

US EPA ARCHIVE DOCUMENT



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

2-13-91

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Malathion Chronic Toxicity/Oncogenicity Testing
Protocols

Tox. Chem. No.: 535
Project No.: 0-2040
Record No.: 268526

FROM: Brian Dementi, Ph.D., D.A.B.T.
Review Section III
Toxicology Branch I-IRS
Health Effects Division (H7509C)

Brian Dementi 2/8/91

TO: Joanne Edwards, Review Manager
PM Team #74
Special Review and
Reregistration Division (H7508C)

THRU: Henry Spencer, Ph.D., Acting Section Head
Review Section III
Toxicology Branch I-IRS
Health Effects Division (H7509C)

Heck 2/11/91 KB 2/13/91

By way of letter from Robert L. Linkfield, Ph.D., dated October 3, 1990, to Ms. Lois Rossi, Branch Chief, Document Processing Desk, American Cyanamid has submitted to the Agency two protocols for life-time studies of malathion (AC6,601) (rat, mouse) and one protocol for such study on malaoxon (CL28,967) (rat), for review by the Agency.

In response to the request, Tox Branch would remind the Registrant that the primary responsibility for the design and conduct of studies that satisfy toxicology Guideline requirements rests with the Registrant. Tox Branch will comment upon the protocols and may suggest certain modifications in order to obtain information on possible hazards. However, the ultimate responsibility for the overall suitability/acceptability of the study to address possible hazards concerns rests with the Registrant. The following comments are offered with respect to the protocols in question.

In the cases of the malathion and malaoxon chronic/carcinogenicity study requirements, the registrant(s) shall be required to perform interim sacrifices (e.g. 3, 6 and 12 months). The interim sacrifices shall include, but not be limited to, the performing of assays for cholinesterase activity (plasma, erythrocyte, brain) and shall include assessments of possible effects upon the ocular system. The assessment of ocular effects shall include, but not be limited to:

- Retinal electrical activity (electroretinography)
- Ophthalmoscopic observations
- Fundus observations/photographs
- Clinical observations of potential cholinergic signs
- Body weights
- Histopathology of the eye; light and EM, including intra- and extraocular muscle, optic nerve and retina.

The registrant(s) shall be required to discuss with Toxicology Branch I the protocols for these particular studies prior to initiating the studies. Dates for the necessary discussions shall be established as soon as is practicable.

Toxicology Branch I reserves the decision to require a chronic dog study for the purposes of assessing the potential for malathion to elicit ocular effects.

Toxicology Branch I does not have toxicological data on the end product (malathion/bait formulation) being used in California and is unable to perform a hazard assessment on the product. It is recommended that acute toxicity data (ref. 40 CFR 158.340) on the end use formulation be provided by the responsible party(ies). The testing requirements are:

- Oral Toxicity (81-1)
- Dermal Toxicity (81-2)
- Inhalation (81-3)
- Eye Irritation (81-4)
- Dermal Irritation (81-5)
- Dermal Sensitization (81-6)

In the case of the eye irritation study, the protocol (81-4) shall be revised to extend the period of observation to 28 days and to include at study termination the assessment of ocular effects. The assessment of ocular effects shall include, but not be limited to histopathology of the eye, light and EM, including intra- and extraocular muscle, optic nerve and retina.

Toxicology Branch I here affirms that the registrant(s) shall also satisfy the subchronic (90-day) inhalation study in the rat and domestic animal safety testing requirements as originally set forth in the 1988 registration standard on malathion.

Non-dietary Exposure Branch will be forwarding to you via separate memorandum a summary statement of the data requirements for that Branch.

cc: Joanne Edwards
Lois Rossi
Penelope Finner-Crisp

TABLE A
GENERIC DATA REQUIREMENTS FOR FENTHION

Sec. 158.340 Toxicology - Footnotes (cont'd)

- 9/ Acute Tests in Rats: (Recommended; acute sublethal doses; tests performed pretest, at 4 days and repeated at intervals until full recovery). Observations should include:
- cholinesterase activity (blood); and
 - retinal electrical activity (electroretinography).
- 10/ Subchronic Study in Rats: (Recommended; 3 orally treated and 1 control group, 10 rats/sex/group. Observations pretest and at intervals for at least 90 days; doses based on results of acute study). Observations should include:
- cholinesterase activity (blood, brain at termination);
 - retinal electrical activity (electroretinography);
 - ophthalmoscopic observations;
 - fundis observations/photographs;
 - clinical observations of potential cholinergic signs;
 - body weights; and
 - histopathology of the eye; light and EM, including intra- and extraocular muscle, optic nerve and retina.
- 11/ Nonrodent (Dog/Rabbit/Monkey) Study: (Recommended; 3 orally treated and 1 control group, 5 animals/sex/group. Observations pretest and at intervals for at least 6 months). Observations should include:
- cholinesterase activity (RBC, plasma; at termination brain, oculomotor muscle, retina);
 - retinal electrical activity (electroretinography);
 - corneal sensitivity;
 - slit lamp biomicroscopic examinations;
 - corneal thickness;
 - corneal curvature;
 - ophthalmoscopic/fundis observations/photographs;
 - intraocular pressure;
 - refractivity of cornea and lens;
 - clinical observations of potential cholinergic signs;
 - body weights; and
 - histopathology of the eye; light and EM, including intra- and extraocular muscle, optic nerve and retina.

United States Environmental Protection Agency
Washington, D.C. 20460

Form Approved
OMB No. 2070-0107
Approval Expires 12-31-92

REQUIREMENTS STATUS AND REGISTRANT'S RESPONSE

INSTRUCTIONS: Please type or print in ink. Please read carefully the attached instructions and supply the information requested on this form. Use additional sheet(s) if necessary

1. Company name and Address BONIDE CHEMICAL CO. INC. 2 WURZ AVE. YORKVILLE NY 13495	2. Case # and Name 0248 Malathion Chemical # and Name 057701 Malathion	3. Date and Type of DCI GENERIC
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4. Guideline Requirement Number	5. Study Title	Progress Reports			6. Use Pattern	7. Test Substance	8. Time Frame	9. Registrant Response
		1	2	3				
71-4 (b)	Avian repro. duck	Y			ABCDE	TGAI	24 MOS.	
72-5	Life cycle fish	Y			ABCDE	TGAI	24 MOS.	
81-8-SS	ACUTE NEUROTOXICITY Protocol				AB	TGAI	12 MOS. 3 MOS.	
82-4	90-day inhal.-rat	Y	Y		ABCDEI	TGAI	24 MOS.	
83-1 (b)	Chronic tox - non-rodent	Y	Y	Y	ABCDEI		36 MOS.	
83-2 (a)	Onco-genicity - rat	Y	Y	Y	ABCDEI		3 MOS. 36 MOS.	draft last guidelines for performing - 1B under toxicity paper - 2 weeks (undergoing review) no derivative Cal. Reg. - reassessed

10. Certification
I certify that the statements made on this form and all attachments are true, accurate, and complete.
I acknowledge that any knowingly false or misleading statement may be punishable by fine, imprisonment or both under applicable law.

Signature and Title of Company's Authorized Representative _____

11. Date _____

12. Name of Company Contact _____

13. Phone Number _____



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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Summary of Malathion Reregistration Data Requirements
for Purposes of Data Call-In

FROM: Brian Dementi, Ph.D., D.A.B.T
Review Section I
Toxicology Branch I - IRS
Health Effects Division (H7509C)

Brian Dementi 9/7/90

TO: Lawrence Schnaubelt, Section Head
Reregistration Branch
Special Review and Reregistration Division (H7508C)

THRU: Roger Gardner, Acting Section Head
Review Section I
Toxicology Branch I - IRS
Health Effects Division (H7509C)

Roger Gardner 9/11/90
KB 9/11/90

This memorandum summarizes for Special Review and Reregistration Division the toxicology data requirements for a malathion DCI.

With respect to carcinogenicity and chronic toxicity testing requirements, Toxicology Branch I advises that the registrant(s) shall conduct the following studies:

- a) A chronic/oncogenicity study of malathion in the F344 rat. *rat oncogenicity - DCF (standard only call) for slide reevaluation*
- b) A chronic/oncogenicity study of malaoxon in the F344 rat.
- c) An oncogenicity study of malathion in the B6C3F1 mouse.

In addition to the new long term studies to be conducted as listed above, the registrant(s) shall sponsor a re-reading of the histopathologic slides for the 1980 Food and Drug Research Lab's study: "The Evaluation of the Chronic Toxicity Effects of Cythion Administered in the Diet to Sprague-Dawley Rats for 24 Consecutive Months", as previously set forth in the 1988 malathion registration standard.

I. "Chronic Dietary Toxicity and Oncogenicity Study with AC6,601 in Mice"; Protocol No. 971-90-161. (126)

malathion

This particular protocol, contrary to that implied by the title, is not written for the conduct of a combined chronic/oncogenicity study as defined in Section 83-5 of the FIFRA Guidelines, but rather is written to satisfy the oncogenicity Guideline requirement, Section 83-2. Since Tox Branch is requiring only an oncogenicity study in the mouse, the protocol in that sense is appropriate.

In general the protocol appears to adequately reflect the Guideline testing requirements for oncogenicity testing. The following additional points are made. In item 14, the protocol specifies four study groups consisting of a control (0 ppm) and three dosed groups (35, 3500 and 7000 ppm AC6,601 via the feed). This study is being required to address questionable carcinogenicity findings of the liver of male animals as identified in the 1978 National Cancer Institute carcinogenicity study in mice (NCI Technical Report Series No. 24), where the dosage levels were 0, 8,000 and 16,000 ppm via the feed. Since the doses in the NCI study exceeded the limit dose of 7,000 ppm Tox Branch considers it necessary to advise that the higher dosage levels (8,000 and 16,000 ppm) be employed in the new study, a modification considered necessary to resolve the question of possible carcinogenicity of malathion in the mouse. This decision to employ the higher doses, which exceed the limit dose, is not without precedent as a measure to resolve a question of carcinogenicity. To this end, Tox Branch would cite the July 15, 1988 memorandum of Dr. Theodore Farber, then Tox Branch Chief, to Dr. Larry Andrews of American Cyanamid Company with respect to carcinogenicity testing of glyphosate in the mouse in which case a study with a high dose of 30,000 ppm was considered necessary in order to resolve questionable kidney findings. (copy of memorandum appended.)

With respect to the topic of data retention, item 21 in the protocol, the Registrant is referred to 40 CFR 160.190 for further information on the subject.

II. "Chronic Dietary Toxicity and Oncogenicity Study With AC6,601 in Rats"; Protocol No. 971-90-162.

malathion

In general, the protocol appears to reflect the Guideline testing requirements for a combined chronic/oncogenicity study, Section 83-5 of the FIFRA Guidelines. The protocol specifies dosage levels of 50, 5000 and 10,000 ppm. The rationale for this dosage selection rests with a 13-week subchronic study where there was extensive mortality and compromised weight gain at 16,000 ppm, but not at the next lowest dose of 8,000 ppm. In view of the findings in the subchronic study, the dosage

selection appears proper. However, we should note in the 1979 NCI 2-year carcinogenicity study of malathion in the F344 rat (NCI Technical Report No. 192) where dosage levels of 2,000 and 4,000 ppm were employed, mortality was extensive at the high dose, particularly in males (survival at 103 weeks: males-54, 28 and 0%; females-74, 62 and 50% for control, low and high dose groups, respectively). Hence before initiating another 2-year study at doses as high as 5,000 and 10,000 ppm, perhaps another 13-week subchronic study in the same strain of rat from the same supplier as contemplated for the proposed chronic study would be appropriate.

III. "Chronic Dietary Toxicity and Oncogenicity Study with CL28,967 in Rats." Protocol No. 971-90-163.

This protocol also appears to reflect the Guideline testing requirements for a combined chronic/oncogenicity study in the rat, Section 83-5 of FIFRA Guidelines. The protocol specifies dosage levels of 15, 1,500 and 3,000 ppm. The dosage selection appears to be reasonable given the findings in a 13-week subchronic study in rats which revealed extensive mortality at 4,000 ppm, but none at 2,000 ppm, the next lower dose tested. We should note that in the 1979 NCI 2-year carcinogenicity study of malaoxon in the F344 rat (NCI Technical Report Series No. 135), dosage levels employed were 500 and 1,000 ppm, but there was no evidence an MTD had been reached in terms of altered body weight gain. There was some evidence of increased mortality among males at the high dose, but this was inconclusive.

Tox Branch recommends that the Registrant contact SRRD to arrange a time with TOX Branch representatives for discussing changes in the design of the protocols aimed at obtaining more definitive assessments of cholinesterase inhibition for these chemicals. Pursuant to ocular effects testing recommendations as set forth in the TOX Branch memorandum of 9/7/90 (copy appended), the discussion at the recommended meeting should also address revisions in the protocols for the two rat studies which would be designed to assess the potential for malathion and malaoxon to elicit ocular toxicity.

cc: Flora Chow

United States Environmental Protection Agency
Washington, D.C. 20460

*** COMMENTS FOR GUIDELINE REQUIREMENTS**

Case # and Name
0248 Malathion
Chemical # and Name
057701 Malathion

GUIDELINE COMMENT

- 83-1(b) chronic toxicity dog using malathion- emphasis for testing ocular effects
- 83-2(a) chronic tox/onco of malathion in F344 rat
chronic tox/onco of malaaxon in rhe F344 rat
study due Feb 1994



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

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MAR 12 1991

MEMORANDUM

SUBJECT: Meeting to Discuss Malathion Protocols
FROM: Joanne Edwards, Review Manager *JDE*
Special Review and Reregistration Branch
TO: Addressees

A meeting has been scheduled for Thursday, March 21 at 1:00 PM in CM-2 Conference Room 1112, to the malathion chronic toxicity/oncogenicity testing protocols. Attending for Cyanamid will be Bob Linkfield, Jane Harris, Bill Steller, and Michelle Bassler. If you have any questions concerning this meeting, or have a conflict with the scheduling, please call me at 308-8046.

Addressees: Brian Dementi
Carl Baetcke
Hank Spencer
Bill Burnam
Larry Schnaubelt
Marilyn Mautz