



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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA ID No. 89-CA-26
Amendment to Section 18 Quarantine Exemption For The
Use of Malathion In California To Include All Crops
Which Grow In Treatment Areas

Project No.: 0-1164A
Tox. Chem. No.: 535
Record No. 255928

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Conclusion

In consideration of this proposed Section 18 amendment to the quarantine exemption for the use of malathion in aerial spraying of urban areas in Southern California for purposes of medfly eradication, Toxicology Branch has determined that the toxicology data base does not support the proposed amendment, particularly in the absence of a definitive exposure assessment. The concerns at issue are summarized below.

Carcinogenicity

The Health Effects Division Carcinogenicity Peer Review Committee convened on February 7, 1990 to assess the evidence of carcinogenicity of malathion as derived essentially from five National Cancer Institute bioassays (including three malathion and two malaoxon studies) plus one malathion assay performed by a contract laboratory. In evaluating this data base, plus accessory information from the areas of mutagenicity, metabolism and structure activity relationships, the Peer Review Committee placed malathion in carcinogenicity category "D". The Committee agreed with the NTP reanalysis that there was no clear evidence of carcinogenicity due to malathion or malaoxon administration in most of these studies (the NTP concluded equivocal evidence in the malaoxon rat study). This is also consistent with past Agency positions. However, the Committee felt there were many issues regarding the adequacy of each study from which a firm conclusion on the carcinogenic potential of malathion could not be made. (April 12, 1990 report on the Peer Review of Malathion). The "D" category is defined in EPA's Cancer Risk Assessment Guidelines as "not classifiable as to human carcinogenicity" (FR Vol. 51 No. 185, p. 34000, 1986). The peer review document summarizes the particular findings the Peer Review Committee considered as constituting at least some evidence of carcinogenicity (p.25). In placing malathion in category "D", the Peer Review Committee also reaffirmed those requirements of the February 1988 malathion Registration Standard which require the registrant(s) to perform an additional mouse carcinogenicity study with malathion and an additional rat chronic/carcinogenicity study with malaoxon. The committee also determined that the required malathion chronic study in the rat be revised to that of a requirement for a combined chronic/carcinogenicity study (p.1). In addition, as noted in the Peer Review Document (p.10) the Registration Standard requires a reexamination of histopathologic slides from the Food and Drug Research Lab's 1980 malathion life time (2-year) bioassay in the rat.

Subsequent to the completion of the Peer Review, Toxicology Branch received and reviewed a relevant 1975 journal publication where evidence was obtained in the rat that malathion, when administered along with dimethylbenzanthracene (DMBA), enhanced mammary tumor and leukemia incidences relative to those increases obtained with DMBA alone. The study authors speculated that malathion may potentiate DMBA induction of mammary tumors and leukemia by inhibiting DMBA metabolizing enzymes. Since the investigators did not evaluate malathion alone, a clear distinction cannot be made between the possibilities that malathion acted as potentiator of DMBA or contributor in part to the direct induction. (K. C. Silinskis and A. B. Okey, J. National Cancer Institute, 55,

653-657, 1975.) EPA's Cancer Risk Assessment Guidelines make no distinction for regulatory purposes as to the mechanism (induction, potentiation, promotion, etc.) by which chemical substances function in eliciting tumorigenic responses. The particular responses identified in this journal publication were among those listed in the Peer Review Document as possibly related to malathion exposure (p. 25). It is unlikely that these published findings would have altered the basic conclusion of the Peer Review Committee, although this publication does contribute to the weight-of-the-evidence.

In the face of the unresolved issue of the carcinogenicity of malathion as reflected in the "D" classification by the Peer Review Committee, in concert with the existing requirements for three additional carcinogenicity bioassays and reassessing of histopathologic slides from one study, all of which is anticipated to require an additional four years or more for completion, Toxicology Branch considers the toxicology data base to be inadequate to support the spraying of malathion on populous urban areas in the absence of a definitive exposure/risk assessment. The fact that large human populations, perhaps millions of individuals, experience direct exposure render the exposure assessment particularly compelling.

Hence, Toxicology Branch defers to Non-dietary Exposure (NDEB) Branch the development of the needed exposure assessment. Toxicology Branch notes that populations in the area of application are potentially exposed to malathion not only by direct contact but by ingestion of crops that are locally cultivated. Such exposures would be in addition to those most Americans experience via residues of malathion in foods in commerce. All sources of exposures to malathion should be factored into the exposure assessment. (Note: by way of discussion with Curt Lunchick and Michael Firestone of NDEB, Registration Division is advised to require the California Department of Food and Agriculture and/or the malathion registrant(s) to submit the necessary information for NDEB to develop an exposure assessment for use by Toxicology Branch in risk assessment. The data to be submitted should include: 1) amount of malathion and malaaxon being deposited per unit surface area during application, presented as both the amount of malathion and malaaxon in the spray tank and the amounts actually deposited; 2) residues on local crops resulting from aerial spraying; 3) ambient air monitoring after application, including assessment of malathion and malaaxon; and 4) estimates of oxidation of malathion to mala^{ox}on, including that of possible photo-oxidation. Protocols should be submitted for items 1-4 above and approved by NDEB prior to initiating field testing. Existing data may be submitted for evaluation by NDEB as possible submissions to satisfy items 1-4. In addition the application rates, number of applications per year in a spray zone, and hours per day and spray season that pilots spray will be required).

Ophthalmological Effects

There is a lengthy and complex body of scientific information developed primarily by Japanese investigators which indicates that exposures to organophosphates, of which malathion is an example, can cause serious damage to the visual system. This is a subject which cannot be fully presented in this Section 18 response. Briefly, uncertainties exist at this time as to the likelihood that malathion at levels being applied in the aerial medfly eradication program will induce damage to the visual system analogous to that reported to have resulted from organophosphate aerial spraying in Japan. Thus, for this reason also, Toxicology Branch does not consider the toxicology data base to be adequate to support the Section 18 amendment at this time. Needed is a thorough and critical review of the existing work by various authors on the organophosphate-ocular effects syndrome with particular attention directed to assessing the likelihood that malathion will elicit the effects, and if so, at what level of exposure. The exposure assessment called for under the carcinogenicity topic will be necessary in order to determine the likelihood that exposures would occur in the dosage range where ocular effects were identified in Japan following organophosphate aerial treatment. Toxicology Branch has advised that the registrant(s) be required to conduct ocular testing of malathion in an animal model. Toxicology Branch must advise that information thus far examined suggests that malathion may elicit the ocular effects, reinforcing the need for a precautionary and conservative approach until such time as the issue has been resolved.

Additional Concerns

The carcinogenicity and ocular effects considerations as stated above constitute the principal reasons for recommending against granting this Section 18 amendment at this time. However, there are other issues which require review and clarification before malathion can be adjudged to be safe for application to large human populations. Toxicology Branch is here making a distinction between uses of malathion in agriculture where professional applicators control their own exposures and those among urban populations where individuals of all age groups, health status, living circumstances, etc. are potentially exposed. Additional issues of concern to Toxicology Branch which will require evaluation might be described as follows:

- o Certain impurities in malathion samples are recognized as being of toxicological concern, e.g. malaoxon, isomalathion, O,O,S-trimethylphosphorodithioate, diethyl fumarate, etc. Toxicology Branch defers to Dietary Exposure Branch an assessment designed to assure that samples which are being used in aerial sprayings contain no additional impurities, nor an enhanced level of any one impurity, with respect to those present in particular samples which were used

in toxicological studies submitted to HED to satisfy Guideline testing requirements. In this regard, Toxicology Branch notes the several registered products of malathion given by name in the 9/1/89 letter of Douglas Campt appended to Registration Division's request.

- o Toxicology Branch is also aware of evidence that malathion can be oxidized in the environment to malaoxon, a compound which is a potent cholinesterase inhibitor and a more acutely toxic agent than is malathion. If the public is being exposed to malaoxon at appreciable fractions of malathion being administered, then malaoxon exposures should constitute a component of the proposed exposure assessment.
- o Toxicology Branch recognizes considerable uncertainty from the information in hand as to the relative quantity of malathion being applied in California to that which was applied in Japan during 1957-1971 when the ocular effects were characterized. This comparison should be resolved through careful review of the available information on this subject.
- o It has come to HED's attention that homeless people living in the spray area may be experiencing untoward health related effects from the spraying operation (March 6, 1990 letter by Robert Cohen, Legal Aid Society of Orange County, Santa Ana, California, to Registration Division, Rich Tinsworth, with attachment). This report requires evaluation. There also may be other individuals who do not find it easy or convenient to avoid direct spraying. The proposed exposure assessment will be of great benefit in evaluating the likelihood of harm to these individuals.
- o Toxicology Branch is aware of evidence that malathion spraying may be eliciting hypersensitivity or immunological effects in some individuals. Information pertaining to these subjects will need to be evaluated, and, again, in the light of the much needed exposure assessment.
- o Toxicology Branch advises that various gaps remain in the toxicology data base with respect to Guideline requirements.

Summary of Toxicology Data Base - Technical Malathion

<u>Study</u>	<u>Results</u>	<u>Tox Category</u>	<u>Classification</u>
Acute oral LD ₅₀ , rat	1522-1650 mg/kg (male) 1546-1945 mg/kg (female)	III	minimum

Acute dermal LD ₅₀ , rabbit	> 2000 mg/kg (male, female)	III	minimum
Acute inhalation LC ₅₀ , rat	> 1.7 mg/liter for 4 hours (male, female)	II	minimum
	> 4.0 mg/liter	III	minimum
Primary eye irritation, rabbit	mild conjunctival reactions, reversible within 7 days	III	minimum
Primary dermal irritation, rabbit	slight dermal irritation	IV	minimum
Dermal sensitiza- tion, guinea pig	nonsensitizing	-	minimum
Chronic feeding, rodent	data gap		
Chronic feeding, dog	supplementary levels tested: 0, 62.5, 125 and 250 mg/kg/day in beagles. ChE NOEL < 62.5 mg/kg/day (plasma & RBC activity inhibited about 25%). <u>62.5 mg</u> - Elevated liver and kidney wts. Dose related elevated combined thyroid/parathyroid wt. Elevated platelet count; reduced creatinine in both sexes; reduced BUN in M; reduced SGPT. <u>125 mg</u> - Elevated liver & kidney wts. Dose related combined thyroid/parathyroid wt.; elevated platelet count; reduced RBC count in female; reduced creatinine in both sexes; reduced BUN in M & F; reduced SGPT. <u>250 mg</u> - Elevated liver and kidney wts.; Elevated combined thyroid/parathyroid wt. & platelet count; reduced RBC count & hematocrit (M & F); reduced creatinine (M & F); reduced BUN in M & F; reduced SGPT; decreased albumin; decreased calcium (F).		
Carcinoge- nicity, rat	data gap		
Carcinoge- nicity, mouse	data gap		

Developmental data gap
toxicity, rat

Developmental toxicity, rabbit minimum
developmental NOEL = 25 mg/kg and LEL = 50 mg/kg
(increased resorption). Maternal NOEL = 25 mg/kg
& LEL = 50 mg/kg (reduced body weight gain during
the period of gestation). Levels tested: 0, 25,
50, & 100 mg/kg/day in NZW strain. At 100 mg/kg
- same effects as 50 mg/kg.

Reproduction, rat data gap

Mutagenicity Studies

Gene mutation (Ames test)	Negative for inducing gene mutation in bacteria	Acceptable
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Structural chromosomal (cytochrome damage, <u>in vivo</u> , rat bone marrow cells)	Negative for inducing chro- mosomal aberra- tions (M, F) up to clinically toxic and cyto- toxic levels (2000 mg/kg)	Acceptable
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Other genotoxic effects (unscheduled DNA synthesis in rat primary hepatocyte cultures)	Negative for inducing UDS at doses up cytotoxic levels, 0.12-0.16 ul/ml	Acceptable
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Metabolism, rat	C-14-Labeled malathion was dosed orally at 40 & 800 mg/kg and 40 mg/kg/d. 90+ percent of the dose was excreted in 72 hrs with 80-90% excreted in the urine. Females excreted slightly more in urine than males. Between 4 and 6% of the dose was converted to the active inhibitor malaoxon.	guideline
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Based upon a study in man in which red blood cell and plasma cholinesterase activity was inhibited at a dose of 0.34 mg/kg (the lowest effect level), an RfD of 0.02 mg/kg/day has been calculated using a 10-fold uncertainty factor.

As used in the aerial application program, technical malathion is admixed, at the concentration level of approximately 22%, in Staley's protein bait, NuLure or other similar bait material cleared for use on food crops. Toxicology Branch defers to Registration Division the question of acute testing requirements for the mixture for purposes of labeling.