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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: ALUMINUM PHOSPHIDE. ID NO. 066501. Request for Reservation of Data Requirements for Acute Neurotoxicity Studies, Chronic/Oncogenicity Study, Reproduction Study and Dominant Lethal Study; Request for Waivers of Subchronic Neurotoxicity, Chronic Toxicity and Reproduction Studies in Rats; Review of Protocols Submitted for the Above Studies.

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CONCLUSIONS:

DATA WAIVER REQUESTS:

The data requirement for a dominant lethal study will be reserved pending evaluation of recent NTP efforts on phosphine, which include a dominant lethal study. These results are expected to become available in the near future and may have impact on this requirement.

The data requirements for oncogenicity, chronic toxicity, and reproduction will not be waived or reserved. These studies

were required based on the triggers of positive mutagenicity data and/or potential for repeated occupational inhalation exposure over a prolonged period.

Data waivers for neurotoxicity studies (acute and subchronic) ~~also~~ will not be granted. These requirements were based on reports of neurotoxic symptoms occurring after acute exposure to phosphine and on potential for repeated occupational exposure.

TB-I does not agree with the Registrant that long-term exposure to applicators is not expected. Although the available mutagenicity data does not provide definitive proof that phosphine is a human mutagen, overall it suggests the need for additional data to better characterize potential risk to persons routinely exposed to phosphine.

The above data requirements are consistent with those required for other fumigants such as methyl bromide, except for the chronic toxicity. TB-I considers a <u>combined</u> chronic toxicity/oncogenicity test a reasonable approach to addressing potential long-term effects of phosphine to applicators.

The rationales for declining the data reservation/waiver requests are discussed in detail below under "Discussion".

<u>STUDY PROTOCOLS</u>:

The study protocols (81-8, acute neurotoxicity in rat; 82-5, subchronic neurotoxicity in rat; 83-4, 2-generation reproduction study in rat; 83-5, combined chronic/oncogenicity study in rat; 84-4, dominant lethal study in rat) appear adequate for each of the proposed studies except for the following points:

1. Recommended dose levels or rationales for dose selection were not specified in any of the protocols.
2. The oncogenicity and chronic toxicity study should be combined (as stated in memo from L. Hansen to K. Dearfield, 7-22-92; Guideline Series 83-5) rather than conducted separately as indicated in the protocols. The subchronic neurotoxicity study may be conducted as a satellite group in the chronic/oncogenicity study, if desired.
3. In the acute neurotoxicity study, FOB and MA testing should be performed preexposure and at time of peak effect after dosing, rather than a single 20-hr post-exposure evaluation. It seems unlikely that peak effect would occur at 20 hrs.
4. If neurotoxic effects are observed in the acute and/or subchronic neurotoxicity studies, recovery testing should be conducted for some animals after termination of exposure (eg. at 7 and, if necessary, 14 days post-exposure).

5. Tabulation of body weight gain data (in addition to body weights) is recommended.

ACTION REQUESTED:

The Phosphine Task Group requested reservation of requirements for oncogenicity and dominant lethal studies in rats pending evaluation of a new in vivo lymphocyte chromosomal aberration study in rats and reservation of the acute neurotoxicity studies in rats pending evaluation of an acute neurotoxicity study in rats on zinc phosphide. Waivers of the rat chronic toxicity, subchronic neurotoxicity and 2-generation reproduction studies were also requested. Protocols for the studies were submitted for comment if the data requirements were not waived. Several articles were submitted in support of the waiver request. These requests were presented in memos to Joanne Edwards from Donald G. Shaneen on behalf of Degesch America, Inc. dated 7-12-93 and from Gary L. Burin on behalf of the Metal Phosphide Task Force dated 7-22-93.

DISCUSSION:

DATA REQUIREMENTS FOR PHOSPHINE AND OTHER FUMIGANTS:

In the 1986 Reregistration Standard for Aluminum and Magnesium Phosphides (which supercedes the 1981 Registration Standard), it was stated that "new information has been submitted which shows that exposure to phosphine gas can occur during application", "the Agency has re-examined the need for chronic toxicity and exposure data" [since the 1981 Registration Standard] and "the Agency does not have adequate data to determine whether phosphine gas may cause any long term adverse (chronic) effects on humans and the environment." The requirements for reproductive toxicity, chronic toxicity and oncogenicity studies were "reserved pending results of subchronic, teratology and mutagenicity studies." Based on the apparent mutagenic potential of phosphine (see below) and the lack of data on effects of repeated exposure over periods of several years, those studies are now requested.

The Registrant is correct that chronic inhalation studies were not required by the Agency for other fumigants. However, oncogenicity, reproduction and acute/subchronic neurotoxicity studies have been required for other fumigants, including methyl bromide. TB-I had intended that a chronic toxicity study be conducted in combination with the oncogenicity study to maximize information obtained from the study.

EXPOSURE OF APPLICATORS TO PHOSPHINE:

Potential for Long-Term Applicator Exposure: The Registrant states that long-term inhalation exposure to phosphine by

applicators is not expected. TB-I does not agree, based on exposure estimates calculated from findings of the exposure study on phosphine by S.Z. Mansdorf and Associates on phosphine exposure (MRID No. 407172-01; memo from J. Smith of OREB to K. Dearfield, dated 7-24-92). Exposures lasting more than 1 hr/day and exceeding the STEL (1 ppm) were reported for several use patterns. While turnover of personnel may indeed be rapid in some cases, there are undoubtedly many applicators who may be exposed over a relatively large percentage of their lifetime.

According to "average" exposure patterns for workers as described by the Registrant in the waiver request, exposures of 1 hr/day, 100 days/yr and 5 yrs employment could occur. TB-I considers this a significant exposure duration and expects that there are workers (eg. on farms, in port authorities) who perform fumigations over longer time periods.

Furthermore, since usage of aluminum phosphide may be expected to increase as methyl bromide is phased out, TB-I considers assessment of effects from long-term exposure to phosphine of increasing importance.

Biogenic Sources of Phosphine: The study on biogenic sources of phosphine (Angew. Chem. Int. Ed. Engl. 1993, 32:761-763) does not, in the opinion of TB-I, impact on the need to assess toxicity from inhalation exposure to phosphine. Like methyl bromide, biogenic sources account for a significantly greater proportion of total global phosphine production than anthropogenic sources. However, levels of exposure to applicators during fumigation would be greater than exposure due to to biogenically produced phosphine dissipated throughout the biosphere at extremely low concentrations.

Phosphine was detected in human feces at ng/kg levels in this study, indicating the presence of very small amounts in the gastrointestinal tract under normal physiologic, methanogenic conditions. In contrast, inhalation exposures to phosphine during fumigation may reach mg/kg body weight levels.

VALIDITY OF AVAILABLE MUTAGENICITY DATA:

The Registrant has requested that the dominant lethal and oncogenicity studies be reserved pending review of a new chromosomal aberration study in rat lymphocytes. The new study has been conducted with modifications in the experimental protocol (see below for details). However, TB-I believes that, despite the Registrant's objections to the experimental protocols of the in vivo rat lymphocyte cytogenetic study in question, overall the data indicate that phosphine has genotoxic potential.

Effect of Delayed Harvesting of Cells on Control Chromosomal Aberration Frequency: The Registrant discussed the in vivo rat

lymphocyte cytogenetics study performed for American Cyanamid (8E submission to OTS, #8EHQ-0291-1188), in which lymphocytes from control and phosphine-treated rats were cultured for extended times because of cell cycle delays caused by phosphine. The Registrant believes that this may have caused artifactually low levels of chromosomal aberrations in cells from control animals, since controls would not have delays in cell cycle time and aberrations might decrease with additional cell divisions. However, TB-I notes that the mean number of cells with aberrations from the control males were within the historical control range for males and were not exceptionally low; in fact they approached the high range of 1% (0.7%, Experiment 1 and 0.9%, Experiment 2). This suggests that the control values were not significantly reduced by prolonged culture times. In addition to the overall increase in % cells with aberrations, appearance of rare chromosomal abnormalities (triradials and quadriradials) was noted in the treated animals which, according to the study authors, is not usually seen in lymphocytes of healthy young rats.

In another study conducted by Pharmakon (MRID 414343-02), phosphine was clastogenic to CHO cells at non-cytotoxic doses. In vitro exposure of cultured human lymphocytes in the Garry et al. study (Science 1989, 246:251-255) also showed a dose-response in chromosomal aberration frequencies. Although details of the experimental protocol were not given, TB-I considers it unlikely that the number of aberrations in the control cells would approach those seen in treated cells if the controls were harvested earlier (30-100X higher in treated cultures).

Studies on Humans Exposed to Phosphine: TB-I agrees with the Registrant that additional work is needed to clarify the significance of results reported in the study by Garry et al. However, the fact that stable chromosomal rearrangements were detected months after exposure in Giemsa-banded chromosomes from cultured human lymphocytes from the phosphine-exposed group (but not controls) suggests a treatment-related effect and is consistent with the appearance of the rare chromosomal abnormalities in the rat in vivo/in vitro lymphocyte study. Lack of persistence of chromosomal breaks, deletions and gaps may reflect formation of the more complex rearrangements described above following breakage, clearance of lethally damaged cells or repair of DNA damage. A second report, albeit inconclusive, of increased chromosomal aberrations among Houston Port Authority workers exposed to phosphine during grain elevator fumigation (Houston Chronicle, 7-25-92), suggests that this is not a spurious observation.

The Australian study of workers exposed to phosphine submitted by the Registrant (Media Release from National Occupational Health and Safety Commission or Worksafe Australia; study by Anadergh Barbosa et al.) concluded that, with proper

application procedures, there was no evidence of mutagenicity of phosphine as determined by a lymphocyte micronucleus assay (and Ames assay of urine). However, this study was not conclusive in that (1) a different mutagenicity assay was used than in the Garry et al. study (micronucleus vs. chromosomal aberration), making comparison of results difficult and (2) there was no evidence that the investigators determined optimum cell culture time for controls and treated cells, or sampled at more than one time point. It is possible that worker protection measures in this study were more stringent than in the Garry study; however, insufficient information was provided in these studies for comparison. Like the study by Garry, the sample size was relatively small.

NEUROTOXICITY:

The Registrant has requested that the acute neurotoxicity study be reserved pending evaluation of the acute neurotoxicity test on zinc phosphide for the USDA. This study was required based on reports of neurotoxic symptoms (eg. tremor, convulsions, behavioral changes) following acute exposure to phosphine. Although the metabolite of primary interest (phosphine) is the same for zinc and aluminum/magnesium phosphide, TB-I will not grant this request on the basis that the route of administration for zinc phosphide (oral) may not provide appropriate evaluation of neurotoxicity from inhalation exposure.

The subchronic toxicity study waiver will not be granted. Subtle neurotoxic effects such as those identified in the functional observational battery and motor activity tests, which might occur with repeated exposure at lower doses, have not been tested for.