DATA EVALUATION REPORT

Summary

Study Type: Subacute Inhalation Toxicity in Rats

Prepared for:
Office of Pesticide Programs
U.S. Environmental Protection Agency
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Arlington, VA 22202

Prepared by:
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March 19, 1993

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Contract Number: 68D10075
Work Assignment Number: 1-122
Clement Number: 93-107
Project Officer: Caroline Gordon
DATA EVALUATION REPORT

STUDY TYPE: Subacute inhalation toxicity - rat

TEST MATERIAL: Sumilaryv

SYNONYMS: S-31183

STUDY NUMBER: 728

SPONSOR: Sumitomo Chemical Company, Limited
5-33, Kitahama 4-Chome, Chuo-Ku
Osaka 541, Japan

TESTING FACILITY: Same

TITLE OF REPORT: Sumilaryv -- Subacute Inhalation Toxicity Study of S-31183 in Rats

AUTHOR: Shinobu Kawaguchi

REPORT ISSUED: Study completed April 14, 1988

CONCLUSIONS: This study is classified as Supplementary and is not upgradeable. Sprague-Dawley rats (10/sex/group) were administered Sumilaryv by inhalation for 4 weeks, 7 days/week, for 4 hours/day.

NOEL = 482 mg/m³

LEL = 1,000 mg/m³ based on salivation in 3 males and 4 females during the first few days of exposure, body weight was decreased in males throughout the test period, and serum lactate dehydrogenase was elevated 44% in males.

CORE CLASSIFICATION: This study is classified as Supplementary because the stability of the test material and the characteristics of the exposure atmospheres were inadequately characterized and the inhalation equipment did not provide an adequate dynamic air flow rate.
A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

   Name: Sumilarv (technical grade)

   Formula: [4-phenoxypenyl (RS)-2-(2-pyridyloxy) propyl ether

   Structure: Not available

   Batch number: PTG-86011

   Purity: 97.0%, impurities not identified

   Physical property: White solid

   Stability: Not reported

   Storage: Not reported

   Vehicle: Corn oil

2. Rationale for Dose Selection

   The exposure levels used in the current study were selected based on an acute inhalation study that showed salivation and urinary incontinence in rats exposed to atmospheres generated from a 50% solution of the test chemical in corn oil.

3. Test Article Analyses for Purity and Stability

   The test material was prepared as 12.5% (Group 3), 25% (Group 4), or 50% (Group 5) solutions in corn oil. No information was provided regarding how frequently these solutions were prepared. There is no indication that the prepared solutions were analyzed for content or stability at any time.

   No information was provided regarding analysis of the test material for purity. Two times/week, at each exposure level, breathing zone samples for analysis of the test material were collected on silica gel sampling tubes by aspirating chamber air at a rate of 20 L/minute for 10 minutes, and analyzed by gas chromatography for test material concentration. (The EPA Pesticide Assessment Guideline Series 82-4 suggests that the concentration of test atmospheres be determined at least once per exposure period.) The actual mean concentrations of Sumilarv measured in the breathing zone were as follows:
269 ± 20.6 mg/m³
482 ± 38.3 mg/m³
1,000 ± 70.7 mg/m³

The vehicle-control atmospheres were generated using corn oil without added Sumilary. See Table 1 for the actual concentration data for test material and vehicle.

4. Exposure Conditions

Exposures (4 hours/day, 7 days/week, for 4 weeks) were conducted in a whole-body exposure system (Figure 1). (EPA Pesticide Assessment Guideline Series 82-4 recommends that exposures be conducted for 6 hours/day, 5 days/week, for 90 days.) Ten animals were placed in cages inside the inhalation chamber. Exposure atmospheres were generated by using a glass atomizer. Atmospheres were passed through a 3-L container to remove coarse droplets before atmospheres entered the chamber. Air flow through the chamber was reported to have been 50 L/min, but the report did not state that air flow was monitored during the experiment. (EPA Pesticide Assessment Guideline Series 82-4 suggests that air flow be monitored at least every 60 minutes.) The rate of air exchange within the chamber, calculated by the reviewers, was approximately 5 exchanges/hour \((0.050 \text{ m}^3/\text{min} \times 60 \text{ min} + 0.64 \text{ m}^3)\). This rate of exchange is below the 12-15 exchanges/hour recommended in EPA Pesticide Assessment Guideline Series 82-4. Temperature and relative humidity in the exposure chamber were reported to have been measured at 10-minute intervals during every exposure period using a system by Elwa Seiko Co., Ltd. The temperature and humidity data were not presented in the study report.

The aerosol droplets generated were in the respirable range (see Table 1 for MMAD and GSD data). Particle size distribution was determined 2 times/week at 30-80 minutes after the the beginning of exposure using a Microscopic Sedimentation Analyzer (SA-M1D type, Simadzu Corp). The twice-weekly analysis of particle size in this study is less than the recommended analysis frequency of at least 1 time per exposure (EPA Pesticide Assessment Guideline Series 82-4). Chamber oxygen content was not measured, and the flow rate through the chamber may have been insufficient to ensure adequate oxygenation.

5. Animals

The animals used in this study were Sprague-Dawley rats received from Clea Japan, Inc. The rats were identified by painting the fur with picric acid. Rats were acclimatized to the caging and animal room conditions for 8-9 days prior to the initiation of exposures. During this period, the animals were examined for general physical condition. Based on the results of these examinations, 50 males and 50 females (10/sex/group) were selected for the study from a pool of
Guideline Series 82-4: Subchronic Inhalation Toxicity in the Rat

Fig. 1 Diagram of mist generator and animal exposure system for inhalation toxicity test.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Vehicle Control</th>
<th>Untreated Control</th>
<th>Low Dose</th>
<th>Mid Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual Sumilarv Tech. concentration (mg/m³)</td>
<td>NA</td>
<td>NA</td>
<td>269 ± 20.6</td>
<td>482 ± 38.3</td>
<td>1000 ± 70.7</td>
</tr>
<tr>
<td>MMAD (µm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower limit</td>
<td>0.71</td>
<td>NA</td>
<td>0.66</td>
<td>0.66</td>
<td>0.55</td>
</tr>
<tr>
<td>Upper limit</td>
<td>1.10</td>
<td>NA</td>
<td>1.17</td>
<td>1.11</td>
<td>0.97</td>
</tr>
<tr>
<td>Geometric S.D. (µm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower limit</td>
<td>1.23</td>
<td>NA</td>
<td>1.16</td>
<td>1.22</td>
<td>1.06</td>
</tr>
<tr>
<td>Upper limit</td>
<td>1.66</td>
<td>NA</td>
<td>1.67</td>
<td>1.78</td>
<td>1.54</td>
</tr>
<tr>
<td>Chamber temp. (°C)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Relative humidity (%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Oxygen content (%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Data extracted from Study #728, Table 2 and Appendix A

bMean ± standard deviation

NA = not applicable
NR = not reported
unspecified size. Throughout the acclimatization and exposure
periods, the animals were housed 5 to a cage in aluminum cages with
net floors which were changed twice per week. Pulverized feed (CE-2,
Clea Japan, Inc.) and filtered tap water were provided ad libitum
except during exposures. Animal room conditions were maintained as
follows: temperature, 23°C ± 2°; relative humidity, 55% ± 10%;
>10 air changes per hour; and a 12-hour light/dark cycle.

At the initiation of exposures, rats weighed between 172 and 201 g
(males) and between 120 and 177 g (females).

The 100 animals selected for the study were randomized using a
computerized random numbering scheme and assigned to the following
groups:

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent Solution in Corn Oil</th>
<th>Number of Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (vehicle control)</td>
<td>0% solution</td>
<td>10 Male</td>
</tr>
<tr>
<td>2 (untreated control)</td>
<td>Not applicable</td>
<td>10 Male</td>
</tr>
<tr>
<td>3</td>
<td>12.5% solution</td>
<td>10 Male</td>
</tr>
<tr>
<td>4</td>
<td>25% solution</td>
<td>10 Male</td>
</tr>
<tr>
<td>5</td>
<td>50% solution</td>
<td>10 Male</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 Female</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 Female</td>
</tr>
</tbody>
</table>

At the start of the study, mean body weights of all of the groups
were within 6% of their respective controls.

6. **Statistical Analyses**

Body weight, food and water consumption, and organ weights were
analyzed for homogeneity of variances using the F-test. Data with
homogeneous variances were compared using Student’s t-test. Data
with heterogeneous variances were compared using the Fisher-Behrens
test. (Such tests are more appropriate for comparing two groups.
When comparing more than two groups, as was the case in this study,
an analysis of variance would have been more appropriate.)
Hematology and clinical chemistry values were analyzed using an
analysis of variance. If a significant difference between groups was
observed, the groups were compared to the vehicle control using the
LSD method. Urinalysis data were compared using the Mann-Whitney U-
test.

7. **General Observations**

(a) **Mortality/moribundity/survival**

Animals were observed for mortality/moribundity each day prior to
the start of exposure and then after 0.5, 1, 2, 3, and 4 hours of
exposure.
No deaths occurred in treated animals. One female each from the untreated control and the vehicle control died during the study.

(b) **Clinical observations**

Animals were observed for adverse clinical signs each day prior to the start of exposure and then after 0.5, 1, 2, 3, and 4 hours of exposure. If toxic signs were manifest, animals were observed hourly after termination of exposure for a total of 4 hours or until the toxic signs subsided.

Salivation was observed in 3 males and 4 females in the high-dose group at least once during the first few days of exposure. No toxic signs were observed in treated rats after exposure day 5.

(c) **Body weights/food and water consumption**

**Body weights**--Individual body weights were determined immediately prior to the first exposure and 2 times per week throughout the study.

Body weight gain in males appeared to be lower than in controls throughout the period of exposure, but was significantly decreased only on days 10 and 24, respectively (Table 2). Body weight gain was significantly decreased in females on day 9.

**Food consumption**--Food consumption was measured 1 time per week throughout the study.

No effect on food consumption was observed.

**Water consumption**--Water consumption was measured 1 time per week throughout the study.

Water consumption was slightly (but significantly) increased in the high-dose females during study week 4 compared to the vehicle control. However, this appears to be of no biological significance.

(d) **Ophthalmoscopic examination**

Ophthalmological examinations, using an ophthalmoscope (Valifocal Ophthalmoscope, Rud. Rieter Co.), were performed on all surviving rats in the vehicle control group and the low- and high-dose groups. Males were examined on study day 25 and females were examined on study day 26. No preexposure examinations were reported. (EPA Subdivision F Guideline Series 82-4 suggests that animals be examined both prior to exposure and at termination.)
Table 2. Mean Body Weight Gains for Rats Exposed to Atmospheres Containing Sumilarv Technical for 4 Weeks\(^a, b\)

<table>
<thead>
<tr>
<th>Exposure level (mg/m(^3))</th>
<th>0-3</th>
<th>0-7</th>
<th>0-10</th>
<th>0-14</th>
<th>0-17</th>
<th>0-21</th>
<th>0-24</th>
<th>0-27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle control</td>
<td>26±5.2</td>
<td>59±7.4</td>
<td>81±7.5</td>
<td>108±8.2</td>
<td>130±10.8</td>
<td>156±12.2</td>
<td>163±13.1</td>
<td>182±15.2</td>
</tr>
<tr>
<td>Untreated control</td>
<td>30±4.9</td>
<td>64±6.1</td>
<td>88±9.6</td>
<td>114±12.8</td>
<td>135±15.1</td>
<td>157±16.4</td>
<td>165±18.2</td>
<td>186±20.4</td>
</tr>
<tr>
<td>269</td>
<td>25±4.3</td>
<td>58±7.4</td>
<td>81±9.1</td>
<td>107±12.2</td>
<td>127±15.0</td>
<td>150±18.2</td>
<td>156±20.5</td>
<td>179±21.8</td>
</tr>
<tr>
<td>482</td>
<td>28±4.8</td>
<td>59±5.5</td>
<td>81±3.7</td>
<td>108±7.2</td>
<td>130±9.4</td>
<td>153±9.2</td>
<td>157±12.1</td>
<td>181±13.3</td>
</tr>
<tr>
<td>1,000</td>
<td>19±9.6</td>
<td>50±12.7</td>
<td>69±16.8(^*)</td>
<td>95±22.2</td>
<td>115±22.5</td>
<td>137±25.6</td>
<td>143±26.4(^*)</td>
<td>160±31.6</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle control</td>
<td>12±7.0</td>
<td>19±8.7</td>
<td>29±8.0</td>
<td>32±9.7</td>
<td>44±7.1</td>
<td>49±7.7</td>
<td>56±13.9</td>
<td>64±14.5</td>
</tr>
<tr>
<td>Untreated control</td>
<td>9±6.7</td>
<td>20±6.9</td>
<td>29±9.3</td>
<td>36±10.3</td>
<td>45±8.7</td>
<td>55±7.2</td>
<td>56±9.3</td>
<td>65±7.5</td>
</tr>
<tr>
<td>269</td>
<td>11±3.0</td>
<td>18±7.4</td>
<td>25±7.1</td>
<td>35±7.8</td>
<td>45±8.3</td>
<td>52±12.3</td>
<td>58±9.6</td>
<td>67±6.7</td>
</tr>
<tr>
<td>482</td>
<td>16±5.5</td>
<td>19±6.7</td>
<td>27±6.8</td>
<td>35±8.3</td>
<td>44±7.2</td>
<td>52±8.9</td>
<td>59±8.2</td>
<td>69±11.7</td>
</tr>
<tr>
<td>1,000</td>
<td>10±4.0</td>
<td>16±7.0</td>
<td>23±4.3(^*)</td>
<td>32±6.9</td>
<td>40±9.3</td>
<td>47±11.0</td>
<td>53±9.7</td>
<td>60±8.3</td>
</tr>
</tbody>
</table>

\(^a\) Data extracted from study 728, Tables 6 and 7  
\(^b\) N=10 for all groups except N=9 for untreated control females from weeks 6 until the end of the study  
\(^*\) Significantly different from control, p < 0.05.
No treatment-related effects on the eye were observed.

8. Clinical Pathology

The hematology, clinical chemistry, and urinalysis parameters marked with an X below were examined in this study. Hematology and clinical chemistry parameters were examined in all surviving animals after a 16-hour fasting period following the final exposure. Blood samples were collected from the abdominal aorta. Urine samples were collected prior to the 25th exposure (method not reported). Both summary and individual data were provided for all of the groups.

(a) Hematology

X Hematocrit (HCT)*  X Leukocyte differential count*
X Hemoglobin (HGB)*  X Mean corpuscular HGB (MCH)
X Leukocyte count (WBC)*  X Mean corpuscular HGB concentration (MCHC)
X Erythrocyte count (RBC)*  X Mean corpuscular volume (MCV)
X Platelet count*  

* = Recommended by Subdivision F (November 1984) Guidelines

No treatment-related effect on any hematological parameter was observed.

(b) Blood (clinical) chemistry

Electrolytes               Other

X Calcium*  X Albumin*
X Chloride*  X Albumin/globulin ratio
   - Magnesium  X Blood creatinine*
   - Phosphorus*  X Blood urea nitrogen*
X Potassium*  X Globulins
X Sodium*  X Glucose*

Enzymes

X Leucine aminopeptidase  X Phospholipid
X Alkaline phosphatase (ALP)  X Triglycerides
X Serum cholinesterase  X Uric acid
X Lactic acid dehydrogenase
X Serum alanine aminotransferase (SGPT)*
X Serum aspartate aminotransferase (SGOT)
X Creatinine phosphokinase

* = Recommended by Subdivision F (November 1984) Guidelines

A 44% increase in serum lactate dehydrogenase was observed in high-dose males (Table 3). Other statistically significant changes were observed but were probably incidental.
Table 3. Lactate Dehydrogenase Activity (U/L) in Rats Exposed to Atmospheres Containing Similar Technical for 4 Weeks\(^a,b,c\)

<table>
<thead>
<tr>
<th>Exposure Level (mg/m(^3))</th>
<th>Vehicle Control</th>
<th>Untreated Control</th>
<th>269</th>
<th>482</th>
<th>1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH</td>
<td>72 \pm 13</td>
<td>93 \pm 45</td>
<td>59 \pm 15</td>
<td>88 \pm 24</td>
<td>104 \pm 41*</td>
</tr>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH</td>
<td>71 \pm 20</td>
<td>87 \pm 39</td>
<td>66 \pm 12</td>
<td>83 \pm 31</td>
<td>79 \pm 47</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data extracted from Study #728, Tables 18 and 19

\(^a\)Mean ± standard deviation

\(^b\)N = 10; except vehicle control males, untreated control males, and 269-mg/m\(^3\) males where N = 8

\(^c\)Significantly different from vehicle control (p<0.05)
(c) Urinalysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Test</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>X Appearance</td>
<td>X Sediment</td>
<td>X Bilirubin</td>
<td></td>
</tr>
<tr>
<td>- Volume</td>
<td>X Protein</td>
<td>X Blood</td>
<td></td>
</tr>
<tr>
<td>- Specific gravity</td>
<td>X Glucose</td>
<td>- Nitrate</td>
<td></td>
</tr>
<tr>
<td>X pH</td>
<td>X Ketones</td>
<td>X Urobilinogen</td>
<td></td>
</tr>
</tbody>
</table>

There were no treatment-related changes in any of the parameters examined.

9. Sacrifice and Pathology

Following blood collection, animals were subjected to gross necropsy. All tissues were fixed in a 10% aqueous formaldehyde solution except for the eyes, which were fixed using Davidson's fixative. Those organs marked below with an X were examined histologically for both control groups and the high-dose group. In addition, tissues of all animals with grossly observable lesions were examined microscopically. Organs marked with XX were weighed at necropsy of all animals in all groups.

<table>
<thead>
<tr>
<th>Respiratory</th>
<th>Cardiovascular/</th>
<th>Neurologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>X Nasal cavity*</td>
<td>Hematologic</td>
<td>XX Brain*</td>
</tr>
<tr>
<td>X Trachea*</td>
<td>XX Heart*</td>
<td>X Peripheral nerve*</td>
</tr>
<tr>
<td>XX Lungs (perfused)*</td>
<td>X Bone marrow*</td>
<td>XX Pituitary*</td>
</tr>
<tr>
<td>XX Bronchial bifurcation</td>
<td>XX Thymus*</td>
<td>X Eye*</td>
</tr>
<tr>
<td>X Larynx</td>
<td>X Aorta*</td>
<td>X Spinal cord</td>
</tr>
<tr>
<td></td>
<td>X Lymph node*</td>
<td>(thoracic)</td>
</tr>
<tr>
<td></td>
<td>XX Spleen*</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Digestive System</th>
<th>Urogenital System</th>
<th>Glandular</th>
</tr>
</thead>
<tbody>
<tr>
<td>X Small intestine*</td>
<td>XX Kidneys*</td>
<td>XX Adrenals*</td>
</tr>
<tr>
<td>X Large intestine*</td>
<td>X Urinary bladder*</td>
<td>XX Thyroid*</td>
</tr>
<tr>
<td>X Tongue</td>
<td>XX Testes*</td>
<td>- Parathyroids*</td>
</tr>
<tr>
<td>X Salivary gland*</td>
<td>X Uterus*</td>
<td>X Harderian glands</td>
</tr>
<tr>
<td>X Esophagus*</td>
<td>X Vagina</td>
<td>X Mammary gland</td>
</tr>
<tr>
<td>X Stomach*</td>
<td>X Seminal vesicles</td>
<td>Other</td>
</tr>
<tr>
<td>XX Liver*</td>
<td>X Epididymides</td>
<td>X Skeletal muscle*</td>
</tr>
<tr>
<td>XX Pancreas*</td>
<td>XX Prostate</td>
<td>X Bone (femur)*</td>
</tr>
<tr>
<td></td>
<td>XX Ovaries</td>
<td>X Skin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X Subcutaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>X Tissues with gross lesions</td>
</tr>
</tbody>
</table>

*Recommended by Subdivision F (November 1984) Guidelines
(a) **Macroscopic**

Both summary and individual macroscopic data were available. The incidence of gross lesions was very low overall, and none of the findings appeared to be treatment related.

(b) **Organ weights and organ-to-body-weight ratios**

Both summary and individual organ weight data were available. The relative liver weight was significantly increased (9%) in the high-dose males. However, this effect may have been due to the lower body weight of high-dose males since absolute liver weights were not increased in this group.

(c) **Microscopic Examination**

Histopathological data from all animals on the study were presented in the study report.

Very few lesions were observed microscopically, and the incidence of lesions in the high-dose group was comparable to the incidence of these lesions in both the untreated and vehicle controls.

The reviewers have no other comments regarding the materials and methods sections.

A description of the statistical analysis employed was included in the report.

A signed Good Laboratory Practice Compliance Statement and a list of Quality Assurance Inspections were included. No signed Quality Assurance Statement was located.

**B. DISCUSSION**

Based on the information provided, several tentative conclusions can be made regarding the toxicity of Sumilarv. It causes mild systemic toxicity in rats with a NOEL and LEL of 482 and 1,000 mg/m³, respectively. Adverse effects observed at 1,000 mg/m³ include transient salivation in 30%-40% of the animals and increased serum lactate dehydrogenase in males.

This study is classified as Supplementary. The following deficiencies have been noted:

1. **Stability of test material.** No information was provided in the report regarding the stability of the test material.

2. **Inadequate characterization of exposure atmospheres.** Samples of the test atmospheres were collected for analysis of test material concentration and particle size only 2 days/week. EPA Pesticide
Assessment Guideline Series 82-4 recommends that such analyses be conducted at least once during each exposure period. Also no data were provided regarding the temperature, humidity, or oxygen content of the exposure atmospheres. EPA Pesticide Assessment Guideline Series 82-4 recommends that temperature be recorded every 60 minutes. The study author noted that temperature and humidity of the exposure atmospheres were measured every 10 minutes, but the temperature and humidity values were not presented in the study report.

3. **Inadequate dynamic air flow in the exposure chamber.** Air flow through the chamber was reported to have been 50 L/min. It is unclear from the study report whether this was a measured value since the report did not state whether the air flow rate was monitored. EPA Pesticide Assessment Guideline Series 82-4 recommends that the air flow rate be monitored at least every 60 minutes. At 50 L/min, the rate of air exchange would be approximately 5/hour ($0.050 \text{ m}^3/\text{min} \times 60 \text{ min} = 3.0 \text{ m}^3$). This is well below the recommended dynamic air flow rate of 12-15 air changes/hour (EPA Pesticide Assessment Guideline Series 82-4).

4. **Inappropriate statistical tests.** Body weight and food and water consumption were analyzed using an F-test followed by a Student's t-test (if variances were homogeneous) or a Fisher-Behren's test (if variances were heterogenous). This type of analysis is most appropriate for comparing two groups. When more than one group is compared with controls (as was the case in this study), an analysis of variance should be used.

5. **Insufficient duration of exposure.** The exposures in this study were conducted for 4 hours/day, 7 days/week, for 4 weeks. EPA Pesticide Assessment Guideline Series 82-4 recommends exposing animals for at least 6 hours/day, 5 days/week, for at 90 days.