8-6-86

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

8/6/86

005415

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Application for Registration of SN 584 (Methyl-Isothiocyanate, MITC) for Utility Pole Fumigation
EPA File Symbol 45639-OE. Caswell #573

TO: Henry Jacoby (21)
Registration Division (TS-767C)

FROM: Winnie Teeters, Ph.D. Winnie Teeters 8-24-86
Pharmacologist, Section V
TOX/HED (TS-769C)

THRU: Laurence D. Chitlik, D.A.B.T. LDC 8/6/86
Head, Section V
TOX/HED (TS-769C)
and
Theodore M. Farber, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

Action Requested: Review studies submitted to support a use of SN 584 (Methyl Isothiocyanate) as a utility pole fumigant.

Recommendations: At this time, Toxicology Branch does not find the request for registration of SN 584 as a utility pole fumigant supported by the available data. All of the studies reviewed for this action are either unacceptable or have been classified as Core Supplementary Data and, as such, must be repeated and/or require additional data or clarification of issues (see summaries and individual reviews). Furthermore, 11/13 previously reviewed studies (memo of Bui to Jacoby, 8-20-84) submitted to support this registration were also classified as Core Supplementary Data (see pages 4 & 5 of this memo) and no attempts have been made by the sponsor in the meantime to upgrade these studies.

Background: SN 584 for this use will be applied by placing [redacted] capsules containing 90% technical MITC and 10% inert ingredients into holes drilled into utility poles. Each capsule contains 13 grams MITC [redacted]

005415

[redacted] Only qualified persons employed or contracted by utility companies would apply the product. Since the system is completely enclosed, applicator exposure would be expected to be low if appropriate protective measures are taken.

The sponsor, NOR-AM Agricultural Products, has also requested registration of another product (which contains 20% methylisothiocyanate) as a utility pole fumigant. EFB concluded (memo of J. Reinert, 12-28-82) the following regarding exposure from this use:

> Since the product "may only be applied to utility poles by trained applicators employed or contracted by utility companies, and since both protective clothing and a closed application system must be used, EFB concluded that applicator exposure would be very low and an exposure monitoring study need not be carried out."

Requirements for this use have been predicated on this conclusion of very low exposure. However, on 10-24-84, the EPA published its Final Rule for Data Requirements for Pesticide Registration, and for a terrestrial, non-food use, the requirements included the acute battery and mutagenicity testing and conditional requirements for subchronic, chronic, general metabolism, dermal penetration and domestic animal safety (40 CFR Part 158.135, pages 42892 and 42893).

Furthermore, it is noted that on 6-4-85, the EPA issued a "Special Data Call In Notice for Groundwater, Residue, and Chronic Toxicological Data for Methyl Isothiocyanate" to registrants of pesticide products containing MITC.

The following is a summary of the studies reviewed for this action. Although no toxicological issues of concern have been raised so far in the data available, the limited usefulness of the pivotal studies as submitted, precludes a definitive assessment of the toxicity of MITC.

1. Evaluation of Methyl Isothiocyanate in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay, Litton Bionetics Inc. Project No. 20991, Feb. 1985.

   Although MITC appears negative in this test, the study is judged to be <u>Unacceptable</u> since the raw data do not permit independent confirmation of the results. Additional information regarding the positive control and reasons for requirement of three trials is requested.

2. Mutations Affecting the Hypoxanthine-Guanine Phosphoribosyl Transferase Locus In V 79 Cells: HGPRT-Test. Laboratorium für Mutagenitatsprufung Technische Hochschule Darmstad -

2

Study LMP075A, November 30, 1984

Methylisothiocyanate was judged to be negative for induction of mutagenicity on the HGPRT locus, but this study is considered to be Inconclusive due to the lack of a comprehensive cytotoxicity/cytogenicity dose-response curve. Additional data from testing doses at and above the highest dose used (2.5 ul/ml) are requested. See pages 5 and 7 of this mutagenicity review.

3. Testing of ZK3.318 (Methylisothiocyanate) for Mutagenic Potential In The IN VITRO Chromosome Aberration Test. Laboratorium für Mutagenitatsprufung Technische Hochschule Darmstadt Study LMP 075B. November 30, 1984

This study was positive and clearly demonstrated the production of chromosomal aberrations, including an excess of chromatid exchanges at the two highest doses. However, the study is designated Inconclusive due to the lack of a complete dose-response curve for cytotoxicity. Additional concerns are listed in the "Methods" section. See pages 8 and 9 of this mutagenicity review.

4. Methyl Isothiocyanate (MITC) Oral (Gavage) Teratology Study in the Rat with Amendment to the Final Report. Hazelton Lab, Europe, Final Report No. 3193-14/10 Feb. '83; Addendum, Jan. '84. EPA Accession No. 257765.

A maternal NOEL was established at 5 mg/kg/day but a developmental toxicity NOEL could not be determined due to the lack of individual litter data and a disparity relative to the classification of lens opacity. This study is classified as Core Supplementary Data and submission of additional data and an explanation relative to several issues listed in the "Discussion" section of the review are required. See pages 4 and 8 of this review.

5. Methyl Isothiocyanate (MITC) Oral (Gavage) Teratology Study in the New Zealand Rabbit. Hazelton Lab, Europe, Final Report No. 3637-14/30; June '84. EPA Accession No.257764.

Apparently, a maximum maternal tolerated dose was not used in this study. Accurate assessment of potential developmental toxicity effects (including teratology) cannot be completed in the absence of individual litter data and due to the questionable validity of the concurrent control data. Additional data are requested to provide explanation to several issues (#3, 4, 5, 6, 7, 8 and 9) listed on page 10 of this review. The study is classified as Core Supplementary Data, and although additional data are requested for clarification, it is the reviewer's opinion that the study cannot be upgraded to a classification that would meet the registration requirement for a rabbit teratology study.

6. Methylisothiocyanate: A chronic oral (drinking water) toxicity and carcinogenicity study in the rat. Hazelton Lab, Europe; Feb. 1984, Report # 2611-14/1R, EPA Accession No. 257766

   There are many problems with this study consequently it has been classified as Core Supplementary Data. The histopathological data must be provided in a summary form which includes the actual number of tissues examined/sex/group. It does not appear that a maximum tolerated dose was used unless the requested histopathological data provide this evidence. Also see items 2, 6, 7, 8, 9, 10 and 11 under "Methods" on page 2 of this review. Tentatively, this study is negative for chronic toxicity and oncogenicity at 50 ppm, the highest dose tested.

7. Two-Year Chronic Oral Toxicity and Oncogenicity Study with Methyl Isothiocyanate in Albino Mice (106 weeks final report) and Eight Separate Water Stability Studies; Dec. 1980; EPA Accession No. 257763 and Nos. 257759-62.

   This study is classified as Core Supplementary Data because the actual number of tissues examined/sex/level must be provided. Furthermore, information on compound preparation and analytical data for the test compound in the water offered the mice are required. The requested data on the numbers of tissues examined are necessary to fully assess a possible histopathological effect. With the data available so far, the only compound effect established is a slight depressant effect on body weight of the 80 and 200 ppm males and the 200 ppm females. Tentatively, this study is negative for oncogenicity at 200 ppm, the highest dose tested.

Summary of recently reviewed studies conducted with MITC (SN 584); memo of Bui to Jacoby, 8-20-84.

1. Acute oral LD_{50}, rats: LD_{50} = 95 mg/kg (males and females) Tox. Cat. II, Minimum Data; Schering AG., 7/6/79.

2. Acute oral LD_{50}, rats: LD_{50} = 175 mg/kg (males), Supplementary Data*; Tokyo Dental College, 1970.

3. Acute oral LD_{50}, mice: LD_{50} = 90 mg/kg (males), Supplementary Data*; Tokyo Dental College, 1970.

4. Acute oral LD_{50}, mice: LD_{50} = 104 mg/kg (females), Minimum Data; Matsumoto Dental School, 1974.

5. Acute oral LD_{50}, rabbit: LD_{50} undetermined, Supplementary Data, Hazelton Lab., 4-28-76.

005415

6. Acute oral LD_{50}, dogs: LD_{50} undetermined, Supplementary Data, Hazelton Lab., 4-28-76.

7. Acute oral LD_{50}, monkeys: LD_{50} undetermined, Supplementary Data, Hazelton Lab., 4-38-76.

8. 30-Day dermal, rats: Systemic NOEL < 120 mg/kg/day Supplementary Data; Nara Medical College.

9. 31-Day dermal, rats: Systemic NOEL undetermined, Supplementary Data*; Schering AG., 11-26-75.

10. Acute subcutaneous LD_{50}, rats: LD_{50} = 60 mg/kg (males) and 59 mg/kg (females). Supplementary Data*; Matsumoto Dental College, 1974.

11. Acute subcutaneous LD_{50}, mice: LD_{50} = 75 mg/kg (males) and 89 mg/kg (females). Supplementary Data *; Matsumoto Dental College, 1974.

12. Acute intraperitoneal LD_{50}, rats: LD_{50} = 54 mg/kg (males) and 56 mg/kg (females); Supplementary Data*; Matsumoto Dental College.

13. Acute intraperitoneal LD_{50}, mice: LD_{50} = 82 mg/kg (males) and 89 mg/kg (females); Supplementary Data*; Matsumoto Dental College.

Supplementary Data*: study that may be upgraded if additional requested data are submitted.

Other available data in TOX. Branch files are as follows:

A. Methyl isothiocyanate

1. W. Dykstra's memo of 1-31-78 (EPA registration #2139-55)

   a) Acute inhalation, rat: LC_{50} = 1.9 mg/L/1 hour, Tox. Cat. II, Minimum Data, Huntingdon Res. Cen., 7-4-77.

   b) Eye irritation, rabbit: Tox. Cat. I, Minimum Data* Huntingdon Res. Cen., 12-23-76.

2. G. Burin's memos of 12-21-82 and 4-15-83 (EPA registration #2139-55)

   a) Eye irritation - antidotal study, rabbit: Supplementary Data; Sodium bicarbonate and Cortisone enanthate are effective.

b) *Eye irritation, rabbit: Huntingdon Res. Cen., 12-23-76, reclassified as Supplementary Data. However, no new study is requested and the chemical is classified as Tox. Cat. I.

c) Dermal irritation, rabbits: Unspecified testing lab., study report, and final date. Invalid Data.

B. Vorlex (Methylisothiocyanate, 20%, and chlorinated, C_3 hydrocarbons, 80%)

1. W. Dykstra's memo of 1-31-78 (EPA registration #2139-55)

a) Acute inhalation, rats: LC_{50} = 11 mg/L/1 hour, Tox. Cat. III Huntingdon Res. Cen., 8-22-77, Minimum Data.

b) Eye irritation, rabbit: Tox. Cat. I, Huntingdon Res. Center, 12-23-76, Minimum Data**

2. G. Burin's memos of 12-21-82 and 4-15-82 (EPA registration #2139-55)

a) Acute oral, rats: LD_{50} = 538 mg/kg, Tox. Cat. III, Schering AG, 4-12-79, Minimum Data.

b) Acute dermal, rabbits: LD_{50} = 470 mg/kg, Tox. Cat. II, Schering AG, 5-11-79, Minimum Data.

c) Acute dermal, rats: LD_{50} = 961 mg/kg, Tox. Cat. II, Schering AG, 4-11-79; Minimum Data.

d) Acute intraperitoneal, rats: LD_{50} = 259 mg/kg, Schering AG, 5-26-79; Minimum Data.

e) **Eye irritation, rabbits: Huntingdon Res. Cen., 12-23-76. Reclassified as Supplementary Data. However, no new study is requested and the compound is classified as Tox. Cat. I.

f) Dermal irritation, rabbits: Testing lab., date and study no. are unknown, Invalid Data.

g) ***13-Week inhalation, rats: Schering AG., #9678, 4-10-79. Supplementary Data.

3. Q. Bui's memo of 8-6-84

*** 13-Week Inhalation Study, Rats, (additional information), Schering Ag, #9678, 4-10-79 Supplementary Data.

Data Evaluation Record

Study Title: Methylisothiocynate: A chronic oral (drinking water) toxicity and carcinogenicity study in the Rat

Study Type: Chronic/oncogenicity

Accession No.: 257766 Caswell No.: 573

Sponsor/Contracting Lab.: Nor-Am (Schering AG)/Hazelton Lab. Europe, Ltd

Report Date/Submitted: February 1984/April 26, 1985

Test Material: Methylisothiocynate (MITC), Technical 95.4-96.1%

Test Animal: Sprague-Dawley, CD strain rat [Charles River (UK)Ltd]

Test Doses: 0, 2, 10 and 50 ppm in drinking water

Reviewed by: Winnie R. Teeters, Ph.D. W. Teeters
Section V, TOX Branch/HED

Approved by: Laurence D. Chitlik, D.A.B.T. 8/8/86
Head, Section V
TOX Branch/HED

Classification and Conclusions: This study is classified as Core Supplementary Data. The histopathological data must be provided in a summary form which includes the actual number of tissues examined/sex/group, not just the number of animals so examined. Also see items 2, 6, 7, 8, 9, 10 and 11, under "Methods" on page 2. Furthermore, it does not appear that a maximum tolerated dose was used in the study, unless the requested histopathological data provide this evidence. The weak, non-dose-related effect seen on body weight of males is judged to be insufficient evidence of a compound-related toxic effect, and no other effects were seen.

Methods: The methods from the report have been copied and are appended. Comments on the methods and reporting include the following:

1) The tables summarizing histopathological data did not indicate the number of each kind of tissue examined per group per sex; only the numbers of animals examined were given. In the presentation of individual results, missing tissues were indicated and should have been tabulated in the summary tables.

2) Liver, lungs and kidneys were not routinely examined histopathologically for animals in the low and middle levels. EPA Guidelines indicate that these tissues should be examined for all animals on study as an indication of their health status.

3) Baseline ophthalmological examination was not performed for some rats until the first few days of treatment had begun.

4) Test material was not given to animals that were isolated due to injury or illness.

5) The beginning body weight ranges for males were 136-216 g and for females were 82-196 g; these are unusually wide ranges.

6) The report did not provide a tabulation of clinical signs.

7) Individual food and water consumption data were not provided.

8) There was no summary of necropsy findings for rats that died during the second year or that were sacrificed terminally.

9) The test material was described both as a liquid and as a crystalline solid.

10) The report states that the plastic water bottles were modified to limit loss of MITC by volatilization. Yet, it is also stated that occasionally glass water bottles were used. It is important to know if all water bottles used were modified to preserve the concentrations of MITC and if not, to what extent unmodified bottles were used.

11) The analyzed concentrations of MITC presented to the rats for the first 22 weeks were not provided. Furthermore, the probable widest disparity between nominal and actual concentrations during the study was not given.

Quality Assurance: The report contained a list of audit dates (8 for the in-life phase, 1 for the final report and 1 for the revised report) and was signed by the Quality Assurance Manager.

Results:

A. Test Material - The rat study was conducted with two batches of MITC, batch number 28.166 and 29.482. The percentage purity for five analyzed samples (one of the former batch and four of the latter) ranged from 95.41 to 96.06% MITC. Although the material was described as "a light brown crystalline solid",

another description included in the report and stated to be from previous toxicological studies gave the appearance as a "colorless, yellow brownish liquid". This disparity in physical appearance should be explained. Can it be simply a matter of ambient temperature?

The test material was administered in the drinking water in plastic water bottles specially modified to limit loss of MITC by volatilization. The report states that occasionally glass water bottles were used. It is pertinent to know if all water bottles used were modified to limit loss of MITC since it is acknowledged to be so volatile; i.e., the report states that "the loss of MITC from solutions kept in conventional drinking bottles was shown to be almost complete after 24 hours".

Appparently, there was a particular problem regarding stability with the first batch of stock solutions; these stock solutions were used from study initiation through week 9. No analytical results for this batch were reported but it was stated that they were "poor" and test solutions were prepared daily, rather than weekly, from week 5 to week 9, when a fresh sample of test material (new batch?) was analyzed. The first reported results of analyses of the stock solutions and test solutions in the animal drinking water bottles were for week 23 and subsequent results were given approximately each three months thereafter. Results for the water bottle analyzes are shown in Table 1 (a reproduction of Report Table 13, page B-43). Some of the results show marked differences between nominal and analyzed values, e.g. the 2 ppm level for week 36 was only about 8% of nominal and several others were as low as only 50-65% of nominal, particularly for the 2 and 10 ppm levels. These results are for the day of preparation and 2-3 days later; the water bottles were filled on Fridays, Mondays and Wednesdays from stocks prepared each Friday. It is not clear whether the table values were from fresh solutions made on Friday or from solutions dispensed on Mondays or Wednesdays. This can be an important difference, for reported results show that there even was deterioration of the frozen stock solutions stored in the dark. Furthermore, the table values are means of 6 individual bottles (3 male and 3 female) and there was wide variability among these individual results, e.g. the means of 50.0% and 54.2% of nominal reported for 3 days after preparation for 2 and 10 ppm solutions for week 75 had ranges of 16-59% and 24-78%, respectively.

The worst cases would have been the water bottle concentrations on Fridays before fresh solutions were dispensed that day. There was no indication that any of the reported results were from this time period. Consequently, probably the widest differences between nominal and actual concentrations are not known.

As the table indicates, analysis of control solutions for weeks 23 and 36 suggested contamination with MITC, but the

Table 1- Compound analyses in drinking water.

TABLE 11

Summary of HETC analysis on samples taken from drinking bottles

Week	Group and nominal HETC concentration											
	1 0 ppm			2 2 ppm			3 10 ppm			4 50 ppm		
	On day of preparation Mean ppm	%	3 days after preparation Mean ppm	%	On day of preparation Mean ppm	3 days after preparation Mean ppm	%	On day of preparation Mean ppm	%	3 days after preparation Mean ppm	On day of preparation Mean ppm	%	3 days after preparation Mean ppm	%
23*	0.30	-	0.20	-	1.52	75.3	1.22	60.0	7.90	79.0	7.35	73.5	40.13	80.2	34.11	68.3
36	0.10	-	0.13	-	0.11	7.67	0.18	8.17	9.13	91.3	8.60	86.0	45.3	90.5	40.9	81.8
50*	-	-	-	-	1.90	95.2	1.72	86.2	9.23	92.3	8.23	82.3	44.05	88.0	43.9	87.8
62	-	-	-	-	2.07	103.1	1.60	80.0	10.86	108.6	9.85	98.5	53.77	107.6	50.55	101.0
75	-	-	-	-	1.60	80.2	1.02	50.0	9.02	90.2	5.42	54.2	42.52	85.0	39.93	79.8
88	-	-	-	-	1.58	79.7	1.38	68.7	8.7	87.0	6.4	64.0	41.02	82.0	35.50	71.0
101	-	-	-	-	1.21	61.3	0.98	49.8	7.33	73.3	6.05	60.5	37.35	74.8	35.28	70.7
Overall means	-	-	-	-	1.45	71.8	1.15	57.6	8.88	88.8	7.41	74.1	43.45	86.87	40.02	80.1

* Samples taken on day of preparation and 2 days after preparation.

investigators stated these results were due to an impurity in a solvent and after the analytical procedure was modified there was no further indication of contamination of the control water.

In conclusion, the analyzed dose levels presented the rats for the first 22 weeks of the study were not provided. Furthermore, the widest disparity between nominal and actual concentrations was not defined. Since there is an acknowledged problem with maintaining the concentration of MITC during dosing because of the high vapor pressure, assurance that the rats received the intended concentrations is particularly critical for this study.

B. Survival - Survival was good in this study, with the following percentages of rats alive at 18 months: 94, 92, 90 and 86 for males and 90, 80, 97 and 95 for females of the 0, 2, 10 and 50 ppm groups, respectively; however, by termination at 105 weeks the percentages alive had dropped precipitously to 65, 63, 58 and 64 for males and 43, 33, 53 and 53 for females for the same groups, respectively. Survival did not appear to be affected by MITC treatment.

C. General Observations: The investigators did not present a tabulation of clinical signs but stated that the incidence and severity of the following most frequently observed signs did not appear to be affected by treatment: epilation, tooth malocclusions with associated soft tissue damage, staining around the eyes and of fur generally, staining or swelling around the genitals and pilorection in females.

D. Body Weight: The spread of body weights at study initiation was very wide, being 81-216 grams. The groups were adjusted so that each female group had a mean of 162 grams and the male groups averaged 185, 186, 185 and 179 grams for the 0, 2, 10 and 50 ppm groups, respectively.

The high level males consistently weighed less than controls, as did the low level, also, after week 8, but the low level weight was not as depressed as that of the high level. The mid level males had lower body weights than controls beginning about week 30, but the effect was less than for the other two male groups. All male groups, including controls, had an unexplained loss of about 20 grams at week 22, with recovery within two weeks. At termination, weights of the treated males were 92, 97 and 91% of the control for the 2, 10 and 50 ppm groups, respectively.

Female bodyweight was not adversely affected by treatment with MITC. The 2 ppm group weighed more than controls beginning early (3rd week) in the study, as did the 10 ppm group beginning about week 50. The highest level females also weighed more than controls during the second year of the study.

Group mean body weights for 2 ppm males were checked and had been correctly tabulated from individual data to report table 2.

E. Food Consumption: Treated males had similar food consumption to controls. All male groups showed a decrease in food consumption for week 22; this ranged from a 6 gram mean/rat difference for the low level to only a 1 gram mean/rat difference for the high level.

Food consumption was similar among all groups of females also. This sex did not show the obvious decrease for week 22 seen for the males.

Individual food consumption data were not provided.

F. Water Consumption: The high level group generally showed a lower water intake than the controls; this was seen more consistently for males than for females. Lower levels occasionally drank less than controls but the 2 ppm females ocasssionally drank more than controls. Consequently, the only group showing a consistent depressed water intake was the 50 ppm group.

Individual water consumption data were not provided.

G. Compound Intake: The report stated that "the majority of the study was conducted with doses of 0.08, 0.37 and 1.60 mg/kg and 0.12, 0.56 and 2.65 mg/kg for males and females" of the low, mid and high levels, respectively and that these doses were calculated from week 26 forward.

On two occasions, rats isolated because of injury or illness were not given MITC in their water; the dates and rats were not identified.

H. Ophthalmology: Ophthalmic findings occurred with similar frequencies for control and treated rats. The total numbers affected were 10 vs 11 males and 8 vs 7 females for control and high levels, respectively. Keratitis, lenticular opacity and hyperreflective retina were the most frequent findings.

Data for Table 6, "Summary of Ocular Abnormalities", were correctly tabulated from the individual data.

I. Hematology: Hematological parameters were not affected in either sex at any level by dosing with MITC.

Mean hematological data of males for week 52 were correctly tabulated from the individual data to the summary table (No. 7).

J. Clinical Chemistry: Treatment with MITC did not affect clinical chemistry values of either sex at any level. One high level male (#199) at termination had an unusually high alkaline phosphatase activity (3198 I.U./l compared to a mean value of

181 I.U./l for control males terminally). This extremely high value caused the mean for the group to be over two-fold that of control males, but other individual values were within the range of the controls.

Mean clinical chemistry data of females for week 103 were correctly tabulated in report Table 8 from the individual data.

K. Urinalyses: Urinary volume for treated high level males was noticably less than for controls for weeks 13 and 78, and for treated females the volume was less for weeks 26 and 52; yet these differences were not reflected in specific gravity values. Treated males had 2 plus urinary blood for weeks 78 and 103 compared to 1 plus for controls but these findings were not reflected by increased erythrocytes noted during microscopic examination nor were they accompanied by presence of casts.

Treatment with MITC did not appear to adversely affect urinary parameters.

L. Organ Weights: There were no indications of a compound-related effect in brain, liver, heart, gonad, thyroid or kidney weights. For both the adrenals and pituitary, the presence of tumors in these tissues precluded the use of organ weight data as an indication of compound toxicity because of the increased degree of weight variability. Likewise, the presence or absence of a thymus was so variable among the groups that these organ weight data were not useful in detecting discrete changes from control data.

Mean terminal organ weights for high level males were correctly tabulated in report Table 11 from the individual data.

M. Macroscopic Pathology: The report presented a summary of macroscopic pathology only for rats of the interim sacrifice at 52 weeks and a separate summary for those rats which died during the first 52 weeks of the study; there was no summary for those rats which died during the second year or that were sacrificed at study termination. A summary is required for all rats in the study and the relationship between macro- and micropathology should be discussed.

Necropsy findings for rats of the interim kill (5 of each sex from the control and high level groups) and for those dying during the first year were not remarkable nor did the findings appear to be compound-related. The highest incidences were for pulmonary findings and these were distributed similarly among all groups. Three pituitary masses and one subcutaneous mass were found in rats that died in the low level and a pituitary mass was found in the sacrificed controls.

Ataxia/lateral deviation and depression/lethargy were each listed for 2 female 2 ppm rats. These findings were listed as

macroscopic observations but they are more commonly grouped as clinical observations rather than as necropsy findings.

N. Histopathology: The report did not summarize the histopathology results on the basis of the number of tissues examined per type/sex/group. The summary tables gave only the total number of animals examined per sex and group, yet in the tabulation of individual data there were notations of missing tissues. Consequently the needed figures could have been compiled from the individual data submitted, but this is a lengthy process that should have been done routinely as part of the report preparation. A definitive assessment of the histopathological results must await review of the data presented in the proper summary form. Therefore, the following discussion of the results must be regarded as preliminary and final conclusions will be made after receipt of proper summaries.

The lungs, liver and kidneys of all animals in the low and middle dose levels were not routinely examined. The EPA Guidelines suggest that these tissues be examined in all rats as an indication of the health status of the animals.

1) Non-neoplastic lesions: The animals showed relatively high incidences of eosinophilic cell alterations and angiectasis of the adrenals (females), Harderian gland adenitis (females), glomerulonephritis (both sexes), myocarditis/myocardial fibrosis/scarring (both sexes), and hepatic vacuolation (females). The incidences for these lesions and for others for which the incidence was increased are shown in the following Table 2 (data taken from report Table 6, Appendix 14.2). For those lesions showing an increased incidence in treated rats there usually was no dose-response relationship and usually only one sex showed the increased incidence. Furthermore, in some of these cases, the controls of the unaffected sex had an equal or higher incidence. Consequently, due to these circumstances, no target organ was identified and administration of MITC does not appear to have influenced the incidence of non-neoplastic lesions in rats of this study.

2) Neoplastic Lesions: Neoplastic lesions which occurred at the highest frequencies are listed in the following Table 3 (data taken from report Table 3, Appendix 14.2).

The most frequent tumors were those of the female mammary gland where the total incidence for benign and malignant tumors were 32, 35, 41 and 36 for 0, 2, 10 and 50 ppm groups, respectively. Females of treated groups had slightly increased incidences of multiple benign tumors (11, 15, 18 and 18) but lower incidences of single benign tumors (20, 15, 17 and 16 for the 0, 2, 10 and 50 ppm groups, respectively), than controls.

There was an unexpected incidence of brain tumors in males; the totals for glial tumors were 1, 2, 4 and 1 for the 0, 2,

TABLE 2 - INCIDENCE OF NON-NEOPLASTIC LESIONS

(Data taken from Report Table 6, Appendix 14.2)

ppm	0		2		10		50	
	M	F	M	F	M	F	M	F
No. of Animals Examined	60	60	55	59	55	60	60	60
Adrenals-Eosinophilic Cell Alteration	6	27	2	22	5	13	10	27
Angiectasis	0	16	0	10	1	8	0	20
Harderian Gland-Adenitis	13	21	4	16	4	11	14	24
Heart-Myocarditis/ Myocardial Fibrosis/ Scarring	30	26	6	10	12	6	35	23
Kidney-Pelvic Microcalculi	0	14	1	15	1	5	1	21
-Renal Scarring	0	2	0	1	0	0	7	0
-Glomerulonephritis	30	26	7	9	7	12	29	20
Liver-Fatty Vacuolation/ Vacuolation	9	17	9	21	2	15	14	23
Biliary Proliferation/ Sclerosis	11	5	3	5	4	6	13	10
Lungs-Calcification/Mineralization of Pulmonary Artery	14	8	6	12	8	5	16	15
Perivascular WBC Infiltration	9	4	5	9	5	7	13	5
Ovaries - Cysts	-	6	-	6	-	9	-	13
Spleen-Hyperplasia/Inc. Hematopoiesis/Lymphopoiesis	8	3	5	6	2	5	5	11

TABLE 3 - TUMOR INCIDENCE - ALL ANIMALS

(Data taken from Report Table 3, Appendix 14.2)

ppm	0		2		10		50	
	M	F	M	F	M	F	M	F
# of rats examined	60	60	55	59	55	60	60	60
Brain								
Glioblastoma					1	0		
Mixed Glioma	1	0	0	1	1	0		
Astrocytoma					1	0	1	0
Oligodendroglioma			2	0	1	0		
Total Glial Tumors	1	0	2	1	4	0	1	0
Fibrous Memingoma							1	0
Histiocytic Memingoma							1	0
Total Memingoma Tumors	0	0	0	0	0	0	2	0
Mammary Gland								
Benign - single	2	20	0	15	1	17	0	16
Benign - multiple	0	11	0	15	0	18	0	18
Malignant - single	0	1	0	3	1	1	0	0
Malig. - single & benign			0	1	0	5	0	2
Malig. - multi & benign			0	1				
Total benign & malignant	2	32	0	35	2	41	0	36
Pancreas								
Islet Cell Carcinoma	1	0			3	0	1	1
Islet Cell Adenoma	2	0	0	1			5	2
Islet Cell Adenoma and Carcinoma	1	0						
Total Islet Cell Tumors	4	0	0	1	3	0	6	3
Exocrine Adenoma	4	0	0	0	0	0	0	0
Exocrine Adenocarcinoma	2	0	0	0	0	0	0	0
Total Exocrine Tumors	6	0	0	0	0	0	0	0
Pituitary								
Adenoma	19	44	15	39	12	41	20	38
Adenoma/carcinoma			0	1			0	2
Total Tumors	19	44	15	40	12	41	20	40
Subcutaneous Tissue								
Fibroma- single	3	2	3	0	2	6	8	3
Fibrosarcoma	2	0	3	0	3	2	2	2
Lipoma	2	3	2	2	4	1	2	2
Histiocytic sarcoma	1	1	1	0	2	0	0	1
Cutaneous histiocytoma			1	0				
Sarcoma-unspecified/ undifferentiated/anaplastic			1	0	2	0		
Hibernoma			1	0				
Hemoangiosarcoma							1	0

CONTINUED Table 3

ppm	0		2		10		50	
	M	F	M	F	M	F	M	F
# of rats examined	60	60	55	59	55	60	60	60
Skin								
Papilloma/Squamous papilloma	2	0	4	1	7	0	2	0
Basal Cell Tumor			1	0	2	1	0	1
Baso-squamas Carcinoma	1	0						
Dermal Fibroma-single	2	0	1	0	7	0	2	0
Dermal Fibroma-multiple	1	0			1	0		
Thyroid								
C-Cell Adenoma	6	6	2	3	2	3	7	8
C-Cell Carcinoma	3	2	1	0	0	2	5	2
TOTAL	9	8	3	3	2	5	12	10
Follicular Adenocarcinoma/ carcinoma	0	1					4	0
Follicular Adenoma			1	0	1	1		
TOTAL	0	1	1	0	1	1	4	0
Uterus								
Endometrial Polyp		1		1		2		5
Adrenals								
Pheochromocytoma	9	4	2	1	2	0	7	1
Cortical Adenoma							0	1
Cortical Carcinoma					0	1		

10 and 50 ppm males, respectively. One female in the low dose group had a glial tumor and two males each of the high dose group had a meningoma.

Pituitary adenomas were prevalent in both sexes but females had over twice the incidence found in males; the incidences were 19-44, 15-39, 12-41 and 20-38 for males-females of the control, low, mid and high levels, respectively.

Thyroid tumors were also numerous in both sexes with the totals for C-cell adenomas/carcinomas being 9-8, 3-3, 2-5 and 12-10 for males-females of the 0, 2, 10 and 50 ppm groups, respectively. Males of the high level had 4 follicular carcinomas/adenocarcinomas compared to none in the controls.

Pheochromocytomas were also frequent; the numbers were 9-4, 2-1, 2-0 and 7-1 for males-females of the 0, 2, 10 and 50 ppm levels, resepctively.

As is obvious from the above discussed tumor incidence and from the table data, there is no indication for an increased tumor incidence due to treatment with MITC; however, final assessment will have to await review of the requested data summarizing the incidence on the basis of the number of tissues examined/sex/group.

Discussion: No compound-related or dose-related effects were seen in the rats of this study as a result of ingestion of MITC in their drinking water up to a level of 50 ppm; however, final assessment of histopathological data must await requested summarized data which are to include the actual number of tissues examined/sex/group.

This study does not appear to have included a maximum tolerated dose. Barring the possibility that the requested proper summary of histopathological data will indicate a compound-related effect, no clear-cut evidence for one has been seen in the data so far. Treated males showed slightly depressed body weights compared to controls, but the effect was not dose-related since the mid-level was the least affected and similar degrees of weight depression were seen for the low and high levels. Females did not show any depression of body weight; in fact, all levels of treated females weighed more than their controls.

MITC toxicology review

Page _____ is not included in this copy.

Pages 19 through 42 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Data Evaluation Record

Study Title: Two-year Chronic Oral Toxicity and Oncogenicity Study with Methyl Isothiocyanate in Albino Mice (106 weeks final report) and Eight Separate Water Stability Studies with Methyl Isothiocyanate

Study Type: Chronic/Oncogenicity and Test Material Water Stability
Caswell No. 573, Accession No. 257763 and Nos. 257759-62

Sponsor/Contracting Laboratories: NOR-AM Chemical Co. (Schering AG)/ Nippon Experimental Medical Research Institute Co, Ltd., Japan

Report Date/Submitted: Dec. 1980/4-26-85

Test Material: Methyl Isothiocyanate, technical (MITC)
Lot # MS 25206, purity 93.14%, November 22, 1977;
Supplier: [redacted]

Test Animal: ICR: JCL mice supplied by Clea, Japan
70 each males and females/group

Test Doses: 0, 5, 20, 80 and 200 ppm

Study Reviewed by: Winnie R. Teeters, Ph.D. W. Teeters
Section V, TOX. Branch/HED

Approved by: Laurence D. Chitlik, D.A.B.T. 8/5/86
Head, Section V
Toxicology Branch/HED

Classification and Conclusions: This study is classified as Core Supplementary Data. The actual number of tissues examined/sex/level must be provided. Furthermore, information on compound preparation and analytical data for the test compound in the water offered the mice are required.

Assessment of a possible histopathological compound effect must await receipt of requested data. The only compound effect established thus far is a slight depressant effect on body weight of the 80 and 200 ppm males and the 200 ppm females.

Methods: The methods from the study have been copied and appended. The following items were noted during review of the study.

1) The report failed to provide the actual number of each type of tissue examined histologically per group per sex; only the number of animals examined per group per sex was given.

2) Dosing was accomplished via the drinking water but analysis of the test compound in the water offered the mice was not

reported nor was there any discussion regarding compound preparation. However, there were eight separate stability studies of the test compound in water submitted with this study. This issue is further discussed more fully under the "Results" section in the subpart titled "Test Material".

3) Male mice weighed 14-23 grams at initiation of the study; this is an unusually wide range. Females weighed 15-19 grams.

4) There was no tabulation of daily clinical signs; there was only a summarizing statement on this subject for the entire duration of the study.

5) The following Guideline tissues were not examined: trachea, salivary glands, female mammary gland, esophagus, caecum, colon, rectum, spinal cord, gall bladder and aorta.

6) Some reporting "items" apparently resulted during translation, e.g. the report stated the "Four-week-old male and female ICR: JCL mice were purchased from Clea Japan, Inc. and were preliminarily bred for one week"; it is assumed that the mice were "held" for one week rather than bred for this period. There was also a statement that "The intake of the chemical was calculated based on the daily average intake of water, which was adjusted every day (the intake in a 24-hour period)"; it is assumed that "adjusted" means that the treated water was made up fresh daily, which is so stated in another part of the text.

Quality Assurance: There was a statement to the effect that the report had been audited by Nippon Medical Research Quality Assurance Unit and was considered to be an accurate presentation of the data produced during the course of the study.

Results:

A. Test Material - The test material was presented to the mice in their drinking water. The report stated that "MITC was mixed with drinking water every day to obtain definite concentrations based on the calculation of effective components. The water was given ad libitum from a glass bottle with a silicone stopper."

No analytical data of the solutions given to the mice were provided. Eight separate stability studies of MITC in water accompanied this oncogenicity study. They were all conducted at the Nippon Experimental Medical Research Institute Co., Ltd. and although dated 12-16-1980, represented analyses done about every three months over approximately the same two-year period as the mouse study; however, the first analyses were dated three months after initiation of the mouse study.

The stability studies were well documented and contained standard curves and chromatograms for the data. The studies consisted of analyses of water solutions of the same concentrations as used in the

animal study; the solutions were made up twice a day (morning and afternoon) and analyzed immediately and at twice daily intervals up to 3 days for studies 3-8 and up to 21 days for studies 1 and 2. In all studies, stability of 5, 20, 80 and 200 ppm concentrations was determined with storage in a glass animal water bottle and stability of the highest concentration was studied with storage in a commercially available polycarbonate animal water bottle (glass water bottles were used in the mouse study) and a glass volumetric flask. The first study also contained data on percent recovery and data comparing each of the two water bottles with and without an air space present above the liquid level, as would necessarily result during use of a bottle in an animal study.

The twenty-four hour data for the four concentrations in the glass water bottle (without an air space) showed that the concentrations were mostly within 90% of the mean concentration of the two analyses performed immediately after preparation. The glass water bottle was found to be superior to the polycarbonate one in maintaining the MITC concentration and the concentration was best maintained in the volumetric flask. For each type of water bottle, the presence of an air space above the liquid promoted the loss of MITC from the liquid.

The logic of continuing to investigate the same parameters after the first stability study, for a repetition of seven times, is incomprehensible, particularly in light of the fact that not one analysis was conducted to answer the critical point, that being the concentrations the mice received and, particularly, data on the concentrations in the water bottles just before they were replenished with fresh solutions. It is logical to expect that under the pressing needs of the study daily routine which required that fresh solutions be given 360 mice each day that the same care would not be given to preparing and maintaining the stability of the animal solutions as would be given, in the less hectic pace and environment of the analytical laboratory, for preparation and maintenance of the solutions scheduled for analyses.

Can an explanation for the apparent redundant stability studies and the critical lack of analytical data on the animal solutions, be that during translation important, critical information has been lost.

Pertinent to an evaluation of the animal study, however, and additional to the stability issue, is the fact that the animal study report, itself, does not contain any information on compound preparation; there is only the statement regarding daily presentation of fresh solutions to the animals.

B. Clinical Signs: There was no tabulation of periodic clinical signs in the report; there was only a summary statement in the text that no abnormal findings were seen in the 5 and 20 ppm groups and that equal numbers of each sex in the 80 and 200 ppm groups showed raised hair and a dull coat beginning 30 days into the study and lasting "a long time".

C. Mortality: Treatment with MITC did not appear to affect mortality. At 18 months, there had been only one death among males (200 ppm group) whereas 7, 6, 3, 10 and 4 females had died in the 0, 5, 20, 80 and 200 ppm groups, respectively. By study termination at 106 weeks, mortality among the groups was comparable, being 35, 25, 29, 28 and 37 for males and 37, 38, 37, 39 and 37 for females for 0, 5, 20, 80 and 200 ppm groups, respectively, which had contained 58 mice/group/sex initially (not including 6/sex/group, each sacrificed at 26 and 52 weeks).

D. Body Weight: After only the first week of dosing, males of the 200 ppm group showed a significantly ($p<.001$) lower body weight and after the second week, males of the 80 ppm group also had significantly ($p<0.01$) lower body weights than controls. This situation persisted with only a few exceptions through week 98. The 20 ppm males occasionally had lower weights; the differences from controls were consistently significant for weeks 84-98 and from week 96 to study termination (week 106) this group had the lowest weight of all male groups. Body weight gains at weeks 26 and 52 were significantly less than controls for the 80 and 200 ppm groups but overall gains (weeks 0-106) for none of the treated males were significantly different from their controls.

The only female group showing a similar effect to the males was the 200 ppm group. The lower body weight ($p<.01$) for this group was first seen at week two and occurred quite regularly (42/67 periods) thereafter. Lower level female groups occasionally had mean body weights that were greater than their control. Body weight gains at week 26 and 52 were significantly less than controls only for the 200 ppm females, but overall gains (week 0-106) for none of the treated females were significantly different from control.

Although body weight changes for 200 ppm males were significantly less than controls, even to the $p<0.001$ level, there was only one period, week 90, for which the weight difference amounted to 10% less, and for the other periods the differences were usually only 5-7% less than control. For females, also, the week 90 weight was the only period for the 200 ppm group for which the difference from control, although at the $p<0.01$ level, approached 10% less (actually 9.1%). For females, the differences were usually less than 5% lower than control. Consequently, the biological significance of the effect is unclear, yet it did occur in both sexes at the high level (200 ppm) rather consistently, particularly for males, and was seen persistently in the next lower level (80 ppm) of males, also.

E. Food Consumption and Food Efficiency: There were no significant differences between treated groups of either sex and their controls for food consumption or food efficiency.

F. Water Intake and MITC Dose: There appeared to be only small differences for mean water intake for either sex between treated groups and their controls. (These data were not analyzed statistically nor were any statistical measures of variability provided for them.)

Male mice of the 2 lower levels (5 and 20 ppm) generally consumed similar or slightly more water than controls but there appeared to be a dose-related lower water consumption for the 80 and 200 ppm males. A similar pattern was found for the females, with there being a dose-related lower water intake for the 80 and 200 ppm groups. Consequently, there was a general parallel between the depressant effect on water consumption and body weight, but no relationship seen between body weight and food consumption.

The overall average (male and female) compound intake for the entire study was 0.87, 3.48, 12.43 and 27.37 mg/kg/day for the 5, 20, 80 and 200 ppm groups, respectively (data taken from report table 12). As is usually the case, females had a slightly higher per weight intake than the males.

G. Ophthalmology: All mice were examined for ocular effects at 13, 26, 52 and 106 weeks. Findings appeared random with no relation to dose and included cataract, bulb atrophy, localized corneal and lens opacity and corneal keratitis. The total numbers with lesions were 2, 2, 3, 2, and 3 for males and 5, 2, 1, 1 and 5 for females of the 0, 5, 20, 80 and 200 ppm groups, respectively.

H. Hematology: The only notable hematological differences between treated groups and controls were the tendencies of both sexes of the 80 and 200 ppm groups to have a decreased erythrocyte count and an increased reticulocyte percentage and hemoglobin and hematocrit values tended to parallel the erythrocyte depression. These differences were significant only at the 52 week determination and only for males (RBC:$p<0.05$ for 80 and 200 ppm; hematocrit: $p<0.01$, 80 ppm; reticulocyte percentage: $p<0.05$, 200 ppm). At 26 weeks, the high level females had an increased platelet count, but the control appeared slightly low for the period. No differences from controls were noted for either sex of treated mice at any level at 106 weeks.

I. Clinical Chemistry: At 26 weeks, there were significant decreases for total protein ($p<0.05$ for all) for males and females of the 80 and 200 ppm groups, for blood urea nitrogen ($p<0.01$) for males of these groups and for cholesterol ($p<0.05$) for females of the 200 ppm group. At later periods of 52 and 106 weeks there were not even tendencies for these effects.

Terminally (106 weeks), the 200 ppm females had slightly increased glutamic oxaloacetic transaminase activity (110.86$\pm$ 16.04 and 138.38$\pm$ 32.19 K.U. for controls and treated, respectively) and males of this level showed the same tendency. Both sexes of this level at 52 weeks and the females at 26 weeks had shown a similar tendency for increased activity. There was also a tendency for slightly increased glutamic pyruvic transaminase activity at early intervals (both sexes of the 200 ppm group at 52 weeks and females only at 26 weeks) but neither sex had elevated values at 106 weeks when the study was terminated.

The increased transaminase activity was minimal and the changes in total protein, blood urea nitrogen and cholesterol were temporary, occuring only at the first determination; furthermore, there was no histological or other evidence of toxicity which corroborate these findings. Consequently they are assumed to have very little biological significance.

J. Urinary Findings: There were no notable differences terminally between treated and control mice for any of the urinary parameters. Increases in sodium and potassium had been seen earlier. At 52 weeks, potassium increases were significant for 80 ppm males ($p<0.01$) and for 80 and 200 ppm females ($p<0.05$) and slightly increased but not significant for 200 ppm males and 20 ppm females, but these changes were not dose related. Slight sodium increases were noted for 200 ppm males at 26 and 52 weeks and there were dose-related slight increases for 80 and 200 ppm females at 52 weeks but none of the sodium increases was significant.

Although some of the electrolyte increases were significant, they were not dose related nor persistent and thus are of uncertain biological significance.

K. Organ Weights: Relative, but not absolute, brain weight was significantly ($p<0.01$) increased for 20 ppm males at termination; a similar but not significant, effect was seen also for 80 ppm males. In both cases this effect may be explained by the slight decrease in body weight of these groups compared to their control. At 26 weeks, males of the 20 ppm group had shown a significant ($p<0.05$) absolute brain weight increase without an accompanying increase in relative weight, but the change was an increase of only 6%.

Terminal male relative liver weights were significantly increased ($p<0.05$) for the 80 ppm group; there were also absolute increases for males of this group and the 200 ppm group, but neither attained significance. There were no significant changes for this organ in males at either interim sacrifice.

At 106 weeks, males of the 200 ppm group had an increased ($p<0.05$) relative urinary bladder weight; this group also had an increased absolute weight, as well, although not signficant, and the 80 ppm group had slightly increased, but not significant, both absolute and relative urinary bladder weights. Individual weights were checked for the highest levels and it appears that some of the bladders may have been weighed when they were distended by urine as 4/6 of this group showing markedly elevated weights also had a necropsy finding of "distended" but none had a reported histological finding to explain the increased weight.

At the 52 week interim sacrifice, males of the 80 and 200 ppm groups had several significant organ weight changes (e.g., absolute and relative weights of pituitary, thyroid and spleen were increased in the 200 ppm group and urinary bladder absolute, spleen relative and left thyroid absolute and relative were increased for the 80 ppm group) but for each of these an apparent explanation is provided by

the fact that the controls were unusually low; this judgement is based on observing that for several male organs the weights for controls were less than for control females of about 9 grams lower mean body weight sacrificed at this period, and urinary bladder weights for 52 week male controls were less than those of control males of similar weight sacrificed at 26 or 106 weeks.

Therefore, in summary, although there were several significant organ weight changes at interval or terminal sacrifices, either they appear to have logical explanations that are not related to compound administration, they are not dose-related or they appear to have no biological significance; furthermore, none is supported by evidence of histological alteration.

L. Necropsy: There were no dose-related necropsy findings; all findings appeared random among the groups.

In those instances among mice sacrificed at termination in which treated mice had a higher incidence than the control, the lowest dose had an equal or higher incidence than the highest group. As examples of this, ovarian cystoma was prevalent with an incidence of 6/21, 12/20, 9/21, 8/19 and 9/21, as was myomatous appearance of the uterus with an incidence of 5/21, 10/20, 3/21, 4/19 and 5/21 for the control, 5, 20, 80 and 200 ppm groups, respectively. Additional prevalent findings were pulmonary hyperemia, nodes and liver-like changes for lungs of both sexes; hepatic tumors, distention of the urinary bladder, testicular softening and enlargement of the seminal vesicles of males; swelling and turbidity (?) of the spleen and renal discoloration in both sexes; and uterine relaxation, ovarian hemotoma and mesenteric lymph node enlargement in females.

The most prevalent finding among animals that died was splenic enlargement among females, and although the incidence was higher in treated mice, again the lowest dose level had the highest incidence: 3/37, 14/38, 5/37, 6/39 and 9/37 for the control, 5, 20, 80 and 200 ppm groups, respectively.

M. Histopathology: The report did not contain a tabulation of the histopathological results as a ratio of the number of mice with positive findings to the number examined for that particular tissue per group per sex. The report only presented the total numbers of mice examined per group per sex. It is common to lose a few tissues to autolysis or other management factors in a long term study, particularly for a small animal such as the mouse. Tables listing the individual tissues examined by animal number were present but these only listed positive findings; therefore the crucial total number examined per tissue/sex/group could not be determined from the report.

The following EPA Guideline tissues were not routinely examined: trachea, salivary glands, female mammary gland, esophagus, caecum, colon, rectum, spinal cord, gall bladder and aorta.

1) Non-neoplastic: The data did not indicate a target organ. For those tissues of treated mice sacrificed at 106 weeks having

a higher incidence of lesions than in the controls, the group incidence appeared random, with no indication of a dose-relationship since often the highest incidence was in the lowest dose group. There did appear, however, to be a weak dose-related incidence of cystic ovaries: the incidence was 2/21, 4/20, 3/21, 5/19 and 10/21 for the control, 5, 20, 80 and 200 ppm groups, respectively. Yet, this is a common lesion and the dose-response was poor, at best. Uterine cysts were also prevalent but the incidence was similar among the controls and the 5 and 20 ppm groups, with a lower incidence in higher level groups.

The two most common findings were small cell infiltration of multiple organs and amyloid degeneration of multiple organs, both of which are to be expected in aging mice. The most prevalently affected organs for small cell infiltration were the liver, spleen, kidney, urinary bladder, stomach, pancreas, thymus, bone marrow and mesenteric lymph node and for amyloid degeneration the organs affected most often were the spleen, kidney, duodenum, small intestine, thyroid, adrenal, skin and ovaries.

2) Neoplastic: The most prevalent neoplastic findings were pulmonary adenocarcinomas of males and leukemia of females, but for both lesions the incidence was similar among control and treated mice. These incidences and those for other neoplasms for which there were multiple types of tumors in an organ/tissue are shown in the following table.

TUMOR INCIDENCE

(When > 1/group, or there are other tumors of same organ)

M A L E

# Mice LUNG	64 control	64 5 ppm	64 20 ppm	64 80 ppm	63 200 ppm
Adenoma	2	0	0	0	0
Adenocarcinoma	19	19	19	22	18
LIVER Adenoma	1	3	0	5	2
Hepatic carcinoma	2	4	1	4	2
TOTAL	3	7	1	9	4
SKIN Fibrosarcoma	0	0	0	0	2
Carcinoma of Squamous Cell	0	0	0	0	1
TESTES Seminoma	7	8	3	7	0
Interstitial Cell Tumor	0	0	0	1	0
LEUKEMIA	6	8	9	13	5

F E M A L E

#Mice	64 Control	64 5 ppm	64 20 ppm	64 80 ppm	63 200 ppm
LUNG					
Fibroma	0	0	1	0	0
Sarcoma	0	0	0	1	0
Giant Cell Sarcoma	0	0	1	0	0
Adenocarcinoma	8	5	11	7	10
Metastasis of Hepatic Carcinoma	0	0	0	1	0
LIVER					
Angioma	0	0	0	1	0
Adenoma	0	1	0	0	0
Hepatic Cancer	1	0	0	1	2
Metastasis of pulmonary adenocarcinoma	0	0	1	0	0
SKIN					
Tumor	0	1	0	0	0
Fibrosarcoma	0	0	0	0	3
Adenocarcinoma	1	0	1	2	0
Round Cell Sarcoma	0	1	0	0	0
HIND LEGS					
Sarcoma	0	1	0	0	0
RIGHT THIGH					
Round Cell sarcoma	0	0	0	1	0
UTERUS					
Uterine polyp	1	1	5	2	1
Sarcoma	0	0	1	0	1
Myoma	2	2	1	2	1
Leukemia	27	29	24	24	30

There is no evidence from these data of an oncogenic effect for MITC; however, a final evaluation must await review of these results on the basis of the actual numbers of each tissue examined/sex/group.

Discussion: The possibility of histopathological evidence of a compound effect cannot be definitely evaluated until additional data for the actual numbers of tissues examined are provided. Other than the possibility of a histopathological effect, the only compound effect seen was a slight depressant effect on body weight, and this was minimal. Both sexes of the 200 ppm level showed significant depression of body weight and males of the next lower level (80 ppm) did also. Body weight gains at 26 and 52 weeks for these groups were also significantly less than controls but overall gains (0-106 weeks) were not significantly different for any of the groups. Additionally, the body weight changes for the groups showing the most depression - both sexes of the 200 ppm level - were seldom less than 5-7% lower than their controls.

The biological significance of such a minimal effect can be controversial. Yet it did occur in both sexes of the high level and did show a weak dose-response relationship in that males of the next lower dose level were also affected. Moreover, the slight effect on body weight complies with the concept of a maximum tolerated dose as defined in "Toxicity Potential (Guidance for Anaylsis and Evaluation of Subchronic and Chronic Exposure Studies), EPA - 540/9-85-020, June 1985".

MITC toxicology review

Page _____ is not included in this copy.

Pages 54 through 60 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product quality control procedures

___ Identity of the source of product ingredients

___ Sales or other commercial/financial information

___ A draft product label

___ The product confidential statement of formula

___ Information about a pending registration action

X FIFRA registration data

___ The document is a duplicate of page(s) _____

___ The document is not responsive to the request

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.