
**ENVIRONMENTAL PROTECTION
AGENCY**

[OPTS-47003C; FRL-2642-3]

**Acrylamide; Decision Not To Require
Health Effects Testing**

AGENCY: Environmental Protection
Agency (EPA).

ACTION: Notice.

SUMMARY: This notice presents EPA's final decision not to require health effects testing for acrylamide at this time. Public comments received in response to the Agency's tentative decision not to require health effects testing of acrylamide indicated that the proposed decision should be made final. This notice addresses only the health effects testing of acrylamide. The Agency has addressed the need for environmental effects testing of acrylamide in a separate notice (48 FR 725, January 6, 1983).

FOR FURTHER INFORMATION CONTACT:
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SUPPLEMENTARY INFORMATION.

I. Background

Section 4(e) of the Toxic Substances Control Act (TSCA) (Pub. L. 94-469, 90 Stat. 2003; 15 U.S.C. 2601 *et seq.*) established an Interagency Testing Committee (ITC) to recommend a list of chemicals for EPA to consider for promulgation of testing rules under Section 4(a) of the Act.

The ITC designated acrylamide for priority testing of health and environmental effects in its Second Report published in the Federal Register on April 19, 1978 (43 FR 16684). The ITC based its testing recommendations on high production (1978 production volume of 64 million pounds), anticipated 12 percent production growth rate over the following decade, exposure of an estimated 20,000 workers, possible widespread and low-level exposure of the general population due to its various uses, and insufficient testing information on the recommended effects.

The Agency published in the Federal Register of July 18, 1980 (45 FR 48510) its response to the ITC's testing recommendations covering health effects testing of acrylamide and requested comments on its tentative decision not to initiate rulemaking to require such testing. This decision was based on EPA's opinion that, because there was evidence that exposure of humans and several animal species to very low levels of acrylamide consistently induced neurotoxicity [the no effect level observed in cats is 0.3 to 1.0 mg/kg/day (Ref. 1)], any controls adopted on this basis would be likely to provide a reasonable degree of protection from any other potential acrylamide health hazards. Oncogenic effects were noted to be the one possible exception to this reasoning. However, because the Dow Chemical Company had initiated oncogenicity testing of acrylamide (Ref. 2), EPA concluded that it was not necessary to require additional oncogenicity testing at that time. The Agency also included in that notice its decision to initiate an assessment of acrylamide based upon existing toxicity data.

II. Response to Public Comments

The majority of comments received by the Agency on its tentative decision concurred with EPA's proposed rationale. These commenters recognized that EPA's decision would: (1) Not endanger human health because additional test data would be unlikely to change any control actions based on existing health effects information; (2) be a cost-effective approach to defining the potential hazard of acrylamide to humans; (3) avoid continued study for one chemical that could tie up scarce testing resources better used for others; and, (4) allow EPA to address other recommended chemicals more expeditiously.

In addition to these supportive comments, the Agency received two opposing opinions as well. The first of these argued that any control measures based on currently available information alone (i.e., neurotoxicity) may not adequately protect human health from uncharacterized health effects (e.g., reproductive and teratogenic effects). In response, EPA believes that when all test results from the known ongoing studies are available there will be sufficient data on acrylamide's toxic effects to reasonably determine or predict the health risks it presents to humans, and that the exposure levels consistent with protecting against neurotoxicity and oncogenicity would be so low that they

would be unlikely to produce an unreasonable risk from other health effects.

The second opinion stated that through EPA's decision a precedent for generating significant health effects information only would be established, versus a more general approach to testing for all health effects, which might limit the data base available for identifying options for controlling toxic chemicals. In response to this argument, EPA believes that a decision on whether further testing is necessary for a chemical substance must be approached on a case-by-case basis. For acrylamide, EPA is taking into account the potency of the known effects, likely control levels and probability that other adverse effects will occur at still lower levels. EPA believes that no information essential to potential regulatory activities would be gained from requiring additional health effects testing at this time.

III. Additional Test Data

In a status summary of the oncogenicity study (Ref. 3), Dow reported that test animals from an interim sixth-month sacrifice at the dose level 2.0 mg/kg/day (the highest exposure dose) had no gross or histopathologic effects that were ascribable to acrylamide; however, there were increased numbers of nerve fibers having invaginations of the axolemma and adjacent Schwann cells into the axoplasm. At the twelfth-month sacrifice of the 2.0 mg/kg/day group, the incidence and degree of involvement of focal degeneration of individual nerve fibers was examined. Male rats in this group had increased numbers of myelinated nerve fibers with degeneration or regenerative changes, as well as axolemma invaginations. One of three female rats at the highest dose level sacrificed in the twelfth month of the study had ultrastructural changes similar to those noted in males. Slight focal degeneration of nerve fibers was also seen in rats at 2.0 mg/kg/day at the twelfth-month sacrifice. Preliminary histopathologic examination of peripheral nerves from rats sacrificed after 18 months revealed degenerative changes attributed to ingestion of acrylamide at the highest dose; this was noted especially in male rats. These lesions were consistent with those present at 12 months but more nerve fibers were affected. No carcinogenic effects from exposure to acrylamide were apparent through month 12.

In a second report from Dow (Ref. 4), interim gross pathologic observations from the scheduled 24-month sacrifice of 60 rats/sex/dose level suggests (1) an

increased mortality in female rats at the 2.0 mg/kg/day dose level of acrylamide, and (2) an increased number of female rats with a grossly observed mass in the mammary region at the 2.0 mg/kg/day dose level of acrylamide. Dow has notified its employees and customers, and other producers and users of acrylamide of these preliminary test results.

More recently, the Dow Chemical Company submitted two study reports concerning the oncogenic effects of acrylamide as required under section 8(e) of TSCA (Refs. 5 and 6). In the first submission, Dow reported findings of the histopathological examinations at terminal sacrifice for the female test rats. This report described statistically significant increases in the numbers of neoplasms reported for animals exposed to 2.0 mg/kg/day for the following organs: Central nervous system (brain and spinal cord), mammary gland, clitoral gland, uterus, oral cavity, pituitary gland, and thyroid gland. A statistically significant increase in tibial nerve degeneration, described as a non-neoplastic lesion, was also reported in female rats at the 2.0 mg/kg/day dose level (Ref. 5). Additionally, a statistically significant increase in mortality was reported for male rats given 2.0 mg/kg/day of acrylamide (Ref. 5).

In the second submission, Dow reported the histopathological evaluations for the male rats at the terminal sacrifice from the acrylamide bioassay. This report describes statistically significant increases in the incidence (1) of mesothelioma of the scrotal cavity at 2.0 and 0.5 mg/kg/day, (2) of follicular adenoma (benign) of the thyroid gland at 2.0 mg/kg/day, and (3) of adrenal pheochromocytoma (benign) at 2.0 mg/kg/day (Ref. 6). The report also described an apparent increase, though statistically insignificant, in the number of animals with mesotheliomas of the scrotal cavity at the 0.1 mg/kg/day dose level.

The Agency also received a notice of test results for mutagenicity studies conducted by the American Cyanamid Company (Ref. 7). Data from an Ames test, Chinese Hamster Ovary/Sister Chromatid Exchange (CHO/SCE), and Mouse Micronucleus assay were all negative for acrylamide. However, the BALB/3T3 assay test results show that acrylamide does increase the transformation frequency when exogenous metabolic activation is provided.

Oncogenicity testing of acrylamide was also conducted by EPA at its Health

Effects Research Laboratory in Cincinnati, Ohio. In one study, acrylamide was shown to be capable of initiating tumors in mouse skin when a single 30 mg/kg dose of the chemical was injected intraperitoneally into female SENCAR mice followed two weeks later by repeated applications of 1 mg 12-o-tetradecanoyl phorbol-13-acetate (TPA) 3 times weekly for 20 weeks (Ref. 8). In a follow-up dose-response study of acrylamide in the mouse skin and lung adenoma assays, total doses of 300, 150 and 25 mg/kg of the chemical were administered in 8 aliquots over a 2 week period. Cumulative tumor counts 44 weeks following the start of promotion with TPA also showed that acrylamide was capable of initiating tumors in mouse skin (Ref. 9). Although data from the Strain a lung adenoma assay were not available in this reference, the lead investigator stated that study results for this assay are also positive (Ref. 10).

Preliminary results of the neurofunctional study in primates utilizing visual-motor activity measures reveal that when acrylamide was orally administered (10 mg/kg, 5 days/week until first appearance of toxicity, i.e., approximately 320 to 450 mg/kg total dose), test animals experienced gross avioral disturbance and impaired coordination preceding and accompanying decreased body weights. Sensitivity to vibration decreased during dosing and remained affected for several weeks after cessation of dosing and was found to outlast all other effects (Ref. 11). As part of this study, researchers also observed altered visual thresholds and evoked potentials in cortical responses well before overt signs of toxicity occurred. Visual acuity and flicker-fusion thresholds were reduced and the latency of pattern-reversal evoked potentials increased. After dosing was terminated in two monkeys, the latency of evoked potentials and the flicker-fusion thresholds returned to control values within a few weeks. Visual acuity of both monkeys, however, showed some recovery but stabilized below control values (Ref. 12).

IV. Decision Not To Require Testing

EPA had completed a preliminary assessment of acrylamide's neurotoxicity during 1981. The Agency concluded in that assessment (Ref. 13) that the information then available indicated that any control measures (either voluntary or regulatory) based on acrylamide's neurotoxicity would provide reasonable protection from

other toxic effects resulting from exposure to acrylamide, with the possible exception of oncogenicity. The Agency also concluded that available data on exposures to acrylamide through the use of polyacrylamide in drinking water purification and sugar refining do not suggest an unreasonable risk to human health (Ref. 13). Recent changes in acrylamide production methods and growing operations appear to have significantly reduced worker exposure as well. In a more recent update of the preliminary assessment document (Ref. 14), EPA has concluded that there appears to be no significant neurotoxicity risk to workers handling dry acrylamide or to drinking water supplies due to the use of acrylamide soil gouts.

The final histopathology report from the oncogenicity study, expected to become available to EPA within six months will enable a final assessment of acrylamide's health risk. When final histopathological findings are reported regarding acrylamide oncogenicity, EPA will place them into the public docket and then will reevaluate the risk to workers exposed to acrylamide and explore any control actions that may be necessary.

The Agency concludes that completed and ongoing testing can reasonably be expected to provide sufficient and adequate data to assess the risk to human health caused by exposure to acrylamide and that no further testing should be required under TSCA section 4(a) at this time.

V. References

- (1) McCollister, D.D. *et al.* "Toxicology of Acrylamide." *Toxicology and Applied Pharmacology*, Vol. 8, pp. 172-181, 1984.
- (2) U.S. Environmental Protection Agency. "Assessment of Testing Needs: Acrylamide." Support Document for Decision Not to Require Testing for Health Effects. July, 1980. (EPA 560/11-80-016).
- (3) Gorzinski, S.J. and Johnson, K.A. *Acrylamide Monomer: 2-Year Oncogenicity Study Administered Via the Drinking Water to CDF Fischer 344 Rats, 18-month Status.* (Attachment to M.A. Friedman letter of August 3, 1982.)
- (4) Goodman, C.H. "Letter Enclosing Preliminary Data of a Two-year Chronic Toxicity-Oncogenicity Study on Acrylamide." Dow Chemical Company, Midland, Michigan. December 15, 1982.
- (5) Goodman, C.H. "Letter Submitting Information Under Section 8(e) of TSCA." Dow Chemical Company, Midland, Michigan. July 15, 1983.
- (6) Blair, E.H. "Letter Submitting Information Under Section 8(e) of TSCA." Dow Chemical Company, Midland, Michigan. March 14, 1984.

(7) Most, R.W. "Letter Enclosing a Synopsis of Results from Acrylamide Mutagenicity Studies." American Cyanamid Company, Wayne, NJ. August 13, 1982.

(8) Bull, R.J. *et al.* "Acrylamide as a Tumor Initiator in the Mouse Skin." *Toxicology*, 2(1): 103, 1982.

(9) Bull, R.J. *et al.* "Carcinogenic Properties of Acrylamide in the Mouse Skin and Lung Adenoma Assays." Abstract #333 of 1983 Annual Conference found in the *Toxicologist*, Vol. 3, No. 1, January, 1983.

(10) "Contact Report with R.J. Bull." U.S. Environmental Protection Agency, Health Effects Research Laboratory, Cincinnati, OH. January 14, 1983.

(11) Maurissen, J.P.J., *et al.* "Effects of Acrylamide Monomer on Sensory Thresholds in Monkey." Abstract #402 of 1982 Annual Conference found in the *Toxicologist*, Vol. 2, No. 1, January, 1982.

(12) Merigan, W.H., *et al.* "Visual Indices of Acrylamide Neurotoxicity in Primates." Abstract #401 of 1982 Annual Conference found in the *Toxicologist*, Vol. 2, No. 1, January, 1982.

(13) U.S. Environmental Protection Agency. "Preregulatory Assessment, Disposition Document for Acrylamide." (See Public Docket for this action.)

(14) U.S. Environmental Protection Agency. "Preregulatory Assessment, Acrylamide Disposition Document Update." (See Public Docket for this action.)

VI. Public Record

EPA has established a public record for this testing decision, docket number [OPTS-47003C] which is available for inspection in the OPTS Reading Room from 8:00 a.m. to 4:00 p.m. on working days in Rm. E-107, 401 M Street, SW., Washington, D.C. 20460. The record includes the following information:

- (1) Federal Register notice containing the designation of acrylamide to the Priority List.
- (2) Federal Register notice of proposed decision not to require testing.
- (3) Communications (public, intra-agency, and interagency) consisting of non-confidential memoranda and letters, contact reports of telephone conversations, and meetings.
- (4) Public comments on the ITC report and proposed decision not to require testing.
- (5) Published and unpublished data.

(Sec. 4(a) TSCA (Pub. L. 94-469, 90 Stat. 2003; 15 U.S.C. 2601))

Dated: June 7, 1984.

William D. Ruckelshaus,
Administrator.

(FR Doc. 84-20712 Filed 7-30-84; 8:45 am)

BILLING CODE 6560-50-M