UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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MEMORANDUM FEB 4 1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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SUBJECT: Evaluation of a study entitled" THE EFFICACY OF ATROPINE SULFATE AND PRALIDOXIME CHLORIDE (2-PAM) AS ANTIDOTES FOR THE ACUTE ORAL TOXICITY OF MONITOR TECHNICAL (SX-1244) IN RATS", SOCAL 1678, S-1780, August 3, 1982. (Revision of Report Dated March 4, 1982.) EPA Acc. No. 248457, EPA Record No. 80756.

TOX Chem. No. 378A

The above-mentioned study has been evaluated by Toxicology Branch/HED. It is a detailed, well planned and well reported study.

Classification: Core Minimum, as an acute oral toxicity study.

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The Efficacy Of Atropine Sulfate and Pralidoxime Chloride (2-PAM) as Antidotes for the Acute Oral Toxicity of Monitor Technical (SX-1244) in Rats. C. E. Duke, C. M. Cisson and Z. A. Wong. Chevron Environmental Health Center, Richmond, California, Study No. SOCAL 1678; August 3, 1982. (Revision of Report Dated March 4, 1982.)

EPA Accession No. 248457 TOX Chem No. 378A
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Summary:

1. This study was initiated on September 14, 1981 and was completed on January 12, 1982.

2. The test material was a technical grade Monitor, containing 73.1% of O,S-dimethyl phosphoramidothioate, an active ingredient.

3. Sprague-Dawley rats, 10 of each sex per dose, were given single intragastric doses of Monitor alone and with atropine sulfate or pralidoxime chloride (2-PAM). The doses of Monitor ranged from 13 mg/kg to 100 mg/kg for males and from 8.8 mg/kg to 100 mg/kg for the females. Atropine sulfate (10 mg/kg) and 2-PAM (50 mg/kg) were given intramuscularly. All doses were expressed in terms of Monitor Technical and not in terms of an active ingredient.

4. Atropine sulfate or 2-PAM increased the LD50 values of Monitor Technical as follows:

	LD50 (mg/kg)	
	Male Rats	Female Rats
Monitor Technical alone	21.0	16.2
With atropine sulfate	36.7	44.8
With 2-PAM	51.4	42.9

5. The most prevalent toxic symptoms in male and female rats treated with either Monitor Technical alone or with Monitor Technical and atropine sulfate or 2-PAM were tremors, decreased motor activity, weakness, ataxia, decreased food intake and fasciculations (females only). Atropine sulfate or 2-PAM decreased the toxicity of Monitor Technical by decreasing the incidence of deaths, but had no effect on the signs of toxicity, times to death and times to recovery.

6. Male and female rats treated with Monitor Technical alone, and female rats treated with Monitor Technical and atropine sulfate, had lower body weight gains than their controls. Body weight gains were decreased with increased levels of Monitor. Body weights of the remaining rats were unaffected by treatments.

7. No gross pathological changes were observed that could be attributed to the test material.

8. Classification of this study: Core Minimum.

Materials and Methods:

Sprague-Dawley rats, 10/dose/sex, received single intragastric doses of Monitor Technical alone and with atropine sulfate or pralidoxime chloride (2-PAM). The test material, a clear colorless liquid coded SX-1244, contained 73.1% (w/w) of O,S-dimethyl phosphoramidothioate, an active ingredient.

When Monitor alone was used, the doses ranged from 13 mg/kg to 44 mg/kg for the males and from 8.8 mg/kg to 30 mg/kg for the females. In the antidotal studies, the dosages of 30-100 mg/kg (males) and 20-100 mg/kg (females) were used. (All dosages are expressed as Monitor Technical and not in terms of an active ingredient.) Monitor was administered as an aqueous solution and all animals were dosed with a volume of 10 ml/kg of body weight. Atropine sulfate (10 mg/kg) and 2-PAM (50 mg/kg) were diluted with saline and administered intramuscularly. The control groups received distilled water (10 ml/kg) and the antidote control groups received also atropine sulfate or 2-PAM. Antidotes were administered 15 minutes after oral dosing. The observation period was 14 days or 21 days, if the animals still showed toxic signs 14 days after treatment with Monitor.

At the time of dosing, male rats were 67-72 days old and weighed 209-325 g, and the female rats were 81-97 days old and weighed 200-247 g. The rats were obtained from Simonsen Laboratories, Gilroy, California. The animals were housed at temperature of 21°C and relative humidity of 50-77%, and had free access to Purina Laboratory Rodent Chow #5001.

The animals were weighed prior to dosing and at 7, 14, and 21 days (if necessary) after treatment. The body weights of treated animals in groups with complete survival were compared to the controls using a Student t-test (1). Animals that died during the study and all survivors sacrificed following the observation period were examined for gross pathological changes. The following organs and tissues were examined: skin, spleen, pancreas, stomach, small and large

intestine, liver, adrenals, kidneys, gonads, uterus or seminal vesicles, bladder, heart, thymus, salivary glands, lungs, trachea, thyroid, and fat.

The LD50, slope and confidence limits were determined by the procedure of Berkson (2).

(1) Sokal, R. R. and Rohlf, F. J. Biometry. W. H. Freeman, San Francisco, pp. 220-223, 1969.

(2) Berkson, J. Tables for use in estimating the normal distribution function by normit analysis. Biometrika, 44: 411-435, 1957.

Results:

Effects of Atropine Sulfate (10 mg/kg) and 2-PAM (50 mg/kg) on the Acute Oral LD50 Values of Rats.

The LD50s for groups of male and female rats treated with atropine sulfate 15 minutes following oral dosing with Monitor Technical were 1.7 and 2.8 times higher, respectively, than the LD50s of groups receiving no antidote. Similarly, the LD50s of groups of male and female rats treated with 2-PAM 15 minutes following oral dosing with Monitor Technical were 2.4 and 2.6 times higher, respectively, than the LD50s of groups receiving no antidote. These data are summarized below.

THE EFFECTS OF ATROPINE SULFATE AND 2-PAM
ON THE ACUTE ORAL TOXICITY OF MONITOR TECHNICAL[a]
IN ADULT MALE RATS

Treatment Group	LD50 (*)	Slope (*)
Monitor Technical	21.0 (17.3-25.6) mg/kg	1.4 (1.2-1.6)
Monitor Tech. with Atropine Sulfate	36.7 (28.2-48.0) mg/kg	1.5 (1.2-2.0)
Monitor Tech. with 2-PAM	51.4 (41.4-63.9) mg/kg	1.5 (1.2-1.8)

([a]) Doses are not corrected for percentage of active ingredient.

* (95% Confidence Limits)

THE EFFECTS OF ATROPINE SULFATE AND 2-PAM
ON THE ACUTE ORAL TOXICITY OF MONITOR TECHNICAL[a]
IN ADULT FEMALE RATS

Treatment Group	LD50 (*)	Slope (*)
Monitor Technical	16.2 (13.4-19.5) mg/kg	1.4 (1.1-1.7)
Monitor Tech. with Atropine Sulfate	44.8 (36.6-54.8) mg/kg	1.5 (1.2-1.8)
Monitor Tech. with 2-PAM	42.9 (34.8-52.9) mg/kg	1.4 (1.1-1.7)

([a]) Doses are not corrected for percentage of active ingredient.

* (95% Confidence Limits)

Toxic Signs Observed in Male and Female Rats Treated with Single Intragastric Doses of Monitor Technical.

Males in this group received 13, 15, 20, 25, 30 or 44 mg of Monitor Technical/kg of body weight. The test material was administered at 2 different times. The 13, 20, 30 and 44 mg/kg levels were administered on 9/14/81 and the remaining levels on 12/22/81. There was a control group with each administration.

Females in this group received 8.8, 13, 15, 17.5, 20 or 30 mg of Monitor Technical/kg of body weight. The test material was also administered at 2 different times. The 8.8, 13, 20 and 30 mg/kg levels were administered on 9/14/81 and the remaining levels on 12/22/81. There was a control group with each administration.

The following toxic responses were observed in male and female rats, at all dose levels, shortly after exposure to Monitor Technical: tremors, decreased motor activity, weakness, ataxia and reduced food intake. Most of these symptoms, but ataxia were observed in all (or nearly all) animals, at each dose level. As doses of the test material were increased, the incidence of ataxia was also increased and other toxic responses appeared, such as unkempt appearance, hematuria, salivation, ocular and nasal discharge, convulsions and collapse. Dyspnea was observed in most of the male groups only, in 1-3 animals/group. Fasciculations were observed in most of the female groups only, in 5-10 animals/group.

At the lowest levels of Monitor Technical tested, toxic symptoms disappeared within 1-2 days in the females and within 2-3 days in the males, and there were no deaths. There were deaths at other levels and the survivors required up to 14 days to recover.

Monitor Technical was more toxic to female rats than to male rats. In the 15 mg/kg groups, 9 males and 5 females survived. In the 20 mg/kg groups, 6 males and no females survived. Most of the male and the female nonsurvivors died within 30-120 minutes after exposure to the test material.

Effects of Atropine Sulfate on the Toxicity of Monitor Technical to Male and Female Rats.

Males in this group received 0, 0, 30, 35, 44, 50, 58,67 or 100 mg of Monitor Technical/kg of body weight (single intragastric doses), and 10 mg/kg of atropine sulfate (single i.m. dose). The 0, 30, 45, 67 and 100 mg/kg levels were administered on 9/14/81 and the remaining levels (0, 35, 50, and 58 mg/kg) were administered on 12/22/81.

Females were dosed with the following levels of Monitor Technical (mg/kg): 0, 0, 20, 30, 44, 50, 58, 67 or 100; and then with atropine sulfate (10 mg/kg i.m.). The 0, 30, 44, 67 and 100 mg/kg levels were administered on 9/14/81 and the remaining levels (0, 20, 50 and 58 mg/kg) were administered on 12/22/81.

Atropine sulfate diminished the toxicity of Monitor Technical by decreasing the incidence of deaths, but had no effect on the signs of toxicity, times to death and times to recovery. The most prevalent toxic symptoms in male and female rats were tremors, decreased motor activity, weakness, ataxia and decreased food consumption. In the male groups, the incidence of death (%) was 0, 50 and 100 at Monitor levels of 30, 35 and 67 mg/kg, respectively. In the female groups, the incidence of deaths (%) was 0, 60 and 100 at Monitor levels of 20, 50 and 67 mg/kg, respectively. These incidences were considerably lower than those observed when rats were dosed with Monitor Technical alone. In those studies, 20 and 44 mg of Monitor Technical caused 100% deaths among females and males, respectively.

Effects of 2-PAM on the Toxicity of Monitor Technical to Male and Female Rats

Males in this group received 0, 0, 30, 44, 50 58, 67 or 100 mg of Monitor Technical/kg of body weight (single intragastric doses), and 50 mg/kg of 2-PAM (single i.m. dose). The 0, 30, 44, 67 and 100 mg/kg levels were administered on 9/14/81 and the remaining levels (0, 50 and 58 mg/kg) were administered on 12/22/81.

Females were dosed with the following levels of Monitor Technical (mg/kg): 0, 0, 20, 30, 35, 39, 44 and 67; and then with 2-PAM (50 mg/kg i.m.). The 0, 20, 30, 44 and 67 mg/kg levels were administered on 9/14/81 and the remaining levels (0, 35 andd 39 mg/kg) were administered on 12/22/81.

2-PAM had the same effect on the toxicity of Monitor Technical as atropine sulfate, although, in some instances, it was a better antidotal agent that atropine sulfate. 2-PAM diminished the toxicity of Monitor Techniccal by decreasing also the incidence of deaths, but had no effect on the signs of toxicity, times to deaths and times to recovery. In the male groups, the incidence of deaths (%) was 0, 0, 10, 10, 40, 90, 90 and 90 at Monitor levels of 0, 0, 30, 44, 50, 58, 67 and 100 mg/kg, respectively. In the female groups, the incidence of deaths (%) was 0, 0, 0, 0, 0, 40, 60 and 100 at Monitor levels of 0, 0, 20, 30, 35, 39 and 67 mg/kg, respectively.

Effects of Body Weight:

According to the authors of this report (EPA Accession No. 248457, p.3), the body weights of male rats treated with Monitor Technical (30 mg/kg) and atropine sulfate (10 mg/kg) were significantly lower ($p \leq 0.01$) than those of controls at day 7 only (first weighing after the treatments). It was also stated that no other differences in body weights between treated and control rats were observed. The latter statement is true only in the case of rats treated with Monitor Technical and 2-PAM, and, in some instances, rats treated with Monitor Technical and atropine sulfate.

At Monitor levels of 13 (lowest tested), 15 and 20 mg/kg, male rats weighed, respectively, 86, 54 and 52% of their controls, 14 days after the treatment. At Monitor levels of 13, 15 and 17.5 mg/kg, female rats weighed, respectively, 79, 30 and 13% of their controls, 14 days after the treatment. These data indicate a lower (or slower) weight gain with an increased dose of Monitor Technical. The same trend was evident in the females treated with Monitor Technical and

atropine sulfate. At Monitor levels of 20 (lowest tested), 30, 44 and 50 mg/kg and in the presence of atropine sulfate (10 mg/kg), female rats weighed, respectively, 100, 89, 13 and 4% of their controls, 14 days after the treatment.

Necropsy Findings:

All animals, including those that died before the termination of the study, were examined for gross pathological changes. However, these data were not reported. Only a statement was made that, at necropsy, there were no gross pathological changes observed that could be attributed to the test material. Histopathology was not performed.

Classification of this study: Core Minimum.

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