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

MEMORANDUM

DATE: August 12, 1980 OFFICE OF TOXIC SUBSTANCES

SUBJECT: DEF and Merphos, Studies to be Requested from the Sponsors

FROM: Robert Zendzian, Ph.D.
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TO: Robert Brown
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THRU: William L. Burnam
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Attached are descriptions of studies on DEF and merphos which are required to clarify certain ambiquities associated with the delayed neurotoxicity of the compounds. This clarification is necessary in order to determine if a significant risk of delayed neurotoxicity is associated with use of these compounds. It is recommended that 3(c)(2)(B) letters be issued to the registrants of the compounds directing that the necessary data be provided.

The studies requested are as follows:

Merphos - Chemical Conversion to DEF
Merphos - Metabolism Studies
Merphos - Subchronic Neurotoxicity Study

DEF - Metabolism Study
DEF - Subchronic Neurotoxicity Study

Attachments

MERPHOS - CHEMICAL CONVERSION TO DEF

It has been stated that merphos is rapidly converted into DEF in the mixing tank so that exposure during application is essentially equal to exposure to DEF. Since there are significant differences in the animal toxicology of merphos and DEF, it is necessary to verify the conversion and determine its rate.

The agency requires information on the rate and extent of conversion, merphos to DEF, during the application process so that it is possible to determine how much of each compound an individual can be exposed to during the application process. The resistant may accomplish this by sampling and analysis during a field application or by utilizing a model laboratory experiment. In the latter case the company should take care to explain how their model system matches field application. It is suggested that the registrant discuss their protocol with the agency before starting the study.

# MERPHOS - METABOLISM STUDY

Merphos, an organic phosphate is said to be activated *in vivo* by oxidation to DEF. There are significant qualitative and quantitative differences in the toxicity of the two compounds to indicate that this relationship is more complex than simple oxidation. This includes the possibility that both compounds can be metabolized to n-butyl mercaptan a significantly toxic compound. A metabolism study is required to clearify the relationship of merphos to these two toxic metabolites and develop an understanding of the unusual route and rate of application dependent toxicity of merphos. It should be also noted that a metabolism study of merphos is required by the guidelines.

The metabolism study should follow the proposed guidelines published August 22, 1978, Section 163.85-1. In addition to the oral dosing, a single low dose dermal application should be performed on 5 males and 5 females. Plasma level and tissue binding studies need not be performed. The dermal study is of particular importance since the dermus is the main route of exposure in man and Gaines (1969) has reported that merphos is more toxic by the dermal route than the oral route in male and female rats.

It is suggested that the manufacturer discuss his protocol for this metabolism study with the agency before starting the study.

# MERPHOS - SUBCHRONIC NEUROTOXICITY STUDY

Merphos is an organophosphate compound whose toxicity is attributed to its being converted *in vivo* into DEF a cholinesterase inhibitor. Delayed neurotoxicity has been demonstrated following single subcutaneous, and dermal doses of merphos but not by the oral route, in the hen. Subchronic oral administration has been reported to produce a delayed neurotoxicity.

The demonstration of delayed neurotoxicity by the dermal route, the chief route of human exposure, requires a dermal subchronic neurotoxicity study to determine a no observable effect level. It should be noted that a subchronic neurotoxicity study of ~~DEF~~ Merphos is required by the guidelines following a demonstration of neurotoxicity by acute administration.

The subchronic neurotoxicty study should follow the proposed guidelines published August 22, 1978, Section 163.82-5 however, the dermal rather than the oral route should be used. Since this particular section of the guidelines has been reviewed by agency scientists prior to final publication and significant decreases in the task are being proposed, it is suggest that the manufacturer contact the agency before starting the study. Agency scientists will then advise the manufacturer on his experimental design.

# DEF METABOLISM STUDY

DEF is an organophosphate compound whose toxicity is attributed to its anticholinesterase activity. Information exists which indicates that the toxicity of DEF may be in part due to the in vivo production of n-butyl mercaptan. There are significant qualitative and quantitative differences in the toxicity of DEF dependant on rate and route of administration. A metabolism study is necessary to clearify this situation. It should also be noted that a metabolism study of DEF is required by the guidelines.

The metabolism study should follow the proposed guidelines published August 22, 1978, Section 163.85-1. In addition to the oral dosing, a single low dose dermal application should be performed on 5 males and 5 females. Plasma level and tissue binding studies need not be performed. The dermal study is of particular importance since the dermus is the main route of exposure and Gaines (1969) has reported that DEF is essentially equally toxic by the dermal and oral routes in male and female rats.

# DEF - SUBCHRONIC NEUROTOXICITY STUDY

DEF is an organophosphate compound whose toxicity is attributed to its anticholinesterase activity. Delayed neurotoxicity has been demonstrated following single subcutaneous and dermal doses of DEF but not by the oral route, in the hen. Subchronic oral administration has been reported to produce delayed neurotoxicity. The demonstration of delayed neurotoxicity by the dermal route, the chief route of human exposure, requires a dermal subchronic neurotoxicity study to determine a no observable effect level. It should be noted that a subchronic neurotoxicity study of DEF is required by the guidelines following a demonstration of neurotoxicity by acute administration.

The subchronic neurotoxicity study should follow the proposed guidelines published August 22, 1978, Section 163.82-5 however, the dermal rather than the oral route should be used. Since this particular section of guidelines has been reviewed by agency scientists prior to final publication and significant decreases in the task are being proposed, it is suggested that the manufacturer contact the agency before stating the study. Agency scientists will then advise the manufacturer on his experimental design.