

US EPA ARCHIVE DOCUMENT



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

FEB 8 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Preliminary Review of Japanese studies of ocular impairment due to exposure to organophosphates
HED Project No.

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I. Background

Japanese studies conducted in the 1970s have suggested that children exposed to and/or poisoned by organophosphate (OP) insecticides experience increased myopia and other eye-related adverse effects. The purpose of this review is to determine to what extent these studies demonstrate that OP exposure or poisoning is a cause of serious eye problems.

Studies considered for this review include the following articles:

1. Ishikawa S. 1973. Chronic optic-neuropathy due to environmental exposure to organophosphate pesticides (Saku disease): clinical and experimental study. Nippon Ganka Gakkai Sashhi 77:1835-1886. Translation (TR-80-0787) by Scitran, Santa Barbara, California.

2. Ishikawa S, Miyata M. 1980. Development of myopia following chronic organophosphate pesticide intoxication: an epidemiological and experimental study. pp. 233-254 in Neurotoxicity of the Visual System. Edited by Merigan WH and Weiss B. (Raven Press, New York).

When reviewing the first publication, numerous serious errors in the translation were identified. Three times in the first seven pages a year (e.g., 1978) was reported inaccurately. Certain sentences (e.g., page 6 "The patient was found in 1966.") are clearly incorrectly translated. Every effort was made to take into account or adjust for such errors in this review. A retranslation will be needed if further regulatory use is made of this article.

II. Conclusion

In general these reports, apparently intended to review earlier work, are very poorly organized. Information on animal and human studies are mixed and the scientific method of presenting introduction with objectives, methods, results, and discussion is not followed. Although a case definition of the disease under study is presented, it is not at all clear how it would be applied in practice. No where is there a good listing of how many subjects had which symptoms listed in the case definition. Given that the case series was selected as diseased subjects, controls, free of the disease under study, should have been selected from the same population. This was not done. Rather controls were apparently diseased subjects (disease not specified) taken from a different population, selected on an unknown basis with no matching criteria and no known exposure to OPs. This design violates the most basic approach requirements of the case-control study. Therefore, this review recommends that no use be made of the comparisons between cases and controls. Instead these reports may be taken as a description of the results for various case series and analyzed solely on that basis. No attempt was made in this review to consider any of the data presented related to studies of animals.

III. Suggestive Findings

Taking these two reports together, there are some findings that suggest an effect of OP exposure on the eyes. According to the 1980 report, 71 children aged 4 to 16 were seen at Asama Hospital in Saku, an agricultural area in central Japan where rice and a variety of fruits are grown. Reportedly, OP use had been increasing and was quite high in 1969. The following adverse effects were noted in the 71 children:

- 98% had reduced visual acuity
- 95% had narrowing of the visual field
- 88% had refractive anomalies (mainly myopia and astigmatism)
- 71% had positive neurological findings (Note: this finding is contradicted by the report that 66 or 93% had sensorial neuropathy of the glove-stocking type. Therefore, the population of subjects being discussed is not clear and all the statistics provided are open to question)
- 53% had abnormal eye movements
- 52% had abnormal pupils or pupillary responses
- 49% had optic neuritis, temporal pallor of the disc, or optic atrophy

Of these 71 children, 55 had EEGs administered of which 16 were graded as abnormal. Biopsy of the lateral rectus on several of these patients (number not specified) revealed a total inhibition of cholinesterase activity. The report concludes that most Saku patients had myopia with vertical astigmatism that differed from ordinary myopia in that they had mild neurological complications.

The 1973 report by Ishikawa was difficult to follow but one finding was suggestive of OP exposure in the population of patients. Serum cholinesterase was significantly reduced (judging from inspection of the graph on page 14) in both child and adult patients in July suggesting increased exposure to organophosphate pesticides.

IV. Detailed considerations

Many of the associations reported in these reviews are based on grouped data rather than individuals. For example, OP levels in well and municipal water examined in 12 districts of Saku tended to be associated with the reported prevalence of myopia. Surprisingly, this information was presented as a table without performing a correlation test ($r = 0.70$, calculated by this reviewer). Such associations are subject to aggregation bias (also known as the ecological fallacy), which warns that the overall association may not apply to the individuals affected. In the example, we don't know what the dose of OPs from drinking water was for myopia victims or others in the various districts. Typically, such studies are used only to suggest hypotheses, not to confirm effects. Further, nothing is said about the number of water samples collected, their representativeness, or quality assurance on the analyses. There was no statistical analysis of water values; only ranges are presented.

Much is made of the time trend and seasonal trend in the presentation of myopia victims which coincided with increased OP use. But there is no discussion of possible ascertainment bias. Perhaps medical personnel changed or became more vigilant at seeking out cases or maybe news reports, discussions at schools or in parent groups resulted in more people seeking medical care. Again the data are presented only in graphical form without proper statistical testing.

A mapping exercise claimed that more patients were found in the area sprayed by helicopters, but the analysis (dots on a map) was not properly adjusted for population.

One of the more puzzling aspects of these reviews is the initial assertion that malathion and vamidothion are the two principal OPs sprayed in the Saku area, and the subsequent analysis for OPs in blood which totally ignores these two chemicals. Of 59 patients blood samples, all had salithion in their blood, 14 had formothion and 4 had ethyl or methyl parathion, but there is no

discussion whatever of how, where, or when these chemicals were used.

There is little or no discussion of how patients were chosen for any particular analysis. For example, page 4 discusses 59 patients, page 8 discusses 60 and page 11 discusses 63. The reason for these differences is not discussed.

The anecdotal case reports on pages 44-45 provide insufficient documentation to be of much use. For example, a farmer is said to be chronically poisoned by malathion which is detected in blood and urine and the pupil responds weakly to light. But the farmer's symptoms are not listed, the OP levels detected are not discussed, and the circumstances of exposure are not given. Without references or documentation, such case reports are of little value.

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Circulation