6-19-81

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: June 18, 1981

SUBJECT: EPA Reg.#352-372; PP#1F2448; Long Term Feeding Study In Mice with Oxamyl
CASWELL#625A Accession#070136-143

FROM: William Dykstra, Toxicologist
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WJD for LOC 6/19/81

TO: Jay ELlenberger (12)
Registration Division (TS-767)
and
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Hazard Evaluation Divsion (TS-769)

Recommendations:

1. Oxamyl was not oncogenic up to 75 ppm in the diet of mice for two years. The study is acceptable as Core-Minimum Data.

Review:

1. Long Term Feeding Study in Mice with Oxamyl (WiL 77033; 5/29/81)

Test Material: Technical grade Oxamyl, H#10963, 97.1% purity, white crystalline powder

Three hundred and twenty Charles River CD-1 mice of each sex were selected for study on the basis of body weight gain and findings observed during the quarantine period. The animals were randomized into four treatment groups according to body weight. The randomization process was done separately for males and females.

The mice were housed individually. Fresh water and Purina Laboratory meal were provided ad libitim throughout the study.

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The dose levels in the groups were set based upon findings in an eight week range finding study run at MiL, report dated 9/27/77. Four groups consisting of 80 males and 80 females were established and were as follows:

Treatment Group	Dose Level (ppm)	No. of Animals Male	Female
1	0	80	80
2	25	80	80
3	50	80	80
4	100/75*	80	80

*Due to the unexpected high mortality rates in the mid- and high-dose groups during the first few weeks, the 100 ppm group was decreased to 75 ppm on week 6.

Also 22 extra mice, not previously selected for the study but from the same shipment were added 11/28-12/9/77 to provide additional mice for long term evaluation: 721 added to group 2 female 11/28/77; 722 added to group 3 male 11/28/77; 723, 724, 725, 726 added to group 3 female 11/28/77; 727, 728, 729 added to group 4 male 11/28/77; 730, 731, 732 added to group 4 female 11/28/77; 733, 734, 735, 736, 737 added to group 4 male 12/6/77; 738, 739, 740 added to group 4 female 12/6/77; 741 added to group 4 female 12/8/77; 742 added to group 4 female 12/9/77. These animal additions were made at the request of the sponsor after consultation with the study director.

During the study, all mice were observed twice daily for signs of mortality, toxicity and behavioral changes.

All mice were palpated once weekly for the presence of masses. Any positive findings were recorded as to size, location and appearance.

A record was kept on all mice that died or were killed in extremis during the study. Mice which became moribund or had a sudden large weight loss were sacrificed by CO_2 asphyxiation and necropsied according to the original protocol. Tissues from animals dying before the end of the study or sacrificed in extremis were preserved for histopathologic examination. A gross pathological examination was performed and the tissues saved in 10% buffered neutral formalin on all animals that died within the first weeks of dosing. Most of these latter tissues were not evaluated histopathologically as per instruction from the sponsor, since no alterations of a carcinogenic nature were anticipated from such a short exposure to the test diet. A weekly cumulative record of mortality was maintained.

Body weights were measured for all mice once weekly during the first six months (weeks 1 through 29), once every week during the second half of the first year (weeks 31 through 53), and then once a month until study termination (weeks 57 through 105).

Each time the mice were weighed, the amount of diet consumed by each sex of each group was measured. From these data, food efficiency and average intake of Oxamyl per group was calculated.

Ten male and ten female mice randomly selected from each group were bled from the orbital sinus after 1, 3, 6, 12, and 18 months of dosing and prior to termination of the study. Parameters evaluated were: WBC, RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, complete differential WBC.

All surviving mice were weighed, sacrificed with CO_2 asphyxiation ar necropsied on November 14, 15, 16 and 17, 1979 under the supervision of Dr. Fred W. Sigler. The following organs were weighed: liver, kidneys, tests, brain and stem, and heart.

The following tissue specimens were taken and fixed in 10 to 20 volumes of 10% buffered neutral formalin:

Brain
(Forebrain, midbrain and hindbrain)
Eyes with contiguous Harderian glands
Pituitary
Salivary glands
Heart
Thymus
Thyroid (Parathyroid)
Lungs
(2 coronal section with mainstem bronchi)
Trachea
Esophagus
Stomach
Intestine, smal and large
Adrenals glands
Pancreas
Liver, 2 lobes
Gall bladder
Kidneys
Urinary bladder
Testes, epididymides
Prostate
Ovaries
Corpus and cervix uteri
Spleen
Lymph nodes
Skin
Sciatic nerve
Mammary gland
Bone, bone marrow, or tibio-femoral joint
Muscle
Aorta
Uterus
*Nasal cavity and paranasal sinuses
*Spinal cord (2 levels)
*Head (3 coronal sections) nasopharynx, middle ear, tongue and oral cavity
*Seminal vesicle
Gross lesions (with normal tissue)

Prior to the issuance of the proposed regulations tissue specimens were collected from animals found dead and sacrificed moribund throughout the study according to the above list expect for the tissues marked with *.

Some animals died early in the first few weeks of the study and only a gross necropsy was performed, no tissues were histologically examined (see Mortality section). These mice were 210, group 2 male; 346, group 3 male; 489, 556, 495, 514, 503, 510, 500, 481, 547, 492 group 4 male; 269, 308, group 2 female; 438, 409, 436, 410, 443 group 3 female; 570, 605, 624, 626, 616, 600, 738, 592 group 4 female. Also, several mice were judged to be in such an advanced state of autolysis as to preclude histopathologic evaluation. These mice were 540, group 4 male; 111, group 1 female; 308, group 2 female; and 564, 583 group 4 female. Many other mice were found to have advanced postmortem autolysis, but it was not extensive enough to preclude a histopathological evaluation.

One mouse (71, group 1 male) was cannibalized (cages used in the study had center dividers and one mouse penetrated the divider and was canninbalized) and one (600, group 4 female) was not necropsied (technician oversight).

All other mice placed on the study were examined histologically.

Statistical analyses of the data were performed:

Results:

There was no apparent test material-related effect on any clinical observations.

Tissue masses observed and palpated throughout the study and at termination were evaluated histopathologically. No apparent consistent test material-related effect was noted.

Group 4 males mean food consumption was significantly less than that of the control, group 1, males for weeks 11 through 84 with the exception of weeks 12 and 19. From week 88 through the end of the study there was no significant difference. No pattern was shown throughout the study for the other test groups 2 and 3 males and 2, 3, and 4 females.

The mean body weights for group 3 males were significantly less than those of the control from weeks 1-81. The mean body weights for group 4 males were significantly less than those of the controls from weeks 2-43 and were variable thereafter to the end of the study. There was no significant difference throughout the remainder of the study. The mean body weights for group 3 or 4 females were variably significantly different during the first 21 weeks of study, but were only sporadically significantly different after week 21. No other consistent pattern was noted in any of the treated groups compared to the controls throughout the remainder of the study.

No consistent test material related effects were noted in the body weight of the treatment groups compared to that of the controls after the first 81 weeks of the study.

The cumulative life graph data reflected the early mortalities. These deaths appeared to be related to the acute toxic effect of the test material in the diet mixture. Subsequently, life table analysis indicated no further increased mortality due to Oxamyl occurred during the remainder of the study.

Sporadic significant differences in hematology parameters were noted throughout the study. These changes are suggestive of a compound related effect upon red cell mass in group 4 males early in the study week 4 but this did not persist.

There was a slight decrease in absolute weight of the liver in group 3 males and a slight increase of the organ to body weight ratios of the kidney for group 4 males. Based on the absence of histological findings, these effects are not considered significant.

No significant histopathological changes were noted for the test groups when compared to those of the controls except that the chronic interstitial nephritis of the kidney was significantly less for the test groups (group 2, 3 and 4), males, compared to that of the controls. Oxamyl was not oncogenic at any level tested.

Conclusion:

Oxamyl was not oncogenic at dietary levels up to 75 ppm.

Classificatio Core-Minimum Data

TS-769:th:TOX/HED:WDykstra:6-18-81:#2

Test for Significance of Differences Between Proportions 6/15/31

Lung Neoplasms Female Mice

ppm	Resp	Total	% +/-2(S.E.)	One Tail P Statistic Fisher's
0.000	13	79	16.46+/-(8.31)	
25.000	22	79	27.85+/-(10.52)	0.062
50.000	9	79	11.39+/-(7.64)	$>$$$$
75.000	18	78	23.08+/-(10.22)	0.178

Test for a linear trend is not significant