Chemical Name: Methyl Isothiocyanate (MITC)

REVISED REPORT (Replaces Document Dated 1/26/95)

PC Code: 068103

Based a review of the toxicology database for the chemical listed above, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories below. A brief capsule of the study is presented for use in preparation of risk assessments.

Where no appropriate data have been identified or a risk assessment is not warranted, this is noted. Data required to describe the uncertainties in the risk assessment due to the toxicology database are presented. These include but are not limited to extrapolation from different time frames or conversions due to route differences. If route to route extrapolation is necessary, the data to perform this extrapolation are provided.

Reviewer: Mike Ioannou  
Date: 2/24/95

Branch Chief: Marcia van Gemert  
Date: 2/24/95

Dermal Absorption Data (If available)

MRID:

% absorbed: No dermal absorption data are available - Assume 100% absorption

0
Acute Dietary Endpoint (One Day)

Study Selected - Guideline No.: Developmental Toxicity Study - Rat (83-3a)

MRID No.: 00150077

Summary: In a developmental toxicity study, pregnant rats were administered (by gavage) MITC at dose levels of 0, 1, 5 and 25 mg/kg/day, on gestation days 6-15. The developmental toxicity LOEL = 25 mg/kg/day (tentative)* based on decreased mean fetal weight and decreased crown-rump length values at this level. The Developmental NOEL = 5 mg/kg/day (tentative)*. Maternal toxicity, in the form of decreased body weight gain and food intake on days 6-15, was observed at the 25 mg/kg/day dose level. Maternal toxicity NOEL = 5 mg/kg/day (tentative); maternal toxicity LOEL = 25 mg/kg/day.

Endpoint and dose for use in risk assessment: Developmental NOEL = 5 mg/kg/day (tentative)*, based on decreased mean fetal weight and crown-rump length values at the 25 mg/kg/day dose level.

Comments about study and/or endpoint: * This study has been classified as Core-Supplementary and does not fulfill the guideline requirements for a developmental toxicity study (83-3a) in rats. The registrant is required to provide additional data and/or clarifications for possibly upgrading this study.

This risk assessment is required.

Short Term Occupational or Residential Exposure (1 to 7 Days)
A. Dermal Exposure

Study Selected - Guideline No.: Developmental Toxicity Study-Rat (83-3a)

MRID No.: 00150077

Summary: See Summary under "Acute Dietary Endpoint" above.

Endpoint and dose for use in risk assessment: Developmental NOEL = 5 mg/kg/day (tentative) based on decreased mean fetal weight and crown-rump length values observed at the 25 mg/kg/day dose level.

Comments about study and/or endpoint: See comments under "Acute Dietary Endpoint" above.

This risk assessment is required.

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Short Term Occupational or Residential Exposure (1 to 7 Days)

B. Inhalation Exposure

Study Selected - Guideline No.: 90-Day Inhalation Study-Rat (82-4)

MRID No.: 412214-07

Summary: In a 90 day inhalation study, rats were exposed (nose only) to MITC at 0, 2.1, 20.6 and 91.9 μg/L. Systemic toxicity, in the form of decreased body weight gain, decreased food efficiency decreased blood protein value and increased water intake, was observed at the 20.6 μg/L dose level and above. The LOEL = 20.6 μg/L and the NOEL 2.1 μg/L.

Endpoint and dose for use in risk assessment: NOEL = 2.1 μg/L based on decreased body weight gain, decreased food efficiency, decreased blood protein values and increased water intake observed at the 20.6 μg/L dose level.

Comments about study and/or endpoint: None

This risk assessment is required.

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Intermediate Term Occupational or Residential (1 Week to Several Months)

A. Dermal Exposure

Study Selected - Guideline No.: Developmental Toxicity Study-Rat (83-3a)

MRID No.: 00150077

Summary: See Summary under "Acute Dietary endpoint" above.

Endpoint and dose for use in risk assessment: Developmental NOEL = 5 mg/kg/day (tentative) based on decreased mean fetal weight and crown-rump length values observed at the 25 mg/kg/day dose level.

Comments about study and/or endpoint: See comments under "Acute Dietary Endpoint" above.

This risk assessment is required.

Intermediate Term Occupational or Residential (1 Week to Several Months)

B. Inhalation Exposure

Study Selected - Guideline No.: 90-Day Inhalation Study-Rat (82-4)

MRID No.: 412214-07

Summary: In a 90 day inhalation study, rats were exposed (nose only) to MITC at 0, 2.1, 20.6 and 91.9 µg/L. Systemic toxicity, in the form of decreased body weight gain, decreased food efficiency, decreased blood protein values and increased water intake, was observed at the 20.6 µg/L dose level and above. The LOEL = 20.6 µg/L and the NOEL = 2.1 µg/L, in both sexes.

Endpoint and dose for use in risk assessment: NOEL = 2.1 µg/L based on decreased body weight gain, decreased food efficiency, decreased blood protein values and increased water intake observed at the 20.6 µg/L dose level.

Comments about study and/or endpoint: None

This risk assessment is required.
Cancer Classification and Basis: The rat and mouse carcinogenicity studies conducted with MITC, although they were negative for carcinogenicity, they did not satisfy the guideline requirement (not tested at high enough dose levels and/or had major deficiencies) and thus, the carcinogenic potential of MITC is still unknown. The RfD/Peer Review Committee classified MITC as Group D because of inadequate data.

Q1* = None

RfD and basis: No RfD value has been established for this chemical. The HED RfD/Peer Review committee has evaluated MITC in February 1995 and determined that an RfD value does not need to be established at present.

NOEL for critical study: N/A

Study Type - Guideline No.: N/A

MRID: N/A
Acute Toxicity Studies for Methyl Isothiocyanate (MITC)

<table>
<thead>
<tr>
<th></th>
<th>Toxicity Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>81-1</td>
<td>Acute Oral LD50-Rat = 95 mg/kg (female &amp; Male)</td>
</tr>
</tbody>
</table>
| 81-2 | Acute Dermal LD50-Rabbit = 145 mg/kg male  
- Rat = 202 mg/kg female  
- Rat = 181 mg/kg (female) | 1 |
| 81-3 | Acute Inhalation LC50-Rat = <0.0296 mg/L | 1 |
| 81-4 | Primary Eye Irritation-Rabbit - Corrosive | 1 |
| 81-5 | Primary Dermal Irritation-Rabbit - Animals died shortly after treatment | 1 |
| 81-6 | Dermal Sensitization-Guinea Pigs - Mild Sensitizer |
instances approached spontaneous revertant rates when plates were reinoculated for an additional 24 hours. However, this is the expected result for microbial cells exposed to cytotoxic compounds. Furthermore, since methyl isothiocyanate is volatile, it is likely that when the plates were opened for the initial colony counting, the test material evaporated and was not present during the additional incubation time.

As further shown in Table 1, all strains responded to the mutagenic action of the corresponding nonactivated and S9-activated positive controls.

2. **DNA Damage/Repair Test:** In contrast to the severe cytotoxicity for *S. typhimurium* and *E. coli*, the test material had no effect on the survival of DNA repair-competent or DNA repair-deficient strains of *B. subtilis* at doses up to 2000 μg/disc (Table 2). Because no precautions were taken to prevent compound loss, it is possible that little or no methyl isothiocyanate was available to interact with the bacterial cells.

From the overall findings, the study author concluded that methyl isothiocyanate was negative in the rec-assay and also in the reverse-mutation tests.

**D. REVIEWERS' DISCUSSION/CONCLUSIONS:** We assess that methyl isothiocyanate was adequately tested in the mutation assay, and caused moderate-to-severe cytotoxicity at levels ≥50 μg/disc −S9 or ≥100μg/disc +S9, but did not induce a mutagenic effect. A negative in the spot test is generally not considered to be a sufficient indication of nonmutagenicity in *S. typhimurium* or *E. coli* because the procedure is only qualitative and limits the number of microorganisms that can be exposed to the test material. However, the method employed by the study director (i.e., test material dilutions prepared in sealed tubes and individually-sealed dishes) assured that all organisms on a given dish were exposed to methyl isothiocyanate. Similarly, the induced cytotoxic response supports the assessment that conditions were adequate for test material-cell interaction. It is, therefore, doubtful that performance of the more elaborate desiccator assay for gases and/or vapors would substantively alter the outcome of the methyl isothiocyanate gene mutation spot test.

The DNA damage/repair assay, however, is not acceptable for the following reasons:

1. No precautions were taken to prevent compound loss.
2. There was no indication of cytotoxicity at any level.
3. Only a nonactivated test was performed.
4. Only single replicates were used.

Based on these considerations, we conclude that the gene mutation assay is acceptable and that the microbial DNA damage/repair assay is unacceptable.
Table 2: Representative Results of the *Bacillus subtilis* DNA Damage/Repair (REC) Assay with Methyl Isothiocyanate

<table>
<thead>
<tr>
<th>Substance</th>
<th>Dose (µg/disc)</th>
<th>Inhibition Zone (mm)</th>
<th>Difference (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimethylsulfoxide</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Negative Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanamycin</td>
<td>10</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Positive Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>0.1</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Test Material</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyl isothiocyanate</td>
<td>2000</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*a Results were from single plates containing both H17 and M45.*

*b Positive results were assumed by our reviewers to be a minimum of 5 mm difference in the zone of inhibition between the rec<sup>−</sup> and the rec<sup>+</sup> strains (see Hishieko, H. 1975. Mutagenic activities of metal compounds in bacteria. *Mutat. Res.* 31:185-189).*

*c Findings for lower doses (20, 100, 200, 500, and 1000 µg/disc) were negative.*

Data were extracted from the study report, p. 10.
Methylisothiocyanate

SALMONELLA/E. COLI/B. SUBTILIS

E. QUALITY ASSURANCE MEASURES: Was the test performed under GLPs? No (A statement from the sponsor signed and dated August 24, 1989 indicated that the study was conducted prior to the US EPA requirements of GLPs).

F. APPENDIX: None attached
MEMORANDUM

SUBJECT: Methylisothiocyanate (MITC) Phase IV Data Response

FROM: Ray Landolt 9/3/92
Review Section I
Toxicology Branch II
Health Effects Division (H7509C)

TO: Barbara Bischof PM 51
Accelerated Reregistration Branch
Special Review and Reregistration Division (H7509W)

THRU: Mike Ioannou, Section Head
Review Section I
Toxicology Branch II
Health Effects Division (H7509C)

Marcia van Gemert, Branch Chief
Toxicology Branch II
Health Effects Division (H7509C)

Registrant: Degussa Corporation

Action Requested: 1. Data waiver requests for two generation reproduction (83-4) and general metabolism (85-1) studies.

2. Provide comments on protocol for Estimation of Inhalation (231) and Dermal (232) Exposures for MITC at Outdoor Sites.

Conclusion: 1. Data waiver requests for two generation reproduction (83-4) and general metabolism (85-1) studies are not applicable to the Phase IV Toxicology Data Review which concluded that these two studies are not required for the terrestrial nonfood use registered by Degussa Corporation.

2. The protocol for estimation of dermal and inhalation exposure assessment should provide for continuous monitoring during the treatment of each timber.
Consideration Given this Request

1. The Accelerated Reregistration Branch (SRRD) requests review and comment on data waivers for a two generation reproduction (83-4) and general metabolism (85-1) studies.

Methylisothiocyanate is registered as a "Fungicide for Wood". The directions for use recommend treating structural timbers such as utility poles, bridge timbers and laminated wood products (MITC-FUME label).

This use is considered a terrestrial nonfood use. These two studies (83-4 and 85-1) were not data requirements with Phase IV Toxicology data request.

The registrant's correspondence reply to the requirements status for a two generation reproduction and general metabolism study has cited Reregistration Phase III comments that these studies are "not required for the registrant's use pattern". This is correct.

2. Protocol for Estimation of Inhalation (231) and Dermal (232) Exposure for MITC at Outdoor Sites.

To be effective in the control of decay in wooden timbers, MITC would be expected to migrate through the untreated wood. Exposure to the applicator may occur during the application of each vial (5 to 10 seconds) as well as following the release from each broken vial through fissures in the timber. Monitoring for MITC should be continuous for each timber treated.