TOXICOLOGY ENDPOINT SELECTION DOCUMENT

Chemical Name: METHOMYL

PC Code: 090301

Structure

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{N} \quad \text{O} \\
\text{S} & \quad \text{HN} \\
\text{CH}_3 & \quad \text{O} \\
\end{align*}
\]

Methomyl

The Health Effects Division Toxicology Endpoint Selection Committee considered the available toxicology data for Methomyl at a meeting held on October 9, 1996. Based upon 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.

TOXICOLOGIST:  
Yung G. Yang, Ph.D.  
Date: _____

SECTION HEAD:  
K. Clark Swentzel  
Date: _____

ACTING BRANCH CHIEF:  
Yiannakis M. Ioannou, Ph.D.  
Date: _____
DERMAL ABSORPTION DATA:

A dermal absorption rate of 32% was calculated based on the LOEL of 16 mg/kg/day established in the developmental toxicity study in rabbits and the LOEL of 50 mg/kg/day established in the 21-day dermal study in the same species. In the developmental toxicity study, the LOEL was based on clinical signs indicative of neurotoxicity and in the 21-day dermal toxicity study, the LOEL was based on decreases in plasma and brain cholinesterase activity. The 32% dermal absorption rate will be used for the chronic risk assessment since an oral (dietary) study was selected for this exposure scenario.

MRID No: Developmental Toxicity Study in Rabbits (00131257)
21-Day Dermal Toxicity Study in Rabbits (41251501)

% absorbed: 32%

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ACUTE DIETARY ENDPOINT (ONE DAY)

Study Selected - Guideline No.: Developmental Toxicity Study in Rabbits (§83-3)

MRID No.: 00131257

Summary: Methomyl (98.7%, a.i.) was administered via stomach tube to 20 presumed pregnant New Zealand white (DNL:NZW) rabbits per group (19 in the high-dose group) at dosages of 2, 6 and 16 mg/kg/day on gestation days 7 through 19. One rabbit in the 6 mg/kg/day and 7 in the 16 mg/kg/day groups were found dead during the study. It was determined during necropsy that the stomach was perforated near the cardiac sphincter in the mid-dose rabbit. Clinical signs indicated neurological effects in high-dose rabbits which included tremors, hyperactivity, body jerks, excess salivation, aggressive behavior (stamping of hind feet), hyperpnea, convulsions, ataxia, impaired or lost righting reflex, self-inflicted or spontaneous lesions (skin lesion on the neck and pannus), dyspnea, hypersensitivity, pin-point pupils and vocalization. Excess salivation, a clear discharge around the mouth and nose, was seen at necropsy in rabbits which died. There was no evidence of developmental toxicity in this study. Therefore, the NOEL for developmental toxicity is 16 mg/kg/day. The NOEL for maternal toxicity was 6 mg/kg/day and the LOEL was 16 mg/kg/day based on mortalities and clinical signs.

Dose and Endpoint for use in risk assessment: NOEL = 6 mg/kg/day based on deaths in dams on days 1-3 after dosing at 16 mg/kg/day (LOEL).

Comments about study and/or endpoint: For calculating the MOE, an extra safety factor of 3 will be used in addition to the 100 (i.e., MOE = 300) due to the lack of acute and subchronic neurotoxicity studies (data gaps) as well as the severity of effects (death in 1-3 days) seen at the 6 mg/kg/day dose.

This risk assessment is required.

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SHORT TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 TO 7 DAYS)

DERMAL EXPOSURE:

Study Selected - Guideline No.: 21-Day Dermal Toxicity Study in Rabbits (§82-2)

MRID No.: 41251501

Summary: New Zealand White rabbits (10/sex/group for the control and high-dose; 5/sex/group for the low- and mid-dose) were dermally exposed to methomyl (98.35%, a.i.) for 21 days at dose levels of 0, 5, 50 or 500 mg/kg/day. One high-dose female was found dead due to a fracture at the thoracic-cervical junction of the vertebral column. Clinical signs included hyperactivity (increased reaction to stimuli-noise) at the high-dose (both sexes). At Day 21, mid- and high-dose males and high-dose females displayed significantly lower plasma cholinesterase (ChE) activities. Mean RBC ChE activity was also decreased, but only slightly, at the high-dose (both sexes). Brain ChE activity was significantly decreased at the high-dose (both sexes). At the mid-dose, although not statistically significant, inhibition of brain ChE activity was indicated (3/5 males and 4/5 females exhibited brain ChE inhibition when compared with controls). The NOEL for systemic toxicity is 5 mg/kg/day and the LOEL is 50 mg/kg/day based on brain and plasma ChE inhibitions. No dermal irritation was observed.

Dose and Endpoint for use in risk assessment: NOEL = 5 mg/kg/day based on the brain ChE inhibition in both sexes at 50 mg/kg/day (LOEL).

Comments about study and/or endpoint: At 50 mg/kg/day, 3/5 in males and 4/5 in females exhibited brain ChE inhibition and at 500 mg/kg/day (HDT) both sexes exhibited clinical signs (hyperactivity). An MOE of 100 should be adequate for this risk assessment.

This risk assessment is required.
INTERMEDIATE TERM OCCUPATIONAL OR RESIDENTIAL EXPOSURE (1 WEEK TO SEVERAL MONTHS)

DERMAL EXPOSURE:

Study Selected - Guideline No.: 21-Day Dermal Toxicity Study in Rabbits (§82-2)

MRID No.: 41251501

Summary: New Zealand White rabbits (10/sex/group for the control and high-dose; 5/sex/group for the low- and mid-dose) were dermally exposed to methomyl (98.35%, a.i.) for 21 days at dose levels of 0, 5, 50 or 500 mg/kg/day. One high-dose female was found dead due to a fracture at the thoracic-cervical junction of the vertebral column. Clinical signs included hyperactivity (increased reaction to stimuli-noise) at the high-dose (both sexes). At Day 21, mid- and high-dose males and high-dose females displayed significantly lower plasma cholinesterase (ChE) activities. Mean RBC ChE activity was also decreased, but only slightly, at the high-dose (both sexes). Brain ChE activity was significantly decreased at the high-dose (both sexes). At the mid-dose, although not statistically significant, inhibition of brain ChE activity was indicated (3/5 males and 4/5 females exhibited brain ChE inhibition when compared with controls). The NOEL for systemic toxicity is 5 mg/kg/day and the LOEL is 50 mg/kg/day based on brain and plasma ChE inhibitions. No dermal irritation was observed.

Dose and Endpoint for use in risk assessment: NOEL = 5 mg/kg/day based on the brain ChE inhibition in both sexes at 50 mg/kg/day (LOEL).

Comments about study and/or endpoint: At 50 mg/kg/day, 3/5 in males and 4/5 in females exhibited brain ChE inhibition and at 500 mg/kg/day (HDT) both sexes exhibited clinical signs (hyperactivity). An MOE of 100 should be adequate for this risk assessment.

This risk assessment is required.
CHRONIC OCCUPATIONAL OR RESIDENTIAL EXPOSURE (SEVERAL MONTHS TO LIFETIME)

DERMAL EXPOSURE:

Study Selected - Guideline No.: 2-Year Feeding Study in Dogs (§83-1)

MRID No.: 00007091

Summary: Male and female beagle dogs (4/sex/group) were fed diets with methomyl (90%) at levels of 50, 100, 400 and 1000 ppm (1.25, 2.5, 10 and 25 mg/kg/day by conversion, respectively) for 24 months. Two males at the 1000 ppm group exhibited tremors, salivation, incoordination, and circling movements during the 13th week of the study. One female in the 1000 ppm group died in the 9th week of the study. A replaced dog exhibited repeated convulsive seizures after 17 days of dosing and died on day 18. The effects in kidneys seen at 400 ppm in both sexes included swollen/irregular epithelial cells of the proximal convoluted tubules as well as an increase in the amount of pigment in the cytoplasm of these cells. The following effects were observed at the 1000 ppm level in both sexes: 1) in addition to the effects in kidneys seen at 400 ppm, "irregularity" of the luminal border in the proximal convoluted tubules, 2) bile duct proliferation, 3) extramedullary hematopoiesis in liver and spleen and 4) increased hematogenic activity. RBC parameters (hematocrit, RBC count and hemoglobin) were obviously depressed in one male throughout the study and appeared to be slightly depressed in the remaining males, however, it is difficult to make quantitative comparisons between these data since summary tables were not provided in the report. The following increased organ weights were seen in high-dose males only: (absolute/relative to body weight) liver = +4.9/27.6%, spleen= +23.7/36.4%, kidneys = +6.2/22.1%. The histopathologic changes in these organs were noted above. The NOEL is 100 ppm (2.5 mg/kg/day) and the LEL is 400 ppm (10.0 mg/kg/day) based on the noted effects in kidneys.

Dose and Endpoint for use in risk assessment: NOEL = 2.5 mg/kg/day based on renal toxicity in both sexes manifested as swollen/irregular epithelial cells of the proximal convoluted tubules as well as an increase in the amount of pigment in the cytoplasm of these cells at 10.0 mg/kg/day (LOEL).

Comments about study and/or endpoint: This study/dose level was used to establish the RfD. For calculating the MOE, an extra safety factor of 3 will be used in addition to the 100 (i.e., MOE = 300) due to the lack of acute and subchronic neurotoxicity studies (data gaps). The dose of 2.5 mg/kg/day should be corrected for 32% dermal absorption for this risk assessment.

This risk assessment is required.

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INHALATION EXPOSURE (ANY TIME PERIOD):
Study Selected - Guideline No.: Acute Inhalation Study in Rats (§81-3)

MRID No.:42140102

Summary: Crl:CD BR rats (5/sex/group) were exposed nose only for 4 hours to methomyl (97.7%, a.i.) at airborne concentrations of 0.137, 0.181, 0.182, 0.232, or 0.326 mg/L. The MMAD ranged from 1.3 to 3.8 μm. Chamber test atmospheres consisted of particles: 6.2 to 40% which were less than 1 μm, 38 to 84% less than 3 μm and 85 to 99% less than 10 μm. There were no mortalities at the 0.137 or 0.181 mg/L concentration. Mortalities were observed at all of the other concentrations: 1/10, 6/10, and 7/10 at 0.182, 0.232, and 0.326 mg/L, respectively. Clinical signs among rats that died included abnormal gait, tremors, hyperactivity, hyperreactivity, muscle fasciculation and hunched or low posture. The NOEL is 0.137 mg/L and the LOEL is 0.182 mg/L based on mortality and clinical signs of neurotoxicity.

Dose and Endpoint for use in risk assessment: NOEL = 0.137 mg/L based on mortality and clinical signs of neurotoxicity at 0.182 mg/L (LOEL).

Comments about study and/or endpoint: This risk assessment will be performed only if exposure is greater than 1%.

Special Instructions for Combining Risk from Dermal and Inhalation Exposure: The risk due to dermal and inhalation exposure needs to be combined because of a common endpoint (i.e., clinical signs of neurotoxicity seen following dermal and inhalation exposures). The following procedure is to be followed.

Combining MOEs:

The combined risk resulting from dermal and inhalation exposure to methomyl may be calculated by combining MOEs for these routes. The following equation should be used to calculate a total MOE (MOE_T):

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MOE_T = \frac{1}{\frac{1}{MOE_{dermal}} + \frac{1}{MOE_{inhalation}}}
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CANCER CLASSIFICATION AND BASIS:

Group E, i.e. the chemical is not likely to be carcinogenic to human via relevant routes of exposure (RfD Peer Review, 9/5/96).

Qₙ = Not applicable

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RfD AND BASIS:

RfD value is 0.008 mg/kg/day based on a two-year feeding study in dogs and an uncertainty factor of 300.

NOEL for critical study: 2.5 mg/kg/day

Study Type - Guideline No.: Two-year feeding study in dogs (§83-1)

MRID: 00007091

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ACUTE TOXICITY ENDPOINTS:

Acute Toxicity of **Methomyl**

<table>
<thead>
<tr>
<th>Guideline No.</th>
<th>Study Type</th>
<th>MRID #(S.)</th>
<th>Results</th>
<th>Toxicity Category</th>
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<td>81-1</td>
<td>Acute Oral</td>
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<td>LD₅₀ = 34 (M), 30 (F) mg/kg</td>
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<td>Acute Dermal</td>
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<td>LD₅₀ = &gt;2000 mg/kg (M&amp;F)</td>
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<td>Acute Inhalation</td>
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<td>LC₅₀ = 0.258 mg/L (M&amp;F)</td>
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<td>Corneal opacity</td>
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<td>Negative</td>
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