CASWELL FILE

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

MEMORANDUM TO THE FILE (CASWELL #535-MALATHION)

BY: Brian Dementi, Ph.D., D.A.B.T. Brian Dementi 5/4/90

SUBJECT: Memorandum of Dr. Robert Zendzian "Malathion: Allergic and Ocular Effects", March 30, 1990. ATTACHMENT

Concerns over the potential ocular toxicity of malathion were brought to the attention of Dr. Fenner-Crisp and myself at the California Assembly hearing on March 6, 1990. At that time I personally committed that a response to that issue will be submitted to Speaker Brown. In view of that commitment, my prior interests in cholinesterases and my general involvement with the malathion toxicology data base, I consider it incumbent upon me to offer the following comments with respect to Dr. Zendzian's memorandum.

For the most part, I agree entirely with Dr. Zendzian's memorandum. I agree that with respect to the epidemology studies by Ishikawa, which I have seen on the subject, none evaluates malathion alone. Furthermore, I have seen no animal study in which malathion was tested specifically for the ocular effects in question. I agree with Dr. Zendzian that such specific studies on malathion are now indicated. I believe these studies should be required of the registrant on an expedited basis.

Having acknowledged the agreement and that we don't know at this time whether malathion is a causative agent of the ophthalmologic phenomenon in question, it must be acknowledged that while not established as a causative agent, malathion is implicated

in the etiology of the eye phenomenon in the Ishikawa epidemiology studies by virtue of the fact that it was one of the organo-phosphates (OP) used in the areas of investigation. In Ischikawa and Miyata (1980), a copy of which is attached to Dr. Zendzian's memorandum, one should note that during the period 1957 to 1971, the principle OPs used in Japan, when the authors made their observations, were malathion, EPN and ethyl and methyl parathion (pp. 236-237). "The effects of OP pesticides on the visual system were carefully examined in Japan (in the Saku area) in 1969 by Ishikawa. A specific ocular and systemic syndrome has been isolated in agricultural regions of that district, where parathion and malathion are used extensively" (p.237). "The signs presented by these children were first noted in the residents of the area in 1965, shortly after insecticides became used on a massive scale. The OPs malathion and vamidothion were routinely applied by helicopters at a rate of 30 g. per 100 square meters from twice to a maximum of six times each year for 5 years prior to the time of the study." (p.237) Thus, in these passages of this paper, malathion is named as one of the four major compounds used in general in Japan when the eye phenomenon was discovered and was named as one of two sets of two OPs used in the Saku district as quoted above. This does not establish malathion as the causative agent, but in my opinion implicates the compound as an etiologic factor. This publication by Ischikawa and Miyata appears in a reputable publication, "Neurotoxicity of the Visual System", edited by W. H. Merigan and B. Weiss, Raven Press. I am able to

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say nothing more about the article's credibility.

On page 4 of his memorandum, Dr. Zendzian quotes Dr. Shusterman's reasons for the non-applicability of these studies (i.e. Ischikawa and others) to the Medfly eradication program. I believe these reasons given by Shusterman should not be cited so uncritically. For example '"The pesticides used in Japan include parathion and other OPs with acute and subacute toxicities many times that of malathion" '(p.4). This statement neglects to affirm that malathion was in fact one of the principle OPs used in Japan along with parathion and certain other OPs. Also, toxicity is relative. In comparison between LD_{50}s in the rat, that for parathion is much lower than that for malathion (see attached table). However, with respect to cholinesterase inhibition, the likely explanation for the ocular toxicity in question, the human appears to be particularly sensitive to malathion, LOEL=0.34 mg/kg/day (Moeller and Rider, 1962), as contrasted with the dose in the dog of 62.5 mg/kg/day which yielded essentially equivalent cholinesterase inhibition. The rat as well appears less sensitive than the human. Tox branch needs and will be seeking definitive cholinesterase data on malathion, but for now the human would appear to be considerably more sensitive than the dog, for instance, to cholinesterase inhibition by malathion. Whether this contrast could be explained as due to a contaminant in the malathion sample used in the human study cannot be ascertained. Thus, given the information on hand, the human may be considerably more sensitive to the consequences of malathion cholinesterase

inhibiting potential than might be suspected from animal testing. Also, malaoxon, which could be present in the environment following malathion application, has an LD_{50} more closely aligned with that of parathion (see attached table).

Shusterman notes the substantial difference in application rates, 2.6 pounds/acre/application in Japan vs 2.8 ounces/acre/application in California. Important as this comparison is, his statement does not address the relevant question of the number of applications per year, for instance, nor does it discuss whether applications were directed at human populations in comparable ways. The principal point of interest would be the comparative amounts of pesticide to which individuals in the spray zones would be exposed during a 1-year (for instance) exposure scenario under the two sets of circumstances. The California Health Department is now developing a more definitive exposure assessment for malathion as employed in the Medfly program.

Dr. Schusterman indicates that a fine mist was used in Japan as opposed to a "predominantly large particle protein" bait in California. The comparison is very relevant. However, it would be more comprehensible if expressed in the more quantitative terms of actual droplet sizes and number of droplets per unit volume of air. My discussions with persons in California who have witnessed the spraying indicate droplet sizes are considerably smaller than I would suspect from reading this statement by Dr. Shusterman.

Dr. Shusterman concludes: '"It is our conclusion that exposures from the Medfly eradication program will not produce eye effects of the sort described in the Japanese literature" '(p.4). This may be entirely true, and I would certainly hope it is, but until the definitive exposure assessment is worked up, I am not certain how one can make the statement with certainty.

In his memorandum, Dr. Zendzian indicates that, "The human and animal data available clearly establish the OPs as having the potential for significant toxicity on the ocular system. While the human data does not clearly implicate any one compound, the animal studies show ocular toxicity from fenitrothion, ethylthiometon, fenthion and ethyl and methyl parathion." (p.7) Further along, "However, one must note that the compounds, ethyl and methyl parathion, shown by chronic animal studies to have ocular toxicity, are in the order of 200 times more toxic than malathion. If malathion demonstrates ocular toxicity in animal studies, it may occur at doses significantly higher than those of the prototype compounds" (p.7). If one assumes the 200X figure for relative toxicity derives from LD_{50} values for the parathions vs malathion, then it should be noted that fenthion and fenitrothion have LD_{50} values much closer to that of malathion (see attached table), yet these elicit the effect. From another perspective, if this line of reasoning with respect to LD_{50} comparisons followed, then ethylthiometon might be expected to elicit the response at doses significantly lower than those of fenitrothion. Yet, according to Ishikawa and Miyata (1980) when

evaluated by chronic exposure in the dog, ethylthiometon at doses of 25-75 mg/dog/week for two years and fenitrothion at doses of 10-100 mg/dog/week for one year (p.235), both compounds yielded similar ophthalmologic responses (pp. 245-251, 252). One should note that the LD_{50} for malathion is very close to that of fenitrothion. It is also worthy of note that the LD_{50} of malaoxon is very nearly equivalent to those of the parathions. I therefore cannot share the view that if malathion elicited the ocular effect, its potency could be predicted on the basis of its comparative LD_{50}. Only an actual experimental opthalmological evaluation of malathion in the dog, rat or other species will resolve the matter. Even then there may be problems in view of the fact that humans may have a greater sensitivity to cholinesterase inhibition by malathion, as suggested by the Moeller and Rider (1962) data. Nevertheless, this study should be undertaken immediately. Until such time as it is completed and decision rendered, malathion is implicated as having the potential to elicit the ocular problem at doses of unknown magnitude.

Very much needed is an in-depth evaluation and written review of all the scientific information currently available on the OP-ocular toxicity phenomenon.

In the absence of definitive information on malathion, I believe the issue must be viewed in the generic sense. Conservatively, I believe we must consider that OP inhibitors of erythrocyte and/or plasma cholinesterase(s) should be viewed as probable inhibitors of visual system cholinesterases. Hence,

exposure to malathion must be regulated on the basis of the malathion NOEL for cholinesterase inhibition, which at this time is 0.23 mg/kg/day based upon the Moeller and Rider (1962) human study. An appropriate safety factor should be included to take into consideration individual variability and possible differences between men and women, bearing in mind that the Moeller and Rider study evaluated only men, and, yet, girls were more remarkably affected than boys in the Japanese epidemiology studies. A safety factor would also be desirable to address the possibility that ocular effects may occur at doses below those which can be identified to inhibit the erythrocyte or plasma cholinesterases.

cc: Penelope Fenner-Crisp
Bill Burnam
Karl P. Baetcke
Roger Gardner
Robert Zendzian

TABLE

I. From Farm Chemical Handbook (1986)	Oral LD_{50} Rat (mg/kg)
malathion	1000
parathion (ethyl) male	13
female	3.6
parathion (methyl)	9-25
ethylthiometon	2-12
fenthion	255-298
fenitrothion	800

II. From NCI malaoxon carcinogenicity study (1979)	Intraperitoneal LD_{50} Rat (mg/kg)
malathion	900
malaoxon	25

ATTACHMENT

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D C 20460

MEMORANDUM March 30, 1990

SUBJECT: Malathion: Allergic and Ocular Effects

TO: Penelope Fenner-Crisp Ph.D.
Director
Health Effects Division (H7509C)

FROM: Robert P. Zendzian Ph.D. 7/30/90
Senior Pharmacologist
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

THROUGH: Reto Engler Ph.D.
Chief
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

Action Requested

Review and comment on the following documents;

MALATHION REVIEW: ALLERGIC AND OCULAR EFFECTS
Dennis Shusterman MD, MPH
Chapter Outline
Undated

Draft Memo; re. Potential for Malathion Ocular toxicity,
From, Dennis Shusterman MD, MPH,
To, DHS Medfly Working Group
March 8, 1990

Conclusions

1. Allergic effects

The sensitizing agent in technical malathion has been identified as diethyl fumarate. Considering its removal from technical malathion and the lack of clinical reports of sensitization from direct dermal use of malathion, allergic effects from malathion are not considered a potential health problem. However, the possibility remains that a specific formulation or application form of malathion may contain sensitizing agents.

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2. Ocular effects

The human and animal data available to the Agency clearly establish the organophosphate cholinesterase inhibitors as having the potential for significant irreversable toxicity on the visual system. While the human data does not clearly implicate any one compound, the animal studies show ocular toxicity, similar to that observed in humans, from fenitrothion, ethylthiometon, fenthion and ethyl and methyl parathion. At this time we have no evidence from animal toxicology studies of ocular toxicity due to malathion. However, we do not have an acceptable chronic toxicity study with malathion and this is the only type of routine (guideline) study which has demonstrated this type of toxicity with organophosphate cholinesterase inhibitors.

The compounds demonstrating the toxic effects on the ocular system are all irreversable cholinesterase inhibitors and the evidence available strongly indicates that cholinesterase inhibition, at the target organ, is required for these effects. This information does not perclude the possibility that reversable inhibitors, carbamates, can produce functional abnormalities in the visual system. The toxicity testing available at this time is not capable of detecting functional abnormalities.

Note. The compounds which are implicated in the human toxicity and have shown toxicity in the animal tests do not produce organophosphate type delayed neurotoxicity. Their toxicity on the visual system is separate from that unique type of toxicity. However, none of the compounds which produce OP delayed neurotoxicity have been tested for toxicity on the visual system and it is expected that they can produce ocular toxicity.

Recommendations

It is recommended that;

1. Special testing for toxicity to the visual system be required for all irreversable cholinesterase inhibitory compounds. Such testing has been required for ethyl and methyl parthion and fenthion in the respective registration standards.

2. Special testing for toxicity to the visual system be required for malathion with particular attention to additions to the rat chronic toxicity study such as those performed in the second ethyl parathion study. The high dose must be sufficiently high so as to produce signs of cholinergic toxicity in order to assure a sufficiently severe challenge to the visual system. In vivo observations must include direct examination of the eyes and electroretinograms. Histopathology must include light and electron microscopy of the eye and the

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optic nerve.

3. The Agency develop sensitive functional tests for toxicity to the visual system. Such tests must be validated with reversable and irreversable cholinesterase inhibitors including the toxic organophosphates. When validated, the tests must become part of the Agency guidelines for toxicity testing.

Background

1. Dr. Shusterman's Documents.

a. The outline (attachment I) is, as represented, an outline for a chapter on Malathion as follows;

"Evidence for allergic effects
IgE-mediated (e.g. anaphylasis, urticaria, angiodema, atopic dermatitis, allergic rhinitis/conjunctivitis, atopic asthma)
Cell-mediated (allergic contact dermatitis)

Evidence for ocular effects
Irritant/Allergic (e.g., conjunctivitis, keratitis)
Pharmacologic (miosis, accomodative disturbances)
Neuro-opthalmologic (oculomotor abnormalities)
Other (optic neuritis)"

Five references are cited for the allergic effects section. The references were not provided to the Agency. As noted below we do not consider it necessary to obtain and review them.

Nine references are cited for the ocular effects section. The references were not provided to the Agency. We have the four references in Japanese and the one in Slovic, in translation and have obtained the remaining references.

b. The Draft Memo is a one and one-half page document listing 24 references (attachment II). Included with the package are copies of several of the English language papers written by the Japanese investigators, three other papers in English on the subject and 'testimony' of two individuals on the effects of malathion on the visual system. We have most of these papers and, in translation, copies of additional background papers from the Japanese literature.

Dr. Shusterman briefly summarizes the literature and states that there are significant methodologic problems in the studies and concludes "At best, for public health policy-making purposes, the reports should be treated as clinical case series materials suggestive of the need for further study of the opthalmologic effects of chronic high-dose

organophosphate pesticide exposure." He states as "reasons for the non-applicability of these studies to the Medfly eradication program":

1. "The pesticides used in Japan includes parathion and other organophosphates with acute and subacute toxicities many times that of malathion. In the medfly program, the sole pesticide is malathion."

2. Different application rates. "In Japan, rates of more than 2.6 pounds per acre per application were used, whereas in California the application rate is 2.8 ounces per acre per application"

3. Form of spray, fine mist which could remain suspended in Japan, "predominately large particle" protein bait in California.

4. Contamination of drinking water in Japan.

He concludes;

"it is our conclusion that exposures from the Medfly eradication program will not produce eye effects of the sort discribed in the Japanese literature."

2. Agency background.

a. Allergic effects.

On May 9-11, 1988, Dr. Roy Sjoblad of this office attended the Workshop on "The Effects of Pesticides on Human Health" as a member of the "Immunotoxicology Working Group". Dr. Sjoblad has provided a galley proof of "Chapter 5, Immunologic Effects of Pesticides" which will be published as part of the Proceedings of the Workshop in Advances in Modern Toxicology. We believe that the working group's comments on malathion's immunological properties provide the most recent and authoritative evaluation.

b. Ocular effects

In 1979, as part of the EPN Rebuttable Presumption Against Reregistration, I evaluated a review article by Plestina & Liukovic-Plestina (1978) on the toxic effects of organphosphates on the eye. The authors discussed the cholinergic effects of organophosphates on the eye and the production of cataracts following topical administration for glaucoma. In addition they cited an extensive literature from Japan on the toxic effects of organophosphates on the visual system. We obtained the Japanese references and had them translated. We have also obtained additional, more recent, reports directly from Drs Satoshi Ishikawa and Kazui Mukuno. Bibliographies of these references are attached as Human Effects, 55 references,

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attachment III and Animal Studies, 28 references, attachment IV.

We have also received registrant submitted reports of chronic toxicity studies in the rat with ethyl and methy parathion which show significant toxicity to the eye by routine eye examination and histology and, in the second ethyl parathion study, by additional special testing.

Based on these findings we are now requesting specific evaluations of the visual system for organophosphate cholinesterase inhibiting pesticides.

My evaluation of this material is presented in a briefing document, "Toxic Effects of Organophosphate Pesticides on the Eye", attachment V.

Discussion

1. Allergic effects

The following is quoted from the immunologic effects chapter galley proofs;

"The pesticides malathion, captan, benomyl, maneb, and naled are strong to extreme sensitizers by GPMT (Guinea Pig Maximization Test); however, human sensitization data do not always agree. For example, although human maximization test (HMT) data on technical grade malathion support its classification of a strong sensitizer (Kligman, 1966), such a rating was not confirmed by an International Contact Dermatitis Research Group survey of 455 individuals, in which one tested positive (Cronin, 1980). The lack of clinical reports of dermatitis from malathion use (including direct skin contact as a delousing agent) makes it apparent that the animal and human predictive tests (GPMT and HMT) that indicated strong to extreme sensitization potential overestimated the sensitization hazard. Furthermore, the offending chemical in technical malathion is diethyl fumarate (Fisher, 1988: Milby and Epstein, 1964); reduction of this constituent has further lowered the sensitization potential of this pesticide."

Considering the removal of the sensitizing agent diethyl fumarate from technical malathion and the lack of clinical reports of sensitization from direct dermal use of malathion, allergic effects from malathion are not considered a potential health problem.

However, this does not mean that the formulation, bait, used in California is not a sensitizer. In our experience formulations can contain sensitizing agents other than the active ingredient. For this reason the Agency requires sensitization testing for all formulations. We have no information as to whether the California bait formulation has been tested for sensitization potential.

b. Ocular effects

The pharmacologic effects of the organophosphate cholinesterae inhibitors (OPs) on the eye such as miosis and accomodative disturbances are well recognized, as is the production of cataracts following topical administration for glaucoma. The Japanese experience with extensive human poisoning by OPs showed a previously unreported syndrome of effects on vision ranging from myopia to congestion or atropy of the optic nerve.

The ocular syndrome was not typical of myopia, being generally more severe, accompanied by vertical astigmatism, concentric narrowing of the visual field, and abnormal eye movements. It was not correctable. Additional observations included lowered activity of serum cholinesterase, neurological abnormalities characteristic of anticholinesterase poisoning and relatively high levels of organophosphate insecticides in the blood of the patients compared with normal individuals from other areas.

Ishikawa and Miyata (1980) listed the organophosphates malathion, EPN, ethyl and methyl parathion, fenthion, dipterex, fenitrothion and diazinon as having extensive use in Japan. Earlier papers listed these orgaonphosphates and many more but are not clear as to the extent of their use.

In general the association between the toxic syndrome observed in Japan and exposure to organophosphate pesticides is well established but individual compounds could not be clearly connected with individual cases. Use data indicated possible exposure to more than one organophosphate. Urine analysis could only identify the presence of phosphate metabolites which are not indicative of a specific organophosphate or the presence of paranitrophenol which can be indicative of ethyl parathion, methyl parathion or EPN.

Animal experimentation in Japan showed that the OPs fenitrothion, ethylthiometon and fenthion could produce various aspects of the human syndrome. See the briefing paper and Ishikawa 1980 for details (Attachment V).

The Agency has received chronic toxicity studies on ethyl and methyl parathion which showed toxic effects on the eyes. These effects are similar to some aspects of the sydrome reported from Japan. Two studies with ethyl parathion showed effects at the high doses (50 and 32 ppm) consisting of retinal degeneration by direct observation and histopathology, decreased ERG activity, histopathology (EM) indicative of blindness, and a possible increase in cataracts in females. Lesions were observed in the males but there was no compound-related effect. The sex differenc may have been due to significant differences in compound intake. At the 32 ppm

dose the actual dose was 2.47 mg/kg/day females and 1.75 mg/kg/day males. The study with methyl parathion showed retinal degeneration by direct observation and histopathology at the high dose, 50 ppm, again only in the females.

The human and animal data available clearly establish the OPs as having the potential for significant toxicity on the ocular system. While the human data does not clearly implicate any one compound, the animal studies show ocular toxicity from fenitrothion, ethylthiometon, fenthion and ethyl and methyl parathion. The pattern of toxicity is such as to clearly implicate cholinesterase inhibition as a major factor in this toxicity. Since malathion is an organophosphate cholinesterase inhibitor, we must consider whether our lack of data indicating toxicity to the eye is due to an intrinsic lack of this toxicity or to lack of the proper experiment to show such toxicity.

We have no data indicating a toxic effect of malathion on the eyes but this may well be due to the lack of an acceptable chronic toxicity study in the rat with malathion. The chronic rat study is the only routine toxicity study which has shown ocular toxicity, by ethyl and methyl parathion. These studies also show that the dose tested must be sufficiently high as to show signs of cholenergic toxicity to assure adequate testing to demonstrate the presence or absence of structural toxicity to the visual system.

Special testing for toxicity to the visual system is necessary for malathion with particular attention to additions to the rat chronic toxicity study such as those performed in the second ethyl parathion study. The high dose must be sufficiently high so as to produce signs of cholinergic toxicity in order to assure a sufficiently severe challange to the visual system. In vivo observations must include direct examination of the eyes and electroretinograms. Histopathology must include light and electron microscopy of the eye and the optic nerve.

However, one must note that the compounds, ethyl and methyl parathion, shown by chronic animal studies to have ocular toxicity are in the order of 200 times more toxic than malathion. If malathion demonstrates ocular toxicity in animal studies, it may occur at doses significantly higher than those of the prototype compounds.

The following conclusions can be made in relation to the organophosphate cholinesterase inhibitors;

1. Severe functional and structural damage has been demonstrated in human and experimental animals. Such damage can follow a single massive dose or repeated smaller doses.

In general the severe toxicity follows doses which demonstrate cholinergic toxicity.

2. Function and possibly structural damage can occur at doses which produce blood cholinesterase inhibition without signs of cholinergic toxicity.

3. Functional abnormalities can occur at doses which do not produce blood cholinesterase inhibition. These can occur in the highly sensitive cholinergic structures in the retina and in central areas of the brain. Such effects require sensitive and specific testing procedures which are not available for routine testing.

Attachments

I MALATHION REVIEW: ALLERGIC AND OCULAR EFFECTS
Dennis Shusterman, MD, MPH

II Draft Memo, re Potential for Malathion Ocular Toxicity, Dennis Shusterman, MD, MPH to DHS Medfly Working Program Mrr 8 ,1990

III Bibliography Toxic Effects of OPs on the Eye, Human Effects, Japan

IV Bibliography Toxic Effects of Organophosphate Insecticides on the Eye (Animal Experiments 1972-1977)

V Briefing Document Toxic Effects of Organophosphate Pesticides on the Eye, Robert P. Zendzian Ph.D.

cc

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