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

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MAR - 4 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Methylene bis (thiocyanate)

Project No: 0-1860
Tox. Chem. No.: 565
DE BARCODE No.: D155266
Case No: 018721
Submission No: S283243

TO: John Lee, PM # 31
Registration Division (H7505C)

THRU: Roger Gardner, Section Head
Review Section 1
Toxicology Branch
Health Effects Division (H7509C)

Roger Gardner 2/14/91
KP 2/24/91

FROM: Nguyen Bich Thoa, Ph.D
Review Section 1
Toxicology Branch I
Health Effects Division (H7509C)

NB 02/13/91

Registrant: Albright and Wilson, Ltd.

ACTIONS REQUESTED:

1. Review of the mutagenicity study entitled "MBT: Chromosomal Aberrations Assay with Chinese Hamster Ovary cells in-vitro (MRID 415038-01)
2. Review of the mutagenicity study entitled "Methylene bis (thiocyanate) (MBT): Mouse Lymphoma Mutation Assay (MRID 415038-02).
3. Review of the label entitled " A Tenneco Company Methylene bis (thiocyanate) for Formulation of Industrial Microbiocides and Preservatives".

CONCLUSIONS:

1. The mutagenic potential of methylene bis (thiocyanate) was studied using the chromosomal aberrations assay with Chinese hamster ovary cells in vitro. According to the results of the study, methylene bis (thiocyanate) 2 and 4 ug/ml caused a dose-related positive increase in structural chromosomal aberrations (mainly simple breaks and gaps). These concentrations were

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however cytotoxic, and caused respective decreases of mitotic indexes of 28 and 83% in the presence of metabolic activation and of 33 and 91% in the absence of metabolic activation. This positive clastogenic effect is considered presumptive because it was not confirmed in a repeat assay. The study is acceptable and satisfies the toxicological data requirements of guidelines 84-2(b) (Mutagenicity).

2. The mutagenic potential of methylene bis (thiocyanate) was studied using the Mouse Lymphoma mutation assay. According to the results of the study, methylene bis (thiocyanate) induced a positive mutagenic effect in the mouse lymphoma L5178Y tk⁺/tk⁻ cells line, but only at cytotoxic concentrations. In the presence of metabolic activation, 2, 3, and 4 ug/ml caused significant increases in both the mean tk⁺/tk⁻ mutant counts and the mean mutant fraction values. These concentrations decreased cells survival (relative total growth) by 72, 90, and 99% respectively. In the absence of metabolic activation, 1 and 1.5 ug/ml caused dose-related significant increases in both the mean tk⁺/tk⁻ mutant counts and the mean mutant fraction values. These concentrations decreased cells survival by 59 and 94% respectively. The study is acceptable and satisfies the toxicological data requirements of guidelines 84-2(a) (Mutagenicity).

3. The label entitled "A Tenneco Company Methylene bis (thiocyanate) for Formulation of Industrial Microbiocides and Preservatives" is acceptable. The human hazard signal word on the label is DANGER based on the primary eye irritation and primary dermal irritation toxicity category (1) of several methylene bis (thiocyanate) based formulations (see attached OPP/HED/SACB Tox one-liners dated 02/11/91). The child hazard warning statement "KEEP OUT OF REACH OF CHILDREN" appears on the label. The following statement of practical treatment were on the label: IN CASE OF SKIN CONTACT, WASH WITH PLENTY OF SOAP AND WATER REMOVE CONTAMINATED CLOTHING AND WASH BEFORE REUSE. IF PRODUCT GETS IN THE EYE, FLUSH IMMEDIATELY WITH COPIOUS AMOUNTS OF CLEAN COOL WATER AT LEAST 15 MINUTES. GET MEDICAL ATTENTION IMMEDIATELY. IF SWALLOWED CALL A PHYSICIAN OR POISON CONTROL CENTRE. DRINK 1 OR 2 GLASSES OF WATER AND INDUCE VOMITING. DO NOT INDUCE VOMITING OR GIVE ANYTHING BY MOUTH TO AN UNCONSCIOUS PERSON. NOTE TO PHYSICIAN: PROBABLE MUCOSAL DAMAGE MAY CONTAIN/INDICATE USE OF GASTRIC LAVAGE. PRECAUTIONS FOR SHOCK, RESPIRATORY DEPRESSION AND CONVULSIONS MAY BE NEEDED" are present on the label. Precautionary statements on the hazard to humans and domestic animals were: DANGER (based on tox. cat. stated above). CORROSIVE. CAUSES EYE DAMAGE AND SKIN IRRITATION. DO NOT GET IN EYES, ON SKIN, OR ON CLOTHING. WEAR GOGGLES OR FACE SHIELD AND RUBBER GLOVES WHEN HANDLING. HARMFUL OR FATAL IF SWALLOWED. AVOID CONTAMINATION OF FOOD.

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Copies of the following are enclosed:

- (i) OPP/HED/SACB Tox oneliners on MBT dated 02/22/91,
- (ii) The above referenced label, and
- (iii) DERs for the two above referenced studies.

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Guideline Series 84: MUTAGENICITY

Reviewed by: N. B. Thoa, Ph.D. (Pharmacologist)
Section 1, Tox Branch I
Secondary reviewer: Roger Gardner
Section 1, Tox Branch I
Date:

J. L. Luce
02-13-91

DATA EVALUATION REPORT

CHEMICAL: Methylene bis (thiocyanate) Tox. Chem. No.: 565
EPA File Symbol: 33677-1

STUDY TYPE: Mammalian cells in culture gene mutation assay
in (CHO) cells (84-2b)

ACCESSION NUMBER: 415038-01

SYNONYMS/CAS No. MBT

SPONSOR: Albright & Wilson Ltd., West Midlands, UK

TESTING FACILITY: Inveresk Res. International, Scotland, UK

TITLE OF REPORT: MBT: Chromosomal Aberrations Assay with Chinese
Hamster Ovary cells in-vitro

AUTHOR(S): L.M. Holmstrom, Bs, Ms

STUDY NUMBER(S): 4976

REPORT ISSUED: Feb. 16, 1989

CONCLUSION(S) - Executive Summary: The mutagenic potential of methylene bis (thiocyanate) was studied using the chromosomal aberrations assay with Chinese hamster ovary cells in vitro. Under the experimental conditions of the study, the following conclusions were reached:

1. No numerical chromosome aberrations were observed with MBT at any of the doses used (0.25, 0.5, 1.0, 2.0, and 4ug/ml culture medium).
2. Non cytotoxic concentrations of MBT (\leq 1ug/ml) did not induce any structural aberrations, with or without metabolic activation.
3. Cytotoxic concentrations of MBT (2 and 4 ug/ml) caused a dose-related positive increase in structural aberrations (mainly simple breaks and gaps), both with and without metabolic activation. This positive clastogenic effect is

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considered a "presumptive" effect since it was not confirmed in a repeat (complete) assay.

4. the frequencies of chromosome aberrations (structural and numerical) observed in both vehicle and untreated control cultures were within the historical ranges.

5. The reference chemicals CP, 2-AAF, and MMS all induced positive increases in structural chromosomal aberrations. Numerical chromosomal aberrations (number of cells with endoreplicated chromosomes) were increased by only 2-AAF.

CORE CLASSIFICATION: ACCEPTABLE

MAMMALIAN CELLS IN CULTURE GENE MUTATION

A. MATERIALS

1. Test Material: Name: Methylene bis (thiocyanate)
 Description: technical
 Batch #: 4249 Purity: 99%
 Contaminants: None reported
 Solvent used: DMSO (BDH Ltd., Poole, Dorset, UK)
 Other comments: Manufacturer: Tenneco Co.

2. Control Materials:
 Negative: DMSO
 Solvent/final concentration: 1% (50 ul/culture sample)
 Positive: Non-activation:
 methylmethane sulfonate (MMS, Aldrich Chem. Co.,
 Dorset, UK), 20ug/ml culture medium. Solvent is tissue
 culture grade water, 50 ul/dosing.

 Activation:
 i. cyclophosphamide (CP, Koch-Light labs,
 Buckinghamshire, UK), 20ug/ml culture medium.
 Solvent is tissue culture grade water, 50
 ul/dosing.
 ii. 2-acetylaminofluorene (2-AAF, Aldrich Chem. Co.,
 Dorset, UK), 80ug/ml culture medium. Solvent is
 DMSO, 50 ul/dosing.

3. Activation: S9 derived from

<input checked="" type="checkbox"/> Aroclor 1254	<input checked="" type="checkbox"/> induced	<input checked="" type="checkbox"/> rat	<input checked="" type="checkbox"/> liver
<input type="checkbox"/> phenobarbital	<input type="checkbox"/> non-induced	<input type="checkbox"/> mouse	<input type="checkbox"/> lung
<input type="checkbox"/> none		<input type="checkbox"/> hamster	<input type="checkbox"/> other
<input type="checkbox"/> other		<input type="checkbox"/> other	

If other, describe below

The metabolic activation mixture (S-9 mix) consists of:

 - i. 1.00 ml of freshly thawed S-9 fraction (protein content of 30.7 mg/ml in toxicity tests and 25.6 mg/ml in cytogenicity test).
 - ii. 9.00 ml of co-factor solution (serum free Ham's F10 medium containing 4 mM NADP di-Na, 25 mM glucose-6-phosphate di-Na, MgSO₄·7H₂O, 147.9 mg/liter, and KCl, 223.7 mg/liter).

4. Test compound concentrations used (based on the results of 2 preliminary cytotoxicity assays):

 Without activation: 0.25, 0.5, 1.0, 2.0, and 4ug/ml culture medium.

 With activation: same dose range as without activation

MAMMALIAN CELLS IN CULTURE GENE MUTATION

5. Test Cells: mammalian cells in culture
 ___ mouse lymphoma L5178Y cells
X Chinese hamster ovary (CHO) cells
 ___ V79 cells (Chinese hamster lung fibroblasts)
 ___ other (list):

Properly maintained? Y / N (circle one)
 Periodically checked for Mycoplasma contamination? Y / N (circle one)
 Periodically checked for karyotype stability? Y / N (circle one)
 Periodically "cleansed" against high spontaneous background? Y / N (circle one)

Cells were obtained from Dr. Daroudi, The State U. of Leiden, The Netherlands. Stocks of cells were maintained in Nunc tissue culture flasks containing growth medium (Ham's F10 medium supplemented with fetal bovine serum, 15% v/v, glutamine, 146 mg/liter, and "appropriate" antibiotics), at 37°C, and in an atmosphere of 5% CO₂ in air.

B. TEST PERFORMANCE1. Cell Treatment:

- a. Cells exposed to test compound for:
 24 hours (non-activated) 6 hours (activated)
- b. Cells exposed to positive controls for:
 24 hours (non-activated) 5 hours (activated)
- c. Cells exposed to negative and/or solvent controls for:
 24 hours (non-activated) 5 hours (activated)

2. Protocol

a. Preliminary toxicity assay: An inoculum from the stock culture was trypsinized. The resulting cells were resuspended in fresh growth medium (5×10^5 cells/5 ml sample), and incubated for 20 hours in the conditions described above. The resulting established cultures were washed once with serum free medium. Single samples were sequentially reincubated according to the schedule described below:

<u>TREATMENT</u>	<u>EXPOSURE PERIOD*</u>	<u>RECOVERY PERIOD**</u>	<u>COLCEMID PERIOD_a</u>
with S-9 mix	6 hrs	18 hrs	2 hrs
w/o S-9 mix	24 hrs	0 hr	2 hrs

*. For testing with activation, each sample received 4.5 ml serum free medium, 0.5 ml S-9 mix, and either DMSO (50 ul, vehicle controls), or MBT. For testing without activation, each sample

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received 4.5 ml growth medium, 0.5 ml serum free medium, and either DMSO (50 ul, vehicle controls), or MBT.

** At the end of the exposure period, all samples were washed twice with serum free medium, were added with 5 ml growth medium and reincubated.

@. Colcemid (0.1 ug/ml) was added to all samples at the end of the recovery period.

At the end of the assay, both mitotic cells ("recovered by gently tapping of flasks") and monolayer cells ("recovered by trypsinising") were combined for slide preparations (see attached reproduced page 15 for slide preparation methodology) for toxicity assessment (cell necrosis, cell count, and mitotic index).

b. Main chromosome aberration assay: The protocol used was identical to the one used in the preliminary toxicity assay except for the following:

- i. Duplicated samples were used for each experimental point,
- ii. During the exposure period, for testing with activation, the samples received 4.5 ml serum free medium, 0.5 ml S-9 mix, and either DMSO (50 ul, vehicle controls), MBT, or CP/2-AAF (positive controls). For testing without activation, duplicated samples received 4.5 ml growth medium, 0.5 ml serum free medium, and either DMSO (50 ul, vehicle controls), MBT, or MMS (positive controls).

3. Evaluation of the results: Copies of pp. 17-21 of the report describing the assessment of the results (toxicity evaluation and statistical analysis) are attached.

C. REPORTED RESULTS:

1. Cytotoxicity assays: MBT was freely soluble in DMSO and was highly cytotoxic to the CHO cells. In a preliminary cytotoxic assay, a complete absence of metaphases formation was reported when concentrations of 20, 39, 78, 156, 313, 625, 1250, 2500, and 5000 ug/ml were used, with or w/o metabolic activation. In a subsequent assay with a lower dose range (0.1, 0.5, 1.0, 5, 10, 15, and 20 ug/ml), MBT \geq 5ug/ml totally inhibited the formation of metaphases and the mitotic index counts. The total cell counts was reduced by \geq 72% with activation and by \geq 84% w/o activation. In the presence of metabolic activation, 1 ug/ml slightly reduced both the mitotic index and the total cell counts and 0.1-0.5 ug/ml were slightly cytotoxic (small reduction of total cell counts). In the absence of activation, a similar effect was observed in the total cell counts but the mitotic index was reduced even with 0.5 ug/ml. In

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the main assay, in the presence of metabolic activation, MBT concentrations of 2 and 4 ug/ml respectively reduced the average mitotic index by 28 and 83%. In the absence of metabolic activation, the respective reductions were 33 and 91%.

2. Chromosomal aberration assay: (see attached reproduced tables 5-6 and appendices 1-2).

a. Vehicle and untreated control cultures: Without metabolic activation, the frequencies of chromosome aberrations (structural and numerical) observed in both vehicle and untreated control cultures were within the historical ranges. With metabolic activation, one vehicle and one untreated control cultures presented "slightly elevated frequencies of structural chromosome aberration", reportedly due to an increase in gaps, and both untreated controls and the other vehicle control had a "raised number of cells with endoreplicated chromosomes". These facts were duly taken into consideration in the evaluation of the clastogenic effects of MBT.

b. Positive control cultures: CP, 2-AAF, and MMS all induced positive increases in structural chromosomal aberrations. In addition, a numerical form of chromosomal aberrations (number of cells with endoreplicated chromosomes) was induced by 2-AAF.

c. MBT treated cultures: No numerical chromosome aberrations were observed with MBT at any of the doses used. Concentrations of MBT \leq 1ug/ml did not induce any structural aberrations, with or without metabolic activation. These doses were also not cytotoxic (no reduction in total cell counts). A dose-related positive increase in structural aberrations (mainly simple breaks and gaps) were observed with MBT 2 and 4 ug/ml, both with and without metabolic activation. These 2 doses were cytotoxic in a dose-related manner, and the higher dose induced a mean reduction in total cell counts of 91% reduction without activation and of 83% with activation.

d. Was test performed under GLPs (is a quality assurance statement present)? Y / N (circle one)

D. REVIEWER' DISCUSSION/CONCLUSIONS:

Adequate data were presented to support the report's conclusions. The dosage range used was adequate since the HDT, 4 ug/ml, was markedly cytotoxic. The methodology described was adequate, with duplicate cultures used for each experimental point. Under the experimental conditions of the study, MBT induced structural chromosomal damage (mainly simple breaks and gaps), but only at toxic concentrations. This MBT's positive clastogenic

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effect is "presumptive" because it was not confirmed in a repeat (complete) assay.

E. CORE CLASSIFICATION: ACCEPTABLE

F. REFERENCES: A copy of the references is attached.

PAGES 11 THROUGH 23 HAVE BEEN REMOVED. THOSE PAGES CONSIST OF REGISTRANT-SUBMITTED DATA.

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Guideline Series 84: MUTAGENICITY

Reviewed by: N. B. Thoa, Ph.D. (Pharmacologist).
Section 1, Tox Branch I
Secondary reviewer: Roger Gardner
Section 1, Tox Branch I
Date:

John
D. Gardner
02-13-91

DATA EVALUATION REPORT

CHEMICAL: Methylene bis (thiocyanate) Tox. Chem. No.: 565

EPA File Symbol: 33677-1

STUDY TYPE: Mouse Lymphoma Mutation Assay (84-2a)

ACCESSION NUMBER: 415038-02

SYNONYMS/CAS No.: MBT

SPONSOR: Albright & Wilson Ltd., West Midlands, UK

TESTING FACILITY: Inveresk Res. International, Scotland, UK

TITLE OF REPORT: Methylene Bis Thiocyanate (MBT): Mouse Lymphoma Mutation Assay

AUTHOR(S): P.J. Cattanach

STUDY NUMBER(S): 4947

REPORT ISSUED: Feb. 17, 1989

CONCLUSION(S) - Executive Summary: The mutagenic potential of methylene bis (thiocyanate) was studied using the mouse lymphoma mutation assay. Under the experimental conditions of the study, the following conclusions were reached:

1. Cytotoxic concentrations of MBT induced a positive mutagenic effect in the mouse lymphoma L5178Y tk⁺/tk⁻ cells line. In the presence of metabolic activation, concentrations of MBT of 2, 3, and 4 ug/ml caused significant increases in both the mean tk⁻/tk⁺ mutant counts and the mean mutant fraction values (respective increases of mean mutant fraction were 1.6, 2, and 2.5 folds over controls). All 3 doses were greatly cytotoxic, causing respective decreases in cells survival (relative total growth) of 72, 90, and 99%. The positive mutagenic effect of MBT 4 ug/ml was confirmed in a repeat assay. In the absence of metabolic activation dose-related significant increases in both the mean mutant count and the mean mutant fraction were observed with 1 and 1.5 ug/ml

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(respective increases of mean mutant fraction were 2.3 and 15.2 folds over controls). These 2 doses caused 59 and 94% decreases in cells survival.

2. The mutant count of the vehicle cultures were within historical ranges.

3. Both reference chemicals EMS (without S9 mix) and 3-MC (with S9 mix) induced positive increases in both the mean mutant count and the mean mutant fraction values.

CORE CLASSIFICATION: ACCEPTABLE

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A. MATERIALS

1. Test Material: Name: Methylene bis (thiocyanate)
 Description: technical
 Batch #: 160 Purity: 99%
 Contaminants: Not reported
 Solvent used: DMSO (Analar grade, BDH Ltd., Poole, Dorset, UK)
 0.1 ml/MBT concentration/10 ml culture medium.

Other comments:

2. Control Materials:

Vehicle: DMSO

Solvent/final concentration: 1%

Positive: Non-activation:

ethylmethane sulfonate in 0.1 ml DMSO (EMS, Koch-Light
 labs., Colnbrook, Berks, 250ug/ml culture medium).

Activation:

3-methyl-cholanthrene in 0.1 ml DMSO (3-MC, Radian
 Corp., Austin, Texas, US, 2.5 ug/ml culture medium).

3. Activation: S9 derived from

<input checked="" type="checkbox"/>	Aroclor 1254	<input checked="" type="checkbox"/>	induced	<input checked="" type="checkbox"/>	rat	<input checked="" type="checkbox"/>	liver
<input type="checkbox"/>	phenobarbital	<input type="checkbox"/>	non-induced	<input type="checkbox"/>	mouse	<input type="checkbox"/>	lung
<input type="checkbox"/>	none			<input type="checkbox"/>	hamster	<input type="checkbox"/>	other
<input type="checkbox"/>	other			<input type="checkbox"/>	other		

If other, describe below

The metabolic activation mixture (S-9 mix) consists of:

- i. 1.00 ml of freshly thawed S-9 fraction (protein content of 27.6 mg/ml).
- ii. 9.00 ml of co-factor solution (F₀P medium containing 4 mM NADP di-Na and 25 mM glucose-6-phosphate di-Na).

4. Test compound concentrations used (based on the results of a preliminary cytotoxicity assay):

With activation: Test #1: 1, 2, and 4 ug/ml culture medium.
 Test #2: 2, 3, and 4 ug/ml culture medium.

Without activation: Test #1: 0.5, 1.0, and 1.5 ug/ml culture medium.

Test #2: 0.4, 0.8, 1.2, 1.6, 2, and 3.4 ug/ml culture medium.

5. Test Cells: mammalian cells in culture

mouse lymphoma L5178Y tk⁺/tk⁻ cells
 Chinese hamster ovary (CHO) cells

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received 4.9 ml F₀P medium, and either DMSO, MBT, or EMS.

- iii. In test #2, the cultures were incubated for 72 instead of 48 hours following the exposure period to obtain a higher cells count with the HDT.
- iiii. At the end of the 48 hours incubation period (48 and 72 hours in test #2) the cultures were again rediluted to a density of 2×10^5 cells/culture. Three 3.5 ml cell suspensions were aliquoted from each culture into petri dishes containing 0.35% agar and 3 ug/ml trifluorothymidine in cloning medium (total volume = 25 ml). The samples were reincubated (37° C, 5% CO₂ in air) for 11 days (expression period) and the tk/tk mutant colonies were counted using a Artek 880 automated colony counter.

c. Evaluation of the results: Copies of pp. 15-19 and 44 of the report describing the assessment of the results (toxicity evaluation, criteria for a positive mutagenic effect, statistical analysis, and historical control data) are attached.

d. Was test performed under GLPs (is a quality assurance statement present)? / N (circle one)

C. REPORTED RESULTS:

1. Preliminary cytotoxicity assays: Doses of MBT \leq 0.5 ug/ml were not cytotoxic. Cell survival (total suspension growth) decreased in a dose-related manner with 5 and 50 ug/ml (respective decreases below control values were 48 and 73% with activation and 93 and 98% without activation). Precipitates were formed with doses of MBT \geq 500 ug/ml.

2. Mutation assays: (see attached copies of tables 3-6)

a. Vehicle and untreated control cultures: The mutant counts of the vehicle control cultures were within both the historical ranges observed in this laboratory and the normal ranges reported in the literature.

b. Positive control cultures: Significant increases in mutant counts were observed with both EMS and 3-MC. These increases were within the historical ranges observed in this laboratory.

c. MBT treated cultures:

i. Test #1 (tables 3 & 4): In the presence of metabolic activation the HDT (4ug/ml) induced significant increases in both the mean mutant count and the mean mutant fraction (3.3 fold increase over vehicle control values). This dose produced a 75% decrease in cells survival (relative total growth). No mutagenic effect was observed with any of the lower concentrations. In the absence of metabolic activation a dose-related significant increase in both the mean mutant count and the mean mutant fraction was

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observed with 1 and 1.5 ug/ml (respective increases of mean mutant fraction were 2.3 and 15.2 folds over controls). These 2 concentrations were cytotoxic (respective decreases in cells survival were 59 and 94%).

ii. Test #2 (tables 5 & 6): In the presence of metabolic activation a reportedly weak but well-defined dose-related increase in mean mutant fraction was observed with all 3 concentrations (2, 3, and 4 ug/ml) of MBT used (respective increases over controls were 1.6, 2, and 2.5 folds). The increases in mean mutant count were present but were not dose-related. All 3 concentrations were cytotoxic (respective decreases in cells survival were 72, 90, and 99%). In the absence of metabolic activation a significant increase in mean mutant fraction, unaccompanied by a concomittant increase in mean mutant count, was observed with only the HDT (2.4 ug/ml, 2.1 fold increase). This concentration was very cytotoxic (97% decrease in cells survival).

D. CONCLUSIONS: According to the report "MBT from batch No. 160 is mutagenic in mouse lymphoma L5178Y cells, in the presence and absence of S9 ix, when tested in dimethylsulfoxide at concentrations extending into the toxic range".

D. REVIEWER' DISCUSSION/CONCLUSIONS:

Adequate data were presented to support the report's conclusions. The dosage ranges used were narrow due to the highly toxic nature of the test chemical but they were adequate. The methodology described was adequate, with at least duplicate cultures used for each experimental point. Under the experimental conditions of the study, MBT was positively mutagenic to the mouse lymphoma L5178Y tk⁺/tk⁻ cells line, but only at markedly toxic concentrations. The mutagenic effect of MBT 4 ug/ml (HDT in tests with metabolic activation) was confirmed in a repeat assay (test #2).

E. CORE CLASSIFICATION: ACCEPTABLE

F. REFERENCES: A copy of the references is attached.

PAGES 30 THROUGH 41 HAVE BEEN REMOVED. THOSE PAGES CONSIST OF REGISTRANT-SUBMITTED DATA.

PAGE 42 CONSISTS OF DRAFT LABELING AND HAS BEEN REMOVED FROM THIS REVIEW.