

Screening Assessment for the Challenge
2-Propenamide
(Acrylamide)

Chemical Abstracts Service Registry Number
79-06-1

Environment Canada
Health Canada

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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 2-propenamide (acrylamide), Chemical Abstracts Service Registry Number 79-06-1. The substance acrylamide was identified in the categorization of the *Domestic Substances List* as a high priority for action under the Ministerial Challenge. Acrylamide was identified as a high priority because it was considered to pose the greatest potential for exposure of individuals in Canada and had been classified by the European Commission on the basis of carcinogenicity, genotoxicity and reproductive toxicity. The substance did not meet the ecological categorization criteria for persistence, bioaccumulation potential or inherent toxicity to aquatic organisms. Therefore, the focus of this assessment of acrylamide relates primarily to human health risks.

According to information reported under section 71 of CEPA 1999, between 1 million and 10 million kilograms of acrylamide were imported into Canada in 2006. Based upon information presented in the available scientific and technical literature, the majority of acrylamide is used in the manufacture of various polymers, which in turn are used as binding, thickening or flocculating agents in grout, cement, sewage/wastewater treatment, pesticide formulations, cosmetics, sugar manufacturing, soil erosion prevention, ore processing, food packaging and plastic products and in molecular biology laboratory applications. In Canada, polyacrylamide is used as a coagulant and flocculant for the clarification of drinking water; it is also used in potting soils and as a non-medicinal ingredient in natural health products and pharmaceuticals.

The greatest source of exposure of the general population to acrylamide is from its formation from naturally occurring components of certain foods when cooked at high temperatures, such as french fries and potato chips. Intake from environmental media such as drinking water or air and exposures during use of consumer products are very low in comparison.

Based principally upon weight of evidence-based assessments of international and other national agencies, a critical effect for the characterization of risks to human health is carcinogenicity. Increased incidences of tumours were observed at more than one site in two species of experimental animals exposed by oral administration. Acrylamide was genotoxic in a wide range of *in vivo* and *in vitro* assays. Although the mode of induction of tumours by acrylamide has not been fully elucidated, it cannot be precluded that the tumours observed in experimental animals have resulted from direct interaction with genetic material. In addition, the margin between the upper-bounding estimate of intake of acrylamide by the general population and critical effect levels for neurological toxicity in experimental animals may not be adequately protective in light of the profile of serious effects associated with exposure to this substance.

On the basis of the carcinogenic potential of acrylamide, for which there may be a probability of harm at any level of exposure, as well as the potential inadequacy of margins between estimated exposure and critical effect levels for non-cancer effects, it is

concluded that acrylamide is a substance that may be 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.

Based on the information presented for the ecological assessment, it is concluded that acrylamide 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 upon which life depends. In addition, acrylamide 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 *Domestic Substances List* inventory update initiative. In addition, and where relevant, research and monitoring will support verification of assumptions used during the screening assessment and, where appropriate, the performance of potential control measures identified during the risk management phase.

Based on the information available, it is concluded that acrylamide meets one or more 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 to 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 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), which 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 acrylamide was identified as a high priority for assessment of human health risk because it was considered to present the greatest potential for exposure (GPE) and had been classified by other agencies on the basis of carcinogenicity, genotoxicity and reproductive toxicity.

The Challenge for acrylamide was published in the *Canada Gazette* on February 16, 2008 (Canada 2008). 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 acrylamide was determined to be a high priority for assessment with respect to human health, it did not meet the criteria for persistence, bioaccumulation potential or

inherent toxicity to aquatic organisms. 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 and stakeholder research reports and from recent literature searches, up to September 2008 for the sections of the document relevant to human health and up to August 2008 for the ecological sections of the document. 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.

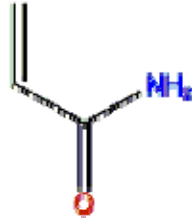
This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. This assessment has undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from H. Gibb, Tetra Tech Services; R. DeWoskin, US Environmental Protection Agency; D. Benford, Food Standards Agency, United Kingdom; and M. DiNovi, US Food and Drug Administration. 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. Additionally, the draft of this assessment was subject to a 60-day public comment period.

The critical information and considerations upon which the assessment is based are summarized below.

Substance Identity

For the purposes of this document, this substance will be referred to as acrylamide. Information on the identity of acrylamide is summarized in Table 1.

Table 1. Substance identity of acrylamide

CAS RN	79-06-1
DSL name	2-Propenamide
NCI names	Acrylamid (German) (EINECS, SWISS) Acrilamida (Spanish) (EINECS) Acrylamide (English, French) (DSL, ECL, EINECS, ENCS, PICCS) 2-Propenamide (AICS, ASIA-PAC, DSL, ECL, NZIoC, PICCS, SWISS, TSCA)
Other names	Acrylamide monomer; Acrylic acid amide; Acrylic amide; Bio-Acrylamide 50; Ethylenecarboxamide; NSC 7785; Propenamide; 2-Propene amide; UN 2074; UN 2074 (DOT); UN3426; Vinyl amide
Chemical group	Discrete organics
Chemical subgroup	Acrylamides and methacrylamides
Chemical formula	C ₃ H ₅ NO
Chemical structure	
SMILES	O=C(N)C=C
Molecular mass	71.08 g/mol

Abbreviations: AICS, Australian Inventory of Chemical Substances; ASIA-PAC, Asia-Pacific Substances Lists; CAS RN, Chemical Abstracts Service Registry Number; DSL, Domestic Substances List; ECL, Korean Existing Chemicals List; EINECS, European Inventory of Existing Commercial Chemical Substances; ENCS, Japanese Existing and New Chemical Substances; NCI, National Chemical Inventories; NZIoC, New Zealand Inventory of Chemicals; PICCS, Philippine Inventory of Chemicals and Chemical Substances; SMILES, simplified molecular input line entry specification; SWISS, Swiss Giftliste 1 and Inventory of Notified New Substances; TSCA, Toxic Substances Control Act Chemical Substance Inventory.

Source: NCI 2008

Physical and Chemical Properties

Acrylamide is a white, odourless, crystalline solid that is highly soluble in water (IPCS 1985). Its physical and chemical properties that are relevant to its environmental fate are presented in Table 2.

Table 2. Physical and chemical properties of acrylamide

Property	Type	Value	Temperature (°C)	Reference
Melting point (°C)	Experimental	84–85		Verschueren 2001
		84.5		Howard 1989
Boiling point (°C)	Experimental	87 (at 2 mmHg or 0.27 kPa)		Howard 1989; Kirk-Othmer 2001
		103 (at 0.67 kPa)		Kirk-Othmer 2001
		116.5 (at 1.4 kPa)		
		136 (at 3.3 kPa)		
Density (kg/m ³)	Experimental	1122 (1.122 g/mL)	30	Kirk-Othmer 2001
Vapour pressure (Pa)	Experimental	0.93 (7×10^{-3} mmHg) ¹	25	Howard 1989
		0.9	25	Kirk-Othmer 2001
		4.4	40	
		9.3	50	
Henry's Law constant (Pa·m ³ /mol)	Calculated ²	3.2×10^{-5} (3.2×10^{-10} atm·m ³ /mol) ¹		Howard 1989
	Modelled	5.98×10^{-4}		HENRYWIN 2000
Log K _{ow} (dimensionless)	Experimental	−0.67		Howard 1989
	Modelled	−0.81		KOWWIN 2000
Log K _{oc} (dimensionless)	Modelled	1.02		PCKOCWIN 2000
Water solubility (mg/L)	Experimental	2 050 000 (2050 g/L)		Verschueren 2001
		2 151 000	30	Howard 1989
		2 155 000 (215.5 g/100 mL)		Kirk-Othmer 2001
pK _a (dimensionless)	Modelled (acid)	15.4		ACD/pK _a DB 2005
	Modelled (base)	−0.83		

Abbreviations: K_{oc}, organic carbon–water partition coefficient; K_{ow}, octanol–water partition coefficient; pK_a, acid dissociation constant.

¹ The value in parentheses is the value originally reported in the reference.

² Calculated from water solubility and vapour pressure (Howard 1989).

Sources

Based on information collected through a survey conducted pursuant to section 71 of CEPA 1999, between 1 million and 10 million kilograms of acrylamide were imported into Canada in 2006, whereas between 100 and 1000 kg of the substance were manufactured in Canada in 2006 (Environment Canada 2008a).

Acrylamide is formed in starchy foods under conditions of high-heat cooking as a processing-induced contaminant (Health Canada 2005a).

Acrylamide is a component of cigarette smoke (Urban et al. 2006). Smith et al. (2000) estimated that the acrylamide content in mainstream cigarette smoke is 1.1–2.34 µg/cigarette. Smoking could possibly be a source of acrylamide in indoor air (NTP 2005a).

Uses

Based upon information identified in the scientific and technical literature, the majority (>90%) of acrylamide is used in the manufacture of various polymers, such as polyacrylamide (NTP 2005a). These polymers are used as binding, thickening or flocculating agents in such applications as water/wastewater treatment, pulp and paper processing and mineral/ore processing (EURAR 2002). Acrylamide polymers are also used in cosmetics, soil conditioning (i.e., stabilizing; EURAR 2002) agents, plastics, specialized grouting agents, food packaging materials and electrophoretic gels (NTP 2005a). Acrylamide polymers or co-polymers are also used in textile industries, as a medium in hydroponically grown crops, in sugar refining and in bone cement (NTP 2005a). Polyacrylamide is also used in crude oil production, coatings for home appliances, building materials, automotive parts, explosives, adhesives, printing inks, adhesive tapes, latex and herbicidal gels and as a clarifier in food manufacturing. It is also used in the manufacture of dyes and in co-polymers used in contact lenses.

According to submissions made under section 71 of CEPA 1999 (Environment Canada 2008a), use patterns in Canada include adhesive, binder, sealant, filler; analytical reagent; coagulant, coalescent; drilling mud additive, oil recovery agent, oil well treating agent; flocculating, precipitating, clarifying agent; flotation agent; functional fluid (i.e., hydraulic, dielectric or their additives); humectant, dewatering aid, dehumidifier, dehydrating agent; monomer; photosensitive agent, fluorescent agent, brightener, ultraviolet absorber; polymer, component of a formulation; processing aid; water repellent, drainage aid; water or wastewater treatment chemical; and residuals.

In Canada, polyacrylamide is used as a coagulant and flocculant for the clarification of drinking water. It is not used in grout for wells (2008 personal communication from Water, Air and Climate Change Bureau, Health Canada; unreferenced). There are currently no pest control products in Canada that contain either acrylamide or polyacrylamide as an active ingredient (2008 personal communication from Pest Management Information Service, Pest Management Regulatory Agency; unreferenced), although acrylamide may be present as a formulant impurity at <0.01% (2008 personal communication from Review and Science Integration Division, Pest Management Regulatory Agency; unreferenced). Polyacrylamide-containing soil amendments must be registered as supplements under the *Fertilizers Act* and the percentage of monomer specified (CFIA 1997). Several polyacrylamides are currently registered in Canada for use in potting soils; the residual acrylamide content is 0.03–0.04% (2008 personal

communication from Canadian Food Inspection Agency; unreferenced). Polyacrylamide is also used in dewatering of sewage sludge; the amount of residual monomer is unknown.

Neither acrylamide nor polyacrylamide is listed on the Cosmetic Ingredient Hotlist, which is a list of prohibited or restricted cosmetic ingredients in Canada (2008 personal communication from Consumer Product Safety, Cosmetics Division, Health Canada; unreferenced). In Canada, polyacrylamide is present as a non-medicinal ingredient in several licensed natural health products (e.g., skin cleansers, moisturizers) (2008 personal communication from Natural Health Products Directorate, Health Canada; unreferenced). Concentrations of polyacrylamide in licensed natural health products range from 0.8% to 3.375%. The concentration of acrylamide in polyacrylamide-containing formulations should not exceed 0.0005%.

Polyacrylamide is also present as a non-medicinal ingredient in several licensed topical therapeutic products, where concentrations range from 0.3% to 1.08% (2008 personal communication from Therapeutic Products Directorate, Health Products and Food Branch, Health Canada; unreferenced). Although acrylamide can be used in gelatine capsules for rigidity, such use is infrequent (2008 personal communication from Bureau of Pharmaceutical Sciences, Health Canada; unreferenced).

In Canada, acrylamide can be found as an impurity in paperboard, polystyrene, polyvinylidene chloride and epoxy coatings at concentrations ranging from 0.000 45 to 29.8 mg/kg; the contribution to intake from this source is negligible (Health Canada 2005d; 2008 personal communication from Food Packaging and Incidental Additives Section, Health Canada; unreferenced).

Polyacrylamide flocculants are used to recover solids from wastewater produced during rendering, meat processing or fish processing (2008 personal communication from Animal Feeds Division, Canadian Food Inspection Agency; unreferenced). These solids may then be added to inedible rendering raw materials at a rate not to exceed 5% of the rendering pit volume, from which various types of protein feeds are produced for addition to livestock feeds at typical rates not exceeding 10%. The concentration of acrylamide in these feeds is estimated to be less than 3 µg/kg.

Releases to the Environment

The breakdown of polyacrylamide into its monomer is energetically unfavourable and unlikely to occur (EURAR 2002). Acrylamide available for release from the polymer is residual (free) acrylamide.

Acrylamide may be released to wastewater during its production and use in the synthesis of dyes, in the manufacture of polymers, adhesives, paper/paperboard, textile additives, soil conditioning agents and permanent press fabrics or in ore processing and oil recovery (Howard 1989). It may also be released in water treated with polyacrylamide as a

flocculating agent. The largest end use is as a flocculant in facilitating liquid–solid separation for processing minerals in mining, waste treatment and water treatment. Other sources of release to water are acrylamide-based sewer grouting and recycling of waste paper. Acrylamide grouts generally consist of a 19:1 mixture of acrylamide and cross-linking agent. When the grout solidifies, it contains less than 0.05% free acrylamide (EURAR 2002).

According to Canada's National Pollutant Release Inventory, 177 kg of acrylamide were reported to be released to the air in 2006, 207 kg were reported as released on-site (medium of release not specified) and 45 kg were reported to be disposed of off-site (NPRI 2008).

Environmental Fate

Based on its physical and chemical properties (Table 2), the results of Level III fugacity modelling (EQC 2003), presented in Table 3, suggest that acrylamide will reside predominantly in water and soil, depending on the compartment of release.

Table 3. Results of Level III fugacity modelling predictions (EQC 2003) for acrylamide

Substance released to:	Fraction of substance partitioning to each medium (%)			
	Air	Water	Soil	Sediment
Air (100%)	0.09	17.2	82.7	0.02
Water (100%)	0	99.9	0	0.1
Soil (100%)	0	9.05	90.9	0.01

If acrylamide is released to air, the Level III fugacity model indicates that a negligible amount of acrylamide would remain in air (see Table 3). An experimental vapour pressure of 0.9 Pa and a negligible Henry's Law constant (estimated at 5.98×10^{-4} Pa·m³/mol and calculated at 3.2×10^{-5} Pa·m³/mol) indicate that acrylamide will partition primarily to soil (>82%) and water (17%) if released solely to air.

Acrylamide is not expected to ionize in natural waters (surface waters, soil or sediment pore waters) based on the predicted pK_a values of 15.4 (acid) and –0.83 (base) (see Table 2).

If released into water, acrylamide is expected to have limited sorption to suspended solids and sediment, based upon a low estimated log K_{oc} (1.02). Volatilization from water surfaces is expected to be an unimportant fate process, based upon this compound's Henry's Law constant. Thus, if water is a receiving medium, acrylamide is expected to remain almost completely in water (>99%; see Table 3).

If released to soil, acrylamide is expected to have low adsorptivity to soil (i.e., expected to be mobile) based upon the estimated log K_{oc} of 1.02 and the experimental log K_{ow} of –0.67. Volatilization from moist and dry soil surfaces seems to be an unimportant fate process, based upon acrylamide's moderate vapour pressure and Henry's Law constant.

Therefore, if released to soil, acrylamide will remain in soil (~90%) and also move into water (9%), as illustrated by the results of the Level III fugacity modelling (Table 3).

Persistence and Bioaccumulation Potential

Environmental Persistence

A number of studies have been conducted to estimate biodegradation. Results generally indicate that there is a widespread microbial ability to degrade acrylamide, but that lag periods of several days may occur prior to significant degradative losses (Croll et al. 1974; Lande et al. 1979; Brown et al. 1982; EURAR 2002; NICNAS 2002). Table 4 presents the empirical biodegradation data for acrylamide.

Table 4. Empirical data for persistence of acrylamide

Medium	Fate process	Degradation value	Endpoint/units	Reference
Water	Hydrolysis	13 870	Half-life, days	Ellington et al. 1988
Water	Biodegradation	70 (ready biodegradability)	% BOD (NH ₃); 28 days	NITE 2002
Water	Biodegradation	100	%, 28 days (1 mg acrylamide/L) ¹	United States Testing Company Inc. 1991
		100	%, 28 days (2 mg acrylamide/L) ¹	
		53	%, 28 days (5 mg acrylamide/L) ¹	
Water	Biodegradation	~80 (river water sample)	%, 100 h	Croll et al. 1974
		~80 (inoculated sample)	%, 20 h	
Soil	Biodegradation	18–45 ²	Half-life, h	Lande et al. 1979
		94.5 ³		
		96 ⁴		

BOD, biological oxygen demand.

¹ The concentration of 1 mg/L was tested to confirm readily degradable material. The concentrations at 2 mg/L and 5 mg/L were tested to confirm partially degradable material. Tested at 20°C.

² Acrylamide concentration of 25 mg/kg soil at 22°C (including soil samples of silt clay, loamy fine sand, loam, silt loam).

³ Acrylamide concentration of 500 mg/kg soil (silt loam) at 22°C.

⁴ Acrylamide concentration of 25 mg/kg soil (silt loam) at 10°C.

A ready biodegradation test for acrylamide was performed according to the test methods of the Ministry of International Trade and Industry in Japan (MITI) set out by the Organisation for Economic Co-operation and Development (OECD) Test Guideline 301C (i.e., MITI-I-OECD TG 301C), with results indicating ready biodegradability (NITE 2002). The 28-day test resulted in a biological oxygen demand (ammonia) of 70% (see Table 4). This test indicates that the half-life in water is less than 182 days (6 months) and that the substance is considered to not persist in this environmental compartment.

Acrylamide was tested for ready biodegradability using the OECD Test Guideline 301D methodology for a closed bottle test (United States Testing Company Inc. 1991). Water samples were inoculated with an inoculum derived from activated sludge bacteria incubated in the dark at 20°C for 28 days and monitored for dissolved oxygen content. Results indicated that acrylamide was readily biodegradable at lower concentrations (≤ 2 mg/L), whereas results at higher concentrations (5 mg/L) indicated that this substance may be toxic to microorganisms, given the lower percentage biodegradation observed (see Table 4).

The biodegradability of acrylamide was also investigated by Croll et al. (1974) using aerated river water. One of the two samples was inoculated with a bacterial culture capable of degrading acrylamide (see Table 4). Lag periods of 5 h for the inoculated river water sample and 50 h for the river water sample only were observed, with approximately 80% degradation being observed in both samples at 20 h and 100 h, respectively (see Table 4). Primary versus ultimate degradation was not specified.

The empirical results for biodegradation of acrylamide (see Table 4) indicate that the half-life in water is less than 182 days (6 months) and that the substance should be considered not to persist in this environmental compartment. The hydrolysis half-life of acrylamide at 25°C has been determined to be very slow, at 13 870 days or 38 years (Ellington et al. 1988). Other studies reviewed by the European Commission (EURAR 2002) also suggest that hydrolysis is negligible in degrading acrylamide, compared with biotic mechanisms.

In soil, the reported ultimate biodegradation half-life is <100 h (Lande et al. 1979) (see Table 4). The measured half-life in soil was influenced by the soil type (loam, silt loam, loamy fine sand, silt clay), the incubation temperature (10°C and 22°C), the acrylamide concentration (25 or 500 mg/kg) and the time of year the soil was collected (March or June). Experimental results indicate that half-lives increased with decreased temperatures and increased acrylamide concentrations. Longer half-lives were also observed in anaerobic studies. The higher acrylamide concentration required more time for degradation, possibly due to saturation or inhibition of enzyme activity by the high substrate concentration. Biodegradation of acrylamide occurred more quickly in samples collected in March compared with those collected in June.

The European Commission (EURAR 2002) estimated a half-life for biodegradation of acrylamide in soil to be 30 days.

Although experimental data on the degradation of acrylamide are available, a quantitative structure–activity relationship (QSAR)-based weight of evidence approach (Environment Canada 2007) was also applied using the degradation models shown in Table 5. Given the ecological importance of the water compartment, the fact that most of the available models apply to water and the fact that acrylamide is expected to be released to and remain in this compartment, biodegradation primarily in water was examined.

Table 5. Modelled data for degradation of acrylamide

Fate process	Model and model basis	Result	Interpretation	Extrapolated half-life (days)	Extrapolation reference and/or source
Air					
Atmospheric oxidation	AOPWIN 2000	$t_{1/2} = 11.46$ h	Degrades quickly in air		
Ozone reaction	AOPWIN 2000	$t_{1/2} = 6.55$ days			
Water					
Hydrolysis	HYDROWIN 2000	$t_{1/2} > 1$ year	Hydrolysis rate extremely slow		
Biodegradation (aerobic)	BIOWIN 2000 Submodel 1: Linear probability	0.92	Biodegrades quickly		
Biodegradation (aerobic)	BIOWIN 2000 Submodel 2: Non-linear probability	0.99	Biodegrades quickly		
Biodegradation (aerobic)	BIOWIN 2000 Submodel 3: Expert Survey (ultimate biodegradation)	2.99	Ultimate degradation in weeks		US EPA 2002; Aronson et al. 2006
Biodegradation (aerobic)	BIOWIN 2000 Submodel 4: Expert Survey (primary biodegradation)	3.95	Primary biodegradation in days		US EPA 2002; Aronson et al. 2006
Biodegradation (aerobic)	BIOWIN 2000 Submodel 5: MITI linear probability	0.65	Biodegrades quickly		Aronson et al. 2006
Biodegradation (aerobic)	BIOWIN 2000 Submodel 6: MITI non-linear probability	0.81	Biodegrades quickly		Aronson et al. 2006
Biodegradation (anaerobic)	BIOWIN 2000 Submodel 7: Linear probability	0.05	Does not biodegrade quickly		
Biodegradation	BIOWIN 2000 Overall conclusion	Yes	Biodegradable		
Biodegradation (aerobic)	TOPKAT 2004 Probability (MITI I)	1	Not persistent in water		TOPKAT developers
Biodegradation (aerobic)	CATABOL ©2004–2008 % BOD (OECD 301C)	54%	Not persistent in water	25	Calculated from BOD assuming first-order rate kinetics

Abbreviations: BOD, biological oxygen demand; MITI, Ministry of International Trade & Industry, Japan; OECD 301C, Organisation for Economic Co-operation and Development Test Guideline 301C; $t_{1/2}$, half-life.

In air, a predicted atmospheric oxidation half-life of 11.46 h (see Table 5) demonstrates that this substance is likely to be rapidly oxidized. The predicted half-life in air for reaction with ozone is longer, at 6.55 days. The short oxidation half-life of acrylamide suggests that the substance is not persistent in air.

In water, a predicted hydrolysis half-life of >1 year (see Table 5) demonstrates that this chemical is likely to be slowly hydrolysed. This result is consistent with the experimental value in Table 4, other studies summarized elsewhere (EURAR 2002) and the fact that acrylamide does not contain functional groups expected to undergo hydrolysis.

The majority of the probability models (BIOWIN submodels 1, 2, 5 and 6) (BIOWIN 2000) suggest that acrylamide biodegrades quickly (see Table 5). All of the probability results, with the exception of BIOWIN submodel 7, are greater than the 0.3 cut-off suggested by Aronson et al. (2006) to identify substances as having a half-life of <60 days (based on the MITI probability models). The same probabilities are also greater than 0.5, exceeding the cut-off suggested by the model developers to indicate fast biodegradation. The half-life result from the primary survey model (BIOWIN submodel 4) of “days” is suggested to mean approximately 2.3 days (US EPA 2002; Aronson et al. 2006), and the ultimate survey model (BIOWIN submodel 3) result of “weeks” is suggested to mean approximately 15 days (US EPA 2002; Aronson et al. 2006). The substance is also expected to degrade rapidly under favourable anaerobic conditions (an anaerobic digester). The overall conclusion from BIOWIN indicates that acrylamide is readily biodegradable.

Other ultimate degradation models (CATABOL and TOPKAT) predict that acrylamide will undergo mineralization in a 28-day timeframe with a probability rate of biodegradation in the range of that of biodegradable chemicals. TOPKAT (2004), which simulates the Japanese MITI 28-day biodegradation test, produced a probability of 1. CATABOL (©2004–2008) predicted a 54% rate of biodegradation. Assuming first-order rate kinetics, the calculated half-life from CATABOL is <182 days.

The results of the model predictions are thus consistent with those from the available experimental studies, indicating that the ultimate biodegradation half-life in water is <182 days.

Using an extrapolation ratio of 1:1:4 for water:soil:sediment biodegradation half-lives (Boethling et al. 1995), the ultimate biodegradation half-life in soil is also expected to be <182 days, and the half-life in sediments is <365 days. These extrapolated model results, as well as the empirical results (Lande et al. 1979; EURAR 2002) for soil, indicate that acrylamide is not persistent in soil or sediment.

Based on the empirical and modelled data (see Tables 4 and 5), acrylamide does not meet the criteria for persistence in air, water, soil or sediment (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

Experimental and modelled $\log K_{ow}$ values of -0.67 and -0.81 , respectively (see Table 2), for acrylamide suggest that this chemical has low potential to bioaccumulate in the environment.

Table 6 presents the empirical bioconcentration factor (BCF) values in fish. The accumulation of acrylamide was studied in fish exposed to 1 mg/L and 10 mg/L solutions of acrylamide over 20–40 days under static conditions (solutions were renewed daily to maintain acrylamide concentrations) (Fujiki et al. 1982). In both carp (*Cyprinus carpio*) and Japanese medaka (*Oryzias latipes*) exposed to 1 mg acrylamide/L, the substance was accumulated slowly during the first 10 days; accumulation then increased rapidly until day 20. At an exposure concentration of 10 mg acrylamide/L, the fish accumulated the substance rapidly until days 10–15, then slowly until days 20–30. The estimated BCFs from these results were <3 . The results for carp are shown in Table 6. These authors also exposed carp and Japanese medaka to 20 mg polyacrylamide/L for 60 days. No accumulation of acrylamide monomer in either of the fish was detected (Fujiki et al. 1982).

Table 6. Empirical data for bioaccumulation of acrylamide

Test organism	Endpoint	Value (L/kg wet weight)	Reference
Carp (<i>Cyprinus carpio</i>)	BCF (1 mg acrylamide/L)	0.26	Fujiki et al. 1982
	BCF (10 mg acrylamide/L)	0.77	
Rainbow trout (<i>Salmo gairdneri</i>)	BCF	<2	Petersen et al. 1985

Uptake of radiolabelled acrylamide was studied in fingerling rainbow trout at two concentrations, 0.338 mg/L and 0.710 mg/L (Petersen et al. 1985). Fish were exposed to acrylamide for 72 h at 12°C and in static conditions. The experimental exposure concentrations were approximately 200–500 times less than the 72-h median lethal concentration (LC_{50}) of 170 mg/L determined for the rainbow trout under similar experimental conditions. The acrylamide BCF was measured in the trout carcass (including kidney, gill and brain) and viscera (heart, gastrointestinal tract, liver and gonads). At the exposure concentration of 0.338 mg/L, the BCFs for this substance were 0.86 and 1.12 in the carcass and viscera, respectively, whereas at the exposure concentration of 0.710 mg/L, the measured BCF values were slightly higher, at 1.44 in the carcass and 1.65 in the viscera (Petersen et al. 1985). Overall, the empirical BCF value for this substance was determined to be <2 in fingerling rainbow trout. Acrylamide was found to be excreted via the gills, urine and bile, with 90% of it in an unchanged form.

As few experimental BCF data and no experimental bioaccumulation factor (BAF) data for acrylamide were available, a predictive approach was applied using available BAF and BCF models, as shown in Table 7.

Table 7. Fish BAF and BCF predictions for acrylamide

Test organism	Endpoint	Value (L/kg wet weight)	Reference
Fish	BAF	1	Arnot and Gobas 2003 (Gobas BAF middle trophic level)
	BCF	1	Arnot and Gobas 2003 (Gobas BCF middle trophic level)
	BCF	10	CPOPs 2008 (no mitigating factors) ¹
		2.5	CPOPs 2008 (with mitigating factors) ¹
		3.2	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.

Metabolism information for this substance was not available, nor was it considered in the BAF or BCF models.

The modified Gobas BAF middle trophic level model for fish predicted a BAF of 1 L/kg, indicating that acrylamide does not have the potential to bioconcentrate and biomagnify in the environment. The results of BCF model calculations presented in Table 7 provide additional evidence supporting the low bioconcentration potential of this substance. Based on the available empirical, kinetic-based and other modelled values, acrylamide does not meet the bioaccumulation criteria (BCF, BAF ≥ 5000) as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Ecological Effects Assessment

Aquatic Compartment

There is experimental evidence that acrylamide causes harm to aquatic organisms at moderate concentrations. Although modelled predictions for aquatic toxicity were performed for this substance, they are not presented here, given the numerous experimental data available.

A large range of experimental aquatic toxicity data for several species exists for acrylamide. In the United States, aquatic toxicity testing of acrylamide was recommended under the *Toxic Substances Control Act* (TSCA) (Walker 1991), and studies in both invertebrate species and fish were sponsored by acrylamide manufacturers (Breteler et al. 1982; Krautter et al. 1986; Walker 1991).

Selected aquatic toxicity data, which were considered reliable for the evaluation of acrylamide toxicity, are summarized in Tables 8 and 9. Acute LC₅₀ as well as median effective dose (EC₅₀) values have been reported for both aquatic invertebrates (i.e., algae, daphnids, midge larvae, opossum shrimp, oyster larvae) and fish (i.e., goldfish, stinging catfish, rainbow trout, fathead minnow, bluegill).

Table 8. Selected empirical data for aquatic invertebrate toxicity of acrylamide

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
Algae (<i>Selenastrum capricornutum</i>)	Acute (72 h)	EC ₅₀	33.8 ¹	SEPC 1997
Daphnids (<i>Daphnia magna</i>)	Acute (48 h)	LC ₅₀	160	Krautter et al. 1986
		EC ₅₀	98	
Midge larvae (<i>Paratanytarsus parthenogenetica</i>)	Acute (48 h)	LC ₅₀	410	
		EC ₅₀	230	
Opossum shrimp (<i>Mysidopsis bahia</i>)	Acute (48 h)	LC ₅₀	109	Breteler et al. 1982
	Acute (96 h)		78	
American oyster larvae (<i>Crassostrea virginica</i>)	Acute (48 h)	EC ₅₀	153 (lab A) 161 (lab D)	Zaroogian 1981 ²

Abbreviations: EC₅₀, concentration of a substance that is estimated to cause some toxic sublethal effect on 50% of the test organisms; LC₅₀, concentration of a substance that is estimated to be lethal to 50% of the test organisms.

¹ As the test was performed on a 50% acrylamide solution, the observed 72-h EC₅₀ of 67.7 mg/L was divided by two to give the toxic effect due to acrylamide.

² Note that the pivotal value of 0.43 mg/L previously reported for this author for categorization was incorrectly cited (i.e., 0.43 mg/L was the value reported for another substance).

Table 9. Selected empirical data for fish toxicity of acrylamide

Test organism	Type of test	Endpoint	Value (mg/L)	Reference
Goldfish (<i>Carassius auratus</i>)	Acute (24 h)	LC ₅₀	460	Bridié et al. 1979
	Acute (96 h)		160	
Stinging catfish (<i>Heteropneustes fossilis</i>)	Acute (24 h)	LC ₅₀	104	Shanker and Seth 1986
	Acute (96 h)		86	
Fingerling rainbow trout (<i>Salmo gairdneri</i>)	Acute (24 h)	LC ₅₀	>300	Petersen et al. 1985
	Acute (48 h)		210	
	Acute (72 h)		170	
	Acute (96 h)		162	
Rainbow trout (<i>Salmo gairdneri</i>)	Acute (96 h)	LC ₅₀	110	Krautter et al. 1986
Fathead minnow (<i>Pimephales promelas</i>)			120	
Bluegill (<i>Lepomis macrochirus</i>)			100	
Rainbow trout (<i>Salmo gairdneri</i>)	Acute (96 h)	EC ₅₀	88	Krautter et al. 1986
Fathead minnow (<i>Pimephales promelas</i>)			86	
Bluegill (<i>Lepomis macrochirus</i>)			85	

Abbreviations: EC₅₀, concentration of a substance that is estimated to cause some toxic sublethal effect on 50% of the test organisms; LC₅₀, concentration of a substance that is estimated to be lethal to 50% of the test organisms.

For invertebrates, acute LC₅₀ values ranged from 78 to 410 mg/L (Breteler et al. 1982; Krautter et al. 1986), whereas EC₅₀ values ranged from 33.8 to 230 mg/L (Zaroogian 1981; Krautter et al. 1986; SEPC 1997) (see Table 8). SEPC (1997) measured acute 72-hour EC₅₀ values based on growth inhibition in a freshwater alga. Krautter et al. (1986) measured acute 48-hour EC₅₀ values based on immobilization and/or bottom migration of *D. magna* and midge larvae. Zaroogian (1981) used a 48-hour oyster embryo-larval assay to measure abnormal shell development for interlaboratory comparisons and test validations for the US Environmental Protection Agency (EPA). Two of the four laboratories that performed the test were deemed to provide reliable results (see Table 8).

In addition to the laboratory data described above, a field study was performed by Brown et al. (1982) to investigate the effect of acrylamide in stream water on the insect fauna living on moss-covered stones in the river. A qualitative assessment of the insect fauna with exposure to 50 µg acrylamide/L showed a decrease in population size and diversity of species within 5 hours. The aquatic invertebrate species surveyed included *Leuctra hippopus*, *Protonemura meyeri*, *Amphinemura sulcicollis*, *Nemura cambrica*, *Chloroperla torrentium*, *Baetis rhodani*, *Hydropsyche instabilis*, *Rhyacophila dorsalis*, *Sericostoma personatum*, Chironomidae species and Philopotamidae species. Within 21 days, only *H. instabilis* was observed in the river. The authors concluded that acrylamide appeared to have a selective adverse effect on aquatic invertebrates, but indicated that more research would be required to fully understand the effects of acrylamide. Uncertainties associated with this study include the lack of upstream control for the duration of the sampling period, changes in river levels that may have resulted in concentrations of acrylamide differing from nominal concentrations, inability to distinguish between toxic effects and avoidance reaction, and seasonal variability in population densities of the sampled invertebrates.

Walker (1991) summarized the potential impact of extended acrylamide exposure on the saltwater organism *Mysidopsis bahia*. Ratios of acute (4-day) LC₅₀ values to chronic (28-day) maximum acceptable toxic concentrations for this saltwater invertebrate were 26 for parent and offspring survival, 115 for female dry weights and 975 for male dry weights. These ratios illustrate that adverse effects on reproduction and growth were produced after extended exposure to acrylamide concentrations that were significantly lower than those suggested by acute LC₅₀ or EC₅₀ values.

In summary, acute empirical LC₅₀ and EC₅₀ values obtained for aquatic invertebrates suggest that acrylamide is moderately toxic to these organisms, with LC₅₀s/EC₅₀s in the 50–500 mg/L range.

Numerous acute empirical LC₅₀ as well as EC₅₀ values are also available for several fish species. Study results for exposure times ranging from 24 to 96 hours are presented in Table 9.

Briefly, 24-hour LC₅₀ values for goldfish, stinging catfish and fingerling rainbow trout ranged from 104 to 460 mg/L (Bridié et al. 1979; Petersen et al. 1985; Shanker and Seth 1986). In fingerling rainbow trout, the 48-hour LC₅₀ was 210 mg/L and the 72-hour LC₅₀

was 170 mg/L (Petersen et al. 1985). Finally, the 96-hour LC₅₀ values for goldfish, stinging catfish, bluegill, fathead minnow and rainbow trout ranged from 86 to 162 mg/L (Bridié et al. 1979; Petersen et al. 1985; Krautter et al. 1986; Shanker and Seth 1986).

In addition, 96-hour EC₅₀ values for fish based on the loss of equilibrium and/or surfacing of the test organisms were reported by Krautter et al. (1986). The resulting EC₅₀ values were similar for the different species tested, including 88 mg/L for rainbow trout, 86 mg/L for fathead minnow and 85 mg/L for bluegill.

In summary, acute empirical LC₅₀ and EC₅₀ values obtained for fish suggest that acrylamide is moderately toxic to these organisms, with LC₅₀s/EC₅₀s in the 50–500 mg/L range.

Other Environmental Compartments

The phytotoxicity of acrylamide was determined in soil and nutrient solution using *Lactuca sativa*, according to OECD Test Guideline 208 (Hulzebos et al. 1993). In soil tests, plants cannot be exposed continuously to the test compound, whereas in nutrient solution, semi-static exposure can be realized, thus providing more information about the actual toxicity of the substance to plants. EC₅₀ values represented the concentration at which growth was 50% of the control, based on harvested shoots. Experimental results are presented in Table 10.

Table 10. Empirical data for soil toxicity of acrylamide

Test organism	Medium	Type of test	Endpoint	Value	Reference
Lettuce (<i>Lactuca sativa</i>)	Soil	Acute (7 days)	EC ₅₀	101 µg/g	Hulzebos et al. 1993
		Acute (14 days)		152 µg/g	
	Nutrient solution	Acute (21 days)		6 mg/L	

The limited data on the toxic effects of acrylamide to terrestrial plants have been summarized in EURAR (2002) and NICNAS (2002). The available data suggest that acrylamide exposure results in a slight toxic effect on plant growth at concentrations of 10 mg/kg. No effect on seed germination was observed.

Contamination of watercourses with acrylamide has followed various grouting applications in construction projects in Europe and Japan (EURAR 2002). In Scandinavia, cattle exposed to acrylamide in their water supply (i.e., a nearby creek) following grout application incidents showed signs of poisoning, with paresis of the hind legs as the main symptom (EURAR 2002). Similarly, adverse effects were observed in cows a few weeks after a grouting application in a tunnel project in Sweden, whereby cows were exposed to acrylamide in their drinking water (EURAR 2002).

Ecological Exposure Assessment

Given the large quantity of acrylamide reported in commerce, the number of notifiers and the wide variety of use codes and applications for the substance (see the sections on “Sources” and “Uses”), there exists the potential for releases to the Canadian environment. Releases to the environment have been reported through the National Pollutant Release Inventory (NPRI 2008) as well as the industrial survey conducted for the calendar year 2006 (Environment Canada 2008a) (see the section on “Releases to the Environment”). However, data regarding concentrations of this substance in environmental media (air, water, soil, sediment) in Canada have not been identified.

Concentrations of acrylamide in the environment elsewhere have been reported. As reported by the European Commission (EURAR 2002), acrylamide was generally not detected (detection limits of 0.2–0.8 µg/L) in surface (river) waters, estuarine waters or seawaters at sites in the United Kingdom and the United States (some of which included sites downstream of production sites). Measured concentrations of 0.3 µg/L and 3.4 µg/L were reported for two other sites in the United Kingdom. No acrylamide was detected in sediments (detection limit of 20–80 µg/kg) at a US site in the vicinity of factories producing or using acrylamide or polyacrylamide (EURAR 2002). Measured levels of acrylamide in process waters (effluent or discharge) between 0.47 and 125 µg/L were reported in the United Kingdom and the United States, whereas no acrylamide was detected at another site (detection limit of 0.2 µg/L) (EURAR 2002).

Characterization of Ecological Risk

As indicated previously, acrylamide does not meet the persistence or bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Furthermore, experimental ecotoxicological data indicate that acrylamide does not cause significant harm to aquatic organisms at low concentrations. For aquatic species relevant to the Canadian environment, acute LC₅₀ and EC₅₀ ecotoxicity values range from 33.8 mg/L for a freshwater alga (SEPC 1997) to 410 mg/L for midge larvae (Krautter et al. 1986). The lowest reported EC₅₀ value of 33.8 mg/L for a freshwater alga (see Table 8) is the critical toxicity value (CTV) used to estimate a predicted no-effect concentration (PNEC). An assessment factor of 100 was applied to this value to account for uncertainty regarding the potential for chronic effects (i.e., lack of data on chronic effects). The resulting PNEC is 0.338 mg/L.

In this screening assessment, a conservative exposure scenario was developed to estimate releases of acrylamide into the aquatic environment from industrial operations and resulting aquatic concentrations (Environment Canada 2008b, c). A quantity of between 1 million and 10 million kilograms of acrylamide was imported in Canada in the year 2006. Other assumptions included a 5% loss of the substance during manufacturing or handling, secondary sewage treatment and releases to a large receiving water body. This scenario resulted in a predicted environmental concentration (PEC) in water that was well below reported values of acrylamide measured in surface waters in other countries (EURAR 2002). The PEC was also well below the PNEC of 0.338 mg/L, resulting in a risk quotient of <1. This conservative exposure scenario indicates that acrylamide is anticipated to pose a low risk to aquatic organisms.

Based on the information available, acrylamide is unlikely to cause ecological harm in Canada.

Uncertainties in Evaluation of Ecological Risk

In evaluating the ecological risk posed by acrylamide, the predicted partitioning behaviour of this chemical indicates that soil is an important medium of exposure. However, limited effects data are available with which to evaluate the risk posed to soil organisms, and limited data are available with which to evaluate phytotoxicity. Indeed, the effects data available apply primarily to pelagic aquatic exposures, and the water column is also a medium of primary concern based on partitioning estimates. There is, however, a lack of chronic toxicity studies evaluating the potential for longer-term effects of exposure of aquatic organisms to acrylamide. The available studies were considered in developing a PEC (i.e., specifically in choosing an assessment factor), as they highlight the potential for longer-term effects (Brown et al. 1982; Walker 1991). In addition, there is concern for potential exposure of mammalian and avian wildlife as a result of acrylamide use in grouting applications in large construction projects, which can potentially result in the contamination of nearby watercourses that may be used as drinking water for mammals and birds. The observed neurotoxicity in cows in Europe exposed to acrylamide in their drinking water (from a contaminated river) resulting from construction projects supports this concern (EURAR 2002).

Potential to Cause Harm to Human Health

Exposure Assessment

Only limited data on concentrations of acrylamide in environmental media were identified. Acrylamide is not expected to be a common contaminant in air, due to its low vapour pressure and high water solubility (WHO 2004). However, it has been identified in a large variety of foodstuffs in many countries (FAO/WHO 2006a, b, c). The major pathway of acrylamide formation in those foodstuffs appears to be a high temperature induced chemical reaction, termed the Maillard reaction, between asparagine and certain reducing sugars, both of which occur naturally in foods (Health Canada 2005a, b;

FAO/WHO 2006a). Foods rich in both these precursors are largely derived from plant sources, such as potatoes and grains. FAO/WHO (2006a) noted that acrylamide formation is particularly likely in carbohydrate-rich foods, baked or fried at temperatures above approximately 120°C. Although several other pathways of acrylamide formation have been identified, they probably contribute relatively little towards overall levels in most foods (Dybing et al. 2005).

In Canada, the highest concentrations of acrylamide have been detected in french fries and potato chips; potatoes contain both asparagine and naturally occurring sugars, and these products are usually cooked at high temperatures (Health Canada 2005a, b, 2006). Acrylamide has not been detected in boiled potatoes, as the cooking temperature is not high enough to cause its formation (Health Canada 2005b). Acrylamide was also detected in breakfast cereals, pastries, cookies, breads, rolls, toast, cocoa products and coffee, although at lower concentrations than in french fries and potato chips. Acrylamide is not present in any ingredient of these food commodities prior to cooking, and it is not a contaminant inadvertently added at any stage of food preparation (Health Canada 2005c).

With respect to other foodstuffs, FAO/WHO (2006a) reported that acrylamide has been detected in coffee, canned black ripe olives, nuts, chocolate, some fish/meat products, roasted vegetables (peppers, onions, broccoli) and prunes. Concentrations of acrylamide have been observed to decline in coffee, cocoa, biscuits, gingerbread and liquorice during storage.

Limited data on concentrations of acrylamide in breast milk were identified. However, no Canadian data on acrylamide in breast milk have been identified. In 15 samples collected in Sweden between 2000 and 2004, acrylamide was detected once (0.51 µg/kg); the concentration in the remaining 14 samples was below the limit of quantification (i.e., <0.5 µg/kg) (Fohgelberg et al. 2005). It was noted that higher concentrations of acrylamide in breast milk (18.8 ng/mL) were reported by Sorgel et al. (2002); however, the two volunteer mothers ingested potato chips prior to sampling, and the resulting peak concentrations are not considered representative of the levels that would be expected over the course of breastfeeding. Analyses of breast milk substitute from Sweden were also carried out by Fohgelberg et al. (2005); the highest concentration among eight samples was 0.7 µg/kg. However, acrylamide was not detected in infant formula in Health Canada's ongoing total diet survey (Health Canada 2005c).

Estimates of daily intake of acrylamide have been prepared, based upon maximum concentrations in relevant environmental media (air, drinking water, soil and food), for various age groups in the Canadian general population (Appendices 1 and 2). Total intakes from food and environmental media ranged from 0.37 µg/kg body weight (kg-bw) per day in infants to 1.76 µg/kg-bw per day in children aged 6 months to 4 years. For most age groups, approximately 90% of the daily intake was from food. No information has been identified on the role of different diets (i.e., cultural differences) on intake of acrylamide (Dybing et al. 2005). Contributions to total intake from air, drinking water and soil, although based upon limited data, were negligible in comparison with that from food.

The dietary acrylamide intakes shown in Appendix 2 were generated by the Statistics and Epidemiology Division, Bureau of Biostatistics and Computer Applications, Food Directorate, Health Products and Food Branch, Health Canada (unpublished) using recent Canadian food consumption values from Cycle 2.2 (Nutrition) of the Canadian Community Health Survey (Statistics Canada 2004) and contaminant levels from various sources. Canadian data (Becalski et al. 2003, 2005; Health Canada 2005c, 2007), generated by the Bureau of Chemical Safety, Food Research Division, Health Products and Food Branch, Health Canada, on contaminant levels in the different food items were supplemented with US (US FDA 2006a, b) and FAO/WHO (2006c) data to create as complete a list as possible of those foods that may be part of the typical diet of Canadians. For samples where acrylamide was not detected, the concentration was conservatively set at the limit of detection. Intakes of acrylamide vary from 0.30 to 1.58 $\mu\text{g/kg-bw}$ per day when using mean consumption levels. French fries and potato chips tend to be the main sources of dietary acrylamide (1997 personal communication from Bureau of Chemical Safety, Food Directorate, Health Canada; unreferenced). Based on the limited study by Fohgelberg et al. (2005) and assuming an intake of 800 ml of breast milk per day (based on consumption data from the 1970s), estimated intake of acrylamide from breast milk would be 0.06 $\mu\text{g/kg-bw}$ per day; therefore, breast milk is not likely to be a significant source of exposure to acrylamide in comparison with food. Health Canada is currently developing additional occurrence data in order to better refine dietary exposure estimates for acrylamide and to inform food-related assessment.

Heudorf et al. (2009) recently calculated estimates of intake of acrylamide by 110 German children, based upon analyses of mercapturic acids of acrylamide and glycidamide in urine. A significant association was observed between consumption of french fries and level of urinary metabolites of acrylamide (i.e., 2–3 times higher concentrations of metabolites in children consuming french fries more than 3 times a week compared with those who consume them less than once a month).

Other sources of potential exposure to acrylamide include smoking and the presence of residual acrylamide in polyacrylamide used in cosmetics, soil conditioners and coagulants and flocculants used in water treatment (Van Landingham et al. 2004; Dybing et al. 2005; FAO/WHO 2006a). Using concentrations of acrylamide measured in cigarette smoke, FAO/WHO (2006c) estimated mean and upper-bound acrylamide exposures of smokers at 0.67 and 1.63 $\mu\text{g/kg-bw}$ per day, respectively. Only a limited number of toiletries and cosmetics in the United States were reported to contain polyacrylamide (4 of 775 skin cleansing products, 24 of 905 moisturizers, etc.; see Appendix 3). Residual concentrations of acrylamide in over 20 product categories ranged from 0.003 to 1.3 mg/kg. Data on residual levels of acrylamide in personal care products in Canada were not identified. Concentrations of polyacrylamide in most of these products sold in Canada are less than 3% (Appendix 4). Estimates of intake resulting from use of cosmetics (e.g., eye makeup, foundation, hand lotion) were calculated using the ConsExpo 4.1 software (ConsExpo 2006). Predicted intakes were negligible compared with dietary intake (e.g., predicted intake of <0.03 $\mu\text{g/kg-bw}$ per day for body lotion; Appendix 5). The European Commission (EURAR 2002) estimated that exposure from non-rinse cosmetics would be

65 µg/day; this is equivalent to 1.1 µg/kg-bw per day for 12- to 19-year-olds and 0.9 µg/kg-bw per day for 20- to 59-year-olds (based upon body weights for these age groups; Health Canada 1998). However, this estimate is based upon a maximum monomer level of 0.01%, whereas the maximum concentration of acrylamide monomer identified in cosmetics in the United States was <0.000 13% (Appendix 3; NTP 2005a). Although data are insufficient to quantify exposure from residual acrylamide used in soil conditioning, coagulants and flocculants, exposures resulting from these uses are expected to be negligible.

There is high confidence in the estimates of intake of acrylamide by the general population, as they were based mainly upon recent, well-conducted analyses by Health Canada (Becalski et al. 2003; Health Canada 2005c, 2007), with supplementary data reported by US FDA (2006b) and FAO/WHO (2006c). Furthermore, there was consistency between the concentrations of acrylamide in french fries and potato chips (foods that contribute the greatest single source of intake) reported by these two agencies.

Health Effects Assessment

An overview of reported health effects of acrylamide in laboratory animals and humans is presented in Appendix 6.

Acrylamide has been classified as *probably carcinogenic to humans* (based upon *inadequate evidence* in humans and *sufficient evidence* in experimental animals; IARC 1994); as a probable human carcinogen, based upon inadequate human data and sufficient evidence in animals (US EPA 2001)¹; as a “non-threshold carcinogen” (EURAR 2002); as a carcinogen (NICNAS 2002); and as *reasonably anticipated to be a human carcinogen* (NTP 2005b). The database for carcinogenicity includes increased incidences of benign and/or malignant tumours at multiple sites in both sexes of rats and carcinogenic effects in 1-year bioassays in mice by several routes of exposure (US EPA 2001).

In Fischer 344 rats administered acrylamide in the drinking water at concentrations equivalent to 0, 0.01, 0.1, 0.5 or 2 mg/kg-bw per day for 2 years, there were significant increases in the incidences of follicular adenomas of the thyroid and peritoneal mesotheliomas in the region of the testis in males (Johnson et al. 1986). Tunica vaginalis testes mesotheliomas are extremely rare in men but are relatively common tumours in the Fischer 344 rat (Wall 2005). In females, there were increased incidences of thyroid follicular tumours, mammary tumours, glial tumours of the central nervous system, oral cavity papillomas, uterine adenocarcinomas and clitoral gland adenomas (Johnson et al. 1986).

Friedman et al. (1995) exposed F344 rats to acrylamide for 106 weeks via drinking water, at concentrations resulting in intakes of 0, 0, 0.1, 0.5 or 2.0 mg/kg-bw per day for males and 0, 0, 1.0 or 3.0 mg/kg-bw per day for females. In males at the highest dose, there was a significant increase in mesotheliomas of the testicular tunic and of thyroid follicular cell

¹ It is noted that the date of last revision of the US EPA assessment was 1991.

adenoma. In the high-dose females, there was a significant increase in the incidence of total number of animals with thyroid follicular neoplasms. In females at both doses, there was a significant increase in the incidence of total animals with mammary gland neoplasms. Rice (2005) noted that seven cases of a morphologically distinctive category of primary brain tumour described as malignant reticulosis were reported by the authors, but were not included in the authors' analyses. Damjanov and Friedman (1998) subsequently reexamined the testicular tumours and suggested that the mesotheliomas might be benign, based upon their cellular uniformity, small lesion size and absence of peritoneal seeding and metastasis.

Acrylamide-induced lung and skin tumours were studied in a series of non-standard carcinogenicity bioassays in mice (Bull et al., 1984b). A/J mice (a strain highly susceptible to development of lung tumours) received acrylamide by oral gavage 3 times a week for 8 weeks at doses of 0, 6.25, 12.5 or 25 mg/kg-bw. Five months after the cessation of exposure, there was a significant, dose-related increase in the number of mice with lung adenomas and in the number of lung adenomas per mouse.

The US Food and Drug Administration (FDA) and the US National Toxicology Program (NTP) began chronic drinking water studies with rats and mice in May 2005 (FAO/WHO 2006c); results have not yet been published.

Although the potential association between exposure to acrylamide and induction of cancer has been investigated in several epidemiological studies, results have been mixed. Marsh et al. (2007) reported the mortality of a cohort of workers with and without exposure to acrylamide at three plants in the United States ($n = 8508$) and one in the Netherlands ($n = 344$). There was no association between exposure to acrylamide and elevated cancer mortality risks, based on comparison with national or local rates or in analyses of work history and exposure indicators within the cohort. Swaen et al. (2007) investigated 696 workers exposed to acrylamide between 1955 and 2001. Exposure was retrospectively assessed based upon personal samples from the 1970s onward and by area samples over the whole study period. No cause-specific standardized mortality ratios for any cancer were exposure related. However, Olesen et al. (2008) analysed blood samples from 374 breast cancer cases in a nested case-control study within a prospective cohort study and reported a positive association between acrylamide-hemoglobin levels and estrogen receptor positive breast cancer.

In a prospective study using data from a cohort of 61 467 women and a baseline between 1987 and 1990 through to 2003, Mucci et al. (2006) found no association between dietary intake of acrylamide and cancer of the colon or rectum. Similarly, Pelucchi et al. (2006) observed no consistent association between dietary intake of acrylamide and risk of cancer of the oral cavity/pharynx, esophagus, large bowel, rectum, breast and prostate using data from a network of Italian and Swiss hospital-based case-control studies. There was also no association between risk of cancer of the large bowel, bladder, renal cell or breast and intake of acrylamide in three case-control studies (Mucci et al. 2003, 2004, 2005).

Hogervorst et al. (2007) chose a random subcohort of 2589 women from the Netherlands Cohort Study on diet and cancer. Acrylamide intake was assessed by a food frequency questionnaire and chemical analyses of relevant foods. After 11.3 years of follow-up, there was an increased risk of postmenopausal endometrial and ovarian cancer with increasing dietary acrylamide intake. There was no increased risk of breast cancer associated with intake of acrylamide. In a similar protocol, Hogervorst et al. (2008) randomly chose a subcohort of 5000 men and women. They reported “some indications” of a positive association between dietary intake of acrylamide and risk of renal cell cancer, but no positive association with either bladder or prostate cancer risk.

Larsson et al. (2009) examined 61 433 women who were cancer-free and who had completed a food frequency questionnaire. During a mean follow-up of 17.4 years, there were 2952 cases of breast cancer in the cohort. There was no significant association between long-term intake of acrylamide and risk of breast cancer, either overall or by estrogen receptor or progesterone receptor status. The association between acrylamide intake and risk of breast cancer did not differ by smoking status.

Acrylamide has been classified as Category 3 for mutagenicity (risk phrase R62: *may cause heritable genetic damage*) by the European Commission (2002). Similarly, the Commonwealth of Australia (NICNAS 2002) has concluded that acrylamide “may cause heritable genetic damage.” Acrylamide was not mutagenic in most bacterial assays, with and without metabolic activation (EURAR 2002); however, positive results were reported in mouse lymphoma assays. Similarly, acrylamide caused chromosomal aberrations in cultured mammalian cells. Both positive and negative results were reported in *in vitro* assays for sister chromatid exchange and unscheduled DNA synthesis. Acrylamide was mutagenic *in vivo*, with mostly positive results reported for micronucleus assays (peripheral blood, bone marrow and spleen) and chromosomal aberrations. Acrylamide also produced positive results in germ cell assays *in vivo* (chromosomal aberrations, micronuclei, heritable translocations) and in dominant lethal assays. Most of the genotoxicity of acrylamide appears to be mediated by its metabolite, glycidamide, a chemically reactive epoxide (FAO/WHO 2006a).

Although a mode of action analysis has not been conducted as part of this screening assessment, the European Commission (EURAR 2002) proposed that the observed tumour types in the animal bioassays showed a possible relationship with disturbed endocrine function, with the possibility of a hormonal mechanism. However, in light of the genotoxicity profile, genotoxic activity could not be discounted from contributing to tumour formation. There were no data to suggest that carcinogenicity would be limited to animals and not relevant to humans. Similarly, the Joint FAO/WHO Expert Committee on Food Additives (FAO/WHO 2006c) concluded that “the evidence currently available was insufficient to support non-genotoxic mechanisms of acrylamide-induced cancer, particularly in light of the consistent evidence for a genotoxic mechanism.” In a European Food Safety Authority colloquium (EFSA 2008), Doerge (2008) concluded that there was “a compelling body of evidence” for a DNA-reactive mechanism for acrylamide carcinogenicity via metabolism to glycidamide.

In addition, the US EPA (2007) recently released an external review draft of a toxicological review of acrylamide, in which it was acknowledged that altered hormonal responses had been proposed as a mode of action; however, the data were considered to be insufficient to make such a determination. The US EPA Science Advisory Board (US EPA 2008) concurred with the conclusion of the US EPA (2007) draft that acrylamide was a “likely human carcinogen” via a mutagenic mechanism. A review of acrylamide is also currently being carried out by the United Kingdom’s Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM 2008).

With respect to other effects, acrylamide has induced neurological effects in acute, short-term, subchronic and chronic studies in experimental animals. In neurotoxicity studies with cats, rats, mice, guinea pigs, rabbits and monkeys, repeated daily exposure at doses from 0.5 to 50 mg/kg-bw per day resulted in hindlimb foot splay, ataxia and skeletal muscle weakness, measured by decreased forelimb and hindlimb grip strength (NTP 2005a).² An increase in duration of exposure was associated with progression in severity of neurotoxicity. In a 2-year drinking water assay with rats, peripheral nerve lesions were observed at 2 mg/kg-bw per day (lowest-observed-adverse-effect level [LOAEL]; no-observed-effect level [NOEL] = 0.5 mg/kg-bw per day) (Johnson et al. 1986). Similarly, electron microscopy revealed slight changes in peripheral nerves of rats administered 1 mg/kg-bw per day (lowest-observed-effect level [LOEL]) in the drinking water for 90 days (NOEL = 0.2 mg/kg-bw per day) (Burek et al. 1980). Examination by electron microscopy was limited to male rats; these effects appeared to have reversed completely after 25 days of recovery. Although histopathological effects were reported in monkeys in short-term studies, study designs did not permit the identification of effect levels (EURAR 2002).

Neuropathological effects, principally peripheral neuropathy, following exposure to acrylamide have also been reported in both case reports and workplace surveys (EURAR 2002). In humans, neuropathies were noted at roughly estimated airborne concentrations that were equivalent to doses lower than effect levels reported in experimental animal studies. However, there was insufficient information with which to establish a dose–response relationship for humans.

The European Commission (EURAR 2002) assessed acrylamide as having “possible risk of impaired fertility.” An NTP (2005a) Expert Panel concluded that acrylamide is a developmental toxicant in both mice and rats. The Panel further assessed acrylamide as a reproductive toxicant to male rats and mice, mediated largely by dominant lethality. More recently, Garey et al. (2005) reported a statistically (i.e., not necessarily biologically) significant decrease in body weight of F344 rat pups, in the absence of a dose–response relationship, in a protocol in which dams were exposed from gestational day 7 to delivery and pups were exposed from postnatal days 1 through 22 to the same dose levels, as low as 1 mg/kg-bw per day. The European Commission (EURAR 2002) noted that although impaired fertility in rats and mice was associated with adverse effects upon sperm parameters, neurotoxic effects may also have played a role. Furthermore, there was no

² It should be noted that statistical analyses were not performed in the assay in which neurological effects were reported at 0.5 mg/kg-bw per day (Tyl et al. 2000a).

evidence of selective developmental toxicity in rats and mice that was not associated with maternal toxicity.

The confidence in the health effects dataset for acrylamide is high, as data were identified for carcinogenicity, genotoxicity, reproductive/developmental toxicity, neurotoxicity and other endpoints.

Characterization of Risk to Human Health

Based principally upon the weight of evidence–based assessments of several international and national agencies (IARC 1994; US EPA 2001; EURAR 2002; NICNAS 2002; NTP 2005b), a critical effect for characterization of risk to human health for acrylamide is carcinogenicity, for which a mode of induction involving direct interaction with genetic material cannot be precluded (EURAR 2002; FAO/WHO 2006c). These classifications were based mainly upon the results of animal bioassays, as the limited number of epidemiological studies available indicated weak or no evidence of increased cancer risk with exposure to acrylamide. Consistently increased incidences of tumours at multiple sites (testes, thyroid, mammary gland) were observed in two drinking water assays with the same strain of rats. Acrylamide is genotoxic *in vivo*, testing positive in somatic cells in a wide range of assays in rodents and inducing transmissible genetic damage in male germ cells of mice.

Epidemiological studies have documented peripheral neuropathy in individuals and workers exposed to acrylamide at airborne exposure levels that might be comparable with, or lower than, oral effect levels reported in experimental animal studies, although data were insufficient for quantification of dose–response. The results of experimental animal studies have been consistent with these observations, with lesions in peripheral nerves observed in rats following both subchronic and chronic exposure via drinking water. The body of literature supports an effect level in the range of the lowest reported LOEL of 1 mg/kg-bw per day (Burek et al. 1980). Adverse reproductive and developmental effects have been reported in laboratory animals, generally at higher levels of exposure, although one recent assay reported reproductive effects in mice at the same level of exposure as the lowest LOEL for neuropathological effects (i.e., 1 mg/kg-bw per day).

Comparison of the critical non-neoplastic effect level for neurological effects in rats (1 mg/kg-bw per day) with the estimated total daily intake for the potentially most highly exposed age group of the general population (1.76 µg/kg-bw per day) results in a margin of exposure of approximately 570. In light of the profile of serious effects associated with exposure to acrylamide, including the observed neurotoxicity in humans, this margin is considered to be inadequate to protect human health.

Additional intake of acrylamide as a result of exposure to cigarette smoke would result in a further decrease in the margin of exposure and corresponding increase of risk to health.

Uncertainties in Evaluation of Risk to Human Health

Although only limited information has been identified on the presence of acrylamide in personal care products such as cosmetics in Canada, intake from such sources is likely to be negligible in comparison with that from food, for which data are much more extensive. Although the evidence for carcinogenicity is limited to short-duration assays in mice and adequate assays in only one strain of rats (i.e., Fischer 344), it is supported by a consistently strong database of *in vivo* mutagenicity studies. Although data from humans are inadequate to contribute to the weight of evidence for carcinogenicity, observations of neurotoxicity in occupational studies are consistent with the results of well-conducted, long-term animal bioassays.

Conclusion

Based on the information presented in this screening assessment, it is concluded that acrylamide 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.

On the basis of the carcinogenicity of acrylamide, for which there may be a probability of harm at any level of exposure, as well as the potential inadequacy of the margin of exposure for other health effects, it is concluded that acrylamide is a substance that may be 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 acrylamide does not meet the criteria in paragraphs 64(a) and 64(b) of CEPA 1999, but it does meet the criteria in paragraph 64(c) of CEPA 1999.

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Appendix 1. Upper-bounding estimates of daily intake of acrylamide for the general population in Canada from air, drinking water and soil

Route of exposure	Estimated intake (µg/kg-bw per day) of acrylamide by various age groups					
	0–6 months ¹	0.5–4 years ²	5–11 years ³	12–19 years ⁴	20–59 years ⁵	60+ years ⁶
Air (ambient and indoor air) ⁷	0.06	0.12	0.09	0.05	0.05	0.04
Drinking water ⁸	0–0.11	0.05	0.04	0.02	0.02	0.02
Soil ⁹	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

- ¹ Assumed to weigh 7.5 kg, to breathe 2.1 m³ of air per day, to drink 0 L of water per day (breastfed), 0.8 L/day (formula fed) or 0.3 L/day (not formula fed) and to ingest 30 mg of soil per day (Health Canada 1998).
- ² 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).
- ³ 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).
- ⁴ 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).
- ⁵ 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).
- ⁶ 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).
- ⁷ No concentrations of acrylamide in ambient air or indoor air in Canada were identified. Monitoring was conducted near six plants in the United States that produced acrylamide and/or polyacrylamide; average acrylamide concentrations were less than 0.2 µg/m³ in either vapour or particulate form (Going 1978). This value was used to calculate a very conservative upper-bounding estimate of potential exposure to acrylamide in air.
- ⁸ No concentrations of acrylamide in drinking water in Canada were identified. Acrylamide was not detected (detection limit = 1 µg/L) in drinking water in the United States (Going and Thomas 1979). The detection limit was used in calculating the upper-bounding estimate of intake. Additional studies included Brown and Rhead (1979), Chu and Metcalfe (2007), Going (1978), Perez and Osterman-Golkar (2003) and Cavalli et al. (2004).
- ⁹ In monitoring in the United States, acrylamide was detected at <0.02 mg/kg in soil or sediment in the vicinity of plants producing acrylamide and/or polyacrylamide (Going 1978).

Appendix 2. Acrylamide usual¹ intakes in food (all sources), based on mean consumption values for all tested categories (2008 personal communication from Bureau of Chemical Safety, Health Canada; unreferenced)

Age/sex group ²	N ³	Mean intake (µg/kg-bw per day) ⁴
0–6 months ⁵	109	0.30 ⁶
6 months–4 years	2860	1.58
5–11 years	4650	1.25
12–19 years, males	3303	0.90
12–19 years, females	3208	0.68
20–59 years, males	5562	0.56
20–59 years, females	6038	0.48
60+ years, males	2478	0.42
60+ years, females	3874	0.41

¹ These results are slightly inflated, as the dilution of acrylamide levels with the addition of water to cooked oatmeal was not accounted for.

² Body weight data from the Canadian Community Health Survey (CCHS), Cycle 2.2 (Statistics Canada 2004); data generated by the Bureau of Biostatistics and Computer Applications, Food Directorate, Health Products and Food Branch, Health Canada (unpublished).

³ The sample size for each age category.

⁴ Non-detected acrylamide concentrations were conservatively set to the limit of detection (range 0.003–0.01 µg/g). Food concentration data from Becalski et al. (2003) and Health Canada (2005c, 2007), generated by the Bureau of Chemical Safety, Health Products and Food Branch, Health Canada, were supplemented with data from USFDA (2006a, b) and FAO/WHO (2006a). Consumption values are from the Canadian Community Health Survey (CCHS) – Cycle 2.2 on Nutrition (Statistics Canada 2004).

⁵ Usual intakes could not be calculated for this age group due to the small sample size. Intakes for 0- to 6-month-olds are 1-day intakes.

⁶ Incorporates intake from breastfed and non-breastfed infants. No Canadian data were available for acrylamide levels in breast milk. Acrylamide was not detected in infant formula; therefore, the concentration was conservatively set to the limit of detection.

Appendix 3. Summary of cosmetics and toiletries available in the United States containing polyacrylamide, and corresponding estimates of concentration of acrylamide

Product category	Number of products containing polyacrylamide in the category ¹ in 2002	Concentration of polyacrylamide (%) ² reported in 2002	Estimated concentration of residual acrylamide, ppm (%) ³
Eye lotion	Not stated	1.6–2.5	<0.1–<1.3 (<0.000 01–<0.000 13%)
Eye makeup preparations	2 of 152	0.05	0.003 (0.000 000 3%)
Hair conditioners	1 of 651	0.7–1	0.04–<0.05 (0.000 004–<0.000 005%)
Tonics, dressings and other hair grooming aids	4 of 598	2	0.08 (0.000 08%)
Hair colours, rinses, conditioners	Not stated	Not stated	Not stated
Non-colouring hair preparations	Not stated	0.9–1.4	0.04–0.06 (0.000 004–0.000 006%)
Foundations	4 of 324	0.2–1.3	0.01–0.2 (0.000 001–0.000 002%)
Other makeup preparations	1 of 201	Not stated	Not stated
Nail and skin care cosmetics	Not stated	Not stated	Not stated
Nail creams and lotions	Not stated	0.6	<0.03 (<0.000 003%)
Underarm deodorants	1 of 247	Not stated	Not stated
Personal cleanliness products	2 of 247	Not stated	Not stated
Aftershave lotion	2 of 231	2	0.2 (0.000 02%)
Skin cleansing products	4 of 775	Not stated	Not stated
Face and neck lotions, powders and creams	17 of 310	0.3–1.6	0.02–1.2 (0.000 002–0.000 12%)
Body and hand lotions, powders and creams	16 of 840	0.2–2.8	0.02–<1.2 (0.000 002–<0.000 12%)
Moisturizers	24 of 905	0.3–1.5	0.01–<0.75 (0.000 001–<0.000 075%)
Night creams, lotions, powders and sprays	6 of 200	0.3–0.8	0.01–0.03 (0.000 001–0.000 003%)
Paste masks/mud packs	6 of 271	0.3–0.7	0.04 (0.000 004%)
Skin fresheners	1 of 184	Not stated	Not stated
Other skin preparations	9 of 725	0.2–2.5	0.01–<0.1 (0.000 001–<0.000 01%)
Suntan gels, creams and liquids	2 of 131	0.5–1	0.06–0.1 (0.000 006–0.000 01%)
Indoor tanning preparations	8 of 71	Not stated	Not stated

¹ Based upon information submitted to the US Food and Drug Administration.

² Based upon information or estimated from the Cosmetics, Toiletries, and Perfumery Association.

³ 1 ppm = 0.0001%.

Source: NTP 2005a

Appendix 4. Ranges of concentrations of polyacrylamide in personal care products available in Canada

Product type	Number of products identified	Number of products in concentration range						
		≤0.1%	>0.1–0.3%	>0.3–1%	>1–3%	>3–10%	>10–30%	>30–100%
Antiwrinkle preparation	171	5	26	102	29	8	1	0
Barrier cream	33	0	3	19	10	1	0	0
Bath preparation	7	1	2	4	0	0	0	0
Body makeup	16	0	0	10	6	0	0	0
Deodorant	4	0	1	1	2	0	0	0
Eye lotion	31	3	6	15	4	3	0	0
Eye makeup	120	1	24	91	3	1	0	0
Face makeup	158	0	28	111	17	2	0	0
Fragrance	2	0	0	1	1	0	0	0
Hair conditioner	17	7	1	4	5	0	0	0
Hair dye	2	0	1	0	1	0	0	0
Hair grooming	70	3	6	21	32	7	1	0
Hair removal	4	0	0	0	4	0	0	0
Hair straightener	7	0	0	2	3	1	1	0
Lipstick	4	0	0	4	0	0	0	0
Manicure preparation	6	0	2	2	1	1	0	0
Shaving preparation	35	7	9	14	5	0	0	0
Skin cleanser	145	8	39	54	34	8	2	0
Skin moisturizer	818	46	175	436	143	16	2	0
Tanning preparation	45	6	1	23	14	1	0	0
Massage oil	16	1	3	11	1	0	0	0
Other	127	5	33	62	24	2	0	1
Total	1838	93 (5%)	360 (19.6%)	987 (53.7%)	339 (18.4%)	51 (2.8%)	7 (0.4%)	1 (<0.1%)
Cumulative percentage			24.6%	78.3%	96.7%	99.5%	99.9%	100%

Source: 2008 personal communication from Sector Strategies Division, Health Canada; unreferenced

Appendix 5. Upper-bounding estimates of exposure to acrylamide in consumer products, based on ConsExpo version 4.1 (ConsExpo 2006)

Consumer product scenario	Assumptions ¹	Estimated exposure (µg/kg-bw per day)
Body lotion	Weight fraction: <0.000 12%; highest estimated concentration of residual acrylamide reported in body and hand lotions, powders and creams (NTP 2005a) Dermal (instant application): Exposed area: 16 925 cm² Body weight: 70.9 kg Exposure frequency: twice daily Applied amount: 8 g Uptake: 11%; highest dermal absorption in study with human volunteers (Van Landingham et al. 2004)	0.03
Eye shadow	Weight fraction: <0.000 000 3%; highest estimated concentration of residual acrylamide reported in eye makeup preparations (NTP 2005a) Dermal: Exposed area: 24 cm² Body weight: 70.9 kg Exposure frequency: twice daily Applied amount: 0.01 g Uptake: 11%; highest dermal absorption in study with human volunteers (Van Landingham et al. 2004)	0.000 000 09
Hair conditioner	Weight fraction: <0.000 005%; highest estimated concentration of residual acrylamide reported in hair conditioners (NTP 2005a) Dermal: Exposed area: 1547.5 cm² Body weight: 70.9 kg Exposure frequency: 2 times weekly Applied amount: 54 g Uptake: 11%; highest dermal absorption in study with human volunteers (Van Landingham et al. 2004)	0.001
Hair mousse	Weight fraction: <0.000 08%; highest estimated concentration of residual acrylamide reported in tonics, dressings and other hair grooming aids (NTP 2005a) Dermal: Exposed area: 637.5 cm² Body weight: 70.9 kg Exposure frequency: 1–2 times weekly Applied amount: 0.3 g Uptake: 11%; highest dermal absorption in study with human volunteers (Van Landingham et al. 2004)	0.0003
Aftershave	Weight fraction: <0.000 02%; highest estimated concentration of residual acrylamide reported in aftershave lotion (NTP 2005a) Dermal:	0.0004

Consumer product scenario	Assumptions ¹	Estimated exposure (µg/kg-bw per day)
	Exposed area: 318.75 cm ² Body weight: 70.9 kg Exposure frequency: daily Applied amount: 1.2 g Uptake: 11%; highest dermal absorption in study with human volunteers (Van Landingham et al. 2004)	
Face cream	Weight fraction: <0.000 12%; highest estimated concentration of residual acrylamide reported in face and neck lotions, powders and creams (NTP 2005a) Dermal: Exposed area: 638 cm ² Body weight: 70.9 kg Exposure frequency: twice daily Applied amount: 0.8 g Uptake: 11%; highest dermal absorption in study with human volunteers (Van Landingham et al. 2004)	0.003
Face pack	Weight fraction: <0.000 004%; highest estimated concentration of residual acrylamide reported in paste masks/mud packs (NTP 2005a) Dermal: Exposed area: 638 cm ² Body weight: 70.9 kg Exposure frequency: twice weekly Applied amount: 20 g Uptake: 11%; highest dermal absorption in study with human volunteers (Van Landingham et al. 2004)	0.0004
Hair spray	Weight fraction: <0.000 006%; highest estimated concentration of residual acrylamide reported in non-colouring hair preparations (NTP 2005a) Dermal: Exposed area: 637.5 cm ² Body weight: 70.9 kg Exposure frequency: twice daily Applied amount: 0.6 g Dermal uptake: 11%; highest dermal absorption in study with human volunteers (Van Landingham et al. 2004) Inhalation (spraying towards person): Spray duration: 0.24 min Exposure duration: 5 min Room volume: 10 m ³ Ventilation rate: 2/h Inhalation rate: 16.2 m ³ /day (Health Canada 1998) Uptake fraction: 100%	Inhalation, mean event concentration: 0.000 08 µg/m ³ Dermal: 0.000 000 08

¹ All defaults from ConsExpo (2006) unless otherwise specified.

Appendix 6. Summary of health effects of acrylamide reported in animal studies

Endpoint	Lowest effect levels ¹ /Results
Acute toxicity	Oral: LD₅₀ (rat): 107–251 mg/kg-bw (NTP 2005a) LD₅₀ (mouse): 107–170 mg/kg-bw (NTP 2005a) LD₅₀ (guinea pig): 150–180 mg/kg-bw (NTP 2005a) Inhalation: LC₅₀ (rat): >6000 mg/m³ (Keeler et al. 1975) Dermal: LD₅₀ (rat): 400 mg/kg-bw (NTP 2005a) LD₅₀ (rabbit): 1148 mg/kg-bw (NTP 2005a) Lowest lethal dose (rat): 400 mg/kg-bw per day (Novikova 1979) [additional studies: Schotman et al. 1978; Cavanagh and Gysbers 1983; Miller and Spencer 1984; Gold et al. 1985; Sabri and Spencer 1990; Crofton et al. 1996; Sumner et al. 2003; Yi et al. 2006]
Short-term repeated-dose toxicity	Oral: LOAEL = 0.0005 mg/kg-bw per day; rat; based upon decreased body weight gain, altered enzyme activity; 10-week drinking water study (Yousef and El-Demerdash 2006) LOAEL = 2 mg/kg-bw per day; rat; based upon endocrine effects (thyroid gland morphometry); 7-day exposure, gavage (Khan et al. 1999) Dermal: LOAEL = 50 mg/kg-bw per day; rabbit; neurotoxicity; 5 weeks (Drees et al. 1976) [additional studies: Hazleton Laboratories 1953; McCollister et al. 1964; Hashimoto and Ando 1973; Kaplan et al. 1973; Suzuki and Pfaff 1973; Edwards 1975; Post and McLeod 1977; Tilson and Cabe 1979; Howland et al. 1980; Dixit et al. 1981; Satchell and McLeod 1981; Von Burg et al. 1981; Cavanagh and Nolan 1982; Gilbert and Maurissen 1982; Merigan et al. 1982, 1985; Aldous et al. 1983; Maurissen et al. 1983, 1990; Miller et al. 1983; Sidenius and Jakobsen 1983; Brimijoin and Hammond 1985; Eskin et al. 1985; Gold et al. 1985; Sickles and Goldstein 1985; Bisby and Redshaw 1987; Harry et al. 1989; Hersch et al. 1989; Medrano and LoPachin 1989; Sabri and Spencer 1990; Schulze and Boysen 1991; Costa et al. 1992; LoPachin et al. 1992, 2002, 2003, 2006; Newton et al. 1992; Xiwen et al. 1992; Abou-Donia et al. 1993; Hughes et al. 1994; Regan et al. 1994; Crofton et al. 1996; Gupta and Abou-Donia 1996, 1997; Torigoe et al. 1997; Lehning et al. 1998; Ko et al. 1999; Regan et al. 2000; Stone et al. 2001; Lafferty et al. 2004; Barber et al. 2007; Olstarn et al. 2007; Bowyer et al. 2008; Doerge et al. 2008; Imai et al. 2008]
Subchronic toxicity	Oral LOEL (reported by FAO/WHO 2006b) = 1 mg/kg-bw per day, based upon morphological changes in nerves, examined by electron microscopy (degenerative changes in nerves at next higher dose) (NOEL = 0.2 mg/kg-bw per day); F344 rats, 90-day drinking water assay; 0, 0.05, 0.2, 1, 5 or 20 mg/kg-bw per day (Burek et al. 1980). Examination by electron microscopy was limited to male rats; the effects at 1 mg/kg-bw per day appeared to have reversed after 25 days of recovery. [additional studies: Hazleton Laboratories 1954; Fullerton and Barnes 1966; Tilson et al. 1979; Tani and Hashimoto 1983; Moser et al. 1992; Crofton et al. 1996; Kim 2005; Garey and Paule 2007]

Endpoint	Lowest effect levels ¹ /Results
Developmental / reproductive toxicity	Oral: LOAEL = 1 mg/kg-bw per day, based upon significant decrease in body weight of pups; Fischer 344 rat; dams were exposed by gavage from day 7 to delivery, pups were gavaged with the same dose levels from postnatal days 1 to 22 (Garey et al. 2005) LOEL = 0.5 mg/kg-bw per day (males), based upon neurodevelopmental effects (hindlimb foot splay and head tilt) in F₀, males only; no NOEL; F344 rat; two-generation drinking water assay; 0, 0.5, 2.0 or 5.0 mg/kg-bw per day (Tyl et al. 2000a). The NTP (2005a) also reviewed this study: "The study table does not indicate statistical significance for any comparisons with the control, and Fisher exact test performed by CERHR confirms a lack of statistical significance for these comparisons." [additional studies: Edwards 1976; Shiraishi 1978; Bio/Dynamics Inc. 1979; Agrawal and Squibb 1981; Hashimoto et al. 1981; Walden et al. 1981; Sakamoto and Hashimoto 1986; Zenick et al. 1986; Husain et al. 1987; Sakamoto et al. 1988; Neuhauser-Klaus and Schmahl 1989; Sublet et al. 1989; Field et al. 1990; Bishop et al. 1991, 1997; Costa et al. 1992; Rutledge et al. 1992; Walum and Flint 1993; Lahdetie et al. 1994; Pacchierotti et al. 1994; Chapin et al. 1995; Wise et al. 1995; Marchetti et al. 1997; Friedman et al. 1999; Adler et al. 2000, 2002; Tyl et al. 2000b; Yang et al. 2005a; Wang et al. 2007; Takahashi et al. 2008]
Chronic toxicity / carcinogenicity	Fischer 344 rats, drinking water, 2 years; 0, 0.01, 0.1, 0.5 or 2 mg/kg-bw/day; males: significant increases in the incidences of follicular adenomas of the thyroid (1/60, 0/58, 2/59, 1/59, 7/59, $p < 0.05$) and peritoneal mesotheliomas in the region of the testis (2/60, 0/60, 5/60, 8/60, $p < 0.05$; 7/60, $p < 0.05$); females: increased incidences of thyroid follicular tumours (1/58, 0/59, 1/59, 1/58, 5/60, $p < 0.05$), mammary tumours (10/60, 11/60, 9/60, 19/58, 23/61, $p < 0.05$), glial tumours of the central nervous system (1/60, 2/59, 1/60, 1/60, 9/61, $p < 0.05$), oral cavity papillomas (0/60, 3/60, 2/60, 1/60, 7/61, $p < 0.05$), uterine adenocarcinomas (1/60, 2/60, 1/60, 0/59, 5/60, $p < 0.05$) and clitoral gland adenomas (0/2, 1/3, 3/4, 2/4, 5/5, $p < 0.05$) (Johnson et al. 1986). F344 rats, 106 weeks, drinking water; 0, 0, 0.1, 0.5 or 2.0 mg/kg-bw per day for males or 0, 0, 1.0 or 3.0 mg/kg-bw per day for females; males, significant increase in mesotheliomas of the testicular tunic (4/102, 4/102, 9/204, 8/102, 13/75, $p < 0.001$) and thyroid follicular cell adenoma (2/100, 1/102, 9/203, 5/101, 12/75, $p < 0.001$); females, significant increase in incidence of total number of animals with thyroid follicular neoplasms (1/50, 1/50, 10/100, 23/100, $p < 0.001$) and total animals with mammary gland neoplasms (7/46, 4/50, 21/94, $p < 0.001$; 30/95, $p < 0.001$) (Friedman et al. 1995). Bull et al. (1984a) administered acrylamide orally at doses ranging from 12.5 to 50 mg/kg-bw per day to female ICR Swiss mice over 3 days for each of 2 weeks. Two weeks later, a subset of animals was administered a dermal application of 2.5 µg 12-O-tetradecanoylphorbol-13-acetate (TPA) per mouse, 3 times weekly. Development of tumours was observed weekly in the skin and in the lungs at 1 year. Acrylamide was reported to initiate squamous cell adenoma and carcinomas in the skin and adenomas and carcinomas in the lung. Skin tumour development was dependent upon TPA, and lung tumour induction was not. Bull et al. (1984b), two protocols: 1. Mouse skin initiation-promotion assay. Acrylamide was administered to female Sencar mice by gastric intubation, intraperitoneal injection and topically to the shaved back, at doses of 0, 12.5, 25 and 50 mg/kg-bw for six applications over a

Endpoint	Lowest effect levels ¹ /Results
	2-week period. After 2 weeks, 1 µg 12-<i>O</i>-tetradecanoylphorbol-13-acetate (TPA; tumour promoter) was applied to the shaved back of each animal, 3 times a week for 20 weeks. They were sacrificed after 9 months. There was a significant dose–response relationship for time to first tumour as well as the appearance of multiple tumours, by all three routes of administration. Acrylamide did not increase tumour yield in the absence of TPA promotion. 2. Mouse lung adenoma bioassay. A/J mice (both sexes) were administered orally 0, 6.25, 12.5 or 25 mg/kg-bw, 3 times a week for 8 weeks. At a separate laboratory, the same strain received by intraperitoneal injection 0, 1, 3, 10, 30 or 60 mg/kg-bw. They were sacrificed after 8 months. In the oral protocol, acrylamide increased the yield of lung tumours in both sexes in a dose-related manner. The dose–response relationship was significant ($p < 0.01$) when both animals with tumours and the multiplicity of tumours were tested using a logit regression model analysis. Results of the intraperitoneal protocol were similar; the number of lung adenomas increased with the dose of acrylamide. [additional studies: Robinson et al. 1986] Non-neoplastic endpoints: Oral LOEL = 2 mg/kg-bw per day, based upon degenerative changes in nerves, examined by light microscopy; NOEL = 0.5 mg/kg-bw per day; F344 rat; 2-year drinking water assay; 0, 0.01, 0.1, 0.5 or 2.0 mg/kg-bw per day (Johnson et al. 1986) Oral LOEL = 2 mg/kg-bw per day (males), based upon degenerative changes in nerves, examined by light microscopy; decreased body weight (males); NOEL = 0.5 mg/kg-bw per day; F344 rat; 2-year drinking water assay; 0, 0, 0.1, 0.5 or 2.0 mg/kg-bw per day for males; 0, 0, 1.0 or 3.0 mg/kg-bw per day for females (Friedman et al. 1995)
Genotoxicity and related endpoints: <i>in vivo</i>	Micronucleus: Positive: Mouse, bone marrow, spleen or peripheral blood (Cihak and Vontorkova 1988; Knaap et al. 1988; Backer et al. 1989; Cao et al. 1993; Russo et al. 1994) Mouse, peripheral blood (Abramsson-Zetterberg 2003; Durling and Abramsson-Zetterberg 2005; Yang et al. 2005b; Manjanatha et al. 2006) Mouse, red blood cells (Paulsson et al. 2002; Ghanayem et al. 2005a) Mouse, reticulocytes (Paulsson et al. 2003); rat, reticulocytes (Paulsson et al. 2003) Mouse, bone marrow (Adler et al., 1988) Negative: Mouse, bone marrow (Sorg et al. 1982) Rat, red blood cells (Paulsson et al. 2002) Chromosomal aberrations: Positive: Mouse, bone marrow (Shiraishi 1978; Adler et al. 1988; Cihak and Vontorkova 1988, 1990) Mouse, first-cleavage embryos (Valdivia et al. 1989) Negative: Rat, bone marrow (Krishna and Theiss 1995) Mouse, splenocytes (Kligerman et al. 1991) Chromatid aberrations and sister chromatid exchange: Positive (but not statistically significant): mouse, spleen lymphocytes (Backer et al. 1989)

Endpoint	Lowest effect levels ¹ /Results
	Aneuploidy and polyploidy: Positive: Mouse, bone marrow (Shiraishi 1978) Unscheduled DNA synthesis: Negative: Rat, liver (Butterworth et al. 1992) LacZ (unvalidated assay): Positive: Transgenic mouse, bone marrow (Myhr 1991; Hoorn et al. 1993) Negative: Transgenic mouse, <i>lacZ</i> (Krebs and Favor 1997) Transgenic mouse Tk^{+/-} Negative: B6C3F1 neonatal mice (Von Tungein et al. 2005) Germ cell assays: Positive: Mouse, dietary or intraperitoneal exposure, spermatogonium, aneuploidy/polyploidy, breaks or chromatid exchanges (Shiraishi 1978) Mouse, spermatocyte, aberrations (Backer et al. 1989) Mouse, chromosomal aberrations during meiosis (Adler 1990) Mouse, spermatid micronuclei (Collins et al. 1992) Mouse; spermatid micronuclei, spermatogonia sister chromatid exchange (Russo et al. 1994) Mouse, sperm, abnormal morphology (Dobrzynska and Gajewski 2000) Mouse, spindle abnormalities (Gassner and Adler 1995) Mouse, spermatogonia, meiotic delay, hypoploidy (Gassner and Adler 1996) Rat, spermatid micronuclei (Xiao and Tate 1994) Negative: Mouse, spermatogonia (Schmid et al. 1999) Rat, spermatid micronuclei (Lahdetie et al. 1994) Dominant lethal assays: Positive: Mouse (Shelby et al. 1986, 1987; Dobrzynska et al. 1990; Ehling and Neuhaeuser-Klaus 1992; Gutierrez-Espeleta et al. 1992; NTP 1993; Holland et al. 1999) Long-Evans rat (Smith et al. 1986; Zenick et al. 1986) Fischer 344 rat (Working et al. 1987; Sublet et al. 1989) Negative: Mouse (Nagao 1994; Adler et al. 2000; Ghanayem et al. 2005b) Fischer 344 rat (Tyl et al. 2000a) Chromosomal aberrations in conceptus after treatment of male: Positive: Mouse (Nagao 1994; Pacchierotti et al. 1994; Marchetti et al. 1997; Titenko-Holland et al. 1998; Holland et al. 1999) Heritable translocations: Positive: Mouse (Shelby et al. 1987; Adler 1990; Adler et al. 1994, 2004) Specific locus: Positive: Mouse (Russell et al. 1991; Ehling and Neuhaeuser-Klaus 1992)

Endpoint	Lowest effect levels ¹ /Results
	Effects on DNA and protamine in male germ cells: Positive: Mouse (Sega et al. 1989, 1990; Generoso et al. 1996) DNA adduct formation: Positive: Mouse, liver, kidney, brain (Segerbäck et al. 1995) Mouse, testis, liver (Sega et al., 1990) Mouse, liver, kidney, lung (Gamboa da Costa et al. 2003) Mouse, liver (Twaddle et al. 2004a, b; Doerge et al. 2005a) Mouse, liver, lung, kidney, testis, leukocytes (Doerge et al. 2005b) Rat, liver, lung, kidney, brain, testis (Segerbäck et al. 1995) Rat, liver, brain, thyroid, mammary, testis, leukocytes (Doerge et al. 2005b) Rat, liver (Doerge et al. 2005c) Rat, liver, brain, testis (Maniere et al. 2005) DNA damage in somatic and germ cells in mice (Dobrzynska 2007) DNA breakage: Positive: Mouse (Sega and Generoso 1990)
Genotoxicity and related endpoints: <i>in vitro</i>	Chromosomal aberrations: Positive: V79 Chinese hamster, with and without activation (Knaap et al. 1988) V79H3 hamster, aberrations and polyploidy, without activation (Tsuda et al. 1993) V79 Chinese hamster, without activation (Martins et al. 2007) Mutation at HPRT locus: Negative: V79H3 Chinese hamster, without activation (Tsuda et al. 1993) Chinese hamster ovary, with and without activation (Godek et al. 1984) V79 cells (Baum et al. 2005) Equivocal: Chinese hamster ovary, with and without activation (Godek et al. 1982b) Mutagenicity at thymidine kinase locus: Positive: Mouse lymphoma, with and without activation (Knaap et al. 1988) Mouse lymphoma, without activation (Moore et al. 1987) L5178Y/Tk(+/-) mouse lymphoma cells without activation (Mei et al. 2008) L5178Y3.2.7c-tk(+/-) mouse lymphoma cells (Yuan et al. 2005) Mutagenicity in CH transgene: Positive: Big Blue mouse embryonic fibroblasts (Besaratina and Pfeifer 2003, 2004) Sister chromatid exchange: Positive: V79 Chinese hamster, with and without activation (Knaap et al. 1988) V79H3 Chinese hamster, without activation (Tsuda et al. 1993) V79 Chinese hamster, without activation (Martins et al. 2007) Negative: Chinese hamster ovary, with and without activation (Sorg et al. 1982) Unscheduled DNA synthesis:

Endpoint	Lowest effect levels ¹ /Results
	Positive: Rat hepatocyte (Naismith and Matthews 1982; Miller and McQueen 1986; Barfknecht et al. 1987, 1988) Negative: Rat hepatocyte (Miller and McQueen 1986); rat hepatocyte, without metabolic activation (Butterworth et al. 1992) Human hepatoma G2 cells: DNA strand breaks and increased frequency of micronucleus (Jiang et al. 2007) DNA repair: Negative: Rat hepatocyte (Miller and McQueen 1986) Cell transformation with BALB/3T3, C3H/10T1/2 or NIH/3T3: Positive: Microbiological Associates 1982a, 1984; Banerjee and Segal 1986; Tsuda et al. 1993 Negative: Microbiological Associates 1982b; Abernethy and Boreiko 1987 Cell transformation, Syrian hamster embryo cells: Positive: Park et al. 2002; Klaunig and Kamendulis 2005 Negative: Kaster et al. 1998 Spindle disturbances: Positive: Chinese hamster V79, without activation (Adler et al. 1993) Effects upon chromosomal segregation, migration: Positive: Human fibrosarcoma (Sickles et al. 1995) DNA amplification: Negative: CO60 Chinese hamster (Vanhorick and Moens 1983) Mutagenicity (histidine operon in <i>S. typhimurium</i> and tryptophan operon in <i>E. coli</i>): Positive: <i>Salmonella typhimurium</i> TA98 and TA100 (Yang et al. 2005b) Negative: <i>S. typhimurium</i> TA1535, TA1537, TA98, TA100, TA102, TA1538; <i>E. coli</i> WP2uvrA, with and without activation (Lijinsky and Andrews 1980; Godek et al. 1982a; Bull et al. 1984b; Hashimoto and Tanii 1985; Zeiger et al. 1987; Knaap et al. 1988; Jung et al. 1992; Muller et al. 1993; Tsuda et al. 1993) Mutagenicity to streptomycin resistance genes: Negative: <i>Klebsiella pneumoniae</i> (Vasavada and Padayatty 1981) Cell division aberration: Positive: Chinese hamster lung cell line DON:Wg3h (Warr et al. 1990); Chinese hamster lung fibroblast LUC2p5 Wg3h (Warr et al. 1990) DNA damage: Positive in V79 and Caco-2 cells but negative in primary rat hepatocytes (Puppel et al. 2005) Germ cell assay: Human, testicular cells, single-stranded DNA breaks (Bjorge et al. 1996)
Sensitization	Positive: Guinea pig (Allan 1995; Stockhausen GmbH 1995)
Studies in humans	
Short-term	Dermal; LOAEL = 3 mg/kg-bw per day; increase in alanine aminotransferase; 3

Endpoint	Lowest effect levels ¹ /Results
	days, one dose level only, in aqueous solution; study with volunteers (Fennell et al. 2005) Inhalation and dermal, 2-month occupational exposure to grout; air samples yielded 0.27 and 0.34 mg/m³ for sum of acrylamide and <i>N</i>-methylolacrylamide (approximately 50% was acrylamide); hemoglobin adducts, peripheral nervous system symptoms (Hagmar et al. 2001)
Subchronic	Acrylamide monomer concentrations and peripheral neurotoxicity investigated in 66 workers at a factory producing polymer; 24-month duration, inhalation; LOAEL = ≥ 0.3 mg/m³; neurotoxicity; likely concurrent dermal exposure (Myers and Macun 1991; Bachmann et al. 1992)
Chronic toxicity and carcinogenicity	Marsh et al. (2007) reported the mortality of a cohort of workers with and without exposure to acrylamide at three plants in the United States (n = 8508) and one in the Netherlands (n = 344). Standardized mortality ratios were calculated (brain and other central nervous system system, thyroid, testis and other male genital organs, respiratory system, esophagus, rectum, pancreas, kidney) using national and local rates and modelled internal cohort rates to assess site-specific cancer risks by demographic and work history factors and by exposure indicators. There was no association between exposure to acrylamide and elevated cancer mortality risks. Swaen et al. (2007) investigated 696 workers exposed to acrylamide between 1955 and 2001. Exposure was retrospectively assessed based upon personal samples from the 1970s onward and by area samples over the whole study period. No cause-specific standardized mortality ratios for any cancer were exposure-related. Mucci et al. (2006) conducted a prospective study of acrylamide in food and risk of colon/rectal cancer with data from a cohort of 61 467 women and baseline between 1987 and 1990 through to 2003. There was no evidence that dietary intake of acrylamide was associated with cancer of the colon or rectum. Olesen et al. (2008) analysed blood samples from 374 breast cancer cases in a nested case-control study within a prospective cohort study. They reported a positive association between acrylamide-hemoglobin levels and estrogen receptor positive breast cancer. Using data from a network of Italian and Swiss hospital-based case-control studies, Pelucchi et al. (2006) analysed the relation between dietary acrylamide intake and cancer of the oral cavity/pharynx (749 cases, 1772 controls), esophagus (395 cases, 1066 controls), large bowel (1394 cases of colon cancer, 886 cases of rectal cancer, 4765 controls), larynx (527 cases, 1297 controls), breast (2900 cases, 3122 controls), ovary (1031 cases, 2411 controls) and prostate (1294 cases, 1451 controls). There was no consistent association between intake of acrylamide and risk of cancer. In three case-control studies for increased risk of cancer of the large bowel, bladder, kidneys, renal cell or breast, there was no association between intake of acrylamide and increased cancer incidence (Mucci et al. 2003, 2004, 2005). Hogervorst et al. (2007) chose a random subcohort of 2589 women from the Netherlands Cohort Study on diet and cancer. Acrylamide intake was assessed by a food frequency questionnaire and chemical analyses of relevant foods. After 11.3 years of follow-up, there was an increased risk of postmenopausal endometrial and ovarian cancer with increasing dietary acrylamide intake. In a similar protocol, Hogervorst et al. (2008) randomly chose a subcohort of 5000 men and women and reported "some indications" of a positive association between dietary intake of

Endpoint	Lowest effect levels ¹ /Results
	acrylamide and risk of renal cell cancer. Michels et al. (2006) conducted a case-control study of 582 women with breast cancer and 1569 controls. Information concerning childhood diet at ages 3–5 was obtained from the mothers of the participants, with a 30-item food frequency questionnaire. Although an increased risk of breast cancer was observed among women who had frequently consumed french fries at preschool age, the authors noted that this may have resulted from bias or chance. Larsson et al. (2009) examined 61 433 women from the Swedish Mammography Cohort who were cancer-free and who had completed a food frequency questionnaire in 1987–1990 and again in 1997. During a mean follow-up of 17.4 years, there were 2952 cases of breast cancer in the cohort. In multivariate analyses controlling for risk factors, there was no significant association between long-term intake of acrylamide and risk of breast cancer, either overall or by estrogen receptor or progesterone receptor status. The association between acrylamide intake and risk of breast cancer did not differ by smoking status.
Neurological effects	Dermal; workers, grouting, 2 years; significant reduction in sensory nerve conduction velocity (Kjuus et al. 2004) Occupational (dermal and inhalation) exposure; 71 workers exposed 1–18 months, 51 unexposed workers; dermal effects and “some potential signs of neurotoxicity” (He et al. 1989) Inhalation (and possibly dermal) exposure of workers resulted in impairment of sensitivity to vibration (Deng et al. 1993) [additional studies: Calleman et al. 1994; Goffeng et al. 2008b]
Genotoxicity <i>in vivo</i>	No increase in chromosome breaks or aberrations in 25 workers exposed to acrylamide-containing grout (25 unexposed control workers); increased frequency of chromatid gaps might indicate “a slight genotoxic effect”; concomitant exposure to <i>N</i> -methylolacrylamide (Kjuus et al. 2005)
Sensitization	One positive reaction among 72 study participants (Geukens and Goossens 2001) Positive case report (Beyer and Belsito 2000)
Miscellaneous studies	Bergmark et al. 1993; Boettcher et al. 2005; Bull et al. 2005; Fennell et al. 2005; Hagmar et al. 2005; Fuhr et al. 2006; Paulsson et al. 2006; Goffeng et al. 2008a

¹ LC₅₀, median lethal concentration; LD₅₀, median lethal dose; LO(A)EC, lowest-observed-(adverse-)effect concentration; LO(A)EL, lowest-observed-(adverse-)effect level; NO(A)EC, no-observed-(adverse-)effect concentration; NO(A)EL, no-observed-(adverse-)effect level.