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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

Oct 5, 1990

SUBJECT: Malathion, Case of Juan Macias

TO: William Burnam
Deputy Director
Health Effects Division (H7509C)

10/5/90

FROM: Robert P. Zendzian Ph.D.
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Evaluate the following documents;

Ltr, re Juan Macias, case report, from Alfrado A. Sadun MD, Ph.D to Kenneth Cohn MD, June 12, 1990.

Ltr, re Juan Macias, re diagnosis, from Shelton L Wagner MD, to Frank Davido, Aug 24, 1990.

Memo, re Case report of alleged 'Saku disease' folowing malathion exposure in the medfly campaign, from Paul J. Papanek Jr. MD MPH to Bill Burnam, Aug 24, 1990 w/incl Ltr, re Toxic epidemiology program, from Paul J. Papanek Jr. MD, MPH to James Stratten MD, MPH, July 17, 1990, w/incl Report, Study of Opthalmologists in Malathion Spray Area, 7/5/90

Conclusions and Recommendations

Juan Macias received a dose of malathion/bait formulation in the eye and subsiquently lost essentialy all vision. The pathology of the loss of vision was diagnosed as due to loss of nerve fibers from the optic nerve. The retina appeared normal. A dose/effect relationship is considered highly likely and the following is recommended to investigate this possibility;

1) The time-course of the development of Mr. Macis' blindness must be determined in order to allow experimental evaluation of this toxic effect.

2) The toxicology of malathion, and other selected compounds, on the visual system following direct instilation must be tested in the rat. The rat demonstrated pathology of

the eye and optic nerve in chronic studies with parathion. A protocol for the test is included in this memo.

Discussion

On March 28, 1990 Juan Macias was exposed to malathion bait sprayed from a helicopter as part of the California Med-fly program. The material entered his eyes. Subsiquently he lost almost all vision to the extent that he is considered legally blind. On June 11, 1990 he was examined by Dr. Alfrado A. Sadun who diaginosed his condition as due to "bilateral optic atropy with severe drop-out of the nerve fiber layers in both the arcuate bundles and the papillomacular bundle." That is, nerve fibers in the optic nerve had been irreversably destroyed. Dr. Sadun diagnosed this case as Saku disease, a toxic response to organophosphate pesticide poisioning observed in Japan.

Dr. Sadun's report and the other documents reviewed describe a series of 'effects' that occured between exposure and examination that appeared to be critical to the development of the pathology. However, the time course of these happenings is only poorly presented. It is necesary to develop a calendar of events in order to understand the time course of the development of Mr. Macias' blindness. This understanding will assist us in developing animal studies to test for cause and effect relationship.

The following information is needed;

During the time period, which days did Mr. Macias attend school and which days was he absent? Why was he absent for each of these days.

Directly following exposure certain signs/symptoms were noticed by Mr. Macias. When (dates) did these things happen?

It is indicated that Mr. Macias visited his school nurse. When (date(s)) and for what causes?

Later Mr. Macias lost his vision. When did this happen, time course, dates? Did he see or speak with anyone during this period who kept records?

Mr. Macias was refered to Dr. Sadun by Dr. Kenneth Cohn. When did Dr. Cohn see Mr. Macias? When did Mr. Macias make his appointment and what was the reason given at that time?

Mr. Macias first went to Dr. Kenneth Sparks. When did Dr. Sparks see Mr. Macias? When did Mr. Macias make his appointment and what was the reason given at that time?

A cause and effect relationship in this case is considered highly likely based on our information concerning the toxicity of organophosphate pesticides to the visual system. An epidemic of damage to human vision was observed in Japan which could be clearly attributed to poisoning by organophosphate pesticides. The Agency has information from chronic feeding studies, in the rat, of the organophosphates methyl and ethyl parathion and tribufos (DEF) showing toxicity to the visual system.

It is strongly recommened that the potential for damage to the visual system following instalation of an organophosphate in the eye be tested. A protocol for such testing is proposed below.

Protocol

Direct Neurotoxicity to the Eye and Visual System

Purpose To determine the effect of a single direct ocular dose of a compound on the macro and microstructure of the eye and associated musculature, the optic nerve and the optic centers of the brain. A single dose, chosen to have minimal or no systemic toxicity, will be instilled into the eye of young adult female rats. Groups of treated and control rats will be periodically sacrificed and samples of the visual system collected for examination by light and electron microscopy.

1) Test material. The technical form of the compound is to be used.

2) Vehicle. The vehicle, if necessary, should have no irritant or toxic effect on the eye and visual system.

3) Test animal. Young adult female rats. Female rats have demonstrated sensitivity to ocular toxicity of an organophosphate by showning damage to the retinal and optic nerve in two chronic studies with ethyl parathion. Prior to use, test animals are to be examined by a veternary opthomologist and only animals having normal eyes are to be placed on test.

4) Dose preparation. The test material should be prepared in a liquid form, preferably as a solution. A suspension may be used if a solution cannot be obtained in a nontoxic vehicle

5) Dose volume. Volume shall be limited so that excess material will not spill out of the eye.

6) Experimental Design

a) Rangefinding study. A rangefinding study must be performed to determine the dose for the definative study. Test animals are to be given a single dose of test material in one eye. A

range of doses are to be tested so as to determine the largest dose that can be administered without producing excessive toxicity. The dose selected should produce minimal or no observable signs of toxicity.

b) Definative study. 1) Five control and five treated animals are to be used for each exposure duration.

2) A single dose of test material or vehicle is to be instilled into one eye of the animal. The eye is not to be washed following dosing.

3) Animals are to be maintained individually accordingly to the usual procedures for experimental animals.

4) Animals are to be observed/examined twice daily.

5) Groups of 5 test and 5 control animals are to be sacrificed periodically following dosing. Sacrifice intervals are to be determined in consultation with the Agency.

6) Animals to be sacrificed are to be anesthatized and a blood sample collected for determination of plasma and RBC cholinesterase activity.

7) Animals are to be perfused in situ with a fixative suitable for fixation of the nervous system.

8) From each animal, both eyes with associated musculature, both optic nerves, the brain and spinal cord are to be collected. Tissue is to be prepared so as to allow examination by light and electron microspy.

9) Selected Tissue is to be examined by light and electron microspy. Tissue to be examined is to be determined in consultation with the Agency but should include at least;

i) from both eyes, cillary muscle, retina, ouclormotor muscles and associated nerves.

ii) cross and longitudinal sections of both optic nerves

iii) representative sections from the optic centers of the brain.

10) Staining. Experience has shown that H & E staining of nervous tissue is usually sufficient but additional specially stained sections may be made on the advice of the pathologist.