

**BASIC ACRYLIC MONOMER MANUFACTURERS, INC.**

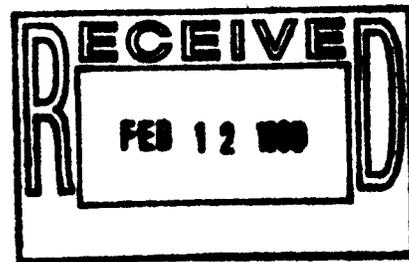
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February 11, 1999

**BY FEDERAL EXPRESS**

Dr. C.W. Jameson  
NIEHS  
MD EC-14  
P.O.Box 12233  
Research Triangle Park, N.C. 27709



Re: Ethyl Acrylate

Dear Dr. Jameson:

The Basic Acrylic Monomer Manufacturers, Inc. ("BAMM") appreciates this opportunity to provide final comments in support of the proposed delisting of ethyl acrylate from the Biennial Report on Carcinogens ("BRC"). See 63 Fed. Reg. 68,783 (Dec. 14, 1998). BAMM represents domestic manufacturers of acrylic acid and acrylate esters, including ethyl acrylate.

BAMM filed a delisting petition in August 1997 which led to the current NTP consideration of delisting ethyl acrylate from the BRC. BAMM also submitted written comments to the NTP Board of Scientific Counselors' Subcommittee on the Report on Carcinogens, dated November 13, 1998, and provided an oral presentation by Dr. Sandra Murphy, Chair of BAMM's Technical Committee, at the Subcommittee's meeting on December 3, 1998.

BAMM is pleased that all three NTP scientific review groups voted overwhelmingly to delist ethyl acrylate from the Report on Carcinogens. Those recommendations are also consistent with the recent report of the Presidential/Congressional Commission on Risk Assessment and Risk Management, which concluded that the rodent forestomach tumors induced by chronic ethyl acrylate gavage dosing are not relevant for humans.

Ethyl acrylate was originally listed as "reasonably anticipated to be a carcinogen" in 1989 based on a NTP chronic gavage study which induced forestomach tumors in male and female mice and rats. However, subsequent data, most prominently that produced in mechanistic studies by NTP/NIEHS scientists, now provide compelling evidence that the forestomach tumors produced by gavage dosing result from a toxicity-mediated mechanism that will not occur in humans. This finding, combined with the extensive data set showing that ethyl acrylate does not induce tumors (or significant toxicity) by other routes of exposure, led BAMM to petition for the delisting of ethyl acrylate from the Report on Carcinogens.

Specifically, BAMM's delisting petition and previous comments to the NTP made the following principal points:

1. A series of subsequent mechanistic studies, most prominently those by NTP scientists, demonstrated that gavage dosing of ethyl acrylate produced localized inflammation and hyperplasia only at the site of contact in the rodent forestomach. This response was reversible unless daily gavage dosing continued for six months, in which case the lesions progressed to tumors. The observed response was concentration- rather than dose-dependent. No such toxicity or carcinogenicity was observed in the rodent glandular stomach, which received a comparable dose to that of the forestomach.
2. Chronic animal studies employing other routes of exposure, including inhalation, dermal and drinking water exposure, produced no increase in tumors and no toxic response other than slight irritation at the point of contact. Drinking water exposure involving the same daily dose used in the NTP chronic gavage study produced no carcinogenic or toxic response in the forestomach or any other site.
3. Extensive metabolic data demonstrates that ethyl acrylate is very rapidly metabolized in the body into non-toxic metabolites. Any toxic effects of ethyl acrylate would therefore be expected to occur only at the point of contact. This is confirmed by the lack of any systemic toxicity in any of the numerous studies on ethyl acrylate, as well as the inability to measure ethyl acrylate in the blood stream after exposure.
4. While ethyl acrylate produces a positive response in certain types of *in vitro* genotoxicity assays (*e.g.*, mouse lymphoma assay), it does not produce a genotoxic response in *in vivo* studies. Recent studies demonstrate that the positive *in vitro* results occur only at concentrations associated with high levels of cytotoxicity, consistent with the results for several other non-genotoxic chemicals that are not considered to be carcinogenic.
5. Human ethyl acrylate exposures are almost exclusively via inhalation, with some potential for dermal exposure in occupational settings. Exposures are very low in both occupational and non-occupational settings. Recent occupational exposure data collected from ethyl acrylate producers found that the geometric mean exposure by operations type is consistently below 0.5 ppm, with the upper 95th percentile maximum exposure level at or below 1 ppm. Consumer exposures are even lower, because ethyl acrylate is polymerized in all consumer applications. A recent market basket survey confirmed that residual ethyl acrylate levels in latex paints are very low, resulting in short-term exposures of only 4 ppb when used in an unventilated room under worst-case conditions. The strong, noxious odor of ethyl acrylate at very low concentrations (odor threshold of approx. 0.5 ppb) ensures that human exposure

remains negligible. Human exposure levels therefore never approach the very high concentrations of ethyl acrylate needed to overwhelm the detoxification pathways even in the most sensitive rodent forestomach tissue.

Based on these data, the three NTP scientific review committees each voted to recommend delisting of ethyl acrylate from the Report on Carcinogens. At the Board of Scientific Counselors' Subcommittee meeting considering ethyl acrylate delisting, the only one of the three review committee meetings open to the public, the ethyl acrylate data were thoroughly considered and discussed, with several committee members remarking that the case for delisting ethyl acrylate is particularly strong. This is reflected in the wide margins by which the Subcommittee and the two previous NTP review committees voted in favor of delisting ethyl acrylate.

The only concern raised at the Subcommittee meeting that was not adequately addressed and resolved at the meeting was a transformation study of tracheal cells involving ethyl acrylate that was mentioned by one participant, but no other information on the study was available at the meeting. The uncertainty about this study was cited as a primary reason for their votes by two of the three committee members who either voted against the delisting or abstained on the merits. (A fourth committee member also abstained because he has done research on ethyl acrylate on behalf of a BAMM member company.)

BAMM has now reviewed the transformation study mentioned at the meeting, which involved the evaluation of 17 chemicals in a short-term *in vitro* transformation assay involving cultured rat tracheal epithelial cells.<sup>1</sup> The study observed that ethyl acrylate was "very toxic" and had "an extremely low IC50 level," which is the concentration that reduces the relative colony-forming efficiency ("CFE") by 50 percent. The only transformation results reported for ethyl acrylate found a moderate transformation frequency at a concentration slightly below the IC50 level for ethyl acrylate, which likely was also associated with significant cytotoxicity. This result is consistent with the other available data indicating that ethyl acrylate can result in positive *in vitro* genotoxicity results at concentrations involving significant cytotoxicity, but does not produce positive results in *in vivo* genotoxicity assays, likely because ethyl acrylate is so rapidly detoxified in tissue. Further assurance that ethyl acrylate is not carcinogenic or toxic to tracheal cells *in vivo* is provided by the chronic inhalation bioassays that have been completed for ethyl acrylate and its sister compounds (methyl and butyl acrylate) which observed no increased tumors or toxicity in any tissue other than slight nasal irritation. As the majority of the Subcommittee recognized, this study therefore does not affect the conclusion that ethyl acrylate is unlikely to cause human cancer.

The extensive data set available on ethyl acrylate thus provides compelling evidence that ethyl acrylate only causes tumors in the uniquely sensitive rodent forestomach through a toxicity-

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<sup>1</sup> V. Steele, *et al.*, Evaluation of a Rat Tracheal Epithelial Cell Culture Assay System to Identify Respiratory Carcinogens, *Envtl. Molecul. Mutagen.* 14:48-54 (1989).

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mediated mechanism that (1) requires chronic exposure to very high concentrations of ethyl acrylate that is (2) provided only by a gavage bolus, which is (3) needed to overwhelm the normally very effective and efficient detoxification pathways *in vivo*. The NTP should therefore affirm the strong recommendation provided by all three of its scientific advisory committees and delist ethyl acrylate from the Biennial Report on Carcinogens.

Respectfully submitted,

Handwritten signature of Elizabeth K. Hunt, appearing as "E. Hunt/GSM".

Elizabeth K. Hunt  
Executive Director