UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

APR 27 1998

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Triclosan: Review of Toxicology Data Submitted by the Registrant.

TO: Adam Heyward / Portia Jenkins
PM Team # 34
Regulatory Management Branch II
Antimicrobials Division (7510W)

FROM: Timothy F. McMahon, Ph.D. 3/17/98
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THRU: Winston Dang, Ph.D.
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And

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EPA Identification Numbers:

P.C. Code: 054901 DP Barcode: D240164
Submissions: S532102
MRID numbers: 44389701 through 44389711

Registrant: Ciba Specialty Chemicals

Action Requested: Review of non-guideline toxicology data submitted in support of the registration of the active ingredient Triclosan.

Background

The registrant (Ciba Specialty Chemicals) has submitted (at the request of the Antimicrobials Division, USEPA), non-guideline toxicology studies which were conducted with Triclosan, technical grade (>99% a.i.). Also included were mutagenicity studies in support of the 84-2 guideline requirement under Subdivision F Testing Guidelines. The specific studies and executive summaries of these studies are detailed below:

1) CITATION: Eldridge, S. (1993): Cell Proliferation in Rodent Liver. Study performed by Pathology Associates, Inc. For Ciba-Geigy Corporation. MRID # 44389701. Unpublished.

Executive Summary: In this study, liver tissue from mice in the subchronic feeding study (MRID # 43022605) was examined for cell proliferation as a result of Irgasan treatment. The subchronic feeding study used doses of 0, 25, 75, 200, 350, 750, or 900 mg/kg/day for 13 weeks, or 0, 25, 350, and 900 mg/kg/day for 7 weeks. Slides prepared from paraffin embedded tissue were stained with hematoxylin and eosin for histopathology evaluation, or stained with proliferating cell nuclear antigen (PCNA). Histopathology examination and cell proliferation analysis was performed on 5-7 mice/sex/dose excluding the 750 mg/kg/day dose. At 7 weeks (45 days), hepatocellualr hypertrophy was the most consistent and prominent histopathological observation. The lesion was observed at the 25 mg/kg/day dose level in both sexes. At 350 and 900 mg/kg/day, necrosis of hepatocytes was also observed. At 13 weeks, hepatocellular hypertrophy was also observed at 75 mg/kg/day and above in both male and female mice, with increasing severity as the dose increased. Severity scores for histopathology at the high dose appeared higher at 7 weeks than 13 weeks for male and female mice. Cell proliferation was juidged by the reviewer to be increased significantly at 75 mg/kg/day and above in male mice, and at 200 mg/kg/day and above in female mice. The results of this study support a mode of action consistent with cellular regeneration as a result of hepatocellular toxicity. A No Observed Effect Level of 25 mg/kg/day was identified, based on hepatic effects in males observed at 75 mg/kg/day and above. The 75 mg/kg/day dose level is considered a NOEL for female mice. This study is classified as **acceptable (non-guideline).**

2)CITATION: Molitor, E., Persohnm, E., Thomas, H. (1995): The Effect of FAT 80'023/Q (IRGASAN DP300) on Selected Biochemical Liver Parameters Following Subchronic Dietary Administration to Male and Female Mice. Ciba-Geigy Limited, Toxicology Services, Basel, Switzerland. MRID # 44389702. Unpublished.

Executive Summary: In this study, Irgasan DP 300 technical was administered to five groups of young adult male CD-1 mice in a pelleted standard rodent diet at doses of 0, 100, 300, 1200, and 3000 ppm (approximately 0, 25, 75, 350, and 900 mg/kg/day) for 14 days. Two additionhal groups of nine male mice received either 0 or 900 mg/kg/day Irgasan for 14 days followed by a 4 week recovery period. Groups of female mice received Irgasn in the diet at doses of 0, 25, 350, and 900 mg/kg/day for 14 days. Livers were immediately frozen at necropsy in liquid nitrogen for biochemical and immunochemical measurements. Liver weight was significantly increased in male mice at 75 mg/kg/dayand above and in female mice at 350 mg/kg/day and above. At the lowest dose in male mice (18.4 mg/kg/day), signficant increases were observed in microsomal protein (25%), EROD activity (82%), and PROD activity (431%). Total microsomal hydroxylation of testosterone was significantly increased at the low dose in male mice, as was stereoselective hydroxylation of the 6ß-hydroxylated metabolite. In female mice, significant induction of CYP 3A1 and CYP 3A2 as well as CYP4A was observed at the lowest dose in female mice (19.8 mg/kg/day). The low dose of 18.4 mg/kg/day is considered as a LOEL, based on significant increases in serum biochemistry parameters observed in the liver of male mice. A NOEL was not achieved in this study.

3) CITATION: Molitor, E. And Persohn, E. (1995): The Effects of FAT 80'023/Q (Irgasan DP300) On Selected Biochemical Liver Parameters Following Dietary Administration to Male Rats. Study performed by Ciba-Geigy Limited, Switzerland. MRID # 44389703. Unpublished.

Executive Summary: In this study, young adult male Sprague-Dawley rats (230-260 g b.w.) were divided into groups of five rats. Four groups (groups 7-10) received Irgasan in the diet for 14 days at concentrations of 0, 300, 1500, and 6000 ppm (0, 23, 108, and 518 mg/kg/day). Two additional groups (11 and 14) received Irgasn at 0 and 6000 ppm for 42 days. Reversibility of the effect was examined in a single group of five rats, who received 6000 ppm Irgasan in the diet for 14 days followed by a 28 day recovery period. No clinical signs of toxicity were reported in this study. Food consumption at the 6000 ppm dose was decreased by 50% on day 1, but rebounded on days 3-7 to almost 3-fold over control. Decreased food consumption at 300 and 1500 ppm of 10%

and 6% was observed on days 3-7 of the study. Body weight at 6000 ppm was decreased 4-8% over the first 8 days of the study. The recovery group displayed decreased group mean body weight vs control (6%) during the 28 day recovery period. Significantly increased absolute (52%) and relative (52%) weight of the liver was observed at 6000 ppm Irgasan in the diet. Absolute liver weight in rats receiving test article for 42 days was not increased, probably as the result of decreased body weight at study termination in this group. Liver biochemical effects were observed at 6000 ppm, including a doubling of cytochrome P-450 content, increased cytosolic glutathione-S-transferase activity (65% increase), a 3-fold increase in lauric acid hydroxylation activity at the 12 position, and a 10-fold increase in PROD activity. Those rats recovering for 28 days showed no significant induction or inhibition of enzyme activities in the liver, while those rats maintained on the test diet for 42 days continued to show changes in liver biochemistry consistent with the 14-day dose group. Testosterone hydroxylation (formation of the 15α- and 16β-hyroxy metabolites was increased at the high dose. Total testosterone hydroxylation activity was increased at the 1500 and 6000 ppm dose levels. Immunoblot analysis showed a marked dose-dependent increase in Mab be4 immunoreactive protein at 1500 and 6000 ppm, indicative of an increase in cytochromes CYP2B1 and CYP2B2. A slight induction of CYP3A1 was identified at 1500 and 6000 ppm (131% and 209% of control). Mab clo4 immunoreactive protein showed 116% at 1500 ppm and 164% at 6000 ppm after 14 days of treatment. Treatment for 42 days produced a similar effect as that observed after 14 days. Based on these results, a No Observed Effect Level of 23 mg/kg/day can be established, based on liver biochemical effects observed at the next highest dose (108 mg/kg/day).
This study is classified as **acceptable (non-guideline)**.

4) CITATION: Henderson, L.M., S.J. Ransome, C.E. Brabbs, A.J. Tinner, S.E. Davies, and A. Lloyd (1988) An Assessment of the Mutagenic Potential of Triclosan Using the Mouse Lymphoma TK Locus Assay. Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England. Study No. ULR 216/88644. September 15, 1988. MRID 44389704. Unpublished.

EXECUTIVE SUMMARY:

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 (§84-2)**, and satisfies the requirements for FIFRA Test Guideline for in vitro mammalian forward gene mutation data.

5) CITATION: Stankowski, L. F., Jr., et al. (1993) Amended Final Report, Ames/Salmonella Plate Incorporation Assay on Test Article 39316 (CC #14663-09). Pharmakon USA, P.O. Box 609, Waverly, PA. Laboratory Study Report No. PH 301-CP-001-93, December 2, 1993. MRID 44389705. Unpublished.

EXECUTIVE SUMMARY:
In a microbial mutagenicity assay (MRID 44389705), *Salmonella typhimurium* strains TA100 and TA1538 were exposed to tolylfluanid (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 (§84-2)** and satisfies the requirement for FIFRA Test Guideline for *in vitro* mutagenicity (bacterial reverse gene mutation) data.

6) CITATION: Strasser, F.F. and D. Müller (1979) Chromosome Studies in Somatic Cells, Long-Term Study with FAT 80 023/A Chinese Hamster (Test for Mutagenic Effects on Bone Marrow Cells). CIBA-Geigy Limited, Protection of Health and Environment, Toxicology, Basle Switzerland. Laboratory Experiment No. 78-3105. February 15, 1979. MRID 44389711. Unpublished study.

EXECUTIVE SUMMARY:

In an *in vivo* bone marrow chromosome aberration assay (MRID 44389711), 6 male and 6 female Chinese hamsters were given 3 oral doses of triclosan (purity not reported) per week for 12 weeks in 0.7% aqueous carboxymethylcellulose (CMC) at levels of 75, 150, 300, or 600 mg/kg body weight. Bone marrow was sampled 6 hours after the last treatment.

Lethality occurred in 8/12 animals in the 600 mg/kg test group and in 1/12 animals in the 75 mg/kg group. Clinical signs of toxicity or body weight depression were not reported to have been evaluated at any treatment level. There was no significant increase in the incidence of chromosome damage at any treatment level compared to vehicle controls. Only one chromatid break was observed (per 400 metaphase spreads) each at 300 and 600 mg/kg. A positive control was not included in the assay.

This study is classified as **unacceptable/not upgradable (§84-2)** and does not satisfy the guideline requirements for *in vivo* cytogenetic mutagenicity studies because: (i) a positive control was not included in the study, (ii) the form and purity of the active ingredient tested were not reported, (iii) the test system was not fully identified (strain, source, and age of test animals), and (iv) the animals wer sampled only at 6 hours ater the last dosing.

7) CITATION: Thomas, Rer. Nat. H. (1994): The Effect of FAT 80'023/Q and the model inducers Phenobarbitone, 3-Methylcholanthrene, Pregnenolone 16∝-carbonitrile and Nafenopin on Selected Biochemical and Morphological Liver Parameters in the Syrian Hamster. Study conducted by Ciba-Geigy Limited. Study number CB 93/40. Submitted under MRID # 44389706. Unpublished.

EXECUTIVE SUMMARY:

In this special study, Irgasan DP300 technical (purity 99.5%) was administered to 4 groups of young adult male and female Syrian Hamsters (five/sex/group) in a pelleted standard hamster diet (Nafag 924) at concentrations of 0, 700, 5000, and 15000ppm [approximately 0, 49.9, 309.8, 799.0 mg/kg/day (males) and 46, 314.3, 958.8 mg/kg/day (females)] for 14 days. Separate recovery groups of five males and five females received either 0 or 15000 ppm Irgasan DP300 in the diet for 14 days followed by a 28 day recovery period.

Significant treatment-related effects were observed in male and female hamsters at the 5000 (309.8 mg/kg/day in males, 314.3 mg/kg/day in females) and 15000 ppm (799 mg/kg/day in males, 958.8 mg/kg/day in females) treatment levels. At 5000 ppm Irgasan, significant induction of total hepatic microsomal cytochrome P-450 and activities of ethoxyresorufin-o-deethylase (EROD) and pentoxyresorufin-o-depentylase (PROD) was observed, as was an increase in Mab clo4 immunoreactive protein in male hamster liver. At 15000 ppm, the above effects were also observed, and in addition, abnormal histopathology of the kidneys in females (randomly distributed spots or white patches of white pigmentation on the surface of the kidney) was observed after 14 days of treatment. Total activity towards testosterone was not affected by Irgasan feeding in the diet, but specific hydroxylation reactions were affected. Of note in males, formation of androstenedione was increased in a dose-related manner, as was the formation of the 16-β metabolite. A noticeable dose-response was observed only for androstenedione formation, however.

In female hamsters, a dose-related increase in formation of both the 7-∝ and 15-∝ hydroxy metabolites was noted as a result of Irgasan treatment (formation of the 7-∝ metabolite: activities of 22.16, 35.74, 39.33, and 46.66 nmol/min/g at the 0,700, 5000, and 15000 ppm dose levels, respectively; formation of the 15-∝ metabolite: 8.61, 12.78, 18.29, and 29.87 nmol/min/g at 0, 700, 5000, and 15000 ppm Irgasan, respectively). Androstenedione formation was also slightly increased with dose of Irgasan, with a doubling of activity at the high dose (42.72 nmol/min/g) in relation to control activity (21.14 nmol/min/g).

Significant treatment-related increases in lauric acid hydroxylation were observed in male and female hamsters at 15000 ppm Irgasan, as were significant decreases in activity of cytosolic glutathione-S- transferase and increases in bilirubin and morphine glucuronyltransferase activity. Total immunoreactive protein towards the Mab clo4 antibody (indicative

of induction of CYP4A P-450, a peroxisome proliferator inducible form) was observed in male and female hamsters at 15000 ppm. Together with the data presented on the effects of the model inducers phenobarbital, 3-methylcholanthrene, nafenopin, and pregnenolone 16 ∝-carbonitrile, the data suggest that Irgasan acts as a peroxisome proliferator, as observed in other work with rats and mice. Hamsters, however, appear less sensitive to Irgasan treatment relative to rats and mice.

Based on the results of this study, a Systemic NOEL of 700 ppm can be established, with a Systemic LOEL of 5000 ppm, based on induction of total cytochrome P-450, EROD, and PROD in male and female hamsters, and induction of Mab clo4 immunoreactive protein (CYP4A peroxisome proliferator inducible P-450) in male hamsters).

This study is classified as **acceptable (non-guideline)**. The study provides important information on the mechanistic basis of Irgasan induced liver toxicity, and also provides information on the relative sensitivity of the hamster to the hepatic effects of Irgasan.

8) CITATION: Thevanez, Dr. Phil. II ph. (1987): Final Report: FAT 80023: 28-Day Toxicity Study in Mice (Administration in Feed) with Special Reference to Histopathology. Ciba-Geigy Ltd., Basle, Switzerland. MRID # 44389707. Unpublished.

EXECUTIVE SUMMARY: In a twenty-eight day toxicity study, a total of 40 mice (MAGf [SPF], 5/sex/dose) received technical triclosan admixed into pelleted feed at dose levels of 0, 50, and 1000 ppm (6.48 and 135.59 mg/kg/day in males, 8.25 and 168.78 mg/kg/day in females) for 4 weeks. Five males and 5 females were given the high dose and allowed to "recover" (feeding of non-treated feed) for 2 weeks. There were no reported effects on mortality, body weight, or food consumption. Hematological effects were observed at the high dose (135.59 mg/kg/day in males; 168.78 mg/kg/day in females), and included significant decreases in erythrocytes, hemoglobin, and hematocrit in males, and a significant decrease in hemoglobin in females. Both sexes showed significant increases in thrombocytes at this dose, the effects of which were not fully reversible after two weeks recovery. Clinical chemistry alterations (significant increases in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase; significant decrease in glubulin fraction) were observed at the high dose in male and female mice. Elevated serum enzyme activities were evident after the two week recovery period. Absolute weight of the liver and liver/body weight ratio were significantly increased at the high dose in male and female mice. Histopathological examination of the liver showed an increased incidence of liver cell necrosis (as single cells or small cell groups), hemosiderosis of Kupffer cells in the vicinity,

cytoplasmic vacuoles in hepatocytes, and liver cell hypertrophy. The presence of necrosis was still evident (2/5 males and 3/5 females) after the recovery period.
Based on the biochemical and morphological effects of Irgasan treatment on the liver of male and female mice, a systemic LOEL of 135.59 mg/kg/day for males and 168.78 mg/kg/day is assigned. The systemic NOEL is considered to be 6.48 mg/kg/day in males, and 8.25 mg/kg/day in females. This study is classified as **acceptable** and provides relevant toxicologic data on the effects of Irgasan treatment to the liver of male and female mice. This study was not conducted to fulfill a specific guideline requirement, but provides useful data for the risk assessment of Irgasan.

9) CITATION: Burns, J.M. (1997) 14-Day Repeated Dose Dermal Study of Triclosan in CD-1 Mice. Corning Hazleton Incorporated (CHV), 9200 Leesburg Pike, Vienna, Virginia. Laboratory Study No. CHV 2763-100. April 29, 1997. MRID 44389708. Unpublished.

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 suppurative 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 ($p \leq 0.05$) 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 ($p \leq 0.05$) 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,**

11) CITATION: Burns, J.M. (1997) 14-Day Repeated Dose Dermal Study of Triclosan in Rats. Corning Hazleton Incorporated (CHV), 9200 Leesburg Pike, Vienna, Virginia. Laboratory Study No. CHV 6718-102. April 28, 1997. MRID 44389710. Unpublished.

EXECUTIVE SUMMARY:

In a repeated dose dermal toxicity study (MRID 44389710), triclosan (99.3% a.i.) was applied daily in acetone to the clipped skin of ten Crl:CD®BR rats/sex/dose at dose levels of 0, 0.3, 0.6, 1.5, 3.0, or 6.0 mg/animal/day for 14 days.

Treatment-related dermal irritation was observed in both sexes of the 6.0 mg/animal/day group consisting of erythema, scaling, and eschar. Dose-related, non-neoplastic histopathological changes to skin were observed at application sites in the 6.0 mg/animal/day treatment group which consisted of treatment-related acanthosis of eschar in 4/10 males and 3/10 females and hyperkeratosis in 10/10 females. No unscheduled deaths occurred and no clinical signs of toxicity were observed in any treatment group. There were no treatment-related changes in organ weights. There were no significant differences between the terminal body weights or in food consumption in the treated and control groups nor were there any overall differences in body weight changes in treated males and females. **The LOEL for this study is 6.0 mg/animal/day, based on treatment-related dermal irritation at the treatment site. The NOEL is 3.0 mg/animal/day.**

This dermal toxicity study is classified as **acceptable/non-guideline** and was intended only as a rangefinding study for a 90-day dermal study.

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.

This dermal toxicity study is classified as **acceptable/non-guideline** and was intended only as a rangefinding study for a 90-day dermal study.

10) CITATION: Burns, J.M. (1997) 14-Day Repeated Dose Dermal Study of Triclosan in Mice. Corning Hazleton Incorporated (CHV), 9200 Leesburg Pike, Vienna, Virginia. Laboratory Study No. CHV 6718-101. April 28, 1997. MRID 44389709. Unpublished.

EXECUTIVE SUMMARY:
In a repeated dose dermal toxicity study (MRID 44389709), triclosan (>99.3% a.i.) was applied daily in propylene glycol 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.

Dose-related dermal irritation was observed in both sexes of the 3.0 and 6.0 mg/animal/day groups consisting of erythema, eschar, exfoliation, ulcers, alopecia, and/or thickening. In the 1.5 mg/animal/day group, eschar was observed in both sexes and erythema was seen in males only. Dose-related, non-neoplastic histopathological changes to skin were observed at application sites and included ulceration, epidermal debris, epidermal acanthosis, dermal fibroplasia, and chronic active inflammation in both sexes at 1.5, 3.0, and 6.0 mg/animal/day. No unscheduled deaths occurred and no clinical signs of toxicity were observed in any treatment group. 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 these dose levels. 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 ($p \leq 0.01$) at 6.0 mg/animal/day during Week 1 (↓130%) and for females at 3.0 mg/animal/day during Week 2 (↑133%, $p \leq 0.05$) and overall (↑58%/ $p \leq 0.01$). Food consumption was significantly increased ($p \leq 0.05$) for the 6.0 mg/animal/day females only during Week 2 (↑14%) and overall (↑9%). **The LOEL for this study is 1.5 mg/animal/day, based on treatment-related dermal irritation at the treatment site and on hepatocellular hypertrophy. 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.

This dermal toxicity study is classified as **acceptable/non-guideline** and was intended only as a rangefinding study for a 90-day dermal study.