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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

JUN 17 1987

MEMORANDUM

SUBJECT: Aluminum Phosphide - Review of Protocols for the Generation of Phosphine Gas from Aluminum Phosphide, and the Testing of Phosphine Gas in Acute/Subacute Inhalation Studies in Rats and Two Mutagenicity Studies (Ames Salmonella and Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells) - EPA Registration No. 40285-1

Tox. Chem. No.: 31

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and

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Consultant
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TO: Jeff Kempter, PM 32
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THRU: Theodore A. Farber, Ph.D., Chief
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The following memorandum incorporates comments made by Albin B. Kocialski and Frank Vocci with regard to the submitted protocols.

Comments by Frank Vocci on Acute Inhalation Protocols numbered 1 and 2 (No clinical signs, low dose and clinical signs, high dose, respectively).

- Dose/response relationships are usually obtained in inhalation exposures by varying concentration, keeping time of exposure constant.

- Protocols 1 and 2 are written to change both concentration and time of exposure. Tables 1 and 2 below illustrate the point.

Table 1 (No Clinical Signs)

| Conc. (ppm) | Exposure Time (min) | CT (ppm-min$^{-1}$) |
|---|---|---|
| 1.0 | 60 | 60 |
| 0.6 | 120 | 72 |
| 0.3 | 240 | 72 |

Table 2 (Clinical Signs)

| | | |
|---|---|---|
| 150 | 60 | 9000 |
| 75 | 120 | 9000 |
| 37.5 | 240 | 9000 |

These are essentially constant exposure indices (CT). If in table 2 the results followed Haber's Rule, it would result in a single data point, i.e., plotting the probit curve based on CT. If three data points resulted, it would tell us that phosphine does not follow Haber's Rule of Exposure. In either case, one is required to do more exposures to define the probit curve, sorting out the relationship between concentration and exposure time. This is cumbersome requiring a minimum of nine exposures to obtain the appropriate data for each exposure time in table 2. Why not simply call for some definitive time of exposure, i.e., 4 hours at three different dose levels?

Admittedly, there may be something in the rationale I am not aware of. The registrant states in the letter to Jeff Kempter that he already knows the $LC_{100}$ for 1, 2, and 4 hours of exposure. Were the indices the same or different?

One final note on these protocols. Generating phosphine gas from aluminum phosphide may result in aluminum oxide

aerosol. The registrant is aware of this but does not mention how it will be accounted for in these studies.

Comments on Proposed Subchronic Inhalation Study:

- o The objective paragraph I.C. of the protocol does not define repeated inhalation exposure;
- o The duration paragraph I.D. of the protocol does not define time of exposure; and
- o The study design paragraph V.B. gives three exposure levels, one of which is higher than the levels chosen for the acute no-clinical signs study. Shouldn't the dose levels be determined following the acute inhalation study?

The following additional comments/suggestions and/or recommendations were made by Albin B. Kocialski and apply to both acute inhalation study protocols.

- o The method of generating the phosphine gas needs to be detailed.
- o Concentration should be expressed in mg/L as well as ppm.
- o It is suggested that histopathology be conducted on animals showing gross signs, and surviving 14 days.
- o It is recommended that histopathology be conducted on lung, liver, and kidney, regardless of gross findings.
- o A reasonably detailed description of the exposure chambers needs to be included in the report.
- o Analytical and nominal exposure levels, as well as particulate size and distribution need to be included in the report for $PH_3$ and Aluminum oxide.
- o Method of anesthesia should not be by the inhalation route.
- o A summary of incidence table of findings need to be included in the report.
- o All raw data must accompany the report.
- o Will the nose only method or the whole body exposure method be used?

- The material to be tested is the one that is registered by EPA for sale.

- A no-observable-effect level (NOEL) and the lowest-observable-effect level (LEL) should be reported, separately from any phase of the experiment where animals are allowed a recovery period. Any recovery phase of the experiment should have its own NOEL and LEL.

The following comments apply to the subchronic inhalation protocol.

- It is suggested that the lung and bronchial tree be included in the organ weights.

- Tissues should be examined at lower doses for those effects seen at the higher doses.

- Exposure should be reported in ppm and mg/L for $PH_3$ and Aluminum oxide.

- A summary incidence table needs to be included for all effects with the severity of the finding (i.e., grade of severity) also included for histopathology.

- All raw data need to be submitted.

- The duration of exposure in terms of minutes or hours per day and days per week need to be included in the protocol.

- Explain why 2 of 3 doses found in the acute inhalation study (low dose) are identical to 2 of 3 doses found in the subacute inhalation study, and why the third dose is higher.

- Urine should be analyzed for protein or specific gravity.

- A NOEL and the LEL should be reported, separately from that phase of the experiment where animals are allowed a recovery period. This phase of the experiment should have its own NOEL and LEL.

- The material to be tested is the one that is registered by EPA for sale.

- The analytical and nominal exposure levels as well as particle size and distribution need to be included in the report for $PH_3$ and Aluminum oxide.

- Will exposure be by nose only or whole body?

The following comments apply to the teratology study.

- The dose levels should be listed or expressed in terms of the following:
  - A preselected numerical value for a fixed period of time;
  - A final concentration with dose and time duration reported; and
  - The protocol needs to state whether or not exposure will be nose only or whole body.

Comments with respect to the mutagenicity study protocols have been made by Dynamac (EPA contractor) and are attached. Please refer to pages 3 and 4 of each of the Data Evaluation Records.

Note: The purpose of conducting these studies can be found on page 9 of the Guidance Document for the reregistration of pesticide products containing aluminum or magnesium phosphide dated October 8, 1986. A xeroxed copy of the page is attached.

Attachment

However, new information has been submitted which shows that exposure to phosphine gas can occur during application. Surveys conducted by the National Institute for Occupational Safety and Health at three grain elevators in 1985 demonstrated a wide range of exposures. In one elevator, where ventilation was poor, exposures ranged from 0.23 ppm to 1.08 ppm as a time weighted average (TWA), in general exceeding the Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) of 0.3 ppm (8 hour time weighted average). In a second elevator, where ventilation was better, exposures ranged from 0.01 ppm to 0.77 ppm TWA. In a third elevator, with good ventilation, no phosphine was detected. Data submitted by Quaker Oats Company and Phillip Morris Company also show exposures occurring during various types of fumigation.[1] The Agency is also aware that exposures can occur during transfer and handling of treated commodities.

With the knowledge that exposure to phosphine gas can occur during fumigation and transfer and handling of treated commodities, the Agency has re-examined the need for chronic toxicity and exposure data. The current OSHA PEL of 0.3 ppm as an 8 hour time weighted average (TWA) is apparently based on subchronic data showing no deaths in animals exposed to 2.5 ppm phosphine several hours per day for 28 weeks. However, these animals exhibited serious toxic effects in several organs at this level. The Agency has concluded that the available data are not adequate to establish a no observed effect level (NOEL) for phosphine. The following toxicity testing for phosphine is required: a 90 day subchronic inhalation study in rats, an inhalation teratology study in one species and a battery of mutagenicity studies. To quantify exposures to phosphine which may occur, worker/applicator monitoring studies are required for major use sites. These toxicity and exposure studies will be used to assess the margins of safety of worker exposures to phosphine and to determine whether the interim exposure standards described in Section II.B.9. are adequate to protect workers. Another objective of the studies is to attempt to develop short exposure limits (SEL's) which might allow shorter exposures at higher concentrations than currently permitted by the OSHA PEL. Protocols for the toxicology and exposure studies must be submitted to the Agency for review prior to initiation of studies.

6. Restricted Use Classification

End-use pesticides containing aluminum or magnesium phosphide are classified for restricted use and may be applied only by or in the physical presence of an applicator certified in an approporiate category. All training programs leading to certification of applicators must be reviewed and, if

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1 These data were submitted and entered into EPA Public Docket #D-05640.