

NORTH AMERICAN POLYELECTROLYTE PRODUCERS ASSOCIATION

Comments on December 2007 US EPA External Review Draft Toxicological Review of Acrylamide (CAS No. 79-06-1) In Support of Summary Information on the Integrated Risk Information System

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INTRODUCTION

The North American Polyelectrolyte Producers Association (NAPPA) submits the following comments regarding the US Environmental Protection Agency's (EPA) December 2007 draft Toxicological Review of Acrylamide for the Integrated Risk Information System (IRIS)¹ (the "draft Assessment"), as announced in the December 28, 2007 *Federal Register* (72 FR 73813) with respect to Docket No. EPA-HQ-ORD-2007-1141. NAPPA represents the major North American manufacturers and users of acrylamide, which currently includes Ashland Inc., Ciba Specialty Chemicals, Kemira Water Solutions, Inc., Nalco Company and SNF Holding Company. As such, NAPPA has a unique interest in this proceeding.

Issues associated with acrylamide exposure and assessment of potential human health effects, were until recently primarily focused around the monomer and associated polymers. The recent determinations that acrylamide is a natural byproduct of cooking of certain food substances, has shown that the public's exposure to acrylamide is much greater from endogenous sources or from food.

The following comments address several key issues that should be considered as EPA further evaluates and revises its Acrylamide IRIS assessment.

¹ Toxicological Review of Acrylamide (CAS No. 79-06-1) – In Support of Summary Information on the Integrated Risk Information System (IRIS). December 2007, External Review Draft.
http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=470652.

EPIDEMIOLOGY

The draft Assessment correctly concludes that there is a considerable amount of human epidemiology data on acrylamide. While there may be limitations to these epidemiology data related to study designs and available cohorts, overall the available evidence supports the conclusion that there is not an association between acrylamide exposure and cancer in humans.

As highlighted in the draft Assessment, the epidemiology data on acrylamide shows that:

“No association has been established between increased levels of acrylamide in the diet and increased risk for a variety of cancer types.”

“No statistically significant associations were found between increased risks for large bowel, kidney, or bladder cancer and frequent consumption of foods containing high or moderate levels of acrylamide.”

While NAPPA generally supports the Agency’s review of the epidemiology studies, the assessment does not rely on the most up-to-date information and is also missing key references. In particular, NAPPA notes that:

- 1) EPA’s statements regarding a possible increased risk for pancreatic cancer related to the cohort established by Marsh *et al.* does not consider the most recent update to that cohort (Marsh 2007) which found no increased risk for pancreatic cancer in the cohort;
- 2) EPA’s conclusion regarding the lack of reproductive effects information in the epidemiology data is missing a key reference by Costa *et al.* (1994); and finally,
- 3) EPA concerns over the adequacy of the human neurotoxicology data are not accurate and EPA should rely on human neurotoxicity results in establishing the IRIS risk limits.

Marsh *et al.* 2007 Shows No Increased Cancer Risk

The draft Assessment notes that based on Marsh *et al.* (1999) there is a possible association with increased risk of pancreatic cancer and occupational exposure to acrylamide. However, this conclusion is inaccurate and outdated when you consider the

results and conclusion from the recent update of this same cohort that was published by Marsh *et al.* in 2007². The updated study, which expands the years of follow-up through 2002, did not find an increase of any cancer following exposure to acrylamide. The author's state:

“For pancreatic cancer, in particular, we observed a 38% deficit in deaths (nine deaths, SMR = 0.62, CI = 0.28-1.18) yielding a 6% overall deficit for the combined 1925-2002 period.”

This clearly indicates that EPA's conclusions regarding possible pancreatic cancer risks observed in this cohort are not valid. Further, no other statistically significant cancer risks were identified in this study and the only elevated SMR related to respiratory system cancer, has already been attributed to muriatic acid exposure.

When the Agency considers the updated information on this cohort from Marsh *et al.* 2007, which EPA has already concluded is the most comprehensive available epidemiology study, NAPPA believes the Agency will conclude that there is no evidence of an increased cancer risks associated with acrylamide exposure in this or any other study.

Data on Reproductive Effects from Epidemiology Data

EPA concludes in the Assessment that there is a complete lack of information in the epidemiology literature on possible reproductive effects associated with human exposure to acrylamide. However, EPA notes that the study conducted by Calleman *et al.* 1994 includes the collection of a reproductive history from the study participants. The draft Assessment does not further evaluate this aspect of the study and fails to evaluate the report by Costa and Calleman (1994)³, attached, which provides more information on the

² Marsh, G., A. Youk, J. Buchanich, I. Jmert Kant and G. Swaen. (2007). Mortality Patterns Among Workers Exposed to Acrylamide: Updated Follow Up. *Journal of Occupational and Environment Medicine*, 49(1): 82-95.

³ Costa, LG and Calleman, CJ (1994). Determination of Hemoglobin Adducts Following Acrylamide Exposure. EPA/600/R-93/226. February 1994.

reproductive evaluation of this study. Costa and Calleman (1994) state on page 30 of the report that:

“The results of a survey on the reproductive history of each subject showed no difference *in fertility, abortion and birth defects in offspring between the acrylamide workers and referents.*” (emphasis added)

All participants provided their reproductive histories, which is mandatory in China, and which had already been provided to the State. As such, these are likely to be valid and properly reported results. This paper clearly demonstrates that reproductive toxicity was not observed in even heavily exposed individuals.

These results are consistent with EPA’s conclusions in the draft Assessment that reproductive toxicity is expected to be a much less sensitive endpoint than neurotoxicity. This conclusion was also reached by the National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR), which notes in the Monograph⁴ that the “Expert Panel expressed negligible concern for adverse reproductive and developmental effects for exposures in the general population.”

Human Neurotoxicity Data Adequate for Risk Assessment

EPA concludes in the draft Assessment that the available human data on neurotoxicity is not sufficient for establishing the RfC because the studies do not provide adequate information on dose-response, involve mixed inhalation and dermal exposure, involve exposure to confounding chemicals, and the duration of exposure was less than chronic. One of the key studies that EPA assessed in its review of the human neurotoxicity data is Calleman et al. (1994)⁵. As already noted, this study is further described in a paper by Costa and Calleman³ (1994), which EPA should include in its revised IRIS assessment report.

⁴ NTP CERHR (2005). Monograph on the Potential Human Reproductive and Developmental Effects of Acrylamide. NIH Publication 05-4472. February 2005.

⁵ Calleman *et al.* (1994). Relationships between Biomarkers of Exposure and Neurological Effects in a Group of Workers Exposed to Acrylamide. *Tox App Pharm*, 126:361-271.

Drs. Costa and Calleman, working under a cooperative agreement with the University of Washington (Seattle), evaluated a number of aspects of neurotoxicity in workers exposed to acrylamide for more than two years. They determined that neurotoxicity reached a plateau after six months exposure; the researchers were further able to establish a human NOAEL, LOAEL and EL₅₀ for neurotoxicity of acrylamide of 3, 8, and 10 mg/m³, respectively.

Using a neurotoxicity index assessed in a double blind clinical evaluation and exposure from either the biomarkers or area monitoring, Drs. Costa and Calleman showed that the threshold for neurotoxicity is 3.0 mg/kg/day. NAPPA believes that EPA should use the results in this study instead of relying on rodent data.

In considering EPA's concerns about the human epidemiology data, NAPPA believes that these results should not be disregarded as they are directly related to acrylamide exposed workers. In the study, these air concentrations were derived by back-calculating from blood levels of the acrylamide adduct so any potential dermal exposure (which is likely be small relative to inhalation) would be captured by the blood levels of the adduct.

Mutagenicity/Carcinogenicity - NAPPA encourages EPA to perform a more critical evaluation of the extensive mutagenicity literature on acrylamide. NAPPA is providing a critical analysis from Dr. Errol Zeiger which explores all relevant modes of action as called for by EPA's recently issued draft *Framework for Determining a Mutagenic Mode of Action for Carcinogenicity: Using EPA's 2005 Cancer Guidelines and Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens*. As discussed in Dr. Zeiger's analysis, the draft Assessment is deficient by its failure to discuss the evidence supporting alternative modes of action such as kinesin binding and oxidative stress. Additionally, the draft Assessment gives little attention to the available studies that suggest that the genotoxic effects of acrylamide and glycidamide may not be a consequence of the alkylation of DNA by glycidamide.

Other issues discussed by Dr. Zeiger include:

- While acrylamide is a weak genotoxin in mouse somatic cells, and mouse and rat germinal cells, acrylamide is not genotoxic in rat somatic cells although the available carcinogenicity data is all from rat studies.
- Although the metabolite, glycidamide, forms DNA adducts, the WOE of the genetic toxicity data support the conclusion that the genetic effects seen can be explained by effects other than a direct genotoxic mechanism, specifically through interference with the mitotic and meiotic apparatus, through induction of an oxidative stress response and/or through protamine alkylation and disruption.

Additionally, NAPPA encourages EPA to more critically review the available evidence on the carcinogenicity of acrylamide. The draft Assessment suggests that the available evidence supports the conclusion that acrylamide is “likely to be carcinogenic to humans” based on findings of: (1) increased incidences of tumors in male and female rats; (2) the initiation of skin tumors following oral, i.p., or dermal exposure to AA and tumor promotion by TPA in two strains of mice; and (3) increased incidence of lung adenomas in another mouse strain following i.p. injection of AA. NAPPA maintains that a more thorough review of the available data should lead EPA to conclude that typical occupational or general population exposure do not present a cancer risk.

A significant issue that requires more critical evaluation concerns the classification of tumors in the existing cancer bioassays. An analysis of this issue prepared by Dr. McConnell is attached. Dr. McConnell was instrumental in establishing the NTP guidelines for combining tumor types. He concludes with regard to fibroadenomas and adenocarcomas of the mammary gland, “current NTP policy is not to combine adenomas and fibroadenomas for determining a treatment-related effect.” With regard to the malignant reticulosis, he concludes “because of their fundamental difference in histomorphogenesis, they should not be combined with glial cell tumors.” Finally, with

regard to the TVMs, he cites a pathology working group (PWG) report which is also provided as an attachment to this submission. The PWG concluded that the TVMs were not the result of genotoxicity but were secondary to the Leydig cell tumors and unique to the Fischer rat.

Mode of Action – Hormonal

While acrylamide has clearly been shown to cause cancer in rats following high dose exposures, the critical issue to an effective assessment is an understanding of the “mode of action” by which acrylamide exerts its carcinogenic potential. Dr. Annette Shipp has prepared an in-depth review of the issues that support a hormonally mediated mode and in doing so addresses each of the tumor types.

As explained by Dr. Shipp, the key issues that should be evaluated to determine the mode of action in a specific organ are:

- *The basic biology of that organ system along with physiological controls, such as feed back loops, that explains normal functioning;*
- *The key steps in that biological/physiological flow of normal functioning that could be impacted by either changes due to aging or the application of an exogenous chemical resulting in changes in that cell or organ system’s homeostasis; and,*
- *The key step or biological “trigger(s)” (that is the obligatory precursor step) that provides the underlying stimulus, even in the absence of exogenous chemicals that “push” a normally functioning cell in an organ to become a neoplastic cell resulting in a tumor-containing organ. Stated differently, what are the biological/physiological changes that occur in the development of “spontaneously” occurring tumors in specific organs?*

Dr. Shipp’s analysis supports the contention that the tumors in laboratory animals caused by acrylamide exposure are hormone or some other homeostatic related event driven.

Conclusion

NAPPA believes that a more comprehensive and critical review of the existing genotox and mechanistic information, in combination with the extensive information anticipated

from the NCTR studies, is needed prior to completing the IRIS assessment. NAPPA further believes that a more comprehensive review will lead EPA to conclude that acrylamide should be assessed using a threshold, margin of exposure technique.