Attachment 3

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

16 JUN 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM:

SUBJECT: Peer Review of a Document Entitled "Ocular Effects of Organophosphates"

FROM: George Z. Ghali, PhD G. Ghali 4/15/91
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

TO: Anne Lindsay, Director
Registration Division (H7505C)
Office of Pesticide Programs

THRU: Karl Baetcke, PhD, Chief
Toxicology Branch II (IRS)
Health Effects Division (H7509C)

Reto Engler, PhD, Chief
Science Analysis and Coordination Branch
Health Effects Division (H7509C)

and

Penny Fenner-Crisp, PhD, Director
Health Effects Division (H7509C) 6/12/91
Office of Pesticide Programs

The RfD/Peer Review Committee convened on February 21, 1991 to discuss the possible association between ocular effects and organophosphate pesticides. Material available for review by the Committee included a document entitled "Ocular Effects of Organophosphates" prepared by Dr. Brian Dementi addressing the association between exposure to organophosphate pesticides and ocular effects observed in population/clinical and animal studies from the Japanese literature, and other animal studies from data submissions.

Members of the Peer Review Committee felt that the report by Dr. Dementi accomplished the objective of characterizing the body of published works in question.

The Committee agreed that:

1) the population studies, though not satisfactorily conforming to contemporary standards in epidemiology, were helpful in establishing a plausible association between eye effects observed in humans and exposure to organophosphates.

2) the population data, though lacking much information that would be necessary to properly characterize the ocular effects and correlate doses with such effects, when viewed as a whole, are adequate to establish, at least, a working hypothesis, that is, exposure of humans to organophosphates may produce ocular toxicity.

3) the animal studies provided conclusive evidence of the potential of organophosphates to produce adverse ocular effects in mammals, and conclusively demonstrate that both lenticular changes and other serious eye damage (e.g. retinal degeneration) will follow exposure to organophosphates under defined circumstances of dosing. It was recognized, therefore, that data from well-designed animal studies are essential to further assess the above hypothesis.

The report is essentially in agreement with several other previous evaluations by Dr. Robert Zendzian of the Health Effects Division, addressing the same subject.

The Committee concluded that the combined toxicological data from epidemiology studies and from bioassay demonstrate the potential for organophosphates to produce a wide range of ophthalmological effects, and hence support the necessity to establish ocular testing as a registration requirement for this class of chemicals for the purpose of hazard characterization and risk assessment.

Individuals in Attendance:

1. RfD/Peer Review Committee Members and Associates (signatures indicate concurrence with the peer review report unless otherwise stated).

Penny Fenner-Crisp — Penelope A. Fenner-Crisp

William Burnam

Karl Baetcke

Reto Engler

Henry Spencer

George Ghali G. Ghali

Rick Whiting Rick Whiting

2. RfD/Peer Review Members in Absentia (committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the committee).

Marcia Van Gemert Marcia Van Gemert

3. Scientific Observers (Non-committee members; signatures indicate concurrence with the peer review unless otherwise stated).

Robert Zendzian 4/16/91

William Sette Cillian Sette 6/11/91

Jerome Blondell Jerome Blondell 6/11/91

4. Scientific Reviewers (committee or non-committee members responsible for data preparation and presentation of data; signatures indicate technical accuracy of panel report).

Brian Dementi Brian Dementi 4/16/91

George Ghali George Ghali

cc: R. Cool
A. Allan
F. Chow

Attachment 4

Ocular Effects of Organophosphates

Prepared by Brian Dementi, Ph.D., D.A.B.T.

Date: March 27, 1991

PARATHION

a) Zendzian, R. (1984). Ethyl parathion, review of chronic/oncogenic rat study: A memorandum (review) by R. P. Zendzian dated 8/29/84.

b) Zendzian, R. (1986). Electroretinographic evaluation, G.A. Edwards, Monsanto, R.D. No. 693, July 23, 1986, Accession #263986. A data evaluation report dated 8/86.

c) Zendzian, R. (1987). Report of results of findings of electron microscopy of retina, nervus opticus --- chronic toxicology long-term study in rats. A data evaluation reported dated 7/1/87.

d) Zendzian, R. (1989). Parathion, chronic/oncogenicity study in rats. A memorandum (review) by R. P. Zendzian dated 3/15/89.

Two studies are under discussion here. In the first of these, a Biodynamics Inc. study reviewed by Zendzian (1984), parathion was administered via the feed to rats in groups of 60 each at dosage levels of 0, 0.5, 5.0 and 50 ppm. Findings relevant to effects on the eye were: inhibition of plasma pseudo ChE in both sexes at the mid- and high-dose levels, but not at the low dose, brain cholinesterase was inhibited only at the high dose; cholinergic signs, more pronounced in females than in males, occurred at the high dose only; evidence of retinal atrophy was observed in females at the high dose level.

The second study was performed by the Institut fur Tieranatomie der Universitat Munchen. As reviewed by Zendzian (1987) parathion was tested in the rat at 0, 2, 8 and 32 ppm. Plasma pseudo ChE and erythrocyte AChE, LEL = 8 ppm, NOEL = 2 ppm; brain LEL = 32 ppm, NOEL = 8 ppm. Decreased ERGs occurred at the mid- and high-dose levels only. Gross retinal abnormalities were evident in females at the high dose. Of the 50 animals per group, 20 (40%) received ophthalmoscopic examination, 10 (20%) received ERG examinations and one-half, 5 (10%), of the latter group selected at random received retinal histopathologic examinations.

The ophthalmoscopic exam yielded evidence of choroidal pallor in males at all doses, and evidence of cataract in males at the high dose and in females possibly at all doses.

The ERG assessment indicated statistically significant reduced b-wave amplitudes among females at the two high doses accompanied by a numerical increase at the low dose. In males, there was a marginal (20%) reduction in b-wave amplitude in all dosed groups, which was not statistically significant.

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Electron microscopy yielded a compound related toxicity in the retina and optic nerve of males and females at the high dose level.

Zendzian (1989) expressed the view based upon the concerted ERG, ophthalmoscopic and histopathologic effects that most if not all rats in the high dose group are blind.

Dr. Zendzian notes that ophthalmoscopic exams failed to reveal abnormalities which were clearly evident by electron microscopy. Also, ERGs were not as effective as electron microscopy in identifying (characterizing) the problem.

The case report of Dr. Sadun was subsequently submitted to an OPP consultant in this field, Sheldon Wagner, M.D., for an assessment. In his August 24, 1990 letter to Mr. Frank Davido, OPP Pesticide Incident Response Officer, Dr. Wagner expressed his belief that Juan Macias' condition was probably that of Saku disease secondary to malathion exposure. In addition, he expressed his concern that although the condition would probably be rare, it could go unrecognized by most physicians.

We should note that the opinions of Drs. Sadun and Wagner do not establish a cause and effect relationship between malathion spraying and Juan Macias' condition.

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Attachment 5

OFFICE OF PESTICIDE PROGRAMS
REGISTRATION STANDARD BIBLIOGRAPHY
Citations Considered to be Part of the Data Base Supporting
Registrations Under the Malathion Registration Standard

MRID Citation

certain insecticides applied as low volume concentrate and water emulsion sprays. Bulletin of Environmental Contamination & Toxicology 2(6):340-348.

00158055 Rosenfeld, G. (1985) Acute Dermal Toxicity in Rabbits [Using] Test Article: Malathion 95% U.L.V.-Tech: Study #1146B. Unpublished study prepared by Cosmopolitan Safety Evaluation, Inc. 17 p.

00158056 Rosenfeld, G. (1985) Acute Oral Toxicity Study in Rats [Using] Test Article: Malathion 95% U.L.V.-Tech: Study #1146A. Unpublished study prepared by Cosmopolitan Safety Evaluation, Inc. 27 p.

00158057 Rosenfeld, G. (1985) Acute Inhalation Toxicity Study in Rats [Using] Test Article: Malathion 95% U.L.V.-Tech: Study #1146C. Unpublished study prepared by Cosmopolitan Safety Evaluation, Inc. 26 p.

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REGISTRATION STANDARD BIBLIOGRAPHY
Citations Considered to be Part of the Data Base Supporting
Registrations Under the Malathion Standard

MRID CITATION

00058823 Manuel, A.J. (1976) Malathion: Determination of Residues of Malathion, (CL 6,601), S-1,2-Bis(ethoxycarbonyl)ethyl-O,O-dimethyldithiophosphate, and Malaoxon (CL 23,269) in Beef and Pork Muscle, Bread, Cake, Corn Flakes, Milk, Coca-Cola, and Cranberry Sauce by Gas-Liquid Chromatography: Report No. C-919. Includes method M-647 dated Mar 12, 1976. (Unpublished study received Aug 16, 1976 under 241-EX-83; submitted by American Cyanamid Co., Princeton, N.J.; CDL:230458-D)