UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM JUL 2 2 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Aluminum/Magnesium Phosphide, ID# 066501. Additional Toxicology Data Requirements to Support Reregistration.

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CONCLUSIONS:

TB-I has determined that additional toxicology studies are required to support reregistration of aluminum/magnesium phosphide following review of the available toxicology data and discussion with the Phosphine Workgroup. An inhalation combined chronic toxicity/oncogenicity study in rats and a 2-generation reproduction inhalation study in rats will be required. These studies are being required as the result of data indicating that phosphine gas is mutagenic in vivo and in vitro to humans and in vivo to rats and evidence that subchronic and chronic exposure to phosphine gas occurs routinely in several use patterns. Additional neurotoxicity and mutagenicity testing requirements are also required but are not addressed in this memo.

ACTION REQUESTED:

TB-I was asked to determine whether any additional toxicology data requirements should be added to those listed in the 1986 reregistration standard for aluminum and magnesium phosphide. Any additional data requirements shall be included in a forthcoming DCI and a RED shall not be generated at this time as was originally planned.

CC Schnaubelt/Tompkins (PM72)

DISCUSSION:

The rationale for requiring these studies is based on the following information: 1) evidence that phosphine gas is mutagenic both in vitro and in vivo, including in humans following occupational exposure; and 2) evidence that subchronic and chronic exposures to phosphine gas can occur for a number of use patterns.

Chronic toxicity/oncogenicity study in rats: Over the years most of the attention on phosphine has focused on its extreme acute inhalation toxicity. The effects of chronic inhalation exposure have been poorly researched; one study using several species indicated that no significant effects were seen when animals were treated with 2.5 ppm of phosphine for a total of 800 hrs (about 24 weeks), but the toxic endpoints examined were limited. The oncogenic potential of phosphine with chronic low level exposure has not been determined.

Concerns for potential cancer risk to humans arise from recent data indicating that phosphine is mutagenic and can cause chromosomal breaks in lymphocytes (Science 246: 251, 1989). Induction of stable chromosomal aberrations has been demonstrated in cultured human lymphocytes exposed to low levels of phosphine gas. Rats exposed in vivo to phosphine via inhalation also show increased lymphocyte chromosomal rearrangements when compared to untreated rats. Human in vivo effects further support these results: agricultural workers exposed to phosphine gas or to phosphine and other pesticides show similar increases in lymphocyte chromosomal abnormalities. A direct correlation between these rearrangements and increased cancer incidence has not been demonstrated, but since chromosomal rearrangements are often found in neoplastic cells, their significance cannot be ignored.

Exposure estimates for various use patterns (determined by OREB) indicate that repeated exposure to phosphine is not uncommon during application of aluminum/magnesium phosphide and reentry, aeration or handling of treated commodities. Workers who are routinely involved in fumigation or handling of recently fumigated commodities may therefore be at increased risk.

While TB-I is aware of the technical difficulties involved in conducting a 2 year inhalation cancer bioassay with phosphine, it is felt that the exposure and mutagenicity data taken together provide compelling reasons to examine the carcinogenic potential of phosphine. TB-I also recommends that the study be conducted as a combined chronic toxicity and oncogenicity study in order that an RfC can be established and to fully characterize any potential toxic effects from long-term exposure.

Rationale for the 2-generation reproduction study in rats: There is also little information available on the effects of phosphine exposure on reproduction. An in-house developmental toxicity study of phosphine in rats indicated that phosphine had no significant effects on the developing fetus at low doses, but whether phosphine can affect other reproductive parameters is not

known. In particular, the induction of chromosomal aberrations as described above raises the concern for heritable genetic effects. A reproduction study would examine the potential reproductive effects in both males and females. The occurence of subchronic to chronic worker exposures for certain uses as well as the occurrence of accidental exposures to phosphine by passersby (for example those living near fumigated storage bins) suggest the need to assess this potential.

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