n</i>-Hexane was not teratogenic in this study (Marks et al. 1980). No other oral developmental studies identified. No dermal developmental studies identified.
Reproductive toxicity	Lowest inhalation LOEC for male reproductive toxicity: 3524 mg/m³ (1000 ppm) based on bilateral testicular damage (decreased size and weight of testes, atrophy of seminiferous tubules and loss of nerve growth factor-immunoreactive cell population) observed 2 weeks and 10 months after cessation of <i>n</i>-hexane exposure in male Sprague-Dawley rats exposed to 0 or 3523 mg/m³ by whole body inhalation for 18 hrs/day, 7 days/week for 61 days. (Atrophy of hindlimb muscles occurred in all animals with testicular damage). Total loss of germ cell line occurred in a few animals up to 14 months post-exposure (Nylén et al 1989). Other inhalation studies: Male Sprague-Dawley rats were exposed to 0 or 17622 mg/m³ (0 or 5000 ppm) by whole body inhalation for either a single 24 hrs exposure, 16 hrs/day for up to 8 days or for 6 days/week up to 6 weeks. Animals sacrificed at various time intervals after exposure (0, 2, 7, 14, 30 days) for histological examination. Focal degeneration of spermatocytes and mild exfoliation of elongated spermatids were observed and occurred earliest after the 24 hour treatment. Other effects observed at the various time intervals included the presence of degenerating germ cells and inflammatory cells in seminiferous tubules. The severity of the lesions

Endpoint	Lowest effect level/Results
	increased with the length of exposure, and extended treatment resulted in reduction in diameter and collapse of the tubules, including aplastic tubules. The testes and/or epididymides of all rats were affected after 3 weeks in the group exposed up to 6 weeks (De Martino et al. 1987). Male B6C3F1 mice were exposed to 0, 705, 3524 or 17622 mg/m³ (0, 200, 1000 or 5000 ppm) by whole body inhalation (20 hrs/day for 5 days). Animals were sacrificed 5 weeks post-exposure for examination. No significant effects on the morphology of the sperm or on the classes of abnormalities were detected, and no evidence of lesions was noted in the reproductive tract (Mast et al, 1988b). Lowest oral LOEL for male reproductive toxicity: 4000 mg/kg-bw/day based on atrophy of the germinal epithelium in male CD (SD) BR rats exposed to 0, 570, 1140 or 4000 mg/kg-bw/day for 90 days (120 days for the 4000 mg/kg-bw/day group) (Krasavage et al. 1980). Other oral study: Male Sprague-Dawley rats were exposed to 0 or 20000 mg/kg-bw/day for 1 day (administered in 2 separate doses of 10000 mg/kg-bw/day) or 0 or 10000 mg/kg/day for 5 days through oral gavage. Animals were sacrificed on day 2 or 14 in the single day exposure group, and on day 8 or 17 in the 5-day exposure group. Although some statistically significant changes were noted in organ weight, total sperm head count and cauda count for either the 1- or 5-day exposure, the effects were considered not to be due to treatment by the authors because of the small sample size and endpoints which showed unlikely direction of change compared to controls or the lack of effects in related endpoints (Linder et al. 1992). Female reproductive toxicity: No study specifically designed to assess female reproductive system effects have been identified. No dermal studies assessing reproductive endpoints were identified.
Humans	
Neurotoxicity	Three of the most pertinent epidemiology studies are described below. Note that several other inhalation epidemiology studies are described in US EPA (2005). Those mentioned by Huang (2008) are also described in US EPA (2005). Neurophysiological effects were monitored in 95 shoe factory apparently healthy workers (24 males and 71 females) exposed to a hydrocarbon mixture including <i>n</i>-hexane. Mean exposure time was 9.1 years (SD 8.0, range 1-25). Results were compared to a reference group composed of 52 workers from the same factory. Mean employment time was 10.2 years (SD 9.7, range 4 months to 29 years). Exposed workers were separated into two groups according to the exposure in their main jobs. <i>n</i>-Hexane time weighted average (TWA) concentrations for the mild and high exposure group were 243 and 474 mg/m³ (69 and 135 ppm) respectively, and are based on breathing zone samples. Cyclohexane, methyl ethyl ketone and ethyl acetate were also detected and quantified. The following neurological symptoms were more frequent in all exposed workers: sleepiness, dizziness, weakness in limbs, hypoesthesia and paraesthesia. Motor action potential (MAP) was reduced in median, ulnar and peroneal nerves in both mild and high exposure groups. In the high exposure group, MAP duration in the ulnar and median nerves was increased and motor nerve conduction velocity (MCV) was decreased in the median and

Endpoint	Lowest effect level/Results
	peroneal nerves. All effects were statistically significant. An exposure-related trend was noted for median nerve MCV and ulnar nerve MAP duration (Mutti et al.1982). Workers (56 males) from an offset printing factory were examined for evidence of peripheral neuropathy. Mean background time weighted average concentration of <i>n</i>-hexane was 222 mg/m³ (63 ppm, range 30-110 ppm) and personal air concentration from offset machine workers was 465 mg/m³ (132 ppm, range 80-210 ppm), based on a 12 hrs/day, 6 days/week schedule. The concentration of <i>n</i>-hexane in the cleaning solvent used by the workers was 14-20%. Toluene was present in the solvent blend but not quantified. Average duration of employment was 2.6 years (range 1 month-12 years), and average time in the printing trade was 6.4 years (range 1 month-30 years). The exposed workers were divided into three groups according to signs of peripheral neuropathy: healthy workers (n=10), subclinical (n=26), symptomatic (n=20). Nerve conduction study (NCS) values were within normal range in the healthy workers group but sensory action potential (SAP) was significantly reduced compared to 20 age-matched unexposed controls. In the subclinical group (asymptomatic workers with abnormalities in the nerve conduction parameters), no symptoms of peripheral neuropathy were identified. NCS values in this group revealed further reduction in SAP amplitude and MCV, mild reduction in MAP amplitude and mild prolongation in mean distal latency (DL). In the symptomatic group (showing both clinical and electrophysiological evidence of peripheral neuropathy), clinical signs of peripheral neuropathy were observed including numbness, paraesthesia, and pain and weakness in extremities. Further reduction in SAP, MAP amplitudes and MCV were noted as well as obvious prolongation of DL (Chang et al. 1993). Male workers from a tungsten carbide alloys producing factory were evaluated to assess the effects of low level of <i>n</i>-hexane on the peripheral nervous system. Mean duration of exposure was 6.2 years (range 1-12 years). Mean time weighted average concentration from breathing zone samples for the exposed workers was 204 mg/m³ (58 ppm, SD 41 ppm). Acetone was also present but no other solvent was detected. Workers not exposed to any solvents from the same factory were selected as a control group. There was a statistically significant increase in the frequency of headache, dyesthesia in limbs and muscle weakness in the exposed workers. A statistically significant decrease in the following neurological and electrophysiological parameters was noted: muscle strength (jumping on one foot), vibration sensation of the radial processes [as stated in original paper], and maximal MCV and residual latency of motor nerve conduction in the posterior tibial nerve (Sanagi et al. 1980). No oral epidemiology or case report studies identified.
Effects on vision	Visual function was investigated in 26 cases of polyneuropathy following occupational exposure to <i>n</i>-hexane, and compared to 50 healthy controls. Cases worked on average 7.5 years (SD 5.1), while controls worked an average of 7.6 (SD 3.5) years. Exposure was not quantified. All cases had the following symptoms: upper and lower limb weakness, leg pain, asthenia, paraesthesiae in the hand and arms, and difficulty walking. Electromyography indicated myelinic and axonal lesions of distal nerves. Error scores from the FM-100 Hue test were statistically significantly increased in the exposed group compare to controls, indicating colour

Endpoint	Lowest effect level/Results
	vision defects (Issever et al. 2002). Other studies examining vision effects: Raitta et al. 1978, Seppalainen et al. 1979, Carelli et al. 2007.
Carcinogenicity	A case-control study was conducted to assess the relationship between occurrence of intracranial tumours in workers of a petrochemical research facility and exposure to chemical or physical agents, including <i>n</i>-hexane. Gliomas cases (6 men matched to 10 controls) were exposed for an average of 16.8 years (median value) and benign intracranial tumours cases (4 men and 2 females matched to 9-10 controls) for 14 years (median value). Odds ratios (OR) comparing gliomas cases with self-reported exposure (definite or potential) and project-based potential exposure to <i>n</i>-hexane were infinite (CI 1.4-infinity) and 2.3 (CI 0.4-13.7) respectively. When broken down by duration, ORs were 1.2 (CI 0.2-9.0) for short-term (≤ 48 months) and 16.2 (1.1-228) for long-term (>48 months) potential use. ORs for benign intracranial tumours were not significant except for short-term project-based potential exposure to <i>n</i>-hexane (12.6, CI 0.9-174). Although an association was noted between <i>n</i>-hexane exposure and glioma, the small number of cases, coexposure to other substances and presence of alternative explanations for the association precludes from concluding on the carcinogenicity of <i>n</i>-hexane (Beall et al. 2001).