TOXICOLOGY ENDPOINT SELECTION DOCUMENT

Chemical Name: Carbofuran

PC Code: 090601

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 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: ______________________ Date: 3/4/97
William Dykstra

Branch Chief: Mike Metzger _________ Date: 3/4/97
Mike Metzger
Dermal Absorption Data: None available

MRID: None

% absorbed: Use default value of 100%

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ACUTE DIETARY ENDPOINT (ONE DAY)

Study Selected - Guideline No.: Human Study

MRID No.: 00092826

Summary: Nine male volunteers received placebo [1 subject], 0.05 mg/kg BW [2 subjects], 0.10 mg/kg BW [2 subjects], or 0.25 mg/kg BW [4 subjects] as single oral doses. Blood cholinesterase and physical signs were measured. The NOEL is 0.05 mg/kg BW and RBC cholinesterase depression was 22% and 11% after dosing and there were no clinical symptoms. The LOEL is 0.10 mg/kg BW and the clinical symptoms were headache and light-headed. RBC cholinesterase depression was 35% and 31% after dosing. At 0.25 mg/kg BW, there were severe clinical symptoms and signs and RBC cholinesterase depression was 62%, 63%, 46%, and 59%. The placebo had RBC depression of 10%.

Dose and Endpoint use in risk assessment: NOEL = 0.05 mg/kg BW based on the clinical symptoms and cholinesterase inhibition at 0.10 mg/kg BW (LOEL).

Comments about study and/or endpoint: MOE of 100 needed due to single sex, few subjects, steep dose-response, clinical symptoms at LOEL of 0.10 mg/kg BW in addition to RBC cholinesterase depression.

Uncertainty factor: MOE of 100 needed for acute dietary endpoint risk assessment.

This risk assessment is required.

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

Study Selected - Guideline No.: Human Study with Furadan 4 Flowable (4F)

MRID No.: 00092826

Summary: Groups of 2 human male volunteers were treated dermally for 4 hours with Furadan 4F at doses of 0.5 mg/kg BW, 1.0 mg/kg BW, 2.0 mg/kg BW, and 4.0 mg/kg BW. Measurements of RBC cholinesterase were made and reported with peak values occurring at 4 hours post-treatment.  Dose [mg/kg]  % RBC depression  Symptoms

<table>
<thead>
<tr>
<th>Dose [mg/kg]</th>
<th>% RBC depression</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>22%, 7%</td>
<td>stomach upset, burning at site</td>
</tr>
<tr>
<td>1.0</td>
<td>29%, 21%</td>
<td>None</td>
</tr>
<tr>
<td>2.0</td>
<td>42%, 40%</td>
<td>None</td>
</tr>
<tr>
<td>4.0</td>
<td>61%, 49%</td>
<td>Severe</td>
</tr>
</tbody>
</table>

NOEL considered to be 0.5 mg/kg BW and LOEL at 1.0 mg/kg BW with depression of RBC cholinesterase as effect.

Dose and Endpoint and dose for use in risk assessment: NOEL = 0.5 mg/kg BW.

Comments about study and/or endpoint: MOE of 30 required for risk assessment since LOEL does not include clinical symptoms.

This risk assessment is required.

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INTERMEDIATE TERM OCCUPATIONAL OR RESIDENTIAL (1 WEEK TO SEVERAL MONTHS)

Study Selected - Guideline No.: Human study

MRID No.: 00092826

Summary: See Short-Term

Dose and Endpoint for use in risk assessment: NOEL = 0.5 mg/kg BW.

Comments about study and/or endpoint: MOE of 30 required for risk assessment since LOEL does not include clinical symptoms.
This risk assessment is required.
LONG-TERM OCCUPATIONAL OR RESIDENTIAL (1 WEEK TO SEVERAL MONTHS)

Study Selected - Guideline No.: Human study
MRID No.: 00092826

Summary: See Short-Term

Dose and Endpoint for use in risk assessment: NOEL = 0.5 mg/kg BW.

Comments about study and/or endpoint: MOE of 30 required for risk assessment since LOEL does not include clinical symptoms.

This risk assessment is required.

INHALATION EXPOSURE (ANY TIME PERIOD)

In a 1967 WHO reported acute inhalation study with monkeys, the NOEL was 0.00056 mg/L and the LOEL was 0.00086 mg/L based on emesis for a 6 hour exposure to carbofuran dust. Tremors were seen at 0.0013 mg/L and the LC₅₀ was 0.002 mg/L. This is the lowest LC₅₀ for any animal species listed in the one-liners. Discussion with K. Swentzel of the TES Committee resulted in the conclusion that an additional 10-fold modifying factor should be added to the NOEL, due to the steep dose-response, resulting in a NOAEL of 0.000056 mg/L for use in calculating MOEs for worker inhalation exposure.

NOAEL = 0.000056 mg/L for 6 hour inhalation exposure. MOE of 100 required.

The Furadan 4 Flowable (4F) is Danger Toxicity Category I (according to the label). The available LC₅₀ study with the Furadan 4F is based on a 1 hour chamber exposure and nominal concentrations. The reported LC₅₀ was in Toxicity Category IV and was 25.3 mg/L. Based on discussions with W. Burnam on 3/6/97, the TES endpoint based on the monkey study should be used.

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CANCER CLASSIFICATION AND BASIS: Using the revised Carcinogenicity Assessment Guidelines, the RFD/Peer Review Committee has classified carbofuran as "No likely" to be a human carcinogen based on the lack of evidence of carcinogenicity in mice or rats. Q₁* = Not Required

R₃D and basis: 0.0005 mg/kg/day

NOEL for critical study: single dose human oral study

Study Type - Guideline No.: None

MRID: 00092826

<table>
<thead>
<tr>
<th>Guideline #</th>
<th>Study</th>
<th>Results</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>81-1</td>
<td>Acute oral</td>
<td>σ 7.8 mg/kg, φ 6.0 mg/kg</td>
<td>I</td>
</tr>
<tr>
<td>81-2</td>
<td>Acute dermal</td>
<td>250 mg/kg</td>
<td>II</td>
</tr>
<tr>
<td>81-3</td>
<td>Acute inhalation</td>
<td>0.08 mg/L</td>
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</tr>
<tr>
<td>81-4</td>
<td>Primary eye irritation</td>
<td>minimal irrit.</td>
<td>III</td>
</tr>
<tr>
<td>81-5</td>
<td>Primary dermal irritation</td>
<td>PIS/0.25</td>
<td>IV</td>
</tr>
<tr>
<td>81-6</td>
<td>Dermal sensitization</td>
<td>none</td>
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