UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

DATE: May 17, 1978

SUBJECT: Review of The Acute Toxicological Data on Paranitrophenol

FROM: Toxicology Branch, RD (WH-567)

TO: Mr. Robert J. Taylor (PM #25)
Registration Division (WH-567)

Related EPA File Symbol: 40510-E

Submitted by:
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Opinion and Comment:

A. Two sets of experimental data on paranitrophenol were submitted voluntarily this time for our review. One was performed in 1956 on Monsanto sample #174 of Monsanto Project No. Y-56-56 and the other was performed in 1961 on Monsanto ample #113 [CP 5442-(4)] of Monsanto Project No. Y-61-65.

It is our general impression that the experimental designs of these tests might meet the requirements at that time, but apparently they can not meet quite the present-time established guidelines and standards.

For instances, what might be permissible at that time were to use a single animal for each dose level, a single animal of randomly mixed sexes for dose levels in a single test, random dose level of technical solid material (less than the amount of 0.5 gm as being used in the present-time standard procedure) and application of the test material(s) to only intact skin for dermal toxicity studies, random duration of test (less than 14 days for oral LD_{50} test and less than of days for eye irritation test) and other experimental conditions which do not well fit the present EPA guidelines for toxicological evaluations.

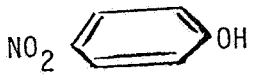
For the aforementioned reasons, most of the old data submitted by Monsanto Company this time are considered invalid. However, there is no action to be taken in this case, because these reports are unsolicited but submitted voluntarily.

B. Younger Laboratories is one of the laboratories whose data must be validated before they can be considered in support of any application for registration.

I. Substance Identification

1. Chemical name and formula:

Paranitrophenol



II. Review of Toxicological Studies

A. Test of Paranitrophenol, Monsanto Sample No. 174, Monsanto Project No. Y-56-56 (Reported by Fred M. Younger, 8/29/56):

1. Oral LD_{50} in Rats

Paranitrophenol was fed by stomach tube to rats as a 25% solution-suspension in corn oil at dose levels of 0.30, 0.35, 0.40 and 0.45 gm/kg b.w. The observation indicated that survival time was 15 minutes to several hours and that some animals were prostrate in 5 minutes after being fed. The autopsy showed the yellow color of the test material present in the liver and kidneys. There was considerable pulmonary congestion and moderate liver congestion.

Evaluation: Oral LD_{50} was about 350 mg/kg (Cat. II).

Comment: The minimum requirements for an oral LD_{50} test are 4 animals per sex per each of 3 dose levels. Only 2 or 3 animals per sex per dose level were used in this test. In general, the animals shall be observed for an appropriate period of time (approximately 14 days) after dosing, but no mention of duration of this test was made.

Classification: Only supplementary value

2. Minimum Lethal Oral Dose in Rabbits

The test material was introduced into the stomach of New Zealand rabbits as a 25% solution-suspension in corn oil at dose levels of 0.20, 0.40, 0.60, 0.90, 1.10, 1.50 and 1.80 gm/kg b.w. Observations were made for toxic symptoms and those sucumbing were autopsied macroscopically.

Evaluation: The minimum lethal oral dose was in the range of 600 to 900 mg/kg.

Comment: Only one male or female animal was used for each dose. No mention of duration of the test was made. It is evident that the number of animals used for each dose was not enough and that one sex of a single animal was used for one dose and other sex of a single animal used in another dose.

Classification: Invalid values

3. Toxicity by Skin Absorption

A 20% solution-suspension in corn oil was applied to the clipped intact skin of New Zealand rabbits at dose levels of 0.50, 1.00, 1.50, 2.25, 3.00 and 3.50 gm/kg b.w. Paranitrophenol was applied also as a 40% aqueous suspension at dose levels of 3.00 and 6.00 gm/kg b.w. in the same manner.

When a 20% (?) suspension was applied, Survival time was 4-6 hours. Lethargy and weakness were apparent in less than 30 minutes following application. The autopsy showed that the tissue surrounding and below the application had absorbed the yellow color of the test substance. A dose of 6.0 gm/kg was non-lethal when applied as a 40% aqueous solution-suspension.

Evaluation: The fatal dose range was 1.50 to 2.25 gm/kg in the case of a 20% (?) oil suspension applied.

Comment: The minimum requirements for a dermal LD_{50} test are 4 dose levels and 4 animals (2 males and 2 females) per dose level with intact skin and 4 animals (2 males and 2 females) per dose level with abraded skin. Only one animal was used for each dose level. It is not a general practice for experiment of this type in which one sex of a single animal was used for one dose level and the opposite sex of a single animal used in another dose level. Furthermore, the information about the percentage of test material in corn oil was contradictory, namely 20% stated in the procedure and 25% mentioned in the conclusion.

Classification: Invalid values

4. Skin Irritation in Rabbits

The finely ground material was applied dry to the intact skin of one male and 2 female white rabbits. The scores of dermal irritation were made according to the method of Draize et. al. (1944).

Evaluation: Overnite two of the rabbits showed slightly more redness with no edema for an average score of 1.6. The application was removed from the skin at this time. This material was considered by them as a mild skin irritant in dry form.

Comment: For a skin irritation test at least 6 animals shall be used and a dose of 0.5 gm of solid material is to be introduced under one inch square gauze patches. The patches shall be applied to one intact and one abraded skin site on each animal. Only three animals were used in this test. The test material was applied to the intact skin only and no mention of the dose level used was made. Furthermore, the test material was kept in contact with the skin only overnite, too soon compared with the established procedure of 24 hrs.

Classification: Invalid vales

5. Eye Irritation in Rabbits

Approximately 10 mg of finely ground material were placed in the conjunctival sac of the right eye of each of 3 (one male and two female) white rabbits. The resulting irritation scores were made according to the method of Draize et. al (1944).

Evaluation: After one hour the average score was 21.0 out of a possible 110. There was moderate erythema, considerable edema and lacrimation as well as slight to moderate corneal dullness. Iris and cornea regained most of their clarity overnite when the average score dropped to 8.6. The eye had absorbed considerable yellow color because some of the test material still present in the conjunctival sac was washed out after 24 hours. Inflamation decreased to an average score of 2.0 in 72 hours. This compound was considered by them as a moderate eye irritant.

Comment: At least 6 animals shall be used and a dose of 50 mg of solid material is to be applied to each test eye for eye irritation test. Only 3 animals were used and 10 mg which is far less than the standard dose level was applied to each test eye.

Classification: Invalid values

B. Test of Paranitrophenol [CP 5442-(4)], Monsanto Sample No. 113, Monsanto Project No. Y-61-65 (Reported by Fred M. Younger, 11/13/61):

1. Skin Absorption MLD in Rabbits

Paranitrophenol was applied as a 7.5% solution in corn oil and in increasing doses (158, 316, 631, 1260, 2510 and 5010 mg/kg b.w.) to the clipped, intact skin of white female rabbits. Observations were made for toxic symptoms and the viscera of the animal that succumbed was examined macroscopically.

Evaluation: The minimum lethal dose by skin absorption in female rabbits was found by them to be greater than 2510 mg/kg and less than 5010 mg/kg. At autopsy no abnormalities of consequence were noted macroscopically.

Comment: In test for lethal dose at least 4 animals per sex and both sexes of animals should be used. Only a single animal for each dose level and only female animals were used in this test. There is no definite information on the surviving time and duration of test for those animals which survived at lower dose levels. Only loose statements were provided concerning observations which are normally required for the afore-described test.

Classification: Invalid values

Thomas S. S. Mao

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R/D Init: GEWhitmore 5/17/78
TM/ccw G.E.W. 5/19/78