

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
5-CHLORO-2-(2,4,-DICHLORO- PHENOXY) PHENOL

Chemical Code # 001371, DPN #: 50291
SB 950 # 568

Original Date: September 10, 2003
Revised: 1/25/05, 7/24/07

DATA GAP STATUS

Combined (Chronic/onco), rat:	No data gap, no adverse effect
Combined (Chronic/onco), hamster:	No data gap, no adverse effect
Oncogenicity, mouse:	Data gap, no study submitted.
Chronic toxicity, dog:	Data gap, no study submitted
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Teratology, mouse:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosomal aberrations:	No data gap, possible adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

All record numbers through 211017 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T070724.doc

Original by: Kishiyama & Silva, 9/10/03; Silva, 1/25/05; Morris 7/24/07.

This chemical is registered as an antimicrobial for use in fabrics. It is also used in skin products.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

**** 50291 - 007, 008, 009, 048; 045802, 221682** AFAT 80'023 2-Year Oral Administration to Rats, @ (Yau, E.T., Green, J.D.; CIBA-GEIGY Corporation, Research Department, Chemicals Division, Greensboro, NC; Report #: 85152; 4/28/86). FAT 80'023 (purity = 99%) was fed in diet to Sprague-Dawley rats [CrI: COBS7 CD7 (SD) BR] (60/sex/dose) at 0, 300, 1000 and 3000 ppm for 104 weeks. At 0, 300, 1000 and 3000 ppm, an additional 5/sex/dose were added for sacrifice at weeks 13, 26, and 78. At 52 weeks, 20/sex/dose were added for sacrifice at 0 and 6000 ppm and 10/sex/dose for all other doses. At week 78 for the chronic study, 60/sex/dose were sacrificed at 0, 300, 1000 and 3000 ppm. Chronic NOEL (M/F) = 1,000 ppm (based on reduced body weight). Male body weights were statistically significantly lower than control weeks 2 - 52 at 6000 ppm and through week 8 at 3000 ppm. Female body weights were statistically significantly lower at ≥ 3000 ppm. There was a statistically significant increase in food consumption at ≥ 3000 ppm in males. Absolute and relative male liver weights were decreased at ≥ 3000 ppm. There was a decrease in absolute heart and a decrease in relative kidney and brain weights in males at 6000 ppm. Absolute brain weights in males were decreased at 3000 ppm. Females showed decreased absolute heart and liver weights and increased relative brain, kidneys, ovaries, heart and adrenals at 6000 ppm and increased absolute and relative ovary weights and decreased relative spleen weights at 3000 ppm. Urinary protein was not statistically significantly decreased, but was lower at ≥ 3000 ppm in females. No evidence of treatment-related oncogenicity. Not acceptable (Silva, 4/9/03) but upgraded to acceptable by submission of a legible copy of "A Pathology Report for Individual Animal@ Appendix VI-7 and the full report for the 90-day study supporting dose selection (S. Morris, 7/24/07).

50291-0048; 221682; "FAT 80'023: 2-Year Oral Administration to Rats (MIN 833005), APPENDIX VI, Pathology Report for Individual Animal." This document is an addendum to DPR doc. #'s 50291-007, 008, 009; rec. # 045802. Evaluation of this document resulted in upgrading the main study to acceptable (Morris, 7/24/07).

Subchronic Study:

**** 50291 – 0030 210966** "90- Day Oral Toxicity Study in Rats with FAT 80'023 (Final Report)," (Goldsmith, L.A.; Litton Bionetics, Inc., Kensington, MD; LBI Project #: 22188; 10/83). FAT 80'023/H (purity not stated) was fed in diet to Sprague-Dawley rats [CrI: COBS CD (SD) BR] (25/sex/dose) at 0, 1000, 3000 and 6000 ppm for 90 days (Intake M: 51 – 92, 159 – 288 or 341 – 634 mg/kg/day; F: 68 – 109, 213 – 322 or 469 – 691 mg/kg/day at 1000, 3000 and 6000 ppm, respectively). At 45 days, 10/sex/dose were terminated. Body weights were statistically significantly decreased throughout the study in males at 6000 ppm. Females showed intermittent decreases in body weights at 6000 ppm throughout the study. Food in 8/25 males and 4/25 females at 6000 ppm was refused temporarily (effect of palpability, rather than of toxicity). Males at 6000 ppm showed an increase in ketones (8/15) as compared with controls (3/15). Males showed increased relative left kidney weights and females showed increased relative liver weights at day 45 at 6000 ppm. At termination, males showed decreased spleen weights and females showed decreased heart weights at ≥ 3000 ppm. At termination, males showed increased relative brain, heart, liver and left testis weights at 6000 ppm and decreased spleen weights at ≥ 3000 ppm. Females, at termination, showed increased relative right and left kidney weights at ≥ 3000 ppm and increased relative liver weights at 6000 ppm. NOEL = 1000 ppm (Histopathologically there was a significant increase in centrilobular cytomegaly in both sexes at ≥ 3000 ppm, beginning at day 45. Males showed fatty metamorphosis at 3000 ppm at day 45, and both sexes at 6000 ppm (day 45, 3/10 males, 1/10 females, 0/10 controls; not statistically significant.) At day 90, 6/15

males and 0/15 females showed fatty metamorphosis. There was no evidence of degeneration or necrosis.) Possible adverse effect. Liver pathology in both sexes beginning at day 45. Acceptable. Silva 1/12/05.

50291 - 023 119775, addendum to: 007, 008, 009 045802 Subchronic Study (in DPR volume/record #: 50291 - 023/119775): "Pathology Working Group Report on Triclosan 90-Day Subchronic Toxicity Study in Sprague-Dawley Rats," was presented in brief summary, submitted in conjunction with the Pathology Work Group (PWG, D.G. Goodman, J.M. Cullen, P.M. Newberne, R.A. Squire, J.M. Ward, R.M. Sauer) review for the definitive 2-Year Chronic Rat Study (DPR volume/record #: 50291 - 007 - 009/045802). Some of the pathology from the 90-day subchronic study was reviewed by Pathco, Inc., Ijamsville, MD, which headed the PWG. Results of the evaluation of the liver pathology for the subchronic study, the PWG deemed 3000 ppm to be an appropriate MTD for the definitive study. Two Year Chronic Study: Liver and lung histopathology from AFAT 80'023 2-Year Oral Administration to Rats" (Yau, E.T., Green, J.D.; CIBA-GEIGY Corporation, Research Department, Chemicals Division, Report 85152; 4/28/86) was evaluated by the PWG and their findings were submitted in DPR volume/record #: 023/119775 ("Irgasan[®] DP 300 Pathology Working Group (PWG) Report on Triclosan/Carcinogenicity Study in Sprague-Dawley Rats; Additional Data to Support Acceptance of MRID 161332" Goodman, D.G.; Pathco, Inc., Ijamsville, MD; 1/23/90). Since data from the definitive study were in question and were re-evaluated by a "PWG" it must be clarified that the term "PWG" does not equate to that term as used by US EPA. "PWG" as defined by US EPA, consists of 3 independent pathologists, who evaluate the data in question, without consulting one another or the original Study Pathologist. Therefore, although some data were re-reviewed by a Pathco, Inc. - devised work group, the information (for the purpose of upgrading the study) is considered supplemental, and the original data (until re-examined by a US EPA PWG) will be the primary data considered by DPR reviewers. As of September 2, 2003, a readable copy of the animal pathology for the definitive study has not been received at DPR. All pathology must be evaluated by DPR prior to determining the acceptability of the 2-Year Chronic Rat Study. The definitive study remains unacceptable but upgradeable with submission of a readable histopathology report. (Kishiyama & Silva, 9/2/03).

COMBINED, HAMSTER

** 50291 - 028 175832 "Potential Tumorigenic and Chronic Toxicity Effects in Prolonged Dietary Administration to Hamsters" (Chambers, P.R.; Huntingdon Life Sciences Ltd., Huntingdon, England; CBG 756/972896; 3/30/99). FAT 80=023/S (purity = 99.5%) was fed in diet to Bio FID Alexander Syrian hamsters (Main group = 60/sex/dose; satellite = 10/sex/dose) at 0 (2 control groups), 12.5, 75, or 250 mg/kg for 90/95 weeks (Main Group; 90 weeks 95 weeks) and 52 weeks (Satellite). Chronic NOEL = 75 mg/kg (Mortality was statistically significantly increased at 250 mg/kg. General clinical condition deteriorated at 250 mg/kg (lethargy, hunched posture, pallor, thin appearance, unsteady gait). Body weight change was lower throughout the dosing period in both sexes at 250 mg/kg. Food consumption during weeks 1 - 3 was decreased in both sexes at 250 mg/kg. However all food consumption decreases were minimal even though they were statistically significant. Water consumption was increased at 250 mg/kg. Urine volume was increased and specific gravity was decreased in both sexes throughout the study at 250 mg/kg. Protein levels and pH values of urine were decreased in both sexes during the first 52 weeks of study at 250 mg/kg. There was an increased incidence in macroscopic irregular cortical scarring and pale coloration of kidneys in both sexes at 250 mg/kg. Females also had a macroscopic increase in white nodules of forestomach at 250 mg/kg. There was a statistically significant increase in distended medullary tubules in males and in radial areas of dilated basophilic kidney tubules in both sexes at 250 mg/kg. The incidence of nephropathy was statistically significantly increased in both sexes at 250 mg/kg. There was a statistically significantly increased incidence in partial depletion of one or more generations of germ cells in testes and in absent spermatozoa, in abnormal spermatogenic cells and in reduced numbers of spermatozoa

in epididymides in males at 250 mg/kg. Focal atypical hyperplasia in the fundic region of the stomach was statistically significantly increased in males at 250 mg/kg. The incidence of distended gastric gland (sometimes containing debris) was statistically significantly increased in both deceased and terminal females at 250 mg/kg. Platelets, GPT and urea nitrogen were decreased at 250 mg/kg in both sexes. PCV, RBC and Hb were decreased in females at 250 mg/kg. WBC and triglycerides were increased in both sexes at 250 mg/kg.) There was no treatment-related oncogenicity. Acceptable, with no adverse effect. (Kishiyama & Silva, 9/4/03).

CHRONIC, BABOON

50291 - 010 045805 "A 1 Year Oral Toxicity Study in Baboons with Compound FAT 80 023/A" (Drake, J.C.; CIBA-GEIGY Pharmaceuticals Wilmslow, Cheshire, UK; Report #: 169/75/S.L.; 7/28/75). FAT 80 023/A (purity not stated) administered orally in gelatin capsules to Papio Baboons (7/sex/dose) at 0 (600 mg lactose + 0.5% magnesium stearate), 30, 100 and 300 mg/kg. After 6, 12 and 13 months (including 28-day recovery period), 2, 3 and 2 baboons/sex/dose, respectively, were sacrificed. NOEL = 30 mg/kg (Body weight gain was slightly decreased in males at ≥ 100 mg/kg and in females at 300 mg/kg by study termination (week 52). Diarrhea and vomiting were observed in both sexes at ≥ 100 mg/kg. Food intake was decreased in males at 300 mg/kg, however statistical significance was not achieved at any particular time point. At 300 mg/kg, females showed an increased incidence in loss of condition (3/6) self-inflicted injury to anal pads (1/6), abrasion (1/6), abdominal pain (2/6), ulcers on feet and anal pads (1/6), no feces passed (1/6) and lethargy (1/6). In females there was a statistically significant increase in prothrombin time and a decrease in Hb, RBC and PCV% at 300 mg/kg. There were no treatment-related long term effects to body weight gain, food consumption, clinical signs, necropsy or histopathology after the recovery period.) UNACCEPTABLE (too few animals at scheduled termination and insufficient information) not upgradeable. (Kishiyama & Silva, 4/23/03)

CHRONIC TOXICITY, DOG

No study submitted

ONCOGENICITY, RAT

See combined (Chronic/Oncogenicity), rat

ONCOGENICITY, MOUSE

No study submitted

REPRODUCTION, RAT

** 50291 – 0029 210965 "Two-Generation Reproduction Study in Rats with FAT 80'02390," (Morseth, S.L.; Hazleton Laboratories America, Inc., Vienna, VA; HLA Study #: 2386-100; 3/18/88). FAT 80'023 (99% Pure) was fed in diet to Crl: CD* (SD) Br rats (25/sex/dose for F0; 30/sex/dose F1 parents) at 0, 300, 1000 and 3000 ppm for 2 generations from premating through weaning of F2 pups. Systemic Parental NOEL = 1000 ppm (There was a decrease in body weights and food consumption at various points during premating, gestation and lactation for both F0 and F1 parents.) Pup NOEL = 1000

ppm (There were incidences of decreased body weights in F1 pups during lactation and in survival in F1 and F2 pups at 3000 ppm.) Reproductive NOEL > 3000 ppm (There were no treatment-related reproductive effects on either parental generation.) No adverse effect. Acceptable. Silva 1/21/05.

50291 - 011 045806 “Two-Generation Reproduction Study in Rats” (Morseth, S.L., Hazleton Laboratories America, Inc., Vienna, VA; Project #: 2386-100 amendment #1; 12/11/85). This volume contains an amendment to a reproduction study protocol. No worksheet. M. Silva, 9/10/03.

TERATOLOGY, RAT

Range-finding Study:

50921 – 0040 210997 “A Range-Finding Study to Evaluate the Toxicity of Irgacare MP (C-P Sample No.: 38328) in the Pregnant Rat,” (Samson, S.; Bio/dynamics, Inc., East Millstone, NJ; Project #: 91-3654; Colgate-Palmolive Study #: 91-013). Irgacare MP (C-P sample #: 38328; 99.8% pure) was administered by gavage to mated CD® (Sprague-Dawley derived) rats (5/dose) at 0 (1% carboxymethylcellulose in 20% glycerin in water suspension), 5, 10, 25, 50 and 75 mg/kg/day for days 6 – 15 of gestation. Maternal NOEL = 50 mg/kg/day (There was a decrease in body weight (1 female) and food consumption at 75 mg/kg/day.) Developmental NOEL = 50 mg/kg/day (There was a decrease in fetal weights at 75 mg/kg/day.) These data are supplemental. No adverse effect indicated. (M. Silva, 12/3/04)

Definitive Study:

** 50921 – 0041 210998 “A Segment II Teratology Study in Rats with Irgacare MP (C-P Sample No.: 38328),” (Schroeder, R.E., et al.; Bio/dynamics, Inc., East Millstone, NJ; Project #: 91-3665; Colgate-Palmolive Study #: 91-005; 4/16/92). Irgacare MP (C-P sample #: 38328; 99.8% pure) was administered by gavage to mated CD® (Sprague-Dawley derived) rats (24-25/dose) at 0 (1% carboxymethylcellulose in 20% glycerin in water suspension), 15, 50 and 150 mg/kg/day (actual doses: 0, 15.8, 52.3 and 156.6 mg/kg/day) for days 6 – 15 of gestation. Maternal NOEL = 50 mg/kg/day (There was a decrease in food consumption at 150 mg/kg/day.) Developmental NOEL = 50 mg/kg/day (There was an increased incidence in “incomplete ossification” or “not ossified” skeletal variations at 150 mg/kg/day on a per litter basis.) Acceptable. No adverse effect indicated. (M. Silva, 12/3/04)

** **50921 – 0044 & 0045 211011 & 211013** “Triclosan: Effects on Pregnancy and Post-Natal Development in Rats: Volume 1, Volume 2 and Appendices 1 – 17,” (Denning, H.J., Sliwa, S., Willson, G.A.; Environmental Safety Laboratory, Unilever Research Lab., Colworth House, Bedford, UK; Document reference: D92/105; Study #: RT/3/84; 12/92). Triclosan (purity not stated) was administered by gavage to mated female Colworth Wistar rats at 0 (corn oil), 30, 100 and 300 mg/kg/day during gestation days (GD) 6 through 15. At GD 21, 25 maternal females per dose (50 for control) were terminated. Subsequently another group of 5 maternal females per dose (10 for control) were allowed a natural parturition before termination. Maternal NOEL = 100 mg/kg/day (There was an increase in slight diarrhea at 300 mg/kg/day (transitional). There was a statistically significant decrease in body weight gain in dams during treatment (GD 6-15) at 300 mg/kg/day. There was a statistically significant decrease initially in food intake at GD 6-15 and post treatment (GD 15-21) intake was increased at 300 mg/kg/day. Overall food intake (GD 6-21) was statistically significantly decreased at 300 mg/kg/day. Food efficiency was statistically significantly decreased from GD 6-10 at 300 mg/kg/day. Water intake was statistically significantly increased throughout the study beginning with the first day of treatment

(GD 6) at 300 mg/kg/day.) Fetal NOEL < 30 mg/kg/day (There was 1 pup with cleft and misshapen palate at 100 mg/kg/day (GA14), 1 pup at 300 mg/kg/day with misshapen palate and 1 pup at 30 mg/kg/day with misshapen palate (S010). There were no such effects observed in control animals, nor were any observed in pups from the postpartum phase. In addition these effects were not described in the historical controls. These effects in the palates of treated animals may be incidental (eg. not statistically significant), however it should be noted.) Pup NOEL = 100 mg/kg/day (There was a statistically significant increase in mean litter size on post partum day 7 and day 14 at 300 mg/kg/day.) Acceptable. Possible adverse effect (palate effects in pups). (M. Silva, 12/3/04)

50291-0048; 221681: This document contains tables of historical control data for palate malformations in rat fetuses and pups. Evaluation of these data did not change the status for the study above (Morris, 3/16/06).

TERATOLOGY, MOUSE

Rangefinding Study:

50921 – 0042 211009 “Dosage-Range Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of C-P Sample No. 38328 Administered Orally Via the Diet to CrI:CD®-1 (ICR)BR Presumed Pregnant Mice,” (Hoberman, A.M.; Argus Research Laboratories, Inc., Horsham, PA; Protocol #: 403-010P; Sponsor’s study #: 91-016; 7/22/92). Irgacare MP (C-P sample #: 38328; 100% pure) was fed in diet to presumed pregnant CrI:CD®-1 (ICR)BR mice (8/dose) at 0 (diet), 5, 10, 20, 40, 80 and 160 mg/kg/day (average consumed dose: 0, 4.8, 9.4, 17.1, 39.0, 71.6 and 127.8 mg/kg/day) during days 6 through 15 of gestation. Maternal NOEL = 40 mg/kg/day (At 160 mg/kg/day, there were reduced body weight gains on GD 12 to 16 and post dose GD 16 to 18. Body weights were decreased at 160 mg/kg/day at GD 18. There was an increase in absolute (g/day) and relative (g/kg/day) food consumption at 160 mg/kg/day throughout dosing and the entire gestation period (GD 0 – 18). The doses (mg/kg/day) consumed by the mice were generally lower than target throughout the study. At 160 mg/kg/day, the doses gradually decreased by 11% up to 24% less than targeted dose during treatment. Consumed doses for the entire treatment period at 5, 10, 20, 40, 80 and 160 mg/kg/day, were 4%, 6%, 14%, 2%, 10% and 20% below target dose. There was an increase in absolute maternal liver weights and relative liver weights (for both brain and body weights) at ≥ 80 mg/kg/day.) Developmental NOEL = 20 mg/kg/day (At ≥ 40 mg/kg/day fetal body weights were statistically significantly decreased ($p < 0.01$). Litter average for resorptions (early and late), percent of resorbed conceptuses and the number of dams with resorptions were increased at 160 mg/kg/day.) Possible adverse effect indicated: Increased resorptions and decreased fetal weights. Data are supplemental. Silva, 12/7/04

Definitive Study:

**** 50921 – 0043 211010** “Developmental Toxicity (Embryo-Fetal Toxicity and Teratogenic Potential) Study of C-P Sample No. 38328 Administered Orally Via the Diet to CrI:CD®-1 (ICR)BR Presumed Pregnant Mice,” (Hoberman, A.M.; Argus Research Laboratories, Inc., Horsham, PA; Protocol #: 403-010; Sponsor’s Study #: 92-001; 10/22/92). Irgacare MP (C-P sample #: 38328; 100% pure) was fed in diet to mated CrI:CD®-1 (ICR)BR mice (25/dose) at 0 (diet), 50, 125, 375 and 1750 ppm (approximately equivalent to 0, 10, 25, 75 and 350 mg/kg/day target or 0.0, 11.2, 26.1, 81.8 and 372 mg/kg/day actual) during days 6 to 15 of gestation. Maternal NOEL = 25 mg/kg/day (The number of mice appearing normal at necropsy was statistically significantly decreased at 350 mg/kg/day. Tan

areas in liver were increased at 350 mg/kg/day. Liver weights, liver/body weights at ≥ 75 mg/kg/day and liver/brain weights at 350 mg/kg/day were increased. Maternal body weights were statistically significantly increased during GD 9 – 14 and 17 at 350 mg/kg/day. Maternal body weight gain was statistically significantly increased at GD 6 – 9 at 350 mg/kg.) Developmental NOEL = 25 mg/kg/day (Fetal body weights were statistically significantly decreased at ≥ 75 mg/kg/day. There was a statistically significant increase in delayed ossification in skull and forelimb phalanges at 350 mg/kg/day.) Acceptable. No adverse effect. (M. Silva, 12/10/04)

50291 - 011 045808 A Irgasan DP 300: Effect of GP 41'353 on Pregnancy of the Mouse,@ (A.K. Palmer, G.M. Scarles; Huntingdon Research Centre, Huntingdon, England, Report #: 2374/68/251; 8/26/68) GP 41'353 (Batch #: Mg2, purity not stated) was administered via oral gavage to mated CD-1 mice (16 - 21) at 0, 10, 50 and 100 mg/kg during gestation days 1 through 16. Maternal NOEL = 10 mg/kg (There was an increased incidence in maternal death at ≥ 50 mg/kg (1 at 50 mg/kg & 6 at 100 mg/kg). Clinical observations (found only in the animals that died) were pilo-erection, weight loss and respiratory distress and were reported to be related to tympanites (enteric disorder causing gas/air in intestine or peritoneal cavity). There were no statistically significant treatment-related effects on body weight and body weight gain, however they were depressed at 100 mg/kg.). Developmental NOEL = 10 mg/kg (There was an increased incidence in percentage of skeletal effects (sternebrae bipartite and/or asymmetrical) in fetuses at 100 mg/kg. There was an increased incidence in percentage of extra ribs in fetuses at ≥ 50 mg/kg. Total percentage of fetuses with variants was statistically significantly increased in all treated groups. However there was no analysis of data on a per litter basis and there were no historical controls for the above effects to fetuses or litters.) Possible adverse effect indicated (Increased fetal variations and maternal death at ≥ 50 mg/kg). Not acceptable and not upgradeable (numerous deficiencies). The data are supplemental. (Kishiyama & Silva, 6/11/03).

TERATOLOGY, RABBIT

Range-finding Study:

50921 – 0038 210991 “A Range-Finding Study to Evaluate the Toxicity of Irgacare MP (C-P Sample No.: 38328) in the Pregnant Rabbit,” (Schroeder, R.E., et al.; Bio/dynamics, Inc., East Millstone, NJ; Project #: 91-3655; Colgate-Palmolive Study #: 91-014). Irgacare MP (C-P sample #: 38328; 99.8% pure) was administered by gavage to mated New Zealand White rabbits (5/dose) at 0 (1% carboxymethylcellulose in 20% glycerin in water suspension), 5, 10, 25, 50 and 75 mg/kg/day for days 6 – 18 of gestation. Maternal NOEL = 50 mg/kg/day (There was a decrease in body weight and food consumption in females at 75 mg/kg/day.) Developmental NOEL = 75 mg/kg/day (There were no effects in fetuses at any doses.) These data are supplemental. No adverse effect indicated. (M. Silva, 12/3/04)

Definitive Study:

** 50921 – 0034 210994 “A Segment II Teratology Study in Rabbits with Irgacare MP (C-P Sample No. 38328),” (Schroeder, R.E., et al.; Bio/dynamics, Inc., East Millstone, NJ; Project #: 91-3666; Colgate-Palmolive Study #: 91-006; 4/16/92). C-P sample #: 38328 (99.8% pure) was administered by gavage to mated New Zealand White rabbits (18-19/dose) at 0 (1% carboxymethylcellulose in 20% glycerin in water suspension), 15, 50, and 150 mg/kg/day for days 6 – 18 of gestation. Maternal NOEL = 50 mg/kg/day (There was a decrease in body weight and food consumption in females at 150 mg/kg/day.) Developmental NOEL = 150 mg/kg/day (There were no treatment-related effects.) No

adverse effect. (M. Silva, 12/3/04)

50291 - 011 045809 A Irgasan DP 300: Effect of GP 41'353 on pregnancy of the New Zealand White Rabbit,@ (Palmer, A.K., Readshaw, M.A; Huntingdon Research Centre, Huntingdon, England, Report #: 2403/68/280; 9/26/68). GP 41'353 (Batch #: Mg2, purity not stated) was administered via oral gavage to mated New Zealand White rabbits (13/dose) at 0, 10, 25, or 50 mg/kg during gestation days 6 through 18. Maternal NOEL = 10 mg/kg (There was an increase in total litter resorption at ≥ 25 mg/kg and a decrease in number of litters at C-section at 50 mg/kg.) Developmental NOEL = 25 mg/kg (There was an increase in 13 ribs on a per fetus level at 50 mg/kg, however, there were no Aper litter@ calculations. In addition, the increase (although statistically significant) was within historical control range.) Possible adverse effect indicated: There was an increased incidence in total litter resorptions at ≥ 25 mg/kg. Not acceptable and not upgradeable. (Kishiyama & Silva, 6/24/03)

GENE MUTATION

** 50291 – 0034 210982 “An Assessment of the Mutagenic Potential of Triclosan Using the Mouse Lymphoma TK Locus Assay,” (Henderson, L.M., Ransome, S.J., Brabbs, C.E., Tinner, A.J., Davies, S.E., Lloyd, A.; Huntingdon Research Centre Ltd., Huntingdon, Cambridgeshire, UK; Study #: KM 880170; 9/15/88). Triclosan (99% pure) was used on mouse lymphoma L5178Y cells in 2 tests with 2 treated cultures/dose both with and without S9 metabolic activation for 3 hours, to test for the forward mutation from the heterozygous thymidine kinase locus (TK +/-) to the thymidine kinase deficient genotype (TK-/-). Test 1 was performed at 0 (DMSO), 1, 2.5, 5, 7.5, 10, 15, 20, 25 ug/ml (no S9) and 0, 0.5, 1, 2, 3.5, 5, 7.5, 10, 15 ug/ml (+S9). Test 2 was performed at 0, 1, 2.5, 5, 7.5, 10, 15, 20 ug/ml (no S9) and 0, 1, 2.5, 5, 7.5, 10, 15, 20 ug/ml (+S9). The results showed that there was a statistically significant increase in mutant colonies at the high dose, with and without S9 in both tests. However, the requirement for a positive test was not fulfilled since survival was very low and the increase in mutation frequency was barely twice background. Therefore, in this study, Triclosan is not considered to be mutagenic. The positive controls functioned as expected. Acceptable. No adverse effect. (Silva, 1/10/04)

** 50291 – 0032 210980 “Ames Metabolic Activation Test to Address the Potential Mutagenic Effect of Triclosan,” (Jones, E., Wilson, L.A.; Huntingdon Research Centre, UK; Unilever Study #: KA 880169; URL 215/88704; 9/9/88). Triclosan (purity = 99%) was tested on *Salmonella typhimurium* strains TA100, TA98, TA1535 and TA1537 (3 cultures/dose/test) at 0 (DMSO), 0.015, 0.05, 0.15, 0.5 and 1.5 ug/bottle for 60 minutes to test for gene mutation (+/- S9 metabolic activation). The experiment was performed twice. In the first experiment, all doses were tested with 0, 3% and 10% S9 and in the second test all with 0, 10 and 30% S9. After incubation, cells were washed and pelleted, then poured on plates with histidine deficient agar. After 72 hours, revertant colonies were counted. There were no treatment-related increases in gene mutation at any dose. The positive controls functioned as expected. Acceptable. No adverse effect. (Silva, 1/7/05)

** 50291 - 0047 211017 “Ames/*Salmonella* Plate Incorporation Assay on Test Article 39316 (CC# 14663-09),” (Stankowski, L.F., Matthews, R.; Pharmakon USA, Waverly, PA; Pharmakon Study #: PH 301-CP-001-93; Colgate-Palmolive Study #: CP-93-012; 12/2/93). Triclosan (purity = 100.5%) was tested on *Salmonella typhimurium* strains TA1537, TA100, TA98, TA1535 and TA1538 (3 cultures/dose/test) at 0.00167, 0.005, 0.0167, 0.05, 0.10, 0.167 ug/plate (no S9 metabolic activation) and 0.05, 0.167, 0.5, 1.67, 2.5 and 5.0 (with S9). A retest was performed with TA100 at 0, 0.000167, 0.0005, 0.00167, 0.005, 0.010, 0.0167, 0.0333, 0.05, 0.10 and 0.167 ug/plate (no S9). This retest was

repeated. There were no treatment-related increases in gene mutation at any dose. The positive controls functioned as expected. Acceptable. No adverse effect. (Silva, 1/5/05)

50291 - 011 045812 “*Salmonella*/Mammalian-Microsome Mutagenicity Test with FAT 80 023/A,” (Arni P., Müller. D.; CIBA-GEIGY Limited; Basle, Switzerland, Experiment #: 78-2511; 3/1/78). FAT 80 023/A (purity unstated) was tested on *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 at 0, 0.01, 0.03, 0.09, 0.27, 0.81, 2.43 and 7.29 µg/0.1 ml (+ S9 metabolic activation) and at 0.01, 0.03, 0.09, 0.27 and 0.81 µg/0.1 ml (no S9) to evaluate mutagenic potential. In addition 2.43 and 7.29 µg/0.1 ml were tested (no S9) on TA92 (3 plates/test condition).. FAT 80 023/A treatments (+/- S9) did not increase the number of histidine-phototropic mutants. At ≥ 0.09 µg/0.1 ml (no S9) and at 7.29 µg/0.1 ml (+S9) bacterial growth was inhibited. All positive controls showed a significant increase in the incidence of histidine-phototropic mutants. The study is not acceptable and not upgradeable due to numerous deficiencies. No adverse effect indicated. (Kishiyama & Silva, 6/30/03).

50291 - 011 045813 “Mutagenic Effects of A Irgasan@ on *Drosophila melanogaster*,” (Magnusson, J.; Wallenberg Laboratory, University of Stockholm, Sweden, 1/30/79). Irgason (purity not stated) was dissolved in corn oil or sucrose was mixed in corn agar substrate and fed to *Drosophila melanogaster* (3 broods of male fruit flies) at 100 ppm (sucrose) and 1000 ppm (sucrose & corn oil) to test for sex-linked recessive lethals. Three experiments were performed: 1) Mutagenicity Test: Feeding was performed in ordinary vials containing corn agar substrate and males received 1000 ppm (Irgason dissolved in corn oil) for 7 days. 2) Feeding (24 hours) was performed in glass tubes (13 ml) with a piece of Kleenex tissue in the bottom to which 2 ml of the sucrose solution at 100 and 1000 ppm were added. 3) The Irgasan Uptake Analysis: Performed on animals injected with Ringer solution at 1000 ppm or fed with corn oil. Uptake was measured at 0, 24, 48 and 72 hours (feeding) or at 0, 24 and 48 hours (injection). Experiments were performed using three broods of males. No increase in sex-related recessive lethals was reported. This study is not acceptable and not upgradeable (deficiencies too numerous). Without a positive control, conclusions cannot be made. (Kishiyama & Silva, 6/30/03).

50291 - 011 045815 “Point Mutation Assay with Mouse Lymphoma Cells I. *In Vitro*-Test / II. Host mediated Assay with FAT 80 023/A,” (Strasser, F.F., Müller, D.; CIBA-GEIGY Limited; Basle, Switzerland, Experiment: 78-2305 & 78-2306; 5/10/78). FAT 80 023/A (purity not stated) was assayed with L5178Y mouse lymphoma cells (2 flasks/dose/incubation time, 10^6 cells/ml in semisolid agar) at 0 (2% carboxymethyl cellulose), 15.8 µg/ml (18 hour incubation) and 28.9 µg/ml (4 hour incubation), followed by a 3 day, treatment-free incubation to assess incidence of mutants. In a host-mediated assay, 10^6 L5178Y cells were injected intraperitoneally into DBA/2f/Bom (SPF) mice (4/dose, sex not stated). Three days after inoculation, mice were dosed orally at 0 (2%, CMC, 10ml/kg) and 1313 mg/kg. Three days later the cells were removed from the peritoneal fluid and seeded into flasks and the incidence of mutation was determined. Results showed no treatment-related increase in the number of mutant L5178Y colonies after either *in vivo* or *in vitro* exposure. No adverse effect indicated. Not acceptable or upgradeable, due to numerous deficiencies. Kishiyama & Silva, 8/1/03

50291 - 011 045819 “The Effect of Irgasan DP 300 in the AMammalian Spot Test”, an *In Vivo* Method for the Detection of Genetic Alterations in Somatic Cells of Mice,@ (Fahrig, R.; Zentrallaboratorium für Mutagenitätsprüfung der Deutschen Forschungsgemeinschaft; 6/22/78). Irgasan DP 300 (99.7% pure) was injected into the peritoneal cavity of mated C57BL/6JHan female mice on gestation day 10 at 0 (Hank=s balanced salt solution) and 50 mg/kg to 46 or 43 females, respectively. Embryos of the genotype a/a; b/+; c^{ch}p/++; d se/++ and s/+ (heterozygous for 4 different recessive coat-color genes) received treatment *in utero* during the 10th day of gestation when about 200 pigment precursor cells were available. The author of the report stated: “The frequency of color spots in mice in the test and

control groups clearly show that Irgasan DP 300 in a dose of 50 mg/kg is active in the spot test. So it is hardly necessary to use any statistics.” The control frequency of color spots was 0.1%, compared with 2.4% with Irgasan DP 300. The mutagenicity of Irgasan DP 300 was considered in the report to be of medium potency. Possible adverse effect indicated: There was an increased incidence in color spots in treated animals. This study is not acceptable and not upgradeable due to numerous deficiencies and primarily the lack of a positive control. (Kishiyama & Silva, 8/25/03)

50291 - 011 045814 “Intrasanguine Host-Mediated Assay with *S. typhimurium* With FAT 80 023/A,” (Arni, P., Müller, D.; CIBA-Geigy Limited, Basle, Switzerland; Experiment #: 78/2803; 3/27/79). FAT 80 023/A (purity not stated) was administered by gavage at 0 (2% carboxymethyl cellulose), 50, 100, 200 and 400 mg/kg in 3 doses at 2, 1 and 0 hours immediately prior to tail vein injection in male mice (6/dose) of *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA 1537. After 60 minutes, mice were sacrificed and the livers processed. Aliquots were plated for bacterial counts (nutrient broth plates) and mutants (minimal agar plates). There was no treatment-related effect on bacterial count, nor was there an increase in mutation rate. There were, however, no positive controls. Unacceptable (Insufficient information, deficiencies too numerous). Not upgradeable. (Kishiyama & Silva, 7/1/03)

50291 - 011 045820 “Use of the Mouse Spot Test to Investigate the Mutagenic Potential of Triclosan (Irgasan DP 300),” (Russell, L.B., Montgomery, C.S.; Published in: Mutation Research, 79:7-12, 1980). Triclosan (99.7% pure) was administered in a single I.P. dose to impregnated inbred C57BL/E females (3 - 6 months of age) at 0 (60% methanol), 1 - 4, 8 or 25 mg/kg on days 9.25 or 10.25 postconception to assess effects in an *in vivo* somatic mutation test (spot test). Dose ranges overlapped the toxic (8 mg/kg reduced post natal survival and 25 mg/kg was toxic to mothers and fetuses exposed *in utero*). Incidence of recessive spots was not significantly increased with triclosan under the conditions of this study. A comparison was made with the study reported by Fahrig et al. (DPR volume/record #: 50291 - 011 045819), where Irgasan DP 300 was used. The authors claim triclosan is insoluble in HBSS (used as a solvent in the Fahrig study) and that dosages at 50 mg/kg were sufficiently toxic in the current study as to make it impossible to obtain enough survivors for evaluation. These authors claim that in the Fahrig study, little or no Irgasan DP 300 was in solution in the study and the 2.4% incidence in color spots was questioned. Not acceptable and not upgradeable due to the fact that this was an open literature study and not performed according to FIFRA Guidelines. No adverse effect indicated. (no work sheets). (Kishiyama & Silva, 8/25/03).

CONCLUSION: There were adverse effects indicated in one study (50291 - 011 045819), however this study was not acceptable or upgradeable (no positive control). None of the other studies were acceptable or upgradeable either, therefore, it is not possible at this time to determine whether FAT 80'023/S induces gene mutations.

CHROMOSOME EFFECTS

** 50291 - 0037 210986 “Chromosome Aberration Assay in Bone Marrow Cells of the Rat with FAT 80'023/Q (Triclosan),” (Völkner, W.; Cytotest Cell Research GmbH & Co. KG, Roßdorf, Germany; CCR Project #: 218305; 4/25/91). FAT 80'023/Q (Batch #: EN 91390.76; purity not stated) was administered by gavage in a single treatment to Wistar rats (6/sex/dose/time point) at 0 (1% carboxymethylcellulose) and 4000 mg/kg to test for cytogenicity in bone marrow cells after 6, 24 and 48 hours. Chromosomal aberrations were assessed (50 metaphases per animal). Cyclophosphamide served as the positive control. FAT 80'023/Q treatment did not increase the incidence in chromosomal aberrations after 48 hours. The positive control functioned as expected. This study is acceptable. No adverse effects. Silva, 12/24/04

**** 50291 - 0031 210974** “Analysis of Metaphase Chromosomes Obtained from CHO Cells Cultured *in Vitro* and Treated with Troclosan,” (Broker, P.C., Gray, V.M., Howell, A.; Huntington research Centre Ltd., URL 214/88731; Unilever Test #: KC880171; 8/11/88). Triclosan (99% pure) was used on Chinese hamster ovary (CHO) strain K¹ –BH₄ cells (2 cultures/dose) *in vitro* at 0 (DMSO), 0.1, 0.3, 0.5 and 1.0 ug/ml for 24 hours (no S9 metabolic activation) and at 0, 4.8, 9.5, 19, 30 and 38 ug/ml for 6 hours (with S9) before cells were treated with colchicine, harvested and examined for metaphases, mitotic index, and osmolality (duplicate slides prepared/dose, +/- S9; 100 metaphases/culture). There was no treatment-related increase in clastogenicity at any dose. The positive controls functioned as expected. No adverse effect. Acceptable. (Silva, 1/5/05)

**** 50291 – 0039 210984** “Chromosome Aberration Assay in Chinese Hamster V79 Cells *In Vitro* with FAT 80’023/Q (Triclosan),” (Heidemann, H.G.; Cytotest Cell Research GmbH & Co.KG., Roßdorf, Germany; CCR Project 179100; 12/17/90). FAT 80’023/Q (Batch #: EN 91390.76, assumed 100% pure) was added to cultures of V79 Chinese hamster cells *in vitro* for a 4 hour treatment at 0 (ethanol), 1.0 ug/ml (no S9) or 0.3 ug/ml (+S9) for 7 hr post-initiation incubation; at 0.1, 1.0, 3.0 ug/ml (+18 hr post-initiation incubation; +/- S9) and at 3.0 ug/ml (+28 hr post-initiation incubation; +/- S9). There was a treatment-related increase in chromosomal aberrations (+/- gaps) at 3.0 ug/ml at 18 hour fixation interval with and without S9 and at 28 hour fixation without S9 (also at 3.0 ug/ml). At the 18 hour fixation time, the results were dose-dependent, occurring at ≥ 1.0 ug/ml both with and without S9. At 3.0 ug/ml there were 4.5 to 6.5% of treated cells with exchanges compared with the control level of 0.0 – 1.0%. Although the effects were not statistically significantly increased at the 18 hr fixation time, the effect was considered biologically relevant because it was dose-related and 4.5% of cells (+ S9) and 6.5% of cells (no S9) carried exchanges. The positive controls performed as expected. Possible adverse effect. The study is acceptable. (Silva, 12/27/04)

50291 - 011 045816 “Dominant Lethal Study,” (Fritz, H.; CIBA-GEIGY Limited, Basle, Switzerland, experiment 32710200; 10/20/71). GP 41 353, was administered in a single gavage treatment to albino male mice (12/dose) at 0 (2% carboxymethylcellulose), 750, or 1500 mg/kg. Subsequently, the males were mated weekly, for 8 weeks, to untreated females (3 females/male/mating; fresh group of females/mating). Results showed no evidence of treatment-related dominant lethal effects. There were no treatment-related decreases in the number of implantations or increases in embryonic deaths (resorptions). Although there were no statistically significant differences in mating ratio, the number of successful matings overall was reduced approximately 10% for GP 41 353 treated animals. Historical controls were not included. No evidence of dominant lethal on the progeny of males treated with GP 41 353. Not acceptable and not upgradeable due to numerous deficiencies. No adverse effect indicated. (Kishiyama & Silva, 8/4/03).

50291 - 011 045821 “Chromosome Studies on Somatic Cells - GP 41 353 (Triclosan)” (Müller, D., Strasser, F.F.; Pharmaceuticals Division, Toxicology/Pathology; CIBA-GEIGY Limited, Basle, Switzerland; 4/16/73). GP 41 353 was administered to Chinese hamsters (4/dose) by gavage for 2 consecutive days at 0 (0.5% CMC), 150, 300 and 600 mg/kg to test for mutagenic effects on bone marrow cells. Animals were sacrificed 4 hours after the last dose, femoral bone marrow was removed and prepared for chromosomal analyses. There were no treatment-related increases in chromosomal aberrations at any dose. The positive controls performed as expected. No adverse effect indicated. The study is not acceptable and not upgradeable, due to numerous deficiencies. (Kishiyama & Silva, 8/26/03).

50291 - 011 045822 “Chromosome Studies in Somatic Cells -- Long Term Study With FAT 80 023/A Chinese Hamster (Test for mutagenic effects on bone marrow cells)” (Strasser, F.F., Müller, D.; CIBA-GEIGY Limited, Basle, Switzerland, Experiment #78-3105; 2/15/79). FAT 80 023/A (purity not

stated) was administered by gavage to Chinese hamsters (6/sex/dose) 3 times weekly for 12 weeks at 0 (0.7% Carboxymethyl cellulose), 75, 150, 300 and 600 mg/kg to assess the effects on bone marrow cell chromosomes. There were no treatment-related effects observed at any dose. It was not possible to form conclusions in this study due to a lack of positive and historical controls. Not acceptable and not upgradeable due to numerous deficiencies. No adverse effect indicated. (Kishiyama & Silva, 8/27/03).

50291 - 011 045817 "Chromosome Studies in Male Germinal Epithelium" (Hool, G., Strasser, F.F., Müller, D.; CIBA-GEIGY Limited, Basle, Switzerland; Experiment #: 78-2903; 12/1/78). FAT 80 023/A (purity not stated) was administered via gavage to NMRI male mice (8/dose) at 0, 189, 378, 756 and 1512 mg/kg/day for 5 consecutive days. The testes were processed (no details) and drop preparations made. 100 metaphases from each of 6 animals per dose were scored. Results showed a single chromosome aberration in the form of a minute (acentric chromosomal fragment) at 756 mg/kg. Seven animals died at 1512 mg/kg. Subsequently a dose group at 189 mg/kg was added. No adverse effect indicated. This study is not acceptable or upgradeable due to numerous deficiencies. (Kishiyama & Silva, 8/22/03)

50291 - 011 045818 "Chromosome Studies in Male Germinal Epithelium" (Hool, G., Strasser, F.F. Müller, D.; CIBA-GEIGY Limited, Basle, Switzerland, Experiment #: 78-2904; 2/21/79). FAT 80 023/A (Batch #: 652, purity not stated) was administered via gavage to NMRI-derived male mice (8/dose) on days 0, 2, 3, 5 and 9 at 0, 189, 378, 756 and 1512 mg/kg. Three days after the last dose, mice were sacrificed and drop preparations were made of the testicular parenchyma. 100 metaphases of spermatocytes for 6 per group were scored. There were no treatment-related increases in chromosomal aberrations at any dose. The study is not acceptable or upgradeable, due to numerous deficiencies. No adverse effect indicated. (Kishiyama & Silva, 8/22/03).

DNA DAMAGE

** 50291- 0046 211016 "Rat Hepatocyte Primary Culture/DNA Repair Test on 39317," (SanSebastian, J.R., Morgan, J.M.; Pharmakon USA, Waverly, PA; Study #: PH311-CP-001-93; 6/24/93). Triclosan (100.5% pure) was used on primary rat hepatocytes (in triplicate) at 0 (DMSO), 0 (culture medium only), 0.25, 0.5, 1.0 and 2.5 ug/ml for 18 to 20 hours *in vitro*. There was no in UDS in cultured rat hepatocytes at the concentrations tested. The positive controls functioned as expected. Acceptable, with no adverse effect. (Silva, 1/3/05)

** 50291 – 0033 210981 A Mouse Micronucleous Test on Triclosan,@ (Henderson, L.M., Produlock, R.J., Haynes, P., Meaking, K.; Huntingdon Research Centre Ltd., Cambridgeshire, UK; Study #: KC 880168; HRC Schedule #: ULR 213/88492; 8/12/88) Triclosan (99% pure) was administered by gavage to CD-1 SPF Swiss albino mice at 0 (1% aqueous methyl cellulose) and 5000 mg/kg. Subsequently 5/sex/dose/ timepoint were sacrificed at 24, 48 and 72 hours after dosing and the bone marrow was examined for presence of micronucleated cells per 1000 polychromatic erythrocytes per animal. No animals died after treatment. Clinical signs were evident at up to 6 hours post-dosing (pilo-erection, hunched posture, diarrhea) in males but by 5 hours (females) and 22 hours (males) they were no longer evident. There were no statistically significant increases in micronucleated polychromatic erythrocytes or micronucleated normochromatic erythrocytes at any of the kill times. The ratio of polychromatic to normochromatic erythrocytes at 24 and 48 hour sampling times was statistically significantly decreased ($p < 0.05$ Wilcoxon's sum of ranks test). This was reversed by 72 hours and according to the report may have been indicative of slight bone marrow cell toxicity. Acceptable. No adverse effect indicated. (Silva, 1/7/05).

50291 - 011 045823 “Nucleus Anomaly Test on Somatic Interphase Nuclei - GP 41 353 (Triclosan)” (Langauer, M., Müller, D.; CIBA-GEIGY Limited, Basle, Switzerland; 5/31/74). GP 41 353 (purity not stated) was administered by gavage to Chinese hamsters (3/sex/dose) for 2 consecutive days at 0 (0.5% CMC), 150, 300 and 600 mg/kg to assess effects on somatic interphase cells *in vivo*. There was no treatment-related increase in micronuclei. The positive control (cyclophosphamide) functioned as expected. This study is not acceptable and not upgradeable due to numerous deficiencies. No adverse effect indicated. (Kishiyama & Silva, 8/27/03).

50291 - 011 045824 “Nucleus Anomaly Test in Somatic Interphase Nuclei Long-Term Study with FAT 80 023/A; Chinese Hamster (Test for mutagenic effects on bone marrow cells)” (Langauer, M., Müller, D.; CIBA-GEIGY Limited, Basle, Switzerland, Experiment #73-3005; 8/23/78). FAT 80 023/A (purity not stated) was administered by gavage to Chinese hamsters (6/sex/dose) 3 times weekly for 12 weeks at 0 (0.7% CMC), 75, 150, 300 and 600 mg/kg to assess the effects on bone marrow cells. One thousand cells from 3/sex/group were evaluated for micronuclei and polyploidy. There were 7/12 deaths at 600 mg/kg. There were no treatment-related effects observed at any dose. Not acceptable and not upgradeable due to numerous deficiencies. Since there were no positive or historical controls or clinical signs described, it is not possible to make conclusions about the toxicity of FAT 80 023/A under the test conditions. No adverse effect indicated. (Kishiyama & Silva, 8/27/03).

** 50291- 0035 210983 “Triclosan: Assessment of Genotoxicity in an Unscheduled DNA Synthesis Assay Using Adult Rat Hepatocyte Primary Cultures,” (Riach, C.G.; Inveresk Research International Limited, Musselburgh, Scotland; IRI Project #: 738388; Unilever Study #: KU 880258; 9/21/88). Triclosan (white powder, purity not stated) was used on primary rat hepatocytes in 2 Experiments: #1 -- % viability and % survival assay at 0 (DMSO), 0.6, 1.3, 2.5, 5, 10, 20, 40 and 80 ug/ml (200 cells/dose counted); #1 UDS assay at 0, 0.625, 1.25, 2.5, 5, 10 ug/ml (150 cells/dose scored; 20, 40, 80 ug/ml were toxic); #2 - % viability and % survival assay at 0 (DMSO), 0.16, 0.3, 0.6, 1.3, 2.5, 5, 10 and 20 ug/ml (200 cells/dose counted); #2 UDS assay at 0, 0.16, 0.3, 0.6, 1.3, 2.5, 5, 10 and 20 ug/ml (150 cells/dose scored; 20 ug/ml was toxic) in order to assess unscheduled DNA synthesis *in vitro*. All experiments were performed with 4 wells/dose. Treatment was for 18 – 20 hours in the presence of [6³H]-TdR. There were no treatment-related increases in UDS in cultured rat hepatocytes at concentrations extending to the toxic range. The positive controls functioned as expected. Acceptable, with no adverse effect. (Silva, 1/3/05)

50291 - 011 045811 “Mutagenicity Test on *Saccharomyces cerevisiae* MP-1 *In Vitro* with FAT 80 023/A,” (Arni P., Müller, D.; CIBA-GEIGY Limited, Basle, Switzerland; Experiment #: 78/3402; 11/27/78). FAT 80 023/A (purity not stated) was tested on *Saccharomyces cerevisiae* strain MP-1 at 10, 20, 30, 40, 50, 60, and 200 mg/l to evaluate genotoxic potential. Incubation was for 3 2 hours without activation only (20 plates/condition). There were no treatment-related effects at any concentration. The positive control functioned as expected. This study is not acceptable and not upgradeable (numerous deficiencies). No adverse effect indicated. (Kishiyama & Silva, 6/27/03)

50291 - 011 045810 “Genetic Activity of Irgasan DP 300 in the MP-1 Strain of *S. cerevisiae*” (Fahrig, R.; Zentrallaboratorium für Mutagenitätsprüfung der Deutschen Forschungsgemeinschaft; 6/22/78) Irgasan DP 300 (99.7% pure) was tested with *S. cerevisiae* MP-1 strain at 0 and 0.2 mg/ml to evaluate its genotoxic potential. Treatments were tested on complete media for survival and intergenic recombination and on selective media with actidione for mutation and without tryptophan for interallelic recombination data without activation only. Three tests with 20 replicates per condition. This study is not acceptable and not upgradeable. The report stated that AIrgasan DP 300 shows weak, but definite mutagenic and recombinogenic activity in *S. cerevisiae* strain MP-1,@ (page 9). The deficiencies were too numerous and too critical to make this study upgradeable. (Kishiyama & Silva, 6/25/03).