DATE: August 29, 2008

MEMORANDUM


FROM: Timothy F. McMahon, Ph.D., Senior Scientist
Antimicrobials Division (7510P)

PC Code: 054901

On March 10, 1998, the Health Effects Division's Hazard Identification Assessment Review committee evaluated the toxicology data base of triclosan and selected doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments, re-assessed the Reference Dose (RfD) established for chronic dietary risk assessment, and addressed the sensitivity of infants and children as required by the Food Quality Protection Act (FQPA) of 1996. In 2006, the Antimicrobials Division Toxicity Endpoint Committee updated the endpoint document with respect to dermal endpoints based on the dermal irritation policy developed within the Antimicrobials Division. In 2008, new data on the effect of triclosan on rat thyroid homeostasis was considered.
I. INTRODUCTION

On March 10, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of Triclosan and selected doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments, reassessed the Reference Dose (RfD) established for chronic dietary risk assessment, and addressed the sensitivity of infants and children from exposure to Triclosan as required by the Food Quality Protection Act (FQPA) of 1996. The application of the 10x factor for protection of infants and children from exposure to Triclosan, as required by FQPA, will be determined by the FQPA Safety Factor Committee (FQPA SFC). It is noted that a previous FQPA assessment was performed for Triclosan in 1997, with a recommendation for no additional safety factor. The HIARC’s conclusions are presented below.

II. HAZARD IDENTIFICATION

A. Acute Reference Dose (Acute RfD)

Study Selected: Chronic Toxicity - Baboon

MRID. No. 257773

Executive Summaries: In a chronic toxicity study, groups of 7 baboons/sex/dose received Irgasan DP300 orally at doses of 30, 100, and 300 mg/kg/day by capsule for 52 weeks. Two males and 2 females from each dose group were sacrificed at six months, 3 males and 3 females from each dose group at 52 weeks, and the remaining animals after a six week recovery period following cessation of treatment. At the 100 and 300 mg/kg/day dose levels, test animals were observed with signs of vomiting, failure to eat, and diarrhea, which occurred 4-6 hours after dosing or during the night. At necropsy, an effect on the lining of the stomach was observed at the high dose. The systemic NOAEL was determined to be 30 mg/kg/day, and the systemic LOAEL was determined to be 100 mg/kg/day, based on clinical signs of toxicity.

Dose and Endpoint for Risk Assessment: NOAEL = 30 mg/kg/day, based on diarrhea observed 4-6 hours after dosing at the LOAEL of 100 mg/kg/day.

Comments about Study and Endpoint: none

This risk assessment is required.
B. Chronic Dietary  [Reference Dose (RfD)]

The RfD established in 1993 was re-assessed by this Committee and is discussed below:

Study Selected: Chronic Toxicity - Baboon §83-1

MRID No. 257773

Executive Summary: In a chronic toxicity study, groups of 7 baboons/sex/dose received Irgasan DP300 orally at doses of 30, 100, and 300 mg/kg/day by capsule for 52 weeks. Two males and 2 females from each dose group were sacrificed at six months, 3 males and 3 females from each dose group at 52 weeks, and the remaining animals after a six week recovery period following cessation of treatment. At the 100 and 300 mg/kg/day dose levels, test animals were observed with signs of vomiting, failure to eat, and diarrhea, which occurred 4-6 hours after dosing or during the night. At necropsy, an effect on the lining of the stomach was observed at the high dose. The systemic NOAEL was determined to be 30 mg/kg/day, and the systemic LOAEL was determined to be 100 mg/kg/day, based on clinical signs of toxicity.

Dose/Endpoint for establishing the RfD: NOAEL= 30 mg/kg/day based on diarrhea observed at 100 mg/kg/day, and hematologic alterations at 300 mg/kg/day.

Comments about Study and Endpoint: The HIARC concurred with the RfD established. The committee also noted supporting evidence for selection of the RfD from the two-year rat chronic toxicity / carcinogenicity study (MRID # 42027906) in which hepatocellular hypertrophy was observed at a dose of 52 mg/kg/day, consistent with several other studies on triclosan showing the liver to be a target organ of toxicity.

Uncertainty Factor (UF): 100 (10x for inter-species extrapolation and 10x for intra-species variation).

\[
\text{RfD} = \frac{30 \text{ mg/kg/day (NOAEL)}}{100 \ (\text{UF})} = 0.30 \text{ mg/kg/day}
\]

This risk assessment is required.
C. Occupational/Residential Exposure

1. Dermal Absorption

An older rabbit dermal absorption study was available from the one-liner database (HED document # 001958). In this study, up to 48% of an applied dermal dose of 0.89 mg triclosan was absorbed. In addition, literature data available on dermal absorption in the mouse show dermal absorption up to 70%. These data are in agreement with the estimate of dermal absorption of 50% derived from comparison of the LOAEL's from a rat 90-day dermal toxicity study (MRID # 43328001) and a rat 2-generation reproduction study (MRID # 40623701). This estimate was based on reduced mean body weight observed in the reproduction study at 150 mg/kg/day, and occult blood in urine observed at 80 mg/kg/day in the dermal study.

Additional dermal absorption data on triclosan have been submitted and reviewed. *In vitro* dermal absorption studies using human skin preparations and various formulations containing triclosan (MRIDs 47261408 through 47261411) showed dermal absorption values for triclosan both in vivo and in vitro using rats as well as an in vitro human skin study. These data supported the conclusion of dermal absorption of 21-23% in the rat studies, and showed in vitro dermal absorption through human skin in vitro of 6.3%. Taken together, the available data on dermal absorption suggest a lower value, around 20% for rat skin and possibly lower for human skin. Additional verification is needed to revise the currently selected dermal absorption value.

Selected Dermal Absorption Factor: 50%

2. Incidental Oral (short-term [1-7 days]; intermediate-term [30 days- 6months])

Study selected: Chronic Toxicity- Baboon

MRID: 257773

Executive Summary: see summary under chronic dietary assessment

Dose and Endpoint for Risk Assessment: NOAEL = 30 mg/kg/day, based on diarrhea observed 4-6 hours after dosing at the LOAEL of 100 mg/kg/day.

Comments about dose and endpoint: the selection of the NOAEL value of 30 mg/kg/day for the short-term incidental oral is appropriate for the time frame of this risk assessment based on the response observed in the baboon study. For the intermediate-term risk assessment, the NOAEL value is consistent with NOAEL values from several oral subchronictoxicity studies that show NOAEL values of 25 and 50 mg/kg/day. A recently completed study (US EPA, 2008) showed that triclosan decreased circulating T4 levels in
rats administered triclosan orally for 30 days at doses of 30 mg/kg and above. Benchmark dosing analysis derived a BMD and BMDL for the 20% response level of 14.51 mg/kg and 7.23 respectively. Although more work needs to be done in this area, the sensitivity of the rat to thyroid hormone disruption vs. humans, and the similarity in pharmacokinetics to humans would result in a decrease in the total uncertainty factor from 100 to 30, based on a reduction in the interspecies factor from 10x to 3x. Thus, an equivalent oral endpoint of 0.24 mg/kg would be derived, supporting the selection of the current endpoint as health protective.

3. Short-Term Dermal - (1-7 days)

Study Selected: 14-Day Dermal Toxicity study - mouse

MRID No. 44389708

Executive Summary: In a repeated dose dermal toxicity study (MRID 44389708), triclosan (99.3% a.i.) was applied daily in acetone to the clipped skin of ten CD-1 mice/sex/dose at dose levels of 0, 0.3, 0.6, 1.5, 3.0, or 6.0 mg/animal/day for 14 days. Signs of dermal toxicity in both sexes at 3.0 and 6.0 mg/animal/day included erythema, edema, alopecia, fissuring, eschar, thickening and discoloration. At 1.5 mg/animal/day erythema, fissuring, eschar, thickening, and discoloration were observed in males and erythema and fissuring in females. Dermal irritation observed in mice in the 0.3, and 0.6 mg/animal/day treatment groups was comparable to that observed in the controls. Non-neoplastic skin lesions were observed at application sites and included superficial ulceration and supplicative inflammation, slight or minimal acanthosis and/or hyperkeratosis, and mild, diffuse, generally subacute/chronic inflammation of the dermis. The lesions were dose-related and occurred primarily in the 1.5, 3.0, and 6.0 mg/animal/day treatment groups. Systemic responses were observed as dose-dependent increases in plasma levels of the test substance. There were treatment-related increases in absolute and liver to body and brain weights at 1.5, 3.0, and 6.0 mg/animal/day which correlated with centrilobular hepatocellular hypertrophy at 3.0 and 6.0 mg/animal/day. There were no significant differences between the terminal body weights in the treated and control groups. For males, the overall body weight gain was significantly decreased (p<0.05) at 6.0 mg/animal for females (↓32%) and significantly increased for males at 3.0 mg/animal/day (↑64%). Food consumption was significantly increased (p<0.05) for the 3.0 and 6.0 mg/animal/day groups during Week 1 (females only), Week 2 (both sexes), and overall for females only. The LOEL for this study is 1.5 mg/animal/day, based on treatment-related dermal irritation at the treatment site and on increased liver weights in this treatment group. The NOEL is 0.6 mg/animal/day. Based on the results of this study, the highest recommended level for a 90-day dermal study was judged to be 1.2 mg/animal/day with inclusion of at least one level below 0.3 mg/animal/day.
Dose and Endpoint for Risk Assessment: NOAEL = 0.6 mg/animal based on treatment-related dermal irritation at the treatment site and on increased liver weights at 1.5 mg/animal.

Comments about Study and Endpoint: The 14-day study duration is appropriate for selection of a short-term dermal endpoint (i.e., 1-7 days). The NOAEL of 0.6 mg/animal was converted to a concentration of 100 µg/cm² by using the surface area of the applied gauze (2 x 3 cm or 6 cm²) and converted according to the formula:

\[
0.6 \text{mg/animal} \times 1000 \text{µg/mg} \div 6 \text{cm}^2 = 100 \text{µg/cm}^2
\]

This risk assessment is required.

4. Intermediate-Term Dermal (30 days-6 months) and Long-term Dermal (> 6 months)

Study Selected: 90 Day Dermal Toxicity Study in Rats

Executive Summary: In a 90-day dermal toxicity study (MRID 43328001), groups of rats (10/sex/group) received triclosan in propylene glycol by dermal application at dose levels of 10, 40, and 80 mg/kg for 6 hrs/day for 90 days, followed by a 28 day recovery period. Dermal irritation at the application site was found in all dose groups. At the 10 mg/kg/day dose, animals were observed with erythema and edema beginning on day 21 of the study. At the 40 and 80 mg/kg/day dose levels, animals were observed with dermal reactions beginning on day 4 of the study and a greater number of animals were observed with dermal scores of +3 and +4 for erythema and edema. In the satellite group given test material at 80 mg/kg/day and allowed a 28 day recovery period beyond the 90-day dosing period, dermal irritation scores had subsided by the end of the 28-day recovery period. Systemically, an increase in the incidence of occult blood in the urine of 80 mg/kg males and females was found. No other systemic toxicity was observed from the data in this study. Under the conditions of this study, the LOAEL for systemic toxicity was 80 mg/kg; the NOAEL was 40 mg/kg.

Comments about Study/Endpoint: The endpoint is appropriate for the intermediate- and long-term assessment of systemic toxicity from dermal exposure to triclosan. A standard Margin of Exposure (100) is applied to the intermediate-term dermal endpoint, and a Margin of Exposure of 300 is applied to any long-term dermal risk assessments. The extra 3x for the long-term assessment is applied to account for extrapolation from a 90-day time point to a chronic time point.

5. Inhalation Exposure (Short-, intermediate-, long-term)

MRID No. 0087996
Executive Summary: In a subchronic inhalation toxicity study (MRID 0087996), triclosan (purity not reported) was administered to 9 rats/dose/sex at dose levels as described in the table below:

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Rats</th>
<th>Mean Concentration (mg/m$^3$) Air</th>
<th>1st Day</th>
<th>2nd-15th Day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9*</td>
<td>9*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>9</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>9*</td>
<td>9*</td>
<td>227</td>
<td>115</td>
</tr>
<tr>
<td>4</td>
<td>9</td>
<td>9</td>
<td>1300</td>
<td>301</td>
</tr>
</tbody>
</table>

*8 animals (2 males/2 females) from each group were kept for a 17-day recovery period, following the 21-day exposure.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean bodyweight (kg)</th>
<th>Equivalent Dose (mg/kg/day)$^#$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>50 mg/m$^3$ (4.22 ppm)</td>
<td>.271</td>
<td>.193</td>
</tr>
<tr>
<td>115 mg/m$^3$ (9.71 ppm)</td>
<td>.251</td>
<td>.202</td>
</tr>
<tr>
<td>301 mg/m$^3$ (25.4 ppm)</td>
<td>.217</td>
<td>.170</td>
</tr>
</tbody>
</table>

* = (mg/m3 x 24.45)/mw = ppm
$#$ = ((0.0087 m$^3$/hr *mg/m$^3$*hr/day)/bw), where 0.0087 m$^3$/hr is a default inhalation rate for young rats.

A 10% ethanol suspension of triclosan was administered “nose only” as an aerosol (5 days per week, 2 hrs per day) for 21 days. Dose levels of 0, 50, 115, or 301 mg/m$^3$ are equivalent to 0, 3.21, 7.97, and 24.14 mg/kg/day for males, respectively, and 0, 4.51, 9.91, and 30.81 mg/kg/day for females, respectively. Treatment groups 3 and 4 initially received concentrations of 227 and 1300 mg/m$^3$, respectively. These concentrations were reduced after the first day of treatment because they were not tolerated well by the animals.
Twelve high-dose animals (5 males and 7 females) died during the course of the study. Toxicity was observed at all dose levels. Treatment-related effects at 1300/301 mg/m$^3$ included clinical signs of toxicity (dyspnea, nasal discharge, muscle spasms, pallor, and diarrhea), decreased body weight, decreased body weight gain, decreased food consumption, statistically-significant increased total leukocyte count, statistically-significant increased percentage of neutrophils and decreased lymphocytes, statistically-significant increased serum glutamic-pyruvic transaminase (GPT) activity, statistically-significant increased alkaline phosphatase (AP), statistically-significant decreased serum proteins (males), and increased incidence of respiratory inflammation. Additional statistical analyses also showed a statistically-significant decrease in thrombocytes. Macroscopic findings for the high-dose animals that died prior to scheduled sacrifice included severe acute congestion and numerous hemorrhages in all organs. Acute purulent inflammation with focal ulceration of the mucous membrane in the nasal cavity and in the trachea were also observed. Treatment-related effects at 227/115 mg/m$^3$ included slightly decreased body weight and body weight gain, slightly decreased food consumption, increased leukocytes, statistically-significant decreased thrombocytes, statistically-significant increased alkaline phosphatase, statistically-significant decreased serum proteins (males), and slight incidences of respiratory irritation in one male and two females. At the low dose, a statistically-significant decrease in thrombocytes and total serum proteins and a statistically-significant increase in alkaline phosphatase were observed in the males. Consequently, the LOAEL is 3.21 mg/kg/day for males based on changes in thrombocytes, total blood proteins, and alkaline phosphatase; the LOAEL for females is 9.91 mg/kg/day. A NOAEL could not be established for males; the NOAEL for females is 4.51 mg/kg/day.

**Dose and Endpoint for Risk Assessment:** LOAEL=3.21 mg/L (males) based on increased total leucocyte count and increased serum alkaline phosphatase at 3.21 mg/L.

**Comments about Study and Endpoint:** Since this is the only study available, the LOAEL should be used for the Short, Intermediate and Long-Term risk assessments.

**This risk assessment is required.**

**D. Margin of Exposure for Occupational/Residential Exposures:**

A MOE of 10 is applied to the short-term dermal risk assessment (3x interspecies extrapolation, 3x intraspecies variation). For intermediate- and long-term dermal risk assessments, an MOEs of 100 is applied.

An MOE of 1000 was applied to the inhalation endpoint. The inhalation toxicity study lacked sufficient data with which to convert the animal doses to human equivalent concentrations (HECs) in accordance with Agency policy and a LOAEL value was selected as the endpoint for inhalation risk assessment; therefore, the use of the LOAEL value from the animal study and uncertainty in determination of what the HEC would be warrants the MOE of 1000.
E. Recommendation for Aggregate Exposure Risk Assessments

Dietary and incidental oral exposures can be combined based on the use of the same study and endpoint for these risk assessments. Dermal and inhalation exposures are considered separately based on the use of different studies with different endpoints for these risk assessments.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study- Rats

MRID No: 42027906

Executive Summary: In a chronic toxicity/oncogenicity feeding study conducted in male and female Sprague-Dawley rats, FAT 80'023 (triclosan) was administered in the diet at doses of 0, 300, 1000, or 3000 ppm (0, 15.3, 52.4, and 168.0 mg/kg/day in males; 0, 20.0, 66.9, and 217.4 mg/kg/day in females). No treatment-related effects on mortality, clinical toxicity, ophthalmology, urinalysis, gross pathology, or neoplastic pathology were observed at any dose level tested. Erythrocyte count, hemoglobin concentration, and hematocrit were decreased in males at the 15.3, 52.4, and 168.0 mg/kg/day dose levels, and erythrocyte count was decreased in females at 66.9 and 217.4 mg/kg/day. Serum alanine and aspartate aminotransferase activities were increased in males at 168.0 mg/kg/day, and blood urea nitrogen was increased in females at 217.4 mg/kg/day. Hepatocellular hypertrophy was observed in males at 168.0 mg/kg/day, and the incidence of hepatic necrosis was increased in males at all dose levels. The predominant residue of triclosan observed in blood and kidney was the sulfate conjugate of triclosan, while unconjugated triclosan was predominant in liver. Residual levels of triclosan were proportional to the dose administered. No carcinogenic potential was demonstrated for triclosan in this study. The systemic NOAEL was determined to be 52.4 mg/kg/day, based on the increase in non-neoplastic liver pathology observed in male rats at the 168.0 mg/kg/day dose.

Discussion of Tumor Data: There was no evidence of carcinogenicity.

Adequacy of the Dose Levels Tested: The dose levels were adequately tested.

2. Carcinogenicity Study- Mice

A second carcinogenicity study for Triclosan was conducted by the oral route and was reviewed by the Food and Drug Administration.

In a carcinogenicity bioassay in mice conducted by Colgate-Palmolive and submitted to the Food and Drug Administration, 5 groups of male and female CD-1 mice (70 mice/sex/dose) received
Triclosan in the diet at dose levels of 0, 10, 30, 100, or 200 mg/kg/day. Fifty mice/sex/dose received dietary Triclosan for 18 months, while the remaining 20 mice/sex/dose received dietary Triclosan for only 6 months, after which time these mice were sacrificed. Blood samples were obtained from 10 mice/sex/dose from both the 6 month and 18 month dose groups at sacrifice, for determination of Triclosan plasma levels. Time of blood sampling relative to the last dose of Triclosan was not stated. Parameters monitored during this study included mortality, clinical observations, body weight, food consumption, ophthalmology, clinical chemistry, urinalysis, hematology, gross and microscopic pathology, and organ weights. Reduced survival was observed in female mice receiving 200 mg/kg/day for 18 months (34/50 vs. 45/50 in control). There were no significant signs of clinical toxicity at any dose level, and no significant effects of treatment on group mean body weight, food consumption, ophthalmology, or urinalysis. A dose-related increase in activity of alanine aminotransferase and alkaline phosphatase was observed in male and female mice at 100 mg/kg/day Triclosan and above in both the 6 month and 18 month dose groups. Significant decreases in both albumin and total protein were observed in males at 6 months and in females at 18 months at doses of 100 mg/kg/day and above. Serum cholesterol was markedly reduced at all dose levels including the 10 mg/kg/day dose. These data suggest that Triclosan can interfere with liver function. Treatment-related hematological effects included increased reticulocyte count and platelet count in males and females at the 200 mg/kg/day dose. Mean liver weight (absolute and relative) was increased in both male and female mice at 30 mg/kg/day and above at both 6 and 18 months. An increased incidence of nodules and discoloration of the liver was observed in both male and female mice at 100 mg/kg/day and above. A dose-related increase in severity of hepatocellular hypertrophy was observed in both male and female mice at 30 mg/kg/day and above. Dose-related increases in incidence or severity of hepatocellular vacuolation/vesiculation and hepatic inflammation, necrosis, and microgranulomas was also observed.

After 18 months of exposure, a statistically significant increase in the incidence of hepatocellular adenoma and carcinoma was observed in male and female mice at 100 mg/kg/day triclosan and above. The incidence was dose-related in both sexes. Combined incidence of adenoma and carcinoma was 12%, 20%, 34%, 64%, and 84% for males, and 0%, 2%, 6%, 12%, and 40% for females at the 0, 10, 30, 100, and 200 mg/kg/day dose levels, respectively. The incidence of adenoma / carcinoma combined exceeded historical control incidence at the 10 mg/kg/day dose level (17% for males, 1% for females), but became statistically significant at the 30 mg/kg/day dose level. **Therefore, a systemic NOAEL of 10 mg/kg/day can be established from the data in this study, based on increased incidence of liver neoplasms in male and female mice at 30 mg/kg/day.**

This study was not reviewed by the Office of Pesticide Programs but is acceptable for purposes of carcinogenicity assessment.

**870.4300 Chronic Toxicity/Carcinogenicity (Hamster)**

In a chronic toxicity/oncogenicity study (MRID 44874001), FAT 80'023/S (triclosan: 99.5% a.i.; Batch # 505017) was administered in the diet to groups of 70 male and 70 female Bio F1D
Alexander Syrian hamsters at concentrations delivering doses of 0 (control 1), 0 (control 2), 12.5, 75, or 250 mg/kg/day. Actual achieved doses were: 0, 0, 12.6, 75.4 [75.5 F], and 251 mg/kg/day for males and females. Groups of 10 hamsters per sex per dose were killed after 52 weeks for interim evaluations; the remaining 60 hamsters per sex per dose were maintained on treated or control diets for up 90 weeks for females and 95 weeks for males.

No treatment-related clinical signs of toxicity were observed during the first 80 weeks of the study. After this time, high-dose males showed deterioration in their general clinical condition with signs such as lethargy, hunched posture, pallor, thin appearance, and unsteady gait. At termination of the females (week 91) the percent survival in the control 1, control 2, low-, mid-, and high-dose groups was 40%, 38%, 47%, 58%, and 48%, respectively. In contrast, high-dose males had an increase in mortality after week 80 which correlated with their deteriorating clinical condition. At termination of the males (week 96) the percent survival in the control 1, control 2, low-, mid-, and high-dose groups was 65%, 72%, 75%, 80%, and 35%, respectively.

Body weight gains by high-dose males and females were significantly (p≤0.05 or 0.01) less than one or both control groups throughout the study. Overall body weight gains by the high-dose animals through week 90 were 46-53% of the control levels. Final absolute body weights of the high-dose males and females were 84-85% and 89-90%, respectively, of the control groups. Body weights and body weight gains by the mid- and low-dose animals were unaffected by treatment. High-dose males and females had significantly (p≤0.01) reduced food consumption during weeks 1-3 as compared with both control groups. Food conversion ratios during the first 16 weeks of the study for animals in the control 1, control 2, low-, mid-, and high-dose groups were 30.5, 29.0, 29.2, 30.1, and 38.5 mg/kg/day, respectively, for males and 33.2, 32.2, 36.6, 36.5, and 50.1 mg/kg/day, respectively, for females. Water consumption was highly variable between individuals and between groups. However, for the high-dose groups, water consumption tended to be slightly increased throughout the study.

Plasma urea nitrogen was significantly (p≤0.05 or 0.01) increased to 119-156% of the control levels in high-dose males and females as compared to one or both control groups at interim sacrifice and at termination. Statistically significant changes were observed for other clinical chemistry parameters and for hematologic parameters and organ weights, but none were considered treatment related.

Throughout the study, high-dose males and females had a consistent increase in urine volume with corresponding decreases in specific gravity and protein concentration. Statistical significance (p≤0.05 or 0.01) was attained for these parameters at almost every time point when compared to one or both controls.

At interim sacrifice, irregular cortical scarring of the kidney was observed at gross necropsy in 4/10 high-dose males and 9/10 high-dose females compared with none in the control male groups and 3/19 in the control female groups combined. This corresponded to microscopic findings in the kidneys of the high-dose groups of both sexes consisting of distended medullary tubules and radial areas of dilated basophilic tubules with or without eosinophilic colloid/fibrosis.

At terminal sacrifice, no dose- or treatment-related gross findings were observed in males. However, in the control (combined), low-, mid-, and high-dose female groups, white nodules in
the forestomach were observed in 3/46, 3/28, 5/35, and 5/29 animals, respectively, pale kidneys were observed in 14/46, 4/28, 3/35, and 10/29 animals, respectively, and irregular cortical scarring was observed in 24/46, 12/28, 16/35, and 20/29 animals, respectively. Microscopically, a significantly (p<0.01) increased incidence of nephropathy was observed in high-dose males and females (decedents and survivors combined) as compared to both control groups and was considered the main factor contributing to death in animals that died before study termination. The severity of nephropathy, as calculated by the reviewer, in high-dose males and females was 3.2 and 2.8, respectively, compared with control values of 2.5-2.7 and 2.1-2.3, respectively. The incidence of nephropathy in the control 1, control 2, low-, mid-, and high-dose groups was 41/60, 38/60, 35/60, 36/60, and 56/60, respectively, for males and 19/60, 21/60, 26/60, 19/60, and 50/60, respectively, for females.

In males tested at the high dose of triclosan, a significantly increased incidence of absent spermatozoa, abnormal spermatogenic cells, and reduced numbers of spermatozoa was observed in males that died and those that were sacrificed at the end of the study. Increased incidence of partial depletion of one or more generations of germ cells within the testis was also observed in high dose male hamsters that died during the study or were sacrificed at study termination.

Lesions in the stomach were significantly (p<0.01) increased in high-dose males and females at termination; focal atypical hyperplasia of the fundic region was observed in 11/60 males and distended gastric glands with or without debris were observed in 17/60 females. These lesions were observed in none of the control males and only one of the control females, respectively. In addition, high-dose males killed at termination and dying during the study had significantly (p<0.01) increased incidences of abnormal spermatogenic cells and reduced numbers of spermatozoa in the epididymides and partial depletion of germ cells in the testes. The LOAEL is 250 mg/kg/day for male and female hamsters based on decreased body weight gains, increased mortality (males), nephropathy, and histopathologic findings in the stomach and testes. The corresponding NOAEL is 75 mg/kg/day.

No evidence of potential carcinogenicity of the test material was observed at the doses given in this study. Neoplastic lesions did not occur in treated groups at incidences significantly higher than the incidences in control animals. The doses administered were adequate for testing carcinogenicity as evidenced by the systemic toxicity described above.

This chronic toxicity/carcinogenicity study in the rat is Acceptable/Guideline and it satisfies the guideline requirement for a chronic toxicity/carcinogenicity oral study [OPPTS 870.4300 (§83-5)] in hamsters.

3. Classification of Carcinogenic Potential:

On March 10, 1998, the Health Effects Division’s HIARC committee examined the available carcinogenicity data for triclosan and was unable to assign a classification to triclosan at that time since data for only one species (rat) were submitted for evaluation of carcinogenicity. Since this determination, a chronic toxicity/carcinogenicity study in the
hamster (MRID 44874001) and a carcinogenicity study in the mouse reviewed by the Food and Drug Administration were submitted and/or obtained by the Agency. The Agency was not able to obtain the individual animal data records for the mouse carcinogenicity study but was able to obtain the FDA’s review and Expert Panel reports on the significance of the mouse study results. On July 25, 2007, the Health Effects Division’s Carcinogenicity Assessment Review Committee met to discuss the additional data submitted as well as the biochemical studies conducted with triclosan in support of a mode of action involving peroxisome proliferation as a causative factor in the positive tumorigenic results observed in the mouse carcinogenicity study.

The overall weight of the evidence supports activation of peroxisome proliferator-activated receptor alpha (PPARα) as the mode of action of triclosan-induced hepatocarcinogenesis in mice. Key precursor events and the tumor response in mice were concordant with respect to both time and dose. The data did not support either a mutagenic mode of action or a mode of action involving cytotoxicity followed by regenerative proliferation as alternative modes of action. While the proposed mode of action for liver tumors in mice is theoretically plausible in humans, it is quantitatively implausible and unlikely to take place in humans based on quantitative species differences in PPARα activation and toxicokinetic differences between the mouse and human.

In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), the CARC classified triclosan as “Not Likely to be Carcinogenic to Humans”. This decision is based on the weight-of-evidence that supports activation of peroxisome proliferator-activated receptor alpha (PPARα) as the mode of action for triclosan-induced hepatocarcinogenesis in mice. The data did not support either mutagenesis or cytotoxicity followed by regenerative proliferation as alternative modes of action. While the proposed mode of action for liver tumors in mice is theoretically plausible in humans, hepatocarcinogenesis by this mode of action is quantitatively implausible and unlikely to take place in humans based on quantitative species differences in PPARα activation and toxicokinetics. The quantification of risk is not required.

IV. MUTAGENICITY

Triclosan has been tested for mutagenic activity in several assays, including bacterial reverse mutation tests (MRID 43533301 and MRID 44389705), an in vitro mammalian cell gene mutation test (MRID 44389704), two in vitro mammalian chromosome aberration tests (Broker, P.C., Gray, V.M., and Howell, A., 1988 and MRID 43740801), a mammalian bone marrow chromosomal aberration test (MRID 43740802), and an unscheduled DNA synthesis assay in mammalian cells in culture (SanSebastian, J. et al., 1993).

870.5100 Bacterial Reverse Mutation Test
In two independently performed microbial preincubation assays (MRID 43533301), *Salmonella typhimurium* strains TA1535, TA1537, TA98, or TA100 were exposed to triclosan doses of 0.015, 0.050, 0.15, 0.5, or 1.5 μg/plate either in the absence or the presence of 3, 10, or 30% S9 derived from Aroclor 1254-induced rat livers. The test material was delivered to the test system in dimethyl sulfoxide.

Triclosan was cytotoxic at 1.5 μg/plate -S9 and at doses ≥0.5 μg/plate with S9. **There was, however, no indication of a mutagenic response in any strain at any dose either without or with increasing concentrations of S9.** All strains responded in the expected manner to the nonactivated and S9-activated positive controls.

The study is classified as **Acceptable/Guideline.** It satisfies the guideline requirement for a gene mutation assay (§84-2).

### 870.5100 Bacterial Reverse Mutation Test

In a microbial mutagenicity assay (MRID 44389705), *Salmonella typhimurium* strains TA100 and TA1538 were exposed to triclosan (100.5% a.i.) in dimethylsulfoxide (DMSO) at concentrations of 0.005-5,000 μg/plate without mammalian metabolic activation (-S9) and 0.005-50 μg/plate with mammalian metabolic activation (+S9). Strains TA98, TA100, TA1535, TA1537, and TA2538 were evaluated for mutagenicity at 0.05-5.0 μg/plate (+S9) and all except TA100 at 0.00167-0.167 μg/plate (-S9). Without S9, TA100 was evaluated for mutagenicity at 0.00167-0.167 μg/plate. The standard plate incorporation test was performed. S9 homogenates for metabolic activation were made from Aroclor induced rat livers.

Triclosan was tested to cytotoxic concentrations. The test article precipitated from solution at 5,000 μg/plate (-S9). In pre-screen cytotoxicity tests triclosan was not toxic to strain TA1538 at doses of 0.005 to 1.67 μg/plate with S9 activation and 0.005 μg/plate without S9 activation and was not toxic to strain TA100 at doses of 0.005 to 0.50 μg/plate +S9 and at 0.005 and 0.0167 μg/plate -S9. **There were no reproducible, dose-related differences in the number of revertant colonies in any tester strain at any dose level/condition compared to the vehicle controls.** The positive control substances induced marked increases in revertant colonies in their respective strains.

This study is classified as **Acceptable/Guideline** (§84-2) and satisfies the requirement for FIFRA Test Guideline for in vitro mutagenicity (bacterial reverse gene mutation) data.

### 870.5300 In Vitro Mammalian Cell Gene Mutation Test

In a mammalian cell gene mutation assay at the thymidine kinase locus (MRID 44389704), L5178Y TK +/- mouse lymphoma cells cultured in vitro were exposed to triclosan (>99% a.i.) in dimethylsulfoxide (DMSO) at concentrations ranging from 1 to 25 μg/mL without metabolic activation (-S9) and from 1 to 20 μg/mL with mammalian metabolic activation (+S9). Treatment levels were selected based on a preliminary cytotoxicity test conducted at 1 to 250 μg/mL with and without activation.
Triclosan was tested up to toxic concentrations. Mutation frequencies were determined for concentrations selected on the basis of relative growth. The first mutation assay was initiated at concentrations ranging from 1 to 25 and 1 to 20 μg/mL without S9 activation and in a second mutation assay at 1 to 20 and 0.5 to 15 μg/mL with metabolic activation. Redundant or highly cytotoxic concentrations were eliminated during the assays. Only dose levels that resulted in ≥10% survival were used to assess mutagenicity. For the final concentrations tested, relative growth ranged from 8 to 100% without activation and from 7 to 88% with activation.

In order for the test material to be considered a mutagen, it had to produce both a mutant frequency at one or more dose levels that was at least twice that of the vehicle control, as well as a dose or toxicity relationship; in addition, the effects had to be reproducible. By these criteria triclosan was negative for inducing forward mutations at the TK locus in mouse L5178Y cells both with and without metabolic activation. In both the nonactivated and activated conditions, the positive controls induced the appropriate responses.

This study is classified as Acceptable/Guideline (§84-2), and satisfies the requirements for FIFRA Test Guideline for in vitro mammalian forward gene mutation data.

870.5375.1 In Vitro Mammalian Chromosome Aberration Test

In a mammalian cell cytogenetics, chromosome aberration assay (MRID not assigned), Chinese hamster ovary cells (CHO strain K1-BH4) were exposed to triclosan (>99% pure; Unilever sample number S15155 T01) and dissolved with DMSO. Concentrations of 0.1, 0.3, 0.5, and 1.0 μg/mL and 4.8, 9.5, 19.0, 30.0, and 38.0 μg/mL were tested for the cultures without and with metabolic activation from Aroclor 1254-induced rat livers for 24 and 6 hours, respectively. Cells were harvested 24 hours after treatment and analyzed for chromosomal aberrations.

Triclosan was tested up to the toxicity limit of 1.0 and 38.0 μg/mL, -S9 and +S9, respectively, based on a preliminary toxicity test using CHO cells that were treated at dose concentrations of 6.3, 12.5, 25.0, 50.0, 100.0, 200.0, and 400.0 μg/mL. No live cells were observed at ≥50 and ≥100 μg/mL in -S9 and +S9 cultures, respectively. There were no aberrant cells at 12.5 and 25.0 μg/mL, -S9, but the mitotic index was declined to ~29% at 6.3 μg/mL compared to the solvent control. For the cultures with +S9, the mitotic index was reduced by 27 and 77% for 50 and 25 μg/mL, respectively, but was comparable to the solvent control at 6.3 and 12.5 μg/mL. The EC50 value for cultures with +S9 and –S9 were estimated to be 38 and 1 μg/mL. Hence, concentrations of 1 and 38 μg/mL were used as the highest dose for the cultures without and with S9, respectively, for the cytogenetic assay.

In the cytogenetic assay, toxicity was noted at 38 μg/mL, +S9, and was not analyzed for chromosomal aberrations. Precipitation, if observed, was not reported for any dose level. Cultures treated with 0.1, 0.3, 0.5, and 1 μg/mL (-S9) and 4.8, 9.5, 19, and 30 μg/mL (+S9) were evaluated for chromosomal aberrations. No statistically-significant increases in the number of aberrant cells or chromosomal aberrations were reported at any dose level compared to the concurrent solvent/negative control. The percentage mean number of aberrant cells with gaps (excluding and including type) was P>0.05 comparable to the solvent and untreated controls for all dose levels and conditions. The positive controls of mitomycin-C and cyclophosphamide displayed significant increases in the percentage of aberrations, hence eliciting a clear positive
response. There was no evidence of chromosome aberration induced over the background.

This study is classified as Acceptable/Guideline because it satisfies the guideline requirement (OPPTS 870.5375; OECD 473) for in vitro cytogenetic mutagenicity data.

870.5376 In Vitro Mammalian Chromosome Aberration Test

In an in vitro cytogenetic assay (MRID 43740801), Chinese hamster lung fibroblasts were exposed to triclosan (99-100%) nonactivated doses of 1 µg/ml (7-hour cell harvest), 0.1-3 µg/ml (18-hour harvest), or 3 µg/ml (28-hour harvest) and S9-activated concentrations of 3 µg/ml (7- and 28-hour cell harvests) or 0.1-3 µg/ml (18-hour harvest). The S9 fraction was derived from Aroclor 1254 induced Wistar male rat livers and triclosan was delivered to the test system in ethanol.

No mitotic cells were recovered at any harvest time from cultures treated with ≥6 µg/ml -S9 or ≥ 10 µg/ml +S9. Findings with the positive controls confirmed the sensitivity of test system to detect clastogenesis. However, nonactivated triclosan at 1 and 3 µg/ml (18-hour harvest) induced a dose-related increase in the yield of cells with abnormal chromosome morphology. The response was significant (p≤0.001) at the higher concentration. A significant increase (p≤0.001) was also seen at 3 µg/ml (28-hour harvest). The most frequently observed type of chromosome damage was exchange figures. In the presence of S9 activation, nonsignificant but concentration dependent increases in cells bearing exchange figures were also seen at 1 and 3 µg/ml (18-hour harvest). The data are, therefore, sufficient to conclude that triclosan is active in this test system.

This study is classified as Acceptable/Guideline and satisfies the guideline requirements for an in vitro mammalian cell cytogenetic assay (§84-2).

870.5385 Mammalian Bone Marrow Chromosomal Aberration Test

In an in vivo bone marrow cytogenetic assay (MRID 43740802), groups of six male and six female Wistar rats received a single oral gavage administration of 4000 mg/kg triclosan (99-100%). The test material was delivered to the animals as suspensions prepared in 1% carboxymethyl-cellulose. Animals were sacrificed 6, 24, and 48 hours following compound administration and bone marrow cells from ten animals per group (5 males and 5 females) were harvested and examined for the incidence of structural chromosome aberrations.

No signs of overt toxicity or cytotoxic effects on the target organ were seen in any treatment groups. The positive control induced the expected high yield of cells with structural chromosome aberrations. There was also no indication of a clastogenic effect at any sacrifice time.

The study is classified as Acceptable/Guideline and satisfies the requirements for FIFRA Test
Guideline §84-2 for in vivo cytogenetic mutagenicity data.

870.5550 Unscheduled DNA Synthesis in Mammalian Cells in Culture

In an in vitro DNA synthesis assay (MRID not assigned), rat hepatocytes were exposed to triclosan (batch/lot#: CC # 14663-09) dissolved in DMSO. Hepatocytes were isolated from the liver of two male Fischer 344 rats by the two-step in-situ perfusion. Concentrations of 0, 0.05, 0.1, 0.25, 1.0, 2.5, 5.0, 10, 25.0, 50.0, 100.0, or 250 µg/mL were tested for 18-20 hours. Cells were autoradiographed, and unscheduled DNA synthesis was evidenced by a net increase in black silver grain counts using an Artek 880 automated colony counter with microscope and connected to an Apple II computer for data analysis. The difference between the cytoplasmic grain count and the corrected grain count was calculated and the net nuclear grains (NNG) and the percentage of hepatocytes in repair were calculated.

Triclosan was tested up to the toxicity limit of 2.5 µg/mL based on the preliminary toxicity test using rat hepatocytes that were treated at dose concentrations of 10.0, 25.0, 50.0, 100.0, 250.0, and 500.0 mg/mL. Precipitation was observed ≥50 mg/mL, and turbidity was noted at 25 mg/mL. Hence 25 mg/mL was selected as the highest dose concentration for the UDS assay.

In the UDS assay, triplicate cultures were exposed to the test article, untreated control, solvent control or a positive control (2AAF). Toxicity was observed at ≥5 µg/mL in the form of low grain count. Hence dose concentrations of 0.25, 0.5, 1.0, and 2.5 µg/mL were evaluated for UDS assay. No significant increases in mean NNG counts were reported at any dose levels and the percent of cells in repair ranged from 0-6%, comparable to the solvent and untreated controls. The positive control yielded 88.7% of cell in repair and a mean NNG count of 21.2, hence eliciting a clear positive response. There was no evidence of induction of unscheduled DNA synthesis in rat primary hepatocytes over the background.

This study is classified as Acceptable-Guideline and satisfies the guideline requirement (OPPTS 870.5550) for an in vitro UDS assay.

V. Susceptibility CONSIDERATIONS

There are no existing tolerances or tolerance exemptions for Triclosan under 40 CFR 180, and there are no food additive clearances from the Food and Drug Administration. However, as there are expected exposures of infants and children to this chemical as well as potential exposures from indirect food uses, the reproductive and developmental toxicity database is discussed.

1. Reproductive Toxicity Study Conclusions

In a 2-generation reproduction study (MRID # 40623701), triclosan was administered to 25 rats/sex/dose at dietary levels of 300, 1000, and 3000 ppm (nominal doses of 15, 50, and 150 mg/kg/day). Significant body weight reduction was observed in adult rats at the high dose during weeks 0-12, gestation, and lactation. The Systemic NOAEL = 1000 ppm, and the Systemic LOAEL = 3000 ppm, based on reduced mean body weight. Body
weights in high dose F1 pups were significantly lower on days 14 and 21 of lactation. F2 pups displayed significantly lower body weights at birth which did not persist at day 4 of lactation or greater. Viability index was decreased at the high dose in both generations of pups and the weaning index was slightly lower in high dose F2 pups vs control. The Reproductive NOAEL = 1000 ppm, and the Reproductive LOAEL = 3000 ppm, based on reduced pup weights and equivocal reduced pup viability in both generations.

2. Pre-and/or Postnatal Toxicity

In a developmental toxicity study in rabbits, triclosan (100% a.i.) was administered by gavage to pregnant female New Zealand White rabbits (18/group) on gestation days 6-18 at dose levels of 15, 50, or 150 mg/kg/day. Rabbits were observed for signs of toxicity; body weight and food consumption values were recorded. On day 30 of gestation, rabbits were sacrificed and necropsied; gravid uterine weights were recorded. The uteri were examined, implantation sites were counted, and the numbers of corpora lutea were determined. The fetuses were removed, weighed, sexed, and examined for external, visceral and skeletal anomalies. They were then examined by the Staple's dissection procedure. Evidence of treatment-related toxicity at the high dose (150 mg/kg/day) consisted of reduced body weight gain and food consumption over the period of treatment. The Maternal NOAEL = 150 mg/kg/day, based on decreased body weight gain and food consumption during treatment. The Maternal NOAEL = 50 mg/kg/day. No developmental toxicity was observed under the conditions of this study. The Developmental LOAEL = not determined; the developmental NOAEL = 150 mg/kg/day.

Triclosan was administered by gavage to pregnant female Wistar rats (30 rats/group, 60/group in control) on days 6-154 gestation at dose levels of 30, 100, or 300 mg/kg/day. At 300 mg/kg/day, maternal toxicity was evident and consisted of transient diarrhea, decreased body weight gain during treatment, and reduced food consumption and increased water consumption from onset of treatment through gestation. Based on these findings, the Maternal NOAEL = 100 mg/kg/day, and the Maternal LOAEL = 300 mg/kg/day. There was no evidence of pre- or post-natal developmental toxicity at any dose level in this study. The Developmental LOAEL = not determined (> 300 mg/kg/day); the Developmental NOAEL ≥ 300 mg/kg/day.

Determination of Susceptibility

The data base is complete and there are no data gaps pertaining to developmental or reproductive toxicity. The data provided no indication of increased sensitivity of rats or rabbits to in utero and post-natal exposure to triclosan. Two prenatal developmental toxicity studies, one in rats and one in rabbits, failed to show evidence of developmental toxicity in the absence of maternal toxicity. In the two-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity.
**Additional Safety Factor(s):**

A safety factor to account for susceptibility is not needed:

(I) The data provided no indication of increased susceptibility of rats or rabbits to *in utero* and/or postnatal exposure to triclosan.

(ii) No evidence of developmental anomalies, including abnormalities in the development of the fetal nervous system, were observed in the pre- and/or post-natal studies.

(iii) There are no data gaps for evaluation of increased susceptibility to infants and children.

**3. Recommendation for a Developmental Neurotoxicity Study**

The committee considered the available data on triclosan for evaluation of neurotoxicity, including the 14-day neurotoxicity study in rats, developmental and reproductive toxicity studies in rats and rabbits, and subchronic and chronic data in rats and mice. There was no evidence of a neurotoxic effect of triclosan in any of these studies. **Thus, the committee did not recommend a developmental neurotoxicity study for triclosan.**
VI. DATA GAPS

There are no current data gaps for hazard evaluation of triclosan.
VII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected and Margins of Exposures for various exposure scenarios are summarized below.

<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>Dose Used in Risk Assessment</th>
<th>Uncertainty factors for Risk Assessment</th>
<th>Study and Toxicological Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Dietary (gen. pop.)</td>
<td>NOAEL = 30 mg/kg/day</td>
<td>Interspecies = 10x</td>
<td>Chronic Toxicity study in Baboons MRID 257773</td>
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<tr>
<td></td>
<td>aRfD = 0.03 mg/kg/day</td>
<td>Intraspecies = 10x</td>
<td></td>
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<td></td>
<td></td>
<td>DBSS* = 1x</td>
<td></td>
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<td></td>
<td></td>
<td>UF = 100</td>
<td></td>
</tr>
<tr>
<td>Acute Dietary (females 13+)</td>
<td>Endpoint not identified in</td>
<td></td>
<td></td>
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<td></td>
<td>the database</td>
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</tr>
<tr>
<td>Chronic Dietary (all populations)</td>
<td>NOAEL = 30 mg/kg/day</td>
<td>Interspecies = 10x</td>
<td>Chronic Toxicity study in Baboons MRID 257773</td>
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<tr>
<td></td>
<td></td>
<td>Intraspecies = 10x</td>
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<td></td>
<td></td>
<td>DBSS* = 1x</td>
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<tr>
<td></td>
<td></td>
<td>UF = 100</td>
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<tr>
<td>Short-Term/Intermediate-Term</td>
<td>NOAEL = 30 mg/kg/day</td>
<td>Interspecies = 10x</td>
<td>Chronic Toxicity study in Baboons MRID 257773</td>
</tr>
<tr>
<td>Incidental Oral (1-30 days;</td>
<td></td>
<td>Intraspecies = 10x</td>
<td></td>
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<tr>
<td>30 days-6 months)</td>
<td></td>
<td>DBSS* = 1x</td>
<td></td>
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<td></td>
<td></td>
<td>UF = 100</td>
<td></td>
</tr>
<tr>
<td>Dermal (short-term)</td>
<td>NOAEL (dermal) = 0.6 mg/</td>
<td>Interspecies = 3x</td>
<td>14-day dermal toxicity study in the mouse MRID 44389708</td>
</tr>
<tr>
<td></td>
<td>animal (100 µg/cm²)</td>
<td>Intraspecies = 3x</td>
<td>NOAEL (dermal) of 0.6 mg/animal, based on dermal</td>
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<tr>
<td></td>
<td></td>
<td>DBSS* = 1x</td>
<td>irritation at 1.5 mg/animal (erythema, fissuring,</td>
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<td></td>
<td></td>
<td>MOE = 10</td>
<td>eschar, thickening, and discoloration). At 3.0</td>
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<td></td>
<td></td>
<td></td>
<td>mg/animal, increased liver weight and centrilobular</td>
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<td></td>
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<td>hepatocyte hypertrophy was observed in both sexes.</td>
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<tr>
<td>Dermal (intermediate term)</td>
<td>NOAEL = 40 mg/kg</td>
<td>Interspecies = 10x</td>
<td>90-day Dermal Toxicity in Rats MRID 43328001</td>
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<tr>
<td></td>
<td></td>
<td>Intraspecies = 10x</td>
<td>LOAEL = 80 mg/kg/day, based on increased incidence</td>
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<tr>
<td></td>
<td></td>
<td>DBSS* = 1x</td>
<td>occult blood in the urine.</td>
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<tr>
<td></td>
<td></td>
<td>MOE = 100</td>
<td></td>
</tr>
<tr>
<td>Exposure Scenario</td>
<td>Dose Used in Risk Assessment</td>
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<tr>
<td>Dermal (long-term)</td>
<td>NOAEL = 40 mg/kg</td>
<td>Interspecies = 10x</td>
<td>90-day Dermal Toxicity in Rats</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intraspecies = 10x</td>
<td>MRID 43328001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DBSS* = 3x (lack of chronic dermal study)</td>
<td>LOAEL = 80 mg/kg/day, based on increased incidence occult blood in the urine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MOE = 300</td>
<td></td>
</tr>
<tr>
<td>Inhalation (all durations)</td>
<td>LOAEL (males) = 50 mg/m$^3$</td>
<td>MOE = 1000</td>
<td>21-Day Inhalation Toxicity study in the rat</td>
</tr>
<tr>
<td></td>
<td>(4.22 ppm; 3.21 mg/kg/day)</td>
<td></td>
<td>MRID 0087996</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LOAEL = 3.21 mg/kg/day, based on decreased thrombocytes, total derum protein, and increased alkaline phospatase in males.</td>
</tr>
<tr>
<td>Cancer (oral)</td>
<td>In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), the HED CARC classified triclosan as “Not Likely to be Carcinogenic to Humans”.</td>
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</tr>
</tbody>
</table>

$^a = 0.6 \text{mg/animal} \times 1000 \mu\text{g/mg} / 6\text{cm}^2 = 100 \mu\text{g/cm}^2$

UF = uncertainty factor, DBSS = database uncertainty [special sensitivity] factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable