



The Fertilizer Institute

Gary D. Myers
President

May 15, 1998

By Federal Express

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
National Institutes of Health
West Campus, Room 300
MD WC-05
P.O. Box 12233
Research Triangle Park, NC 27709

RE: Ninth Annual Report on Carcinogens

Dear Dr. Jameson:

The Fertilizer Institute (TFI), on behalf of its member companies, submits these comments in response to a March 19, 1998 National Toxicology Program (NTP or Program) notice in the Federal Register soliciting final public comments on NTP's list of substances, mixtures and exposure circumstances for possible inclusion in the Ninth Annual Report on Carcinogens (63 Fed. Reg. 13,418).

Statement of Interest

TFI is a voluntary, non-profit trade association of the fertilizer industry. TFI's nearly 250 member companies manufacture over 90 percent of the domestically produced fertilizer. TFI's membership includes producers, manufacturers, distributors, transporters and retail farm suppliers of fertilizer and fertilizer materials. In the production of phosphoric acid-based fertilizers, large amounts of sulfuric acid are produced and utilized by TFI's members. Thus, TFI and its member companies have a vital interest in any effort by NTP to evaluate the carcinogenicity of strong inorganic acid mists containing sulfuric acid.

Description of the Production Process

Fertilizer manufacturers utilize the wet process to produce phosphoric acid. It is estimated that 95 percent of the commercial grade wet-process phosphoric acid is used to produce fertilizers and animal feed, with a small portion used as a feedstock in chemical processing operations. The wet

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process for the production of phosphoric acid includes three basic operations: digestion; filtration; and concentration. Sulfuric acid is relevant to the first operation, digestion.

As part of the digestion operation, beneficiated phosphate rock is added to a recirculating phosphoric acid stream, generating calcium phosphate. Sulfuric acid is then added to the solution to chemically precipitate calcium sulfate solid (phosphogypsum) and leave phosphoric acid in solution. TFI's members captively produce sulfuric acid at their phosphoric acid production facilities. In fact, 71 percent of the sulfuric acid in the United States is produced captively for use in phosphoric acid production. Thus, any evaluation of the carcinogenicity of sulfuric acid, in any form, is of import to TFI's members.^{1/}

Discussion

TFI offers the following comments on NTP's notice of intent to evaluate strong inorganic acid mists containing sulfuric acid for inclusion in the Ninth Annual Report on Carcinogens.^{2/}

I. NTP Should Undertake a Rigorous Review of the Studies Identified As Relevant to Evaluating Strong Inorganic Acid Mists Containing Sulfuric Acid

TFI urges NTP to conduct a critical, independent review of the studies which NTP ultimately concludes are applicable to strong inorganic acid mists containing sulfuric acid, instead of merely adopting the conclusions reached in those studies. TFI believes that NTP has adopted a contrary approach based on a statement contained in NTP's Seventh Annual Report on Carcinogens (1994), the Program's most recent report. In this Report, NTP "reminds" the public that the Report:

is a condensation of large amounts of data and conclusions made by bodies which peer review the data submitted as evidence about cancer and its relation to specific exposures. As such, the Seventh Annual Report on Carcinogens must be less detailed about the actual tests and their drawbacks. The original monographs on each listing are given in the references, and the reader is advised to turn to these for the specific arguments, both pro and con, which went into the listing decision.

^{1/} The remaining two operations, filtration and concentration, do not entail sulfuric acid use.

^{2/} In providing these comments, TFI incorporates by reference its comments (dated August 25, 1997) on NTP's earlier proposal regarding the Ninth Annual Report on Carcinogens (62 Fed. Reg. 37,272 (July 11, 1997)).

Seventh Annual Report on Carcinogens at 4.

Based upon our review of the RC Draft Background Document for Strong Inorganic Acid Mists Containing Sulfuric Acid, it is evident that NTP is relying almost entirely upon the 1992 IARC Monograph titled "Occupational Exposures to Mists and Vapours from Strong Inorganic Acids; and Other Industrial Chemicals" (hereinafter referred to as "IARC Monograph" or "Monograph") in indicating its intent to identify strong inorganic acid mists containing sulfuric acid as a known human carcinogen. TFI cautions NTP to consider the weaknesses of the conclusions reached and procedures utilized in developing the IARC Monograph before relying on it to form the basis for its listing decision.

There are several factors that detract from the accuracy of the conclusions reached by the IARC Working Group on the Evaluation of Carcinogenic Risks to Humans with regard to mists and vapors from strong inorganic acids. First, it is our understanding that the authors of several of the studies reviewed by the Working Group were also members of the Working Group. The presence of the authors very well could have stifled discussion or opposing viewpoints among the participants. Furthermore, this may have resulted in the dismissal of substantive criticisms of certain studies. It is also more likely that study authors would have predetermined positions and that the weight of the evidence would not be considered fairly by them.

Second, because the IARC Working Group analyzed primary and secondary studies and drew conclusions regarding carcinogenicity in its Monograph, the conclusions reached in the Monograph itself should have been subject to peer review. Moreover, the IARC Working Group, in its analysis, considered studies that were not peer reviewed as long as the studies were written up in their final form and provided important data. Because the conclusions reached in the Monograph have not been subject to peer review, nor have some of the included studies, the conclusions reached in the IARC Monograph should be questioned more rigorously by NTP.

Third, many of the studies relied upon by the Working Group, which were also relied upon by NTP, were flawed. For example, Steenland et al. (1988), who reported on studies of U.S. steel workers, did not consider whether the workers also worked in other areas of the mills where they could have been exposed to nickel or other unknown occupational carcinogens. Also, Beaumont, et al. (1987), who similarly reported on steel workers, found that workers who were not exposed to sulfuric acid also suffered from a higher incidence of lung cancer, yet the IARC Working Group did not place any emphasis on this negative finding. In general, many of the studies inadequately considered factors such as employee mobility, job transfers, or confounding or modifying factors such as smoking, alcohol consumption, and exposure to known and suspected carcinogens.

The IARC Working Group also seemed to discount negative findings and overvalued studies showing a positive correlation. For example, an epidemiological study of mortality in relation to work

experience in the Florida phosphate industry was conducted in the 1980's and updated in 1995 (Checkoway et al.). The study, which included over 22,000 workers employed in the industry between 1949 and 1978, found no evidence of causal associations of lung cancer, laryngeal cancer, or of general mortality with specific exposures, including acid mist. Although mentioned in the IARC Monograph, the significance of the study does not seem to have been fully considered.

TFI urges NTP to utilize its scientific expertise to conduct its own, independent assessment of the "pros and cons" associated with each study. Specifically, NTP should critically evaluate the confounding factors for each study, as well as inconsistencies between one study and another. Unless NTP undertakes such a thorough, in-depth review of each study, it will not properly evaluate a chemical for known, or reasonably anticipated, human carcinogenicity.

II. NTP Should Consider the Fact that There Are Significant Differences of Opinion with Regard to Whether Strong Inorganic Acid Mists Containing Sulfuric Acid Are a Known Carcinogen

TFI notes that the Chemical Substances TLV Committee (TLV Committee) and the American Conference of Governmental Industrial Hygienists (ACGIH) have stated that "available studies of workers exposed in the manufacture of sulfuric acid and exposed in processes producing strong inorganic acid mists containing sulfuric acid provide conflicting or insufficient data to confirm an increased risk of cancer" Letter from Roy M. Buchan to Richard A. Flye regarding designation of sulfuric acid contained in strong inorganic acid mists/liquid aerosols, dated July 12, 1996 (copy enclosed). In fact, the TLV Committee and ACGIH ultimately adopted an A2, Suspected Human Carcinogen, designation for sulfuric acid contained in strong inorganic acid mists. Although TFI disagrees with this designation and believes that the evidence is insufficient to draw this conclusion, TFI would like NTP to recognize that there are differences of opinion with regard to the sufficiency of the evidence to conclude that strong inorganic acid mists containing sulfuric acid are a known carcinogen.

III. NTP Should Promulgate a Definition of "a Significant Number of Persons" for Purposes of the Annual Report on Carcinogens

TFI requests that NTP promulgate a definition of "a significant number of persons" for purposes of its carcinogenicity listing prior to evaluating the 14 substances for inclusion in the Ninth Annual Report on Carcinogens. As NTP is aware, the Public Health Service Act, Section 262,^{3/} provides NTP, through delegation from the Secretary of the Department of Health and Human Services

^{3/} This section is codified at 42 U.S.C. § 241.

(HHS), with the statutory authority to publish a report on carcinogenicity. Specifically, Section 262 requires HHS to publish a biennial report which contains:

- (A) a list of all substances --
 - (i) which either are known to be carcinogens or may reasonably be anticipated to be carcinogens, and
 - (ii) to which a significant number of persons residing in the United States are exposed;

* * * *

Under this statutory listing scheme, NTP must first ascertain whether a substance is either (1) known, or (2) reasonably anticipated, to be a carcinogen. NTP makes this determination through reviewing studies on the substance at issue and accepting public comments on the substance. As reflected in the "Report on Carcinogens Listing/Delisting Procedures," NTP has developed a very elaborate review protocol for assessing a substance's carcinogenicity. However, even if a substance satisfies the "carcinogenicity" test, it still must pass the "significant exposure" test before it may be listed in the report.

Under Section 262, a substance cannot be listed unless NTP concludes that "a significant number of persons residing in the United States are exposed [to it]." Although NTP appears to have devoted considerable resources to establishing a system to implement the first part of the listing decision (i.e., carcinogenicity), NTP has not, to the best of TFI's knowledge, devoted resources to determining how to evaluate the second part of the listing decision (i.e., a significant number of persons exposed to the substance). Because this part of the listing analysis is as crucial as the first part, NTP should not engage in listing determinations without properly establishing a clear definition of the number of persons required to be exposed to the substance for listing purposes.

Also, as part of NTP's efforts to better define the second part of the listing criteria, NTP should focus on the word "exposed." As previously stated, the second part of the listing analysis requires that "a significant number of persons residing in the United States [be] exposed" to the known, or reasonably anticipated to be, carcinogen. NTP should define what is meant by the word "exposed." In other words, is it exposure at a certain concentration? Or rather, is it exposure at any concentration? TFI believes that NTP should define "exposed" in terms of a dose (i.e., exposure at a given concentration for a designated period of time). To develop this definition, NTP should conduct rigorous risk assessments to determine the proper safe exposure for an identified carcinogen.

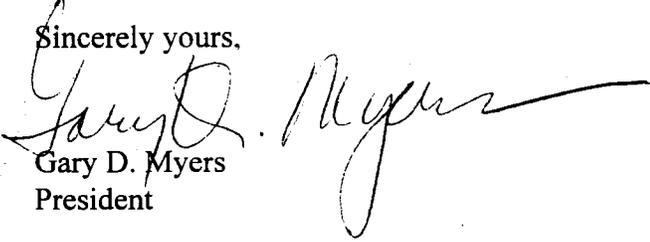
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Defining exposure in terms of dose is very important in the context of strong inorganic acid mists containing sulfuric acid because the manufacture of phosphate fertilizers, which produces the largest quantity of sulfuric acid in the United States,^{4/} actually results in very low concentrations of strong inorganic acid mists containing sulfuric acids according to the studies summarized on page 2-4 of the RC Draft Background Document for Strong Inorganic Acid Mists Containing Sulfuric Acid. Because some of the studies cited in the IARC Monograph indicate that there is a dose/carcinogenicity correlation, NTP should recognize this correlation in making its determination as to whether a significant number of persons residing in the United States are exposed to a potential carcinogen. The NTP's current protocol, which seems to be a "know it when I see it" method of determining significance, should be set aside for a more precise analysis that considers whether a significant number of persons residing in the United States are exposed to a dose that poses a potential cancer risk. Surely, Congress did not intend for NTP to list chemicals or processes from which there is an extremely low risk due to the very low dosages to which people are being exposed.

Because NTP's listing of a substance as a carcinogen, or suspected carcinogen, triggers other regulatory requirements at the federal and state levels, TFI requests that any effort to define what is meant by a "significant number" and "exposed" be addressed in the context of notice and comment rulemaking pursuant to the Administrative Procedure Act.

TFI appreciates the opportunity to submit these comments on NTP's evaluation of strong inorganic acid mists containing sulfuric acid for inclusion in the Ninth Annual Report on Carcinogens. Should you have any questions regarding these comments, please feel free to contact Don Casey of TFI at (202) 608-5909.

Sincerely yours,


Gary D. Myers
President

Enc.

^{4/} In fact, three fertilizer manufacturers together produce more than 37 percent of the sulfuric acid produced in the United States.



American Conference
of Governmental Industrial Hygienists

July 12, 1996

Mr. Richard A. Flye
General Counsel
The Fertilizer Institute
c/o McKenna & Cuneo, L.L.P.
1575 Eye Street, N.W.
Washington, DC 20005

7/17/96
RJ

Dear Mr. Flye:

On behalf of the American Conference of Governmental Industrial Hygienists (ACGIH), this letter is to inform you of the Conference's intent to clarify the recently adopted A2, *Suspected Human Carcinogen*, carcinogenicity designation for sulfuric acid. The A2 designation is to be identified with sulfuric acid contained in strong inorganic acid mists/liquid aerosols and is not intended for sulfuric acid per se. Although available studies of workers exposed in the manufacture of sulfuric acid and exposed in processes producing strong inorganic acid mists containing sulfuric acid provide conflicting or insufficient data to confirm an increased risk of cancer, ACGIH and the TLV Committee consider the data adequate to meet the Committee's definition of *Suspected Human Carcinogen* (enclosure).

Sulfuric acid will be included in the adopted list of substances to be published in the 1996 TLVs and BEIs Booklet. The A2 designation will carry a footnote stating: "Sulfuric acid contained in strong inorganic acid mists."

To further explore the issue of sulfuric acid and its potential as a carcinogen, a meeting has been scheduled for October 5, 1996, by the TLV Dusts and Inorganics Subcommittee with representatives of the Inorganic Acid Mists Panel of the Chemical Manufacturers Association. Substantive data that may evolve from such a meeting or from additional human or experimental animal exposure studies may enable the Committee to reconsider the appropriateness of the recommended TLV and the need for a Notice of Intended Change.

Thank you for your interest and contribution to the activities and deliberations of the TLV Committee.

Sincerely,

Roy M. Buchan
Chair

RMB:cs

Encl.

cc: ACGIH Board of Directors
TLV Chemical Substances Committee

ADOPTED APPENDICES

APPENDIX A: Carcinogenicity

The Chemical Substances TLV Committee has been aware of the increasing public concern over chemicals or industrial processes that cause or contribute to increased risk of cancer in workers. More sophisticated methods of bioassay, as well as the use of sophisticated mathematical models that extrapolate the levels of risk among workers, have led to differing interpretations as to which chemicals or processes should be categorized as human carcinogens and what the maximum exposure levels should be. The goal of the Committee has been to synthesize the available information in a manner that will be useful to practicing industrial hygienists, without overburdening them with needless details. The categories for carcinogenicity are:

- A1 — *Confirmed Human Carcinogen*: The agent is carcinogenic to humans based on the weight of evidence from epidemiologic studies of, or convincing clinical evidence in, exposed humans.
- A2 — *Suspected Human Carcinogen*: The agent is carcinogenic in experimental animals at dose levels, by route(s) of administration, at site(s), of histologic type(s), or by mechanism(s) that are considered relevant to worker exposure. Available epidemiologic studies are conflicting or insufficient to confirm an increased risk of cancer in exposed humans.
- A3 — *Animal Carcinogen*: The agent is carcinogenic in experimental animals at a relatively high dose, by route(s) of administration, at site(s), of histologic type(s), or by mechanism(s) that are not considered relevant to worker exposure. Available epidemiologic studies do not confirm an increased risk of cancer in exposed humans. Available evidence suggests that the agent is not likely to cause cancer in humans except under uncommon or unlikely routes or levels of exposure.
- A4 — *Not Classifiable as a Human Carcinogen*: There are inadequate data on which to classify the agent in terms of its carcinogenicity in humans and/or animals.
- A5 — *Not Suspected as a Human Carcinogen*: The agent is not suspected to be a human carcinogen on the basis of properly conducted epidemiologic studies in humans. These studies have sufficiently long follow-up, reliable exposure histories, sufficiently high dose, and adequate statistical power to conclude that exposure to the agent does not convey a significant risk of cancer to humans. Evidence suggesting a lack of carcinogenicity in experimental animals will be considered if it is supported by other relevant data.

Substances for which no human or experimental animal carcinogenic data have been reported are assigned no carcinogenicity designation.

Exposures to carcinogens must be kept to a minimum. Workers exposed to A1 carcinogens without a TLV should be properly equipped to eliminate to the fullest extent possible all exposure to the carcinogen. For A1 carcinogens with a TLV and for A2 and A3 carcinogens, worker exposure by all routes should be carefully controlled to levels as low as possible below the TLV.