3 METHODS FOR MONITORING EXPOSURES

3.1 EXPOSURE MONITORING

A worker's exposure to airborne acrylamide should be determined by using a personal sampling train consisting of a glass-fiber filter in a Swinnex cassette (13-mm) followed by a silica gel tube. Plastic cassettes (37-mm) yielded poor recoveries of acrylamide and are therefore unsuitable. Samples should be collected at a maximum flowrate of 1 liter/min for a minimum of 2 hr; the maximum air volume should be 120 liters. The silica gel tube should then be treated with methanol to extract the acrylamide. An important step in this method is the transfer of the glass-fiber filters to glass vials containing 1 ml of methanol immediately after sampling to avoid losses of acrylamide from the filter by evaporation. Analysis should be conducted by gas chromatography using a nitrogen/phosphorus detector. The limit of detection for this procedure is 1.3 parts per billion (ppb) (0.004 mg/m^3). This method is described in Method 21 of the *OSHA Analytical Methods Manual* [OSHA 1985].

3.2 BIOLOGICAL MONITORING

The International Programme on Chemical Safety (IPCS) has recommended that a biological monitoring method for acrylamide be developed based on the determination of the adduct formed with hemoglobin [WHO 1985]. However, no biological monitoring test acceptable for routine use has yet been developed for acrylamide.

4 RELATIONSHIP BETWEEN EXPOSURE AND ADVERSE HEALTH EFFECTS

No data are available from studies in humans to establish an occupational exposure limit for acrylamide on the basis of neurotoxic, developmental, reproductive, or carcinogenic effects. However, many studies demonstrate a relationship between exposure and adverse health effects in animals. These studies are the bases for occupational exposure limits recommended by many organizations and government agencies. A few of these studies are described here.

EPA has used results from studies in animals to determine no-observable-effect levels (NOELs) and lowest-observable-effect levels (LOELs). With the use of the appropriate uncertainty factors, EPA has also recommended a "safe" concentration for human exposure (i.e., a concentration that is not expected to produce adverse health effects in exposed individuals) [EPA 1988b].

In 1988, EPA performed a detailed risk assessment of acrylamide based on animal studies of neurotoxicity, carcinogenicity, and reproductive effects [EPA 1988a]. Studies of neurotoxic effects in animals are summarized in Table 6. The NOEL was 0.2 to 2.0 mg/kg per day and the LOEL was 1.0 to 3.0 mg/kg per day. The reference dose (RfD) for acrylamide exposure (formerly acceptable daily intake, ADI) was calculated as 0.0002 mg/kg per day [EPA 1988b]. This value is based on an NOEL for neurotoxicity in a subchronic rat study of 0.2 mg/kg per day [Burek et al. 1980]. The exposure to 0.0002 mg/kg per day corresponds with a TWA concentration of 0.0014 mg/m^3 (assuming an average 70-kg human breathing 10 m^3 of air in an average working day with 100% absorption), which is approximately 20-fold lower than the OSHA PEL of 0.03 mg/m^3. The RfD was obtained by dividing the NOEL by a factor of 1,000 to account for the use of animal data and subchronic exposure. This safety (uncertainty) factor was suggested by the National Academy of Science [NAS 1977].

A designation of B2 (probable human carcinogen) was proposed according to EPA cancer guidelines on the basis of data from studies of two different animal species [EPA 1988a]. Because risks at low exposures cannot be measured directly by experiments in animals or by epidemiologic studies, a number of mathematical models have been developed to extrapolate from high to low doses. To assess the cancer risk posed by acrylamide, EPA used a linear model (i.e., linearized multistage procedure) [EPA 1988a]. Data from the Johnson et al. [1986] study were used to estimate risk from acrylamide exposure. The EPA guidelines for cancer risk assessment recommend pooling tumor incidence data on the grounds that risk estimates derived from the incidence of site-specific tumors may not predict (and may in fact underestimate) whole-body risks that are determined with the pooled animal data. The dose-response curves for each sex are based on the pooled tumor incidence (benign and malignant) and comprise the data sets of choice for risk assessment. The most sensitive sex and species observed in this study (female rats) was chosen to represent possible human risk.

Table 6. Key animal studies of the neurotoxic effects of subchronic and chronic exposure to acrylamide*,+

Reference	Species (route)	Exposure duration	NOEL§ (mg/kg)	LOEL§ (mg/kg)
Burek et al. 1980	Rats	90 days	0.2	1.0
Johnson et al. 1986	Rats	2 years	0.5	2.0
Hamblin 1956	Cats (i.v.)	180 days		1.0
Kuperman 1958	Cats (i.p.)	125 days		1.0
McCollister et al. 1964	Cats	1 year	0.3	1.0
McCollister et al. 1964	Monkeys	1 year	1.0	3.0
Spencer 1979	Monkeys	1 year	2.0	3.0
Schaumburg et al. 1982	Monkeys	1.5 years		1.0

* Adapted from EPA [1988a].
+ All studies here except the two noted used the oral route of administration.
§ NOEL = no-observable-effect level; LOEL = lowest-observable-effect level.

The linearized multistage procedure was followed by EPA [1988a], with GLOBAL 86 as the computer program. Among the models that showed adequate fit with one to six stages, the model that gave the least q_1^* (slope factor) was selected as the model with which to calculate carcinogenic risks using the lifetime average daily exposures provided by the exposure assessment for acrylamide. For the female rats with tumors of the thyroid, oral cavity, uterus, CNS, or mammary glands, this model had two stages. The cancer potency factor obtained for acrylamide by the linearized multistage procedure was 4.5 $(mg/kg\ per\ day)^{-1}$. The cancer potency factor describes the increased risk of developing cancer over a 70-year lifetime per unit of exposure where the unit of exposure is expressed as mg chemical/kg body weight per day. When based on an experimental animal study, the cancer potency factor is the 95% upper confidence limit slope of the dose-response relationship for a carcinogen as the dose approaches zero. Calculated upper-bound excess risks for individuals exposed to acrylamide are presented in Table 7. The highest risks were estimated for sewer repair workers, whose excess risks ranged from 10^{-1} to 10^{-2}. EPA calculated that exposure to airborne concentrations of 0.03 mg/m^3 for a working lifetime of 40 years would result in an excess cancer risk of 2×10^{-3} [EPA 1988a].

The previous American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV®) of 0.3 mg/m^3 [ACGIH 1971] was derived from a study of a small number of cats orally dosed with acrylamide and observed for neurotoxic effects [McCollister et al. 1964]. No effects were observed after feeding the cats acrylamide at the rate of 0.3 and 1 mg/kg per day, 5 days/week for 1 year. On the basis of these data, ACGIH recommended that human exposures not exceed a total intake of 0.05 mg/kg per day. The average 70-kg human who breathes 10 m^3 of air in an average working day would not exceed this recommended exposure limit if he or she were exposed solely to airborne concentrations that did not exceed 0.3 mg/m^3—the TLV adopted by ACGIH.

In 1989, OSHA adopted a new PEL for acrylamide—0.03 mg/m^3 with a skin notation [29 CFR 1910.1000]. This new PEL was based on the increased incidence of cancer in laboratory animals and demonstrated dermal absorption of acrylamide [54 Fed. Reg. 2332]. NIOSH agreed with the proposed PEL of 0.03 mg/m^3 and the supporting evidence of carcinogenicity [NIOSH 1988].

The World Health Organization reviewed cases of acrylamide poisoning in humans [WHO 1985]. Acute exposure to high doses of acrylamide appeared to affect the CNS, and long-term cumulative exposure to smaller doses produced peripheral neuropathy. Signs of peripheral neuropathy appeared after a latent period, which was dose-dependent and decreased with increasing dose.

On the basis of these neurotoxicity data, the World Health Organization recommended that the exposure not exceed a daily intake of 0.012 mg/kg body weight [WHO 1985]. For the average 70-kg human who breathes 10 m^3 of air in an average working day, is occupationally exposed to airborne concentrations only, and has 100% absorption, this intake would result from breathing air with an acrylamide concentration of 0.094 mg/m^3. This recommendation did not consider the risk of cancer or interference with reproduction.

Table 7. Estimates of excess cancer risk for individuals exposed to acrylamide over a lifetime*

Exposure category	Upper-bound individual risk estimates
Manufacturing/processing	10^{-3} – 10^{-2}
Soil grouting (sewer workers)	10^{-2} – 10^{-1}
Drinking water	10^{-6} – 10^{-5}+

* Adapted from EPA [1988a].
+ Worst case to typical case, based on residual acrylamide allowed.

5 RESEARCH NEEDS

Very few studies address dermal absorption of acrylamide, although the dermal route may be the most significant one for acrylamide exposure in the workplace [He et al. 1989]. Therefore, quantitative studies should be performed to assess the absorption of acrylamide through the skin. Because dermal exposure appears to be a significant route of acrylamide uptake and it is difficult to monitor dermal exposures routinely, it is important to develop biomonitoring that can accurately reflect total exposure to acrylamide. A valid biomonitoring technique for acrylamide is presently unavailable. However, the literature on the toxicokinetics of acrylamide indicates that biomonitoring may be feasible either in urine or blood. More than 50% of the given dose is reported to be excreted in urine as the metabolite N-acetyl-S-(3-amino-3-oxy-propyl)cysteine [Miller et al. 1982]. By collecting the urine of workers whose exposure is monitored, it may be feasible to correlate the total exposure (that is, both inhalation and skin) to acrylamide with measured concentrations or total amounts of metabolites in 24-hr urine samples.

Another possibility for biomonitoring is measurement of acrylamide binding to red blood cells. Hashimoto and Aldridge [1970] observed that after rats received a single i.v. dose of ^{14}C acrylamide, the radioactivity in blood after 24 hr was entirely associated with red blood cells. Miller et al. [1982] found that the concentration of ^{14}C in whole blood reached a plateau at 12% of the total dose after 1 hr and remained constant throughout the time period examined (7 days). The binding to erythrocytes accounted for essentially all of the remaining radioactivity in the whole blood. In vitro studies showed that acrylamide was covalently bound to cysteine residues in protein and, on acidic hydrolysis, the adduct yielded a compound with chromatographic properties identified as S-(2-carboxyethyl)cysteine (CEC) [Hashimoto and Aldridge 1970; Bailey et al. 1986].

Bailey et al. [1986, 1987] used gas chromatography to measure the presence of CEC in red blood cells of rats dosed with less than 1 mg/kg. Research is needed to increase the sensitivity of the method (using high-performance liquid chromatography and ion chromotography) and to determine its applicability to human biomonitoring.

Another area that may require more research is elucidation of dose-response relationships for neurotoxic effects. The quantitative data on dose response were adequately addressed in only one species (rat) [Burek et al. 1980]. Better quantitative studies in other species (mice, cats, or rabbits) may be useful.

In light of the reported genotoxicity and carcinogenicity of acrylamide, information on the binding of this compound to DNA is of considerable interest [Moore et al. 1987, Bull et al. 1984a, 1984b; Johnson et al. 1986]. Studies addressing the mechanisms of genotoxicity (in vivo and in vitro DNA binding and effects) would be useful.

Acrylamide is widely used in research laboratories for making polyacrylamide gels. EPA estimated that 100,000 to 200,000 U.S. laboratory workers are potentially exposed [EPA 1988a]. Because exposure data are currently not available on this working population, a survey of potential exposure to acrylamide in research laboratories would be very useful.

6 DISCUSSION AND EVALUATION

Studies in rats and mice indicate an association between the induction of cancer and exposure to acrylamide. Four types of response have been generally accepted as evidence of induction of neoplasms (tumors) [Williams and Weisburger 1986]: (1) the presence of tumors not observed in controls, (2) an increase in the incidence of a specific tumor type observed in controls, (3) the development of tumors earlier than those observed in controls, and (4) an increased number of tumors per animal. Acrylamide satisfies all these criteria. An increased incidence of tumors was observed in one strain of rats (female and male F344) and three strains of mice (male and female A/J, and female Sencar and Swiss-ICR). Increased incidences of lung adenoma and carcinoma occurred in ICR-Swiss female mice dosed by gavage six times over a period of 2 weeks. Similar increases in lung tumor incidence were observed in A/J male and female mice. In female and male rats, the increases in tumor incidence occurred at multiple sites (testes, thyroid, and adrenal gland in males and mammary gland, CNS, oral tissues, uterus, and clitoral gland in females). The incidence of tumors was dose-related both in rats and mice. In A/J mice, acrylamide increased the yield of lung tumors in both sexes in a dose-related manner. In addition, a highly significant dose-response relationship existed for the time to occurrence of first tumors and for the number of tumors per animal in female Sencar mice.

Although carcinogenicity has not been demonstrated in workers occupationally exposed to acrylamide, the limitations of the epidemiologic studies preclude any conclusions regarding the association of exposure to acrylamide monomer and the risk of cancer. Prudent public health practice calls for regarding acrylamide as a potential occupational carcinogen.

On the basis of studies in animals, the International Agency for Research on Cancer (IARC) determined in 1986 that sufficient evidence existed to conclude that acrylamide was carcinogenic in animals and classified it as a 2B carcinogen (a possible human carcinogen) [IARC 1986]. Animal studies also indicate that reproduction is adversely affected by acrylamide exposure. Testosterone levels were depressed in rats [Ali et al. 1983], and decreased fertility was observed in male mice following oral exposure to acrylamide in drinking water [Sakamoto and Hashimoto 1986]. Degeneration of testicular epithelial tissue in male mice treated by gavage has been observed [Hashimoto 1981], as have dominant lethal effects in male rats exposed by drinking water [Smith et al. 1986] and mice exposed i.p. [Shelby et al. 1986]. Oral exposure of male or female mice and rats to acrylamide in drinking water has caused an increased resorption rate [Nalco Chemical Company 1987; Sakamoto and Hashimoto 1986].

7 SUMMARY

Acrylamide is an odorless, white, crystalline solid used as a monomer or as a raw material in the production of polyacrylamides. Workers potentially exposed to acrylamide monomer are employed in acrylamide manufacturing and processing, grouting operations, and research and analytical laboratories.

Only the acrylamide monomer is toxic; polyacrylamide products are generally nontoxic. Acrylamide monomer may be neurotoxic, carcinogenic, genotoxic, and hazardous to reproduction. Recent studies confirm that acrylamide exposures cause cancer and reproductive effects in animals, but epidemiologic studies have not demonstrated these effects in humans.

Key Words: Acrylamide, carcinogenicity, dermal exposures, grouting, neurotoxic effects, occupational exposure, polyacrylamide, reproductive effects.

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9 APPENDIX. INTERNATIONAL STANDARDS FOR WORKPLACE EXPOSURES TO ACRYLAMIDE

This appendix lists occupational exposure limits for airborne acrylamide in various countries (Table A–1), and it contains a discussion of the bases for other recommendations that depart from the frequently cited limit of 0.3 mg/m³.

Table A–1. Occupational exposure limits* for airborne acrylamide in various countries* (mg/m³)

Country	Time-weighted average (TWA)	Short-term exposure limit (STEL)	Ceiling
Austria	0.3	---	---
Belgium	S+ 0.3	---	---
Denmark	S 0.3	---	---
Federal Republic of Germany	S 0.3	---	---
Finland	0.3	0.9	---
Hungary	S 0.3	S 1.5	---
Indonesia	S 0.3	---	---
Italy	S 0.3	---	---
Japan	0.3	---	---
Korea	0.3	0.6	---
Mexico	S 0.3	---	---
Netherlands	S 0.3	---	---
Sweden	S 0.3	S 0.9	---
Switzerland	S 0.3	---	---
Taiwan	0.3	---	---
United Kingdom	S 0.3	S 0.6	---
United States (OSHA)	S 0.03§	---	---
Venezuela	S 0.3	---	S 0.6
Yugoslavia	S 0.3	---	---

* Adapted from Cook [1987].

\+ "S" denotes potential absorption into the body through the skin.

§ In 1989, the Occupational Safety and Health Administration (OSHA) changed its permissible exposure limit (PEL) from S 0.3 mg/m³ to S 0.03 mg/m³ (TWA) [29 CFR 1910.1000].

In 1976, the National Institute for Occupational Safety and Health (NIOSH) recommended an exposure limit (REL) for acrylamide of 0.3 mg/m^3 (0.1 ppm) as a time-weighted average (TWA) for up to a 10-hr workshift (40 hr per week) [NIOSH 1976]. At that time, the available human and animal studies did not provide enough information to alter the previously established OSHA permissible exposure limit (PEL) of 0.3 mg/m^3 as an 8-hr TWA. The original OSHA PEL was based on the 1968 American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value (TLV®) [ACGIH 1971], which was derived mainly from a study of a small number of cats orally dosed with acrylamide and observed for neurotoxic effects [McCollister et al. 1964]. No effects were observed after feeding the cats acrylamide at the rate of 0.3 and 1 mg/kg per day, 5 days/week for 1 year.

The current Swedish standard for acrylamide [TWA = 0.3 mg/m^3] is the same as the previous ACGIH recommendation, with an added short-term exposure limit (STEL) of 0.9 mg/m^3.

Since 1968, ACGIH has designated acrylamide as an A2 substance (suspected human carcinogen) and assigned it a TLV of 0.03 mg/m^3 (0.01 ppm) as an 8-hr TWA with a skin notation [ACGIH 1986]. The revised TLV was based on data indicating a carcinogenic response in rats exposed to acrylamide in drinking water [Johnson et al. 1986]. The skin notation was assigned because of the demonstrated dermal absorption of acrylamide.

On the basis of studies in animals, the International Agency for Research on Cancer (IARC) determined in 1986 that there was sufficient evidence to conclude that acrylamide was carcinogenic in animals [IARC 1986] and classified it as a 2B carcinogen (a possible human carcinogen) [IARC 1987].

The World Health Organization recommended that acrylamide exposure not exceed a daily intake of 0.012 mg/kg body weight [WHO 1985]. For the 70-kg human who breathes 10 m^3 of air in an average workday, is occupationally exposed to airborne concentrations only, and has 100% absorption, this intake would result from breathing air with an acrylamide concentration of 0.094 mg/m^3. It should be emphasized that this value is based solely on the neurotoxicity of acrylamide and does not take into account the risk of cancer or interference with reproduction.

In 1989, OSHA adopted a new PEL for acrylamide—0.03 mg/m^3 as an 8-hr TWA with a skin notation [29 CFR 1910.1000]. This new PEL was based on the increased incidence of cancer in laboratory animals and demonstrated dermal absorption of acrylamide [54 Fed. Reg. 2332 (1989)]. OSHA considered evidence of carcinogenicity derived from the studies by Johnson et al. [1986] and Bull et al. [1984a, 1984b] and stated that the evidence was sufficient to conclude that acrylamide is a carcinogen. In addition, OSHA cited the ACGIH and IARC evaluations of acrylamide as a carcinogen. NIOSH agreed with the proposed PEL of 0.03 mg/m^3 and the supporting evidence of carcinogenicity [NIOSH 1988].

In 1988, the U. S. Environmental Protection Agency (EPA) proposed a reference dose (RfD) for acrylamide exposure (formerly acceptable daily intake, ADI) of 0.0002 mg/kg per day [EPA 1988b]. The RfD is based on a no-observable-effect level (NOEL) in a subchronic rat study of 0.2 mg/kg per day [Burek et al. 1980]. The RfD was obtained by dividing the NOEL by a factor of 1,000 to account for the use of animal data and subchronic exposure. This safety (uncertainty) factor was suggested by the National Academy of Science [NAS 1977]. The designation of B2 (probable

human carcinogen) was proposed for acrylamide according to EPA cancer guidelines on the basis of data from studies of two different animal species [EPA 1988a].

The U.S. Food and Drug Administration has recommended that residual acrylamide monomer not exceed 0.05% in molasses and in beet and cane sugar [37 Fed. Reg. 329 (1972)].

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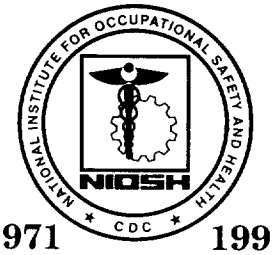

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