Delisting of Ethyl Acrylate from the Biennial Report on Carcinogens

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on behalf of the
Basic Acrylic Monomer Manufacturers, Inc.

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EA - No Systemic Toxicity

- EA is rapidly metabolized to harmless byproducts in tissue
- No EA detected in blood or tissues distant from dosing site
- No systemic toxicity observed in any EA study
- EA is therefore a contact toxicant -- any toxicity expected only at the point of contact

EA - Chronic Animal Studies

- Inhalation - Ethyl, butyl and methyl acrylates
  - no carcinogenicity; slight nasal irritation
- Dermal
  - no carcinogenicity; irritation
- Drinking water
  - no carcinogenicity or toxicity
- Gavage
  - toxicity and carcinogenicity in forestomach
  - no toxicity or carcinogenicity in any other tissue, including glandular stomach with comparable dose

NTP Mechanistic Studies of Gavage Dosing

- Daily gavage exposure for less than 6 months results in reversible inflammation and hyperplasia; no tumors
- After 6 months of daily gavage exposure, lesions become irreversible and progress to tumors
- Toxicity and associated tumors occur only in forestomach, not glandular stomach or other tissues
- Response of forestomach is concentration rather dose-dependent
- Carcinogenicity results from non-genotoxic mechanism associated with chronic toxicity
- Exposure concentration and duration needed to trigger response incompatible with any conceivable human scenario

Genotoxicity

- EA negative in in vitro point mutation assays (e.g., Ames test)
- EA negative in multiple in vivo assays (e.g., micronucleus test, TG•AC transgenic mice, *Drosophila* sex-linked recessive lethal assay, DNA and chromosome assays)
- EA positive for chromosomal aberrations in some in vitro assays (e.g., mouse lymphoma assay)
  - Ciaccio (1998) - in vitro genotoxicity of EA occurs only at high concentrations associated with cytotoxicity
  - Hilliard (1998) - several "non-genotoxic," non-carcinogens produce similar effects in mouse lymphoma assay at concentrations associated with cytotoxicity

Epidemiology Data

- Only study (Walker *et al.*) found increased colorectal cancer mortality at 1 dose level in 1 of 3 cohorts in multi-exposure WWII workplaces
- Cannot be used to support or refute causal association:
    - NTP
    - IARC
    - EPA (MMA)
    - Dr. Walker

Letter from Dr. A. Walker Nov. 11, 1998 (excerpt)

"In the original publication we cited a number of reasons why our data should not be taken on their own as proof of a causal association, and these have been largely summarized, correctly, in the NTP staff document. An increase on the order of two to three fold in risk should have been detectable in the Knoxville cohort, and it was not seen. The exposure indices were crude for all the cohorts. We could not distinguish between EA and MMA in the one cohort that showed an effect (Early Bristol). There were other carcinogens in the workplace. There is (and we can say this more strongly today than seven years ago) no plausible, known causal mechanism for an effect on the colon and rectum resulting from vapor exposures to EA and MMA.

"There was another serious limitation, which we cited in the introduction to our report, that has not been adequately highlighted by either BAMM or the NTP draft. We undertook the analysis because we knew in advance that there was an excess of colon cancer in the cohort. These cohorts had been assembled originally for the evaluation of lung cancer risk, and completely after the fact DeFonso and his colleagues noted a small excess of colon cancer. From that point, we undertook to rigorously structure an analysis that would pinpoint and quantify the elevation. But it remains a post hoc analysis of the unexpected finding. If there were other, supportive human data, I would not think of this as a special drawback. But standing alone, the report is less persuasive than it would have been if colorectal cancers had been identified independently as a concern for these workers.

"For all of these reasons, I find that I agree with the NTP staff that "This study, by itself, can neither establish nor rule out a causal relationship with cancer."

Conclusion

- All plausible routes of exposures evaluated and consistently negative
- Subsequent mechanistic research by NTP scientists provides compelling data that forestomach tumors in chronic gavage study (used to initially list EA) are not relevant to humans
- Presidential Risk Commission concurred that forestomach tumors from EA gavage one of relatively few animal results not relevant to humans