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

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

DATE: September 15, 2008

SUBJECT: **5-Chloro-2-(2,4-dichlorophenoxy)phenol (Triclosan):** Risk Assessment for the Reregistration Eligibility Decision (RED) Document. Case No 2340. DP Barcode 343544. PC Code: **054901.**

FROM: Tim McMahon, Ph.D., Senior Toxicologist
Najm Shamim, Ph.D., Chemist
Srinivas Gowda, Microbiologist/Chemist
Genevieve Angle, Biologist
Timothy Leighton, Exposure/Risk Assessor
Antimicrobials Division (7510C)

TO: Diane Isbell, Team Leader
Heather Garvie, Chemical Review Manager
Regulatory Management Branch II
Antimicrobials Division (7510C)

Attached is the Risk Assessment for Triclosan for the purpose of issuing a Reregistration Eligibility (RED) Decision. The disciplinary science chapters and other supporting documents for the Triclosan RED are also included as attachments as follows:

Toxicology Science Chapter for the Reregistration Eligibility Decision Document, T. McMahon, August 2008

Triclosan: Occupational and Residential Exposure Assessment. From Timothy Leighton, Environmental Scientist, September, 2008.

Triclosan: Dietary Exposure Assessments for the Reregistration Eligibility Decision Memorandum. From Najm Shamim, Ph.D. Chemist, to Tim McMahon, Ph.D. Toxicologist April, 2007.

Product Chemistry Chapter for the Triclosan Reregistration Eligibility Decision (RED) Document. From Srinivas Gowda Microbiologist/Chemist, to Mark Hartman, Branch Chief, July 2007.

Revised Environmental Fate Science Chapter for the Triclosan Reregistration Eligibility Decision (RED) Document. From Srinivas Gowda, Microbiologist/ Chemist, September, 2008

Revised Ecological Hazard and Environmental Risk Assessment Chapter for the Triclosan Reregistration Eligibility Decision (RED) Doocument . From Richard C. Petrie, Agronomist, September, 2008.

TABLE OF CONTENTS

1.0 EXECUTIVE SUMMARY---------- 4
2.0 PHYSICAL/CHEMICAL PROPERTIES ----------17
3.0 HAZARD CHARACTERIZATION ---------- 18
3.1 Hazard Profile ----------18
3.2 Dose-Response Assessment ----------20
3.3 Susceptibility Considerations----------20
3.4 Endocrine Disruption ----------20

4.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION ----------25

5.0 AGGREGATE RISK ASSESSMENT AND RISK CHARACTERIZATION ----------26

5.1 **National Health and Nutrition Surveys (NHANES) for Triclosan** ----------26
5.1.1 NHANES Data and Dose Conversion-------- ----------26
5.1.2 Pharmacokinetics of Triclosan----------28
5.1.3 Uncertainties Associated with the Dose Conversion----------28

5.2 Aggregate Risks----------29
5.2.1 Children (6yrs) to Adult ----------29
5.2.2 Infants----------32
5.2.3 Dermal Irritation----------35
5.2.4 Dermal Systemic----------35

6.0 Cumulative Risk----------37

7.0 OCCUPATIONAL EXPOSURE ----------38
7.1 Occupational Postapplication Exposure ----------40
7.2 Data Limitations/uncertainties ----------40

8.0 ENVIRONMENTAL RISK ----------41
8.1 Ecological Hazard----------41
8.2 Environmental fate and transport----------47
8.3 Environmental exposure and Risk----------48
8.4 Endangered Species----------52

9.0 Incident Report Assessment ----------53
9.1 OPP Incident Data System----------53
9.2 Poison Control Center----------53
9.3 California Data 1982-2003----------53
9.4 National Telecommunication Pesticide Network----------54
9.5 Hazardous Substances Data Bank ----------54

10.0 References----------55

1.0 Executive Summary

Triclosan (2,4,4' –trichloro-2'-hydroxydiphenyl ether) is a chlorinated aromatic compound that has functional groups representative of both phenols and ethers. It is used as a synthetic broad-spectrum antimicrobial agent in the form of a white to off-white powder. It is practically insoluble in water but is soluble in most organic solvents. Only a small portion of the uses of triclosan are regulated by the U.S. EPA and therefore covered in this document.

Triclosan is used as a bacteriostat, fungistat, mildewistat, and deodorizer. The EPA registered products containing triclosan as the active ingredient (ai) are formulated as ready-to-use, pelleted/tableted, emulsifiable concentrate, soluble concentrate, and impregnated materials. Concentrations of triclosan in these products range widely from 0.69% to >99%. Use sites for triclosan include commercial, institutional and industrial premises and equipment, residential and public access premises, and as a material preservative. As a material preservative, triclosan is used in adhesives, fabrics, vinyl, latex, plastics, polyethylene, polyurethane, synthetic polymers, styrene, floor wax emulsions, rope, textiles, caulking compounds, sealants, coatings, polypropylene, rubber, inks, cellulosic materials, slurries, films and latex paints. The residential and public access premises uses include: brooms, mulch, floors, shower curtains, awnings, tents, mattresses, toothbrushes, toilet bowls, urinals, garbage cans, refuse container liners, insulation, concrete mixtures, grouts, air filter materials, upholstery fabrics, and rugs/carpets. The commercial, institutional and industrial premises and equipment uses include: conveyor belts, fire hoses, dye bath vats and ice making equipment.

There are many other uses under the regulation of the US Food and Drug Adminstration (FDA) (e.g., hand soaps, toothpaste, antiseptics for wound care, and medical devices) that are not under EPA's regulatory jurisdiction, however, these exposures have been considered in the aggregate risk assessment within the preliminary risk assessment chapter for triclosan.

Toxicology

The toxicology database for triclosan is complete. Some studies, although cited with certain deficiencies, were considered adequate for regulatory purposes, and thus no new toxicology studies are requested for triclosan. A complete toxicology profile for triclosan can be found in the toxicology chapter .

Acute toxicity studies in experimental animals with technical grade triclosan show that by the oral and dermal routes, triclosan is of low acute toxicity (Toxicity Category IV; MRIDs 43206501 and 94044; 44831105). By the inhalation route of exposure, triclosan was assigned Toxicity Category II for acute exposures and is thus of higher acute toxicity by inhalation exposure than by oral or dermal exposures (MRID 42306902 and 43310501). Triclosan produces moderate irritation to the eyes (MRID 94045) and skin (MRID 42306903) with a Toxicity Category III assigned for both for acute exposures. Triclosan was not a dermal sensitizer in guinea pigs using the Buehler method (MRID 43206502).

Liver toxicity was noted after repeated oral dosing of triclosan to rats, mice, and dogs. In the 90-day rat study, (MRID 43022605, 99.7% a.i.; MRID 133545, % a.i. not stated), fatty metamorphosis and cytomegaly, hypertrophic hepatocytes, vacuolization, inflammation, and pigmentation of Kupffer cells were noted at a dose of 50 mg/kg/day. In the 28-day mouse study, liver cell necrosis and an increase in the liver-body weight ratio were observed at doses of 135 and 158 mg/kg/day for male and female mice respectively (MRID 44389707). In a 90-day oral toxicity study in dogs (MRID 96102), histopathologic examination of tissues from dogs that were killed or died showed evidence of hepatotoxicity resulting in obstructive jaundice at a dose of 25 mg/kg/day.

Dermal irritation is noted after repeated dermal exposure to the technical grade active ingredient (99% a.i.) in a 90-day dermal toxicity study in rats (MRID 43328001) and in two 14-day dermal toxicity studies in rats and mice (MRIDs 44389708 and 44389710). Data from the 90-day rat dermal toxicity study (MRID 43328001) showed irritation at 10 mg/kg/day (500 $\mu g/cm^2$) and a NOAEL for systemic effects at 40 mg/kg/day. Systemic toxicity was also observed in the mouse study with a NOAEL of 0.6 mg/animal/day.

Repeated exposure by the inhalation route to the assumed technical grade of triclosan (MRID 0087996) resulted in inflammation of the respiratory tract as well as changes in several serum enzymes. Acute purulent inflammation with focal ulceration of the mucous membrane in the nasal cavity and in the trachea were also observed. A LOAEL of 50 mg/m^3 or 3.21 mg/kg/day was observed in male rats and no NOAEL was established in males.

Developmental toxicity testing of triclosan in rats and rabbits (MRIDs 43817502/43817503 and MRIDs 43820401/43022607) showed no evidence of pre- or postnatal developmental toxicity at any dose level in either study up to and including 300 mg/kg/day. Developmental LOAELs were therefore not identified. In 2-generation reproductive toxicity testing of triclosan in rats showed effects in offspring (decreased viability and weaning index) only at doses producing toxicity in parental animals (decreased body weights) (MRID 40623701).

Chronic toxicity testing of triclosan in baboons (MRID 133230) showed signs of clinical toxicity (vomiting, diarrhea, failure to eat) at a dose of 100 mg/kg/day with a NOAEL of 30 mg/kg/day. In rats, chronic toxicity testing (MRID 42027906;161332) showed decreases in erythrocyte count, hemoglobin concentration, and hematocrit. 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 52.4 mg/kg/day and above. Chronic toxicity testing of triclosan in hamsters (MRID 44874001/44751101) showed increased mortality, decreased weight gain, increased incidence of nephropathy, and histopathologic findings of the stomach and testes of male hamsters at a dose of 250 mg/kg/day with a NOAEL of 75 mg/kg/day.

In carcinogenicity testing of triclosan in hamsters (MRID 44874001/44751101), there was no evidence of a carcinogenic effect. In carcinogenicity testing in rats (MRID 42027906; 161332), there was no evidence of a carcinogenic effect. In public documents available from the FDA, administration of triclosan in the diet to mice at doses of 10, 30, 100, and 200 mg/kg/day resulted in increases in the incidence of liver tumors at 30 mg/kg/day and above. A systemic NOAEL of 10 mg/kg/day was established from the data in this study, based on increased incidence of liver neoplasms in male and female mice at 30 mg/kg/day.

In several mutagenicity tests including Ames *Salmonella* assays (MRIDs 43533301 and 44389705), a mammalian cell gene mutation assay at the thymidine kinase locus (MRID 44389704), a chromosome aberration assay [Broker, et al. (1988)], an in vivo bone marrow cytogenetic assay (MRID 43740802), and an *in vitro* DNA synthesis assay [SanSebastian, 1993], triclosan was negative for mutagenicity. However, in an *in vitro* cytogenetic assay (MRID 43740801), there was a dose-related increase in the yield of cells with abnormal chromosome morphology. In the presence of S9 activation, nonsignificant but concentration dependent increases in cells bearing exchange figures were also seen.

In a metabolism study in hamsters (MRID 45307501/45307502), urine was the major route of elimination for triclosan radioactivity. Peak plasma and blood concentrations of triclosan-derived radioactivity occurred at one hour post-dose. Area Under the Curve (AUC) measurements indicated that saturation may have been achieved at the high dose, as AUC was not proportional to dose. The major urinary metabolite detected after oral administration was the glucuronide conjugate of triclosan. The major fecal metabolite was parent triclosan. The plasma, kidney, and liver eliminated triclosan equivalent rapidly. Tissue metabolite analyses showed that the glucuronide and sulfate conjugates of triclosan were the major metabolites detected. In a metabolism study in mice, (MRID 45307503), triclosan was eliminated primarily through the feces, via biliary excretion. Bioretention studies indicate that values from C_{max} to $1/8C_{max}$ in the liver were higher than those in plasma following repeated administration at both dose levels, indicating that the liver is the target organ. Primary excreted compounds in the urine following single oral exposures included the unmetabolized parent compound and two parent conjugates; fecal excretion was primarily that of the free parent compound.

In metabolism studies conducted in rats, dogs, and rabbits (MRID 149464), results indicated that at least 70% of an oral dose of triclosan is absorbed from the gastrointestinal tract and that biliary secretion and subsequent fecal elimination is a major excretory route in the rat and dog. Urinary excretion appeared to be a major route of elimination in the rabbit. Tissue accumulation was minimal and primarily associated with highly perfused tissues and organs with excretory function. Metabolite data in rats revealed glucuronide conjugates and unchanged parent compound as biliary metabolites.

Biochemical and cell proliferation studies submitted for triclosan (MRIDs 44389702, 44389703, 44389706, 44389701) suggest that triclosan acts as a peroxisome proliferator

and that the hepatotoxic effect is followed by cell regeneration. For chemicals producing increased cell turnover through cytolethality, a threshold can be inferred below which these effects would not occur.

On July 25, 2007, the Health Effects Division's Carcinogenicity Assessment Review Committee met to discuss the carcinogenicity classification for triclosan and additional data submitted 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. **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 (PPARά) 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 PPARά activation and toxicokinetics. The quantification of risk is not required.

Dose-Response Assessment

On March 10, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee reviewed the available toxicology data for triclosan and selected endpoints for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to triclosan was also evaluated. On October 31, 2006, the Antimicrobial's Division Toxicity Endpoint Committee met to provide additional endpoints for incidental oral and dermal exposures.

For acute and chronic dietary exposure risk assessments, a NOAEL value of 30 mg/kg/day was selected, based on clinical signs of toxicity (vomiting, diarrhea, failure to eat) at a dose of 100 mg/kg/day in a chronic toxicity study in baboons (MRID 133230. For dietary risk assessments, an uncertainty factor of 100 is assigned (10x inter-species extrapolation, 10x intra-species variation). The hazard-based FQPA safety factor is not applied in this case as there are no existing food use tolerances for triclosan. The resulting acute and chronic Reference Dose value is 0.30 mg/kg/day.

For short-term and intermediate-term incidental oral risk assessments (1-30 days and 30 days - 6 months), a NOAEL value of 30 mg/kg/day was selected, based on clinical signs of toxicity (vomiting, diarrhea, failure to eat) at a dose of 100 mg/kg/day in a chronic toxicity study in baboons (MRID 133230). An uncertainty factor of 100 was assigned to this endpoint (10x inter-species extrapolation, 10x intra-species variation).

For short-term dermal risk assessment (1-30 days), a NOAEL of 0.6 mg/animal (converted to concentration of 100 $\mu g/cm^2$ by using the surface area of the applied gauze

(2 x 3 cm or 6 cm^2)) was selected from a 14-day dermal toxicity study in the mouse (MRID 44389708), based on treatment-related dermal irritation at the treatment site and on increased liver weights at 1.5 mg/animal. It is to be noted that the short-term dermal endpoint was derived from a study using the technical grade (99%) test material. Residential uses of triclosan involve exposure to diluted formulations (e.g., 0.5% ai for carpet shampoo further diluted by water). Therefore, the short-term dermal irritation observed for the 99% ai formulation is not applicable for the dermal risk assessment in this case.

For intermediate-term and long-term dermal risk assessments, the endpoint was selected from a 90-day dermal toxicity study in rats with a NOAEL value of 40 mg/kg/day, based on increased occult blood in the urine observed at 80 mg/kg/day..

For inhalation risk assessments, a LOAEL of 50 mg/m^3 (3.21 mg/kg/day) was selected from a 21-day inhalation toxicity study (MRID 0087996), based on increased total leukocyte count and increased serum alkaline phosphatase in male rats at 3.21 mg/kg/day. While this study contained deficiencies that resulted in it not meeting the guideline requirement for a repeat dose inhalation toxicity study, the endpoint was chosen from this study as it was the only data available.

Susceptibility Considerations

There are no food use tolerances for triclosan but in light of residential exposures to triclosan, including exposures of infants and children, the data on developmental, reproductive, and neurotoxic effects of triclosan were examined for any suscepitiblity issues. The data provided no indication of developmental or reproductive effects in offspring of rats or rabbits to *in utero* and post-natal exposure to triclosan. Three prenatal developmental toxicity studies in rats rabbits, and mice, showed no 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. 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 showed no evidence of a neurotoxic effect of triclosan in any of these studies.

Dietary Exposure and Risk

Dietary exposure and risk were assessed for the indirect food uses of triclosan involving pulp and paper use, ice-making equipment, adhesives, cutting boards, conveyor belts, and counter top use. As there were no residue chemistry data submitted for triclosan, methods developed by the Food and Drug Administration were used to estimate

migration of residues. A detailed explanation is found within the dietary risk assessment chapter for triclosan.

For the various indirect food uses of triclosan in this risk assessment, none of the individual scenarios presented with risks of concern for either adults or children.

Drinking Water Exposure and Risk

The environmental fate assessment chapter for triclosan (DP barcode 335393) notes that triclosan was detected in both raw and finished drinking water in Southern California at levels of 56 and 49 ng/L, respectively (Loraine and Pettigrove, 2006). Using the assumption of 2L consumption per day for adults, intake of triclosan is estimated at 98 ng/person/day or 1.4 ng/kg/day for a 70 kg adult. Comparing this intake value to the Reference dose for triclosan selected (0.3 mg/kg/day or 300,000 ng/kg/day), the intake of triclosan in drinking water using the measured value from Loraine and Pettigrove does not present a risk of concern. However, additional monitoring data would be useful in deriving a more accurate estimate that is not based on measurement at one location only.

Residential Handler Exposure and Risk

Residential handler dermal exposure scenarios are best represented by the short-term duration (i.e. painting is intermittent in nature). The short-term dermal duration toxicological endpoint is based on dermal irritation observed during the dosing of mice with a 99% ai product. The in-can paint preservation (1 % ai) is not considered to be as irritating as the more concentrated test substance. The short-term dermal exposures are believed to exhibit minimal skin irritation. This is supported by the lack of incident data and a bounding estimate of film thickness on the skin compared to the dermal irritation endpoint.

For the residential handler inhalation assessment, the inhalation risks were calculated by comparing the daily inhalation dose to the short-term inhalation endpoint. The inhalation MOE of 4000 is above the target MOE of 1000 for the paint brush scenario. However, for the airless sprayer scenario the inhalation MOE of 180 is below the target MOE, and therefore, is of concern. Mitigation options include reducing the application rate in paint or removing the use.

Residential Post-application Exposure and Risk

The residential post-application assessment is protective of long-term exposure. The results of the NHANES aggregate risks using the most conservative methodology option assessed for those 6+ years old indicate mean MOEs ranging from 4,700 to 19,000. At

the 99th percentile the MOEs range from 260 to 1,700. These MOEs are above the target MOE of 100. The NHANES aggregate risks include exposure to both EPA- and FDA-regulated uses.

For infants 6 to 12 months old, the mean NHANES 6-11 year old MOEs combined with bounding estimates for infant-specific activities for nursing, object-to-mouth, and hand-to-mouth exposures indicate an aggregate MOE of 390. At the 99th percentile NHANES distribution combined with the infant-specific activities indicate a MOE of 290. Clearly, including exposures to the FDA-regulated soaps and toothpaste for 6-11 year olds is a conservative assessment of exposure from these products to 6 to 12 month olds. Future refinements to the infant aggregate should focus on this portion of the total exposure.

Based on the low vapor pressure of triclosan and the lack of aerosol generation over time by the application methods (excluding bystanders in the vicinity of airless spraying of paint which triggers risks of concern), inhalation exposure is expected to be minimal. This expectation is confirmed by the MOEs estimated to be in the millions for breathing triclosan-treated dust.

The dermal irritation potential of diluted uses of triclosan impregnated into textiles/fabrics and plastics are also expected to be minimal. This expectation is supported by the low incidents of irritation as well as the screening-level assessment provided herein. The dermal systemic effects were also investigated for children and adults contacting treated articles. The systemic dermal MOE using conservative assumptions is at or above the target MOE for dermal effects.

Aggregate Exposure and Risk

EPA has performed an assessment of the aggregate exposure to triclosan. Aggregate exposure is the total exposure to a single chemical (or its residues) that may occur from dietary (i.e., food and drinking water), residential, and other non-occupational sources including triclosan FDA uses such as hand soaps and toothpaste, and from all known or plausible exposure routes (oral, dermal, and inhalation). An aggregate risk assessment was conducted using the single selected toxicological endpoint for acute dietary, short-term (1-30 days), intermediate-term (1-6 months), and chronic (several months to lifetime) exposure durations. Inhalation aggregate risks are minimal based on the low vapor pressure of triclosan and uses such as tooth paste, hand soap, impregnated textiles, etc that do not involve inhalation as the primary route of exposure. Further discussion of inhalation exposure can be found in the Occupational and Residential Exposure Assessment chapter for triclosan.

In performing aggregate exposure and risk assessments, the Office of Pesticide Programs has published guidance outlining the necessary steps to perform such assessments (General Principles for Performing Aggregate Exposure and Risk

Assessments, November 28, 2001; available at http://www.epa.gov/pesticides/trac/science/aggregate.pdf). Steps for deciding whether to perform aggregate exposure and risk assessments are listed, which include: identification of toxicological endpoints for each exposure route and duration; identification of potential exposures for each pathway (food, water, and/or residential); reconciliation of durations and pathways of exposure with durations and pathways of health effects; determination of which possible residential exposure scenarios are likely to occur together within a given time frame; determination of magnitude and duration of exposure for all exposure combinations; determination of the appropriate technique (deterministic or probabilistic) for exposure assessment; and determination of the appropriate risk metric to estimate aggregate risk

In the case of triclosan, population-based biological monitoring data are available to assess the co-occurrence of uses to develop an aggregate exposure assessment. The population-based biological monitoring data are believed to be a more accurate predictor of aggregate exposure because not only are the data triclosan specific, they are also based on actual consumer use of the various triclosan products as they co-occur in practice. Although the aggregate exposure/risk assessment using the NHANES data provides an encompassing review of all triclosan-treated products, it does not include exposures to children under the age of 6 years old. Children under the age of 6 years exhibit unique activities that do not occur at older ages. Therefore, a separate estimate for children under 6 years old has been included.

The results of the aggregate risk assessment at both the mean and 99th percentile, respectively showed that the combined EPA and FDA uses do not trigger risks of concern. The MOEs at the mean dose range from 4,700 to 19,000. The MOEs at the 99th percentile of the dose range from 260 to 1,700. In fact, applying the lowest (most conservative) percent urinary excretion from the results of the pharmacokinetic data (i.e., 24 percent) to the most conservative dose conversion method (i.e., Geigy's 95th percentile of daily urine volumes), the MOE is 120. In conclusion, even with the reliance of conservative assumptions in estimating risks to account for the considerable uncertainties in converting spot urine concentration to dose, the NHANES data as analyzed for triclosan sufficiently characterizes the aggregate risks as meeting the definition of not resulting in unreasonable adverse effects.

Occupational Exposure

Occupational Handler Risk Summary

The short-term dermal irritation exposures and risks were not estimated for occupational handler exposures. Instead, dermal irritation exposures and risks will be mitigated using default personal protective equipment requirements based on the toxicity of the end-use products. For occupational uses it is OPP practice to mitigate dermal irritation by requiring the user to wear PPE (e.g., chemical resistant gloves and clothing). Mitigating with PPE is only a viable option for pesticide-labeled products (i.e., a label is

needed to inform workers to wear PPE). Therefore, EPA can direct workers using pesticide-labeled products (concentrated form) at the manufacturing setting to wear PPE to mitigate dermal irritation. Conversely, for in-can material preservatives there is no pesticide label that goes with the preserved product to inform the workers/painters that PPE is needed (i.e., there is no pesticide label on a can of paint). Thus PPE is not a viable option to mitigate exposure to products preserved by triclosan such as the in-can paint use.

For the intermediate-term dermal risks, the MOE were above the target MOE of 100, and therefore, not of concern except for commercial painters and material preservative use for paper which will require a closed delivery system. The intermediate-term MOEs for using a paint brush/roller and an airless sprayer are 31 and 1, respectively. Because triclosan is used as a material preservative in the paint, the use of chemical resistant gloves on the label is impractical.

For the occupational handler inhalation exposure and risk assessment, the MOEs were below the target MOE of 1000 for all scenarios except for the brush application for paints. The inhalation MOE for commercial use of an airless sprayer for paints is 54, for liquid pour and liquid pump during paint manufacturing 330 and 290, respectively. For the pulp and paper use a closed delivery system will be required.

Occupational Post Application/Bystander Risk Summary

Based on the low vapor pressure of triclosan and the lack of aerosol generation over time by the application methods, inhalation post-application exposures are expected to be minimal.

Environmental Fate Assessment

Triclosan is hydrolytically stable under abiotic and buffered conditions over the pH 4-9 range based on data from a preliminary test at 50°C. Photolytically, triclosan degrades rapidly under continuous irradiation from artificial light at 25°C in a pH 7 aqueous solution, with a calculated aqueous photolytic half-life of 41 minutes. One major transformation product was identified, DCP (2,4-dichlorophenol), which was present at a maximum of 93.8-96.6% of the applied dose at 240 minutes post-treatment. Triclosan degrades rapidly in aerobic soils maintained in darkness at 20 ± 2°C, with calculated half-lives of 2.9-3.8 days. One major transformation product was identified, methyl triclosan, at maximum averages of 13.5-24.0% of the applied dose at 14-28 days post-treatment. In aerobic water-sediment systems maintained in darkness at 20 ± 2°C, triclosan degraded with calculated nonlinear half-lives of 1.3-1.4 days in the water, 53.7-60.3 days in the sediment, and 39.8-55.9 days in the total system. The major transformation product,

identified as methyl triclosan, was a maximum average of 4.8% of the applied dose at 104 days post-treatment (sediment; sandy loam system).

The Agency has used its databases (EPI Suite) and open literature (TOXNET) to conduct the environmental fate risk assessment.

In soil, triclosan is expected to be immobile based on an estimated K_{oc} of 9,200. Triclosan is not expected to volatilize from soil (moist or dry) or water surfaces based on an estimated Henry's Law constant of 1.5×10^{-7} atm-m^3/mole. Triclosan partially exists in the dissociated form in the environment based on a pKa of 7.9, and anions do not generally adsorb more strongly to organic carbon and clay than their neutral counterparts. In aquatic environments, triclosan is expected to adsorb to suspended solids and sediments and may bioaccumulate (K_{ow} 4.76), posing a concern for aquatic organisms. There is also a low to moderate potential for bioconcentration in aquatic organisms based on a BCF range of 2.7 to 90.

Hydrolysis is not expected to be an important environmental fate process due to the stability of triclosan in the presence of strong acids and bases. However, triclosan is susceptible to degradation via aqueous photolysis, with a half-life of <1 hour under abiotic conditions, and up to 10 days in lake water. An atmospheric half-life of 8 hours has also been estimated based on the reaction of triclosan with photochemically produced hydroxyl radicals. Additionally, triclosan may be susceptible to biodegradation based on the presence of methyl-triclosan following wastewater treatment. Although these data are limited, they indicate triclosan is not likely to contaminate surface or ground waters due to its immobility in soils, and susceptibility to photodegradation, and potentially biodegradation, in soil and water.

From published literature studies on the occurrence of triclosan in waste water treatment plants, treatment plant efficiency, and open water measurements of triclosan, the majority suggest that aerobic biodegradation is one of the major and most efficient biodegradation pathways (70-80%) through which triclosan and its by-products are removed from the aquatic environment with actual efficiencies ranging from 53-99% (Kanda et al., 2003) in activated sludge plants and trickle down filtration, ranging from 58-86% (McAvoy et al., 2002). Another pathway of removing triclosan from water in wastewater treatment plants is through the sorption of triclosan and associated by-products to particles and sludge (10-15%) because of the chemical's medium to high hydrophobicity (Agüera et al., 2003; Gomez et al., 2007; Kanda et al., 2003; Lee and Peart, 2002; Bester, 2003 and 2005; Xia et al., 2005). Benchtop fate testing of triclosan found that 1.5-4.5% was sorbed to activated sludge and 81-92% was biodegraded (Federle et al., 2002).

Activated sludge and/or sludge samples examined for triclosan residue in Ohio showed a range of 0.5 to 15.6 µg/g (dry weight) with higher concentrations of triclosan observed in anaerobic sludge as compared to aerobic sludge (McAvoy et al., 2002). Other countries where sludge samples were analyzed for triclosan are as follows: Canada found 370 ng/g (Lee and Peart, 2002); Germany found 1000-8000 ng/g (Bester, 2003 and 2005); Greece

found 1,840 ng/g (Gatidou et al. 2007); Spain found 420-5400 ng/g (Morales et al., 2005); and 19 WWTP were analyzed in Australia, which had a range of 90-16,790 ng/g dry weight and a median of 2,320 mg/g (Ying and Kookana, 2007).

Effluent concentrations from wastewater treatment plants in the US were 10-21 ng/L in Louisiana (Boyd et al., 2003); 63 ng/L in the upper Detroit river (Hua et al., 2005); 72 ng/L in Arlington, Virginia (Thomas and Foster, 2004); 110 ng/L in North Texas (Waltman et al., 2006); and the highest was 200-2700 ng/L in Ohio (McAvoy et al., 2002). Effluent concentrations from wastewater treatment plants in other countries were measured to be 160 ng/L (Lee et al., 2003) or 50-360 ng/L in Canada (Lee et al., 2005); 50 ng/L (Bester, 2003), 10-600 ng/L (Bester, 2005), or 180 ng/L (Wind et al., 2004) in Germany; 160 ng/L in Sweden (Bendz et al., 2005); 430 ng/L (31.2 μg/g particulate matter), 1120 ng/L (16.1 μg/g particulate matter), or 230 ng/L (22.4 μg/g particulate matter) in three different WWTP in Greece (Gatidou et al. 2007); 80-400 ng/L in Spain (Gomez et al., 2007); 100-269,000 ng/L in Spain (Mezcua et al., 2004); 0.15±0.08 mg/person in 5 European countries (Paxeus, 2004); 340 or 1100 ng/L, for trickle filtration and activated sludge treatment plant in England (Sabaliunas et al., 2003); 42-213 ng/L in Switzerland (Singer et al., 2002); and from 19 WWTP in Australia the range was 23-434 ng/L with a median concentration of 108 ng/L (Ying and Kookana, 2007).

Triclosan was found in approximately 36 US streams (Klopin et al., 2002) where effluent from activated sludge waste water treatment plants, trickle down filtration, and sewage overflow are thought to contribute to the occurrence of triclosan in open water. For this study, the U.S. Geological Survey surveyed a network of 139 streams across 30 states during 1999 and 2000. The selection of sampling sites was biased toward streams susceptible to contamination (i.e. downstream of intense urbanization and livestock production). The median concentration was 140 ng/L and the maximum concentration detected was 2300 ng/L (Klopin et al., 2002). In another study, storm water canal measurements over a 6 month period in Bayou St. John in Louisiana indicated that triclosan ranged from below the detection level to 29 ng/L (Boyd et al., 2004). Raw drinking water in Southern California was found to have 560 ng/L triclosan and 490 ng/L triclosan in finished water (Loraine and Pettigrove, 2006). Other published data on surface water concentrations of triclosan in the US indicated concentrations of 4 and 8 ng/L in the upper Detroit river (Hua et al., 2005) and 56 ng/L in Arlington, Virginia (Thomas and Foster, 2004). Published data on surface water concentrations of triclosan in other countries indicated concentrations of <3-10 ng/L in Germany (0.3-10 ng/L methyl-triclosan) (Bester, 2005); 19±1.4 ng/L in England (Sabaliunas et al., 2003); 11-98 ng/L in Switzerland (Singer et al., 2002); 30 ng/L in Germany (Wind et al., 2004); and in Australia 75 ng/L (Ying and Kookana, 2007).

From published literature on the aquatic toxicity of triclosan in zebrafish, average bioconcentration factors (BCF) for triclosan following a 5-week accumulation period were 4157 at 3 μg/L and 2532 at 30 μg/L (Orvos et al., 2002). Following 2 weeks of depuration, average BCF values decreased to 41 at 3 μg/L and 32 at 30 μg/L. Depuration rate constants were 0.142 and 0.141 per day at 3 μg/L and 30 μg/L, respectively. The predicted bioconcentration factor for triclosan was calculated to be *ca*. 2500. The lethal

body burden was determined to range from 0.7-3.4 mM/kg, indicating a narcosis mode of action. These data indicate that triclosan bioconcentrates in zebra fish, but depuration occurs rapidly once triclosan exposure is removed. Relative to bioaccumulation, there are no data presently available to determine if this occurs. However, some authors (Balmer, M.E. et. al., 2004; DeLorenzo et al., 2008; Heidler, J. and Halden, R. U., 2007; Samsoe-Petersen L. et. al., 2003) suggest that triclosan and methyl triclosan may bioaccumulate in the environment.

Ecological/Environmental Risk Assessment

An ecological risk assessment is not typically conducted for the types of uses registered for triclosan. However, since triclosan has been detected in natural waters, EPA has performed a qualitative environmental risk assessment using monitoring levels of triclosan found in waterways and toxicity values from published literature including USGS montoring data to develop risk quotients (RQs) and compare them to levels of concern (LOCs) for triclosan. LOCs were not exceeded for fish but were exceeded for aquatic plants. There were no acceptable acute toxicity studies for freshwater invertebrates or estuarine and marine organisms nor were there any acceptable chronic toxicity studies available for aquatic organisms. Therefore, risk to these species could not be assessed and data gaps were identified. These data gaps are listed specifically within the Ecological and Environmental Risk Assessment Science Chapter (D343548, from Richard C. Petrie).

Additionally, EPA performed consumer environmental modeling for triclosan as discussed within the Appendix to the Revised Ecological Hazard and Environmental Risk Assessment Chapter of the RED. For this screening level analysis the Down-the Drain (DTD) module of EFAST-2 (Exposure and Fate Assessment Screening Tool, Version 2.0) was used. The DTD module of E-FAST 2 is used to estimate exposure to aquatic organisms from releases of a chemical to surface water from consumer use.
A simplifying assumption used is that all of the triclosan under EPA's jurisdiction is released to surface water as a result of consumer uses. Results of the assessment of exposure and risk to aquatic organisms from uses of triclosan under EPA's jurisdiction for acute risk presumptions for aquatic animals, endangered species risk presumptions for aquatic animals, and acute and endangered species risk presumptions for aquatic plants showed that estimated concentrations of triclosan in surface water did not exceed concentrations of concern for acute risk presumptions for aquatic animals or endangered species risk presumptions for aquatic animals. No exceedances were predicted for the concentration of concern for triclosan for endangered species risk presumptions for aquatic vascular plants, but concentrations of triclosan in surface water were predicted to exceed concentrations of concern for acute risk presumptions for species that represent non-vascular freshwater plants (i.e., algae). Although this evaluation is considered supplemental data, it indicates the need for additional investigation of shifts in algal communities, reductions in biomass, and effects on higher trophic levels (Wilson et al., 2003).

For industrial use scenarios, s discussed within the revised environmental fate chapter, little is known about how much, if any, triclosan is released from industrial sites (where triclosan is incorporated into plastic and textile items) into effluents and the environment (e.g., surface waters). Considering this, the Agency is requiring that the registrants perform environmental modeling and monitoring to address this issue. Until EPA receives these data we are unable to calculate risk quotients specific to these industrial scenarios.

Endangered Species

To facilitate compliance with the requirements of the Endangered Species Act subsection (a)(2) the Environmental Protection Agency, Office of Pesticide Programs has established procedures to evaluate whether a proposed registration action may directly or indirectly reduce appreciably the likelihood of both the survival and recovery of a listed species in the wild by reducing the reproduction, numbers, or distribution of any listed species (U.S. EPA 2004). After the Agency's screening-level risk assessment is performed, if any of the Agency's Listed Species LOC Criteria are exceeded for either direct or indirect effects, a determination is made to identify if any listed or candidate species may co-occur in the area of the proposed pesticide use. If determined that listed or candidate species may be present in the proposed use areas, further biological assessment is undertaken. The extent to which listed species may be at risk then determines the need for the development of a more comprehensive consultation package as required by the Endangered Species Act.

For certain use categories, the Agency assumes there will be minimal environmental exposure, and only a minimal toxicity data set is required (Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs U.S. Environmental Protection Agency - Endangered and Threatened Species Effects Determinations, 1/23/04, Appendix A, Section IIB, pg.81). Chemicals in these categories therefore do not undergo a full screening-level risk assessment.

Preliminary analysis indicates that there is a potential for triclosan use to overlap with listed species and that a more refined assessment is warranted, to include direct, indirect and habitat effects [the Agency is making this statement because triclosan and triclosan transformation products are being detected in various environmental components (see triclosan environmental fate chapter)].

The more refined assessment should involve clear delineation of the action area associated with proposed use of triclosan and best available information on the temporal and spatial co-location of listed species with respect to the action area. This analysis has not been conducted for this assessment. **An endangered species effect determination will not be made at this time.**

Incident Reports

There are no reported incidents for triclosan from a search of the available databases.

2.0 PHYSICAL/CHEMICAL PROPERTIES AND CHARACTERIZATION

Chemical Identity:

Chemical Name:	triclosan
Chemical Family:	diphenoxyether
Common/Trade Name:	2,4,4'-Trichloro-2'-hydroxydiphenyl ether Phenol, 5-chloro-2-(2,4-dichlorophenoxy)- 5-Chloro-2-(2,4-dichlorophenoxy)phenol Irgasan DP-300R Irgaguard B1000 VIV-20
CAS Number:	3380-34-5
Molecular Formula:	$C_{12}H_7C_{l3}0_2$
Chemical Structure:	

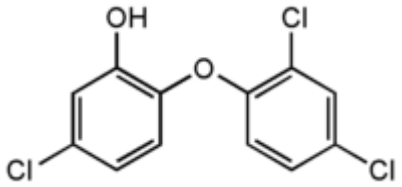

Table 2-1 Chemical Characteristics for Technical Grade Active Triclosan

Molecular Weight	289.541
Color	White crystals
Physical State	White crystalline powder

Specific Gravity	1.55 x 10^3 kg/m^3 at 22˚C
Dissociation Constant	pK_a=8.14 at 20°C
pH	N/A
Stability	Stable at normal conditions
Melting Point	56.5 ^{o} C
Boiling Point	N/A
Water Solubility	0.012 g/l at 20˚C
Octanol-Water Partition constant ($LogK_{OW}$)	4.8 at 25˚C
Vapor Pressure	5.2E-6 mm Hg at 25˚C 2.2E-6 mm Hg at 20˚C

3.0 HAZARD CHARACTERIZATION

3.1 Hazard Profile

Acute Toxicity

Acute toxicity studies in experimental animals with technical grade triclosan show that by the oral and dermal routes, triclosan is of low acute toxicity (Toxicity Category IV; MRID 43206501 and 94044 . By the inhalation route of exposure, triclosan was assigned Toxicity Category II for acute exposures and is thus of higher acute toxicity by inhalation exposure than by oral or dermal exposures (MRID 42306902 and 43310501). Triclosan produces moderate irritation to the eyes (MRID 94045) and skin (MRID 42306903) with a Toxicity Category III assigned for both for acute exposures. Triclosan was not a dermal sensitizer in guinea pigs using the Buehler method (MRID 43206502).

Table 3-1. Acute Toxicity Profile for Triclosan

Guideline Number	Study Type/ Test substance (% a.i.)	MRID Number/ Citation	Results	Toxicity Category
870.1100 (§81-1)	Acute Oral- Rat Triclosan (99.7% a.i.)	43206901	LD_{50}: >5000 mg/kg	IV
870.1200 (§81-2)	Acute Dermal- Rabbit Triclosan (97% a.i.)	94044	LD_{50}: >9300 mg/kg	IV
870.1300 (§81-3)	Acute Inhalation- Rat Triclosan (100.5% a.i.)	42306902, 43310501	LC_{50}: >0.15 mg/L	II

Table 3-1. Acute Toxicity Profile for Triclosan				
Guideline Number	**Study Type/ Test substance (% a.i.)**	**MRID Number/ Citation**	**Results**	**Toxicity Category**
870.2400 (§81-4)	Primary Eye Irritation- Rabbit Triclosan (97% a.i.)	94045	moderately irritating	II
870.2500 (§81-5)	Primary Dermal Irritation- Rabbit Triclosan (% a.i.not provided)	42306903	PII: 3.5 at 72 hours	III
870.2600 (§81-6)	Dermal Sensitization- Guinea Pig Triclosan (99.7% a.i.)	43206502	Not a Sensitizer	NA

3.2 Dose-Response Assessment

On March 10, 1998 the Health Effects Division's Hazard Identification Assessment Review Committee reviewed the available toxicology data for triclosan and selected endpoints for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to triclosan was also evaluated. On October 31, 2006, the Antimicrobial's Division Toxicity Endpoint Committee met to provide additional endpoints for incidental oral and dermal exposures. A summary of the selected endpoints is shown in the table below.

Table 3-2. Summary of Toxicity Endpoints Selected for Triclosan

Exposure Scenario	Dose Used in Risk Assessment	Uncertainty factors for Risk Assessment	Study and Toxicological Effects
Acute Dietary (gen. pop.)	NOAEL = 30 mg/kg **aRfD** = 0.03 mg/kg/day	Interspecies = 10x Intraspecies = 10x DBSS* = 1x UF = 100	Chronic Toxicity study in Baboons MRID 133230
Acute Dietary (females 13+)	No appropriate endpoint identified in the database		

Exposure Scenario	Dose Used in Risk Assessment	Uncertainty factors for Risk Assessment	Study and Toxicological Effects
Chronic Dietary (all populations)	NOAEL = 30 mg/kg **cRfD** = 0.03 mg/kg/day	Interspecies = 10x Intraspecies = 10x DBSS* = 1x UF = 100	Chronic Toxicity study in Baboons MRID 133230 LOAEL = 100 mg/kg/day, based on clinical signs of toxicity
Short-Term/ Intermediate-Term Incidental Oral (1-30 days; 30 days- 6 months)	NOAEL = 30 mg/kg	Interspecies = 10x Intraspecies = 10x DBSS* = 1x UF = 100	Chronic Toxicity study in Baboons MRID 133230 LOAEL = 100 mg/kg/day, based on clinical signs of toxicity
Dermal (short-term)	NOAEL = 0.6 mg/animal (100 $\mu g/cm^2$)	Interspecies = 3x Intraspecies = 3x DBSS* =1x MOE = 10	14-day dermal toxicity study in the mouse MRID 44389708 LOAEL = 1.5 mg/kg/day, based on treatment-related dermal irritation at the treatment site and on increased liver weights
Dermal (intermediate term)	NOAEL = 40 mg/kg	Interspecies = 10x Intraspecies = 10x DBSS* =1x MOE = 100	90-day Dermal Toxicity in Rats MRID 43328001 LOAEL = 80 mg/kg/day, based on increased incidence occult blood in the urine.
Dermal (long-term)	NOAEL = 40 mg/kg	Interspecies = 10x Intraspecies = 10x DBSS* =3x (lack of chronic dermal study) MOE = 300	90-day Dermal Toxicity in Rats MRID 43328001 LOAEL = 80 mg/kg/day, based on increased incidence occult blood in the urine.
Inhalation (all durations)	NOAEL = 50 mg/m^3 or 3.21 mg/kg/day Where mg/kg/day = ((0.0087 m3/hr * mg/m3 * 2 hr/day) /0.271 b.w.	MOE = 1000	21-Day Inhalation Toxicity study in the rat MRID 0087996 LOAEL = 0.115 mg/L, based on increased total leukocyte count and increased serum alkaline phosphatase
Cancer (oral)	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".		

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

3.3 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 data on developmental, reproductive, and neurotoxic effects of triclosan were examined for any suscepitiblity issues. The data provided no indication of developmental or reproductive effects in offspring of rats or rabbits to *in utero* and post-natal exposure to triclosan. Three prenatal developmental toxicity studies in rats rabbits, and mice, showed no 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. 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 showed no evidence of a neurotoxic effect of triclosan in any of these studies. Residual uncertainties regarding exposure to infants and children have not been underestimated but instead conservative assumptions have been used.

3.4 Endocrine Disruption

EPA is required under the Federal Food Drug and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA has authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

There is some evidence that triclosan disrupts thyroid hormone homeostasis and interacts with the androgen and estrogen receptors. The available evidence is summarized below.

Anti-estrogenic/Androgenic Effects

The first studies reported were in medaka fry (Oryzias latipes) where changes in fin length and trends in the sex ratio suggested that triclosan could be weakly anti-estrogenic/ androgenic (Foran et al., 2000). Flaherty and Dodson (2005) studied the aquatic toxicity of several environmentally-detected pharmaceuticals by performing single species laboratory toxicity tests with Daphnia magna, a freshwater zooplankton. Acute exposure to triclosan (1,10, 100 µg/L) yielded no significant effects on survivorship, morphology, ephippium production, fecundity or sex ratio. However, chronic exposure to 10 ug/L triclosan significantly increased the sex ratio of the first brood only. Daphnia exposed to triclosan produced on average about 72% males, over double that of the control counterparts who produced about 31% males in the first brood.

Gee et al. (2007) reported displacement of ^{3}H-estradiol from the estrogen receptor of human MCF7 breast cancer cells by triclosan and inhibition of the estrogen-responsive ERE-CAT reporter gene by triclosan at 10^{-5} M in the presence of 10^{-10} M estradiol. Triclosan was also shown to have anti-androgenic activity in this study as shown by displacement of ^{3}H-testosterone from the rat androgen receptor, although a 1000-fold molar excess of triclosan was needed to produce a 49% displacement of testosterone. Using a mouse mammary tumor cell line with a stably-transfected androgen reporter gene (LTR-CAT), induction of CAT activity by testosterone was inhibited in the presence of triclosan at 10^{-5} M and above. The proliferative response of these mouse mammary tumor cells to testosterone was also inhibited by triclosan.

Ahn et al. (2008) examined the biological activity of triclosan in *in vitro*, cell-based, and nuclear receptor-responsive bioassays for the aryl hydrocarbon (Ah), estrogen (E), and androgen (A) receptors. As reported in the study, triclosan at a concentration of 10 µM induced luciferase expression to 40% of that seen with 2,3,7,8-tetrachloro dibenzo-p-dioxin (TCDD), but it inhibited the induction of luciferase expression by TCDD by approximately 30%. These agonist/antagonist results are consistent with TCS being a partial agonist of the Ah receptor. In both the ER- and AR-responsive bioassays, triclosan exhibited antagonistic activity in this study.

Chen et al. (2007) examined the anti-androgenic potential of triclosan using a cell-based stably transfected cell line lacking critical steroid metabolizing enzymes. Triclosan alone exhibited no androgenic activity at concentrations up to 10 µM, but transcriptional activity in the presence of 0.125 nM testosterone was inhibited by 10 µM triclosan by 92%, and by 38.8% at 1.0 µM triclosan.

Estrogenic Effects

Further work showed that triclosan had high toxicity on the early life stages of medaka and that its metabolite could have weak estrogenic properties with the ability to induce vitellogenin in male medaka (Ishibashi et al., 2004). When the medaka were exposed to triclosan at 20, 100 and 200 µg/L, there was a significant reduction the length of female medakas relative to control. (Not in male). A metabolite of triclosan may be a weak

estrogenic compound with the potential to induce vitellogenin in male medaka but with no adverse effect on reproductive success and offspring. (Ishibashi, et. al., 2004)

Tamura et al. (2006) studied the androgen receptor (AR) activity of listed chemicals, so called SPEED 98, by the ministry of the Environment, Japan, and structurally related chemicals was characterized using MDA-kb2 human breast cancer cells stably expressing an androgen responsive luciferase reporter gene, MMTV-luc. Based on results generated above suggesting that chemicals with diverse structures were capable of disrupting the endocrine systems mediated by AR, a comparative molecular field analysis (C0MFA) model was developed to analyze the structural requirements necessary to disrupt AR function. Triclosan had AR antagonist activity with an IC50 value of 7.5 µM, which was as potent as linuron based on in vitro MDA-kb2 reporter gene assay.

In male South African clawed frogs (Xenopus laevis), intraperitoneal injection of triclosan resulted in reduced plasma vitellogenin and reduced testosterone levels, suggesting that at higher concentrations, triclosan could possess oestrogen antagonist activity (Matsumura et al., 2005).

Effects on Thyroid

Veldhoen et al. (2006) investigated the effects of pre-treatment to environmentally relevant concentrations of triclosan (nominal concentrations of 0, 0.3, 3.0, and 30 µg/L) on the expression of thyroid hormone receptor, basic transcription element binding protein, and proliferating nuclear cell antigen in premetamorphic tadpoles given injections of 1×10^{-11} mol/g body weight triiodothyronine (T3). Premetamorphosis represents a period in tadpole growth that occurs in the absence of endogenous thyroid hormone, characterized by limited development of the hindlmb buds. Exposure to triclosan alone produced no significant changes in hindlimb development or in expression of any of the receptor transcripts. However, pre-treatment with triclosan followed by T3 administration compared to treatment with triclosan alone resulted in significant weight loss, accelerated hind-limb development, elevated brain activity of genes linked with uncontrolled cell growth, and decreased gene activity in the tail fin at level at concentrations of triclosan as low as 0.15 µg/L. These results suggest that changes in thyroid hormone regulated gene expression in the North American bullfrog at a sensitive life stage can occur following exposure to low concentrations of triclosan and are coincident with an accelerated rate of T3-induced development. Thus, triclosan does not mimic thyroid hormone itself but instead accelerates processes associated with exposure to thyroid hormone.

Recent in vivo data from rats provides further evidence that triclosan alters thyroid hormone homeostasis. Crofton et al (2007) demonstrated that short-term (4-day) oral exposure to triclosan decreased serum total T4 concentrations and increased liver weights. Using a benchmark response of 20%, the benchmark dose (BMD) and lower

bound (BMDL) for T4 were 69.7 and 35.6 mg/kg/day, respectively. This study discussed the possibility of more than one mechanism involved in the decrease of T4 levels after oral exposure to triclosan, including activation of the human pregnane X receptor (PXR; Jacobs et al., 2005) resulting in increases in sulfonation or glucuronidation activity.

The effect of triclosan on thyroid has also been investigated using the pubertal assay (US EPA, 2008). Weanling male rats were dosed by oral gavage for 30 days starting on postnatal day 23 with 0, 3, 30, 100, 200 or 300 mg/kg/day of triclosan,. Triclosan did not alter pubertal development, reproductive tract development or gonadal histopathology. , T4 concentrations decreased by 47.4, 49.8, 80, and 81% at 30, 100, 200, and 300 mg/kg respectively. Triiodothyronine (T3) was only significantly decreased at 200 mg/kg, while thyroid stimulating hormone (TSH) levels were unaffected at any dose level. Thyroid histology was also not altered at 100 and 200 mg/kg. Histology at 300 mg/kg is currently under examination. Mean liver weight of dosed male rats was increased significantly at the 100 mg/kg dose and above, suggestive of hepatic enzyme induction and increased clearance of thyroid hormone Using a BMR of 20% and the BMD was calculated as 14.51 mg/kg with a benchmark dose limit (BMDL) of 7.23.

The mechanism of action for the decrease in T4 levels observed in juvenile rats in this study was not investigated. Mean liver weight of dosed male rats was increased significantly at the 100 mg/kg dose and above, suggestive of hepatic enzyme induction and increased clearance of thyroid hormone. However, the study noted no induction of liver UDP-glucuronyl transferase at the 3 or 30 mg/kg dose levels. In a shorter term study in which weanling female Long-Evans rats were exposed by oral gavage for 4 consecutive days to triclosan at 0, 10, 30, 100, 300, or 1000 mg/kg (Crofton et al., 2007), significant decreases in serum T4 concentrations were observed at 100 mg/kg and above in a dose-related manner. This study discussed the possibility of more than one mechanism involved in the decrease of T4 levels after oral exposure to triclosan, including activation of the human pregnane X receptor (PXR; Jacobs et al., 2005) resulting in increases in sulfonation or glucuronidation activity. Further research is needed in this area.

While there are some uncertainties with respect to the pharmacodynamics of triclosan, the pharmacokinetics of triclosan, which has been studied in several animal species and in humans, shows similar half-life of elimination in experimental animal species studied (rat, hamster, mouse) in comparison to humans. In addition, it is also known that the rat is a more sensitive species than the human with respect to perturbations in thyroid homeostasis, based on the shorter half-life of T4 in the rat (12-24 hours) compared to humans (5-9 days), and the lack of the high affinity binding protein thyroxine binding globulin in rats (Capen, 1996).

Further research is needed on the effect of triclosan on thyroid homeostasis and relevance of any perturbations in homeostasis of thyroid hormone levels for human risk. The

BMDL value (7.23) for decreases in T4 in the 30 day study in weanling rats represents the lower bound for a 20% decrease in T4, which is considered applicable to humans based on the association of neurodevelopmental and cognitive deficits with this percentage decrease in thyroid hormone (Haddow et al., 1998). It is not readily apparent from the available toxicology database for triclosan that the effects observed are the direct result of perturbations of thyroid homeostasis. The Agency, however, is aware that research is ongoing on endocrine effects of triclosan, and this further research may require future modification to the existing assessment for triclosan.

4.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION

Based on a review of EPA-registered product labels, triclosan is the active ingredient in textiles and fabrics (e.g., mattresses and clothing/bibs) and plastic products (e.g., toys, cutting boards, etc). Exposures also include those uses where there is the possibility of indirect food migration, including paper/pulp use, use in ice-making equipment, adhesives, cutting boards, and counter tops as well use in conveyer belts. In addition to EPA-regulated uses, the post application assessment also includes an aggregate assessment of the FDA uses such as toothpaste, hand soaps, and deodorants. This assessment includes both EPA- and FDA-registered uses because of the biological monitoring methodology used to collect the samples from the general population does not allow us to separate the contribution of individual products to total exposure.

The National Health and Nutrition Surveys (NHANES) biological monitoring data are available for triclosan to assess aggregate exposure and risk. EPA views the NHANES monitoring data as most representative assessment of aggregate exposures to daily use products. In the case of triclosan, population-based biological monitoring data are available to assess the co-occurrence of uses to develop an aggregate exposure assessment for ages 6 years and older. The population-based biological monitoring data are a more accurate predictor of aggregate exposure because not only are the data triclosan specific, they are also based on actual consumer use of the various triclosan products as they co-occur in practice.

Although the aggregate exposure/risk assessment using the NHANES data provides an encompassing review of all triclosan-treated products, it does not include

exposures to children under the age of 6 years old. Children under the age of 6 years exhibit unique activities that do not occur at older ages. Therefore, a separate estimate for children under 6 years old has been included. Finally, dermal and inhalation route-specific assessments are also summarized.

5.0 AGGREGATE RISK ASSESSMENT

In order for a pesticide registration to continue, it must be shown "that there is reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there are reliable information." Aggregate exposure is the total exposure to a single chemical (or its residues) that may occur from dietary (i.e., food and drinking water), residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal, and inhalation).

In performing aggregate exposure and risk assessments, the Office of Pesticide Programs has published guidance outlining the necessary steps to perform such assessments (General Principles for Performing Aggregate Exposure and Risk Assessments, November 28, 2001; available at http://www.epa.gov/pesticides/trac/science/aggregate.pdf). Steps for deciding whether to perform aggregate exposure and risk assessments are listed, which include: identification of toxicological endpoints for each exposure route and duration; identification of potential exposures for each pathway (food, water, and/or residential); reconciliation of durations and pathways of exposure with durations and pathways of health effects; determination of which possible residential exposure scenarios are likely to occur together within a given time frame; determination of magnitude and duration of exposure for all exposure combinations; determination of the appropriate technique (deterministic or probabilistic) for exposure assessment; and determination of the appropriate risk metric to estimate aggregate risk

In the case of triclosan, population-based biological monitoring data are available to assess the co-occurrence of uses to develop an aggregate exposure assessment. The population-based biological monitoring data are believed to be a more accurate predictor of aggregate exposure because not only are the data triclosan specific, they are also based on actual consumer use of the various triclosan products as they naturally co-occur. Nonetheless, uncertainties in the biological monitoring data also need to be addressed. Converting spot urine concentrations to dose is a difficult endeavor. The population-based biological monitoring data based on spot urine concentrations used in this assessment were obtained from the National Health and Nutrition Surveys (NHANES).

5.1 National Health and Nutrition Surveys (NHANES) Data for Triclosan

5.1.1 NHANES Data and Dose Conversion

The following information has been excerpted from Cohen (2008). The National Health and Nutrition Surveys (NHANES) are a series of US national surveys of the health and nutrition status of the non-institutionalized civilian population conducted by the Centers for Disease Control and Prevention. As part of the 2003-2004 NHANES, urinary concentrations (µg/L) of triclosan (2,4,4'-trichloro-2'-hydroxydiphenyl ether) were measured on a random sample of 2,517 participants of ages 6 and over. These measurements represent concentrations in spot urine samples. The corresponding human dose (mg/kg/day) was not measured or estimated by NHANES. The NHANES urinary metabolite concentration data collection efforts were not designed to directly determine the dose and CDC has not reported dose estimates for triclosan based on NHANES measurement data. The NHANES 2003-2004 data were obtained from the NHANES website: www.cdc.gov/nchs/nhanes.htm

EPA evaluates health effects in terms of toxicity endpoints that represent an exposure level in mg or µg per kilogram body weight that is not expected to be associated with adverse health effects. The conversion of measured spot urine concentrations to daily doses can be difficult because of variable dilution caused by wide fluctuations in fluid intake and excretion. Dose calculation is also difficult because there is no way to determine from the NHANES data from what route of exposure (i.e., oral, dermal, inhalation) and when (i.e., duration and time interval prior to measurement) the exposure to triclosan occurred, and because of uncertainty and variability in the absorption, distribution, metabolism, and excretion (ADME) parameters. If NHANES collected total daily urine excretion for each participant, then that participant's dose could be more accurately estimated by multiplying the triclosan concentration by the total daily urine volume and then dividing by the body weight. However, NHANES only collected spot urine samples so that total urine volume was not measured.

In the absence of total urine volume data, various methods have been proposed to estimate the dose from the measured spot urine concentration. The methods have been categorized into two main groups: one that uses measured pesticide concentrations in urine directly and the other that standardizes urinary concentrations on the basis of creatinine, a by-product of metabolism. There is some debate on whether creatinine is less variable than urinary output. Therefore, at this time, results of both methods are presented. The dose conversion methods are summarized below:

- Mage et al. (2004, 2007) use the estimated daily creatinine excretion for a demographic group; the triclosan concentration is divided by the creatinine concentration, multiplied by the daily creatinine excretion in µg/day, and divided by the body weight.

- Schafer et al. (2004) use the estimated daily urine excretion in L/day and the average body weight for a demographic group; the triclosan concentration is multiplied by the daily urine excretion in L/day, and divided by the average body

weight. Because the data were available in NHANES, actual body weights of subjects were used instead of average body weights as described by PANNA (2004).

- The EPA Office of Research and Development (ORD) does not currently recommend an approach for converting spot urine concentration to a dose. However, the approach used by some ORD researchers is to use the estimated daily urine excretion in L/kg-day for a demographic group; the triclosan concentration is multiplied by the estimated daily urine excretion in L/kg-day. Urine volumes (mean and upper percentile) from Geigy (1981) were used in this method.

Detailed procedures and assumptions used by EPA/OPP/AD to convert spot urine concentrations into dose to assess the tricolsan aggregate risks are provided by Cohen (2008). Cohen (2008) provided the dose conversion from spot urine samples leaving the correction for the pharmacokinetics of triclosan to be done at a later date (see Section 6.1.2 below for pharmacokinetic correction).

5.1.2 Pharmacokinetics of Triclosan

A correction factor to account for the disposition of triclosan, derived from the data of Sandborgh-Englund (2006) was applied to the biological (urine) monitoring data provided by Cohen (2008) and used in this assessment. Sandborgh-Englund (2006) dosed 10 subjects (5M/5F) ranging from 26 to 42 years of age with a single oral dose of 4 mg of triclosan in mouthwash solution. Pre-exposure monitoring to establish baseline exposure levels was also determined. Results indicate that urinary excretion among individuals is variable for triclosan. Urinary excretion ranged from 24 to 83 percent (median of 54 percent) of the administered dose of triclosan in urine in 4 days. The data also indicate that the majority of urinary excretion occurred within 24 hours as illustrated in Figure 1. The urinary excretion half life of triclosan in this study was determined to be 11 hours. Therefore, 54 percent excretion, corrected for baseline exposures, was used by EPA in this assessment to convert the urine concentrations from NHANES to a dose using estimated 24 hour urine void volumes as described by Cohen (2008). The conversion is facilitated by the linear excretion kinetics observed for triclosan in this study. Based on the above, the pharmacokinetic equation used to calculate the triclosan dose is as follows: Triclosan dose (mg/kg/day) / 0.54.

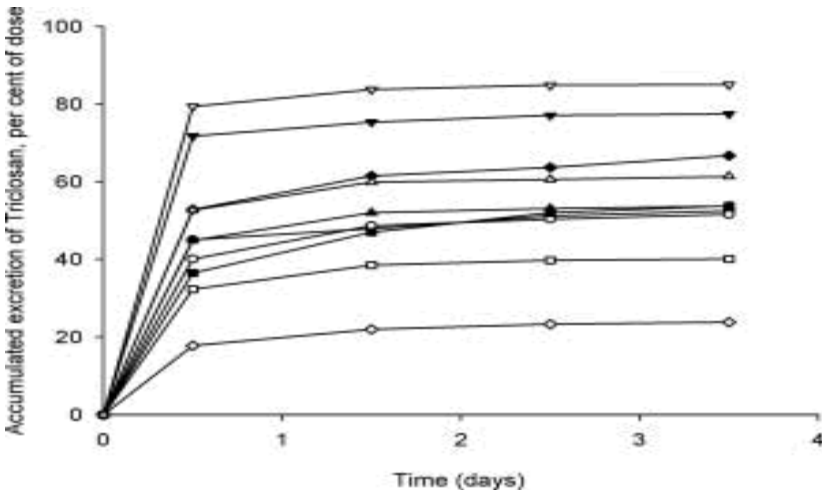

Figure 1. Triclosan Excretion in Urine (taken from Sandborgh-Englund (2006))

5.1.3 Uncertainties Associated with the Dose Conversion

Several uncertainties exist in the aggregate assessment for triclosan that arise from using the biological monitoring data from NHANES. However, these uncertainties are balanced (and perhaps even offset) by the relatively large data set obtained from NHANES; assumptions used by Cohen (2008) for the dose conversion; the characterization of the dose at the lowest (most conservative) urinary excretion; the short urinary excretion half life 11 hours; and use of the upper percentile of exposure. The following uncertainties and data limitations are noted for the aggregate assessment:

- It is assumed that the ADME parameters are the same across all individuals within the NHANES study and are constant within individuals over time. The ADME assumptions are offset by the use of the lowest urinary excretion value available in Sandborgh-Englund (2006) and by characterization of the risks at the 99th percentile of exposure from NHANES using the method which assumes the an upper percentile of daily urine excretion for everyone in the sample.
- Sandborgh-Englund (2006) reported urinary excretion over 4 days post dose. However, from the graphical presentation of the data (raw data not reported) the profile of urinary excretion of triclosan indicates that the results at 24 hours are similar to those at 4 days with a urinary excretion half life of 11 hours.
- NHANES urinary metabolite concentration data are not collected in a way to directly determine the dose, and CDC has not reported dose estimates for triclosan based on NHANES measurement data.
- The conversion of measured spot urine concentrations to daily doses can be difficult because of variable dilution caused by wide fluctuations in fluid intake and excretion. This is offset by one of the dose conversion methods presented that assumed the upper percentile of daily urine volume for all individuals in the NHANES data set.

- Dose calculation is also difficult because there is no way to determine from the NHANES data from what route of exposure (i.e., oral, dermal, inhalation) and when (i.e., duration and time interval prior to measurement) the exposure to triclosan occurred. This is offset by the short half life of triclosan (11 hours in urine).

5.2 Aggregate Risks

5.2.1 Children (6 years) to Adults

The NHANES results are believed to be representative of a range of acute to chronic exposures to children and adults because of the relatively short half-life of triclosan in urine (i.e., 11 hours) and the often daily use of triclosan products such as hand soaps and tooth paste. The upper range of exposures is important because of the uncertainties in converting the spot urine concentrations to a dose; because the pharmacokinetic data appears to be highly variable for triclosan; and because the use of triclosan by the NHANES population is unknown. Interpreting the NHANES data for triclosan as representing a range of acute to chronic exposures is also supported by the fact that the 2,517 samples selected for analyses of triclosan were randomly selected from the total NHANES random population of 9,643, and therefore, *"...the representative design of the survey was maintained"* (Calafat et al 2007). Given the uncertainties in aggregating screening-level single use exposure estimates and assumptions on co-occurrence of uses, the NHANES data are viewed to be a reasonable data set to use for predicting aggregate risks.

All exposure durations were assessed using the selected oral NOAEL of 30 mg/kg/day with a target MOE of 100. The oral endpoint was selected to represent the various oral exposure scenarios that are expected from antimicrobial exposure to triclosan. The calculated MOEs are representative of all exposure durations. The NHANES data show that 74.6% of the samples had detectable levels of total (free plus conjugated) triclosan. Tables 5.1 and 5.2 provide – for each of the three basic concentration to dose conversion methods -- the mean and 99th percentiles, respectively, of the (1) spot urine concentration to dose conversion prior to correcting for the 54% triclosan urinary excretion (in units of ug/kg/day); (2) the pharmacokinetic 54% corrected daily dose converted to units of mg/kg/day; and (3) the MOEs. Aggregate exposures and risks are presented for the following age groups and subpopulations:

- All age groups;
- Ages 6-11;
- Ages 12-19
- Ages 20-59
- Ages >=60
- Male
- Females
- Mexican-American

- White, non-Hispanic
- Black, non-Hispanic

Tables 5.1 and 5.2 report the results of the aggregate risks at both the mean and 99th percentile, respectively. These analyses of the combined EPA and FDA uses do not trigger risks of concern. The mean MOEs range from 4,700 to 19,000. The MOEs at the 99th percentile of the dose range from 260 to 1,700. In fact, applying the lowest (most conservative) percent urinary excretion from the results of the pharmacokinetic data (i.e., 24 percent) to the most conservative dose conversion method (i.e., Geigy's 95th percentile of daily urine volumes), the MOE is 120. In conclusion, even with the reliance of conservative assumptions in estimating risks to account for the considerable uncertainties in converting spot urine concentration to dose, the NHANES data as analyzed for triclosan sufficiently characterizes the aggregate risks as meeting the definition of not resulting in unreasonable adverse effects.

Table 5-2a. Acute, Short, Intermediate-, and Long-term Aggregate Risks for Triclosan (Mean)

Group	Mage (2007) Obese Correct			Schafer (2004) Actual BW			Geigy 1981 Mean Urine Vol			Geigy (1981) 95% Urine Vol		
	ug/kg	mg/kg/day	MOE	ug/kg	mg/kg/day	MOE	ug/kg	mg/kg/day	MOE	ug/kg	mg/kg/day	MOE
All	1.373	0.0025	11801	1.5700	0.0029	10318	1.551	0.0029	10442	2.413	0.0045	6714
6-11	0.872	0.0016	18582	1.0511	0.0019	15412	0.901	0.0017	17986	1.304	0.0024	12426
12-19	1.431	0.0027	11318	1.7404	0.0032	9308	2.189	0.0041	7400	3.361	0.0062	4820
20-59	1.543	0.0029	10501	1.7187	0.0032	9426	1.635	0.0030	9911	2.562	0.0047	6322
>= 60	1.013	0.0019	15996	1.2108	0.0022	13380	1.152	0.0021	14065	1.806	0.0033	8972
Male	1.684	0.0031	9618	2.0316	0.0038	7974	1.963	0.0036	8254	2.997	0.0056	5405
Female	1.076	0.0020	15062	1.1306	0.0021	14329	1.160	0.0021	13969	1.857	0.0034	8726
Mexican-American	1.863	0.0035	8694	2.2781	0.0042	7111	2.220	0.0041	7297	3.455	0.0064	4689
White, Non-Hispanic	1.355	0.0025	11956	1.4850	0.0028	10909	1.477	0.0027	10969	2.303	0.0043	7035
Black, Non-Hispanic	1.082	0.0020	14967	1.5665	0.0029	10342	1.512	0.0028	10714	2.327	0.0043	6962

See Cohen (2008) for details of the dose conversion methods. Geigy (1981) 95% urine vol is the upper percentile of daily urine volume.

Table 5-b. Acute, Short, Intermediate-, and Long-term Aggregate Risks for Triclosan (99th Percentile)

Group	Mage (2007) Obese Correct			Schafer (2004) Actual BW			Geigy 1981 Mean Urine Vol			Geigy (1981) 95% Urine Vol		
	ug/kg	mg/kg/day	MOE	ug/kg	mg/kg/day	MOE	ug/kg	mg/kg/day	MOE	ug/kg	mg/kg/day	MOE
All	15.51	0.029	1044	23.59	0.044	687	23.56	0.0436	688	38.06	0.070	426
6-11	10.85	0.020	1493	24.62	0.046	658	9.70	0.0180	1670	14.17	0.026	1143
12-19	16.63	0.031	974	25.46	0.047	636	28.77	0.0533	563	46.48	0.086	349
20-59	19.08	0.035	849	29.07	0.054	557	29.87	0.0553	542	48.25	0.089	336

>= 60	14.42	0.027	1123	17.15	0.032	945	14.78	0.0274	1096	22.70	0.042	714
Male	18.96	0.035	855	35.15	0.065	461	35.20	0.0652	460	54.07	0.100	300
Female	14.74	0.027	1099	17.77	0.033	912	17.62	0.0326	920	28.47	0.053	569
Mexican-American	20.56	0.038	788	42.37	0.078	382	40.64	0.0753	399	62.42	0.116	260
White, Non-Hispanic	14.98	0.028	1081	16.30	0.030	994	18.97	0.0351	854	29.13	0.054	556
Black, Non-Hispanic	13.72	0.025	1181	26.12	0.048	620	28.25	0.0523	573	45.64	0.085	355

5.2.2 Infants

While NHANES data are measured exposures that represent the real world co-occurrence of triclosan-treated products, it is necessary to use screening-level deterministic assessments as well as to make assumptions of potential co-occurrence of triclosan-treated products for younger children. USEPA (2005), in an internally and externally scientific peer reviewed document, provides the basis of the age group selection: *"This document recommends a set of age groupings based on current understanding of differences in lifestage behavior and anatomy and physiology that can serve as a starting set for consideration by Agency risk assessors and researchers. In specific situations, it is recognized that exposure factors data may not be available for many of the recommended age groupings or that a specific age group may not need to be the subject of a particular assessment, so flexibility and professional judgment are essential in applying these generic age groupings."* One age group was selected to represent behavioral activities of children younger than 6 years old that are exposed to triclosan-treated products.

An assessment of infants in the 6 to 12 month old age group has been selected to represent the high end of exposure activities of children less then six years old to triclosan-treated products. This age group is considered the high end of exposure based on the characteristics discussed in Table 2 presented in USEPA (2005) and the likelihood of these activities co-occurring. USEPA (2005) indicates that this age group includes behaviors that would lend themselves to potentially expose children to triclosan-treated products. Characteristics of children at this age that potentially exposes children to triclosan that would not have been captured by the 6-11 year old age category in NHANES include nursing, increasingly likely to mouth nonfood items, and *"development of personal dust clouds"* as a characteristic relevant to inhalation exposure.

The younger age groups recommended by USEPA (2005) such as birth to 3 months and 3 to 6 months are less likely to be the high exposure groups to triclosan because of less contact with treated objects (not to say there is no contact, but the 6 to 12 month age group are *"increasingly likely to mouth nonfood items"*). The older age groups recommended by USEPA (2005) include 12 to 24 months and 2 to less than 6 years old. These age groups reflect the cessation of nursing and a reduction in hand-to-mouth activities. The activities in the 12 to 24 month age group as well as the 2 to 6 year age group reflect decreasing frequency of mouthing of objects, nursing, etc and decreasing potential for co-occurrence (e.g., nursing) in comparison to the 6 to 12 month old age group.

Infant-specific activities resulting in potential exposures that are not accounted for by the 6-11 year old age group in NHANES that are likely to co-occur include:

- Nursing (i.e., triclosan-contaminated breast milk);
- Object-to-mouth exposures (e.g., mouthing of plastic items such as toys, combs & brushes, playground equipment);
- Hand-to-mouth exposure (e.g., residues in dust stuck to children's hands); and
- Inhalation of triclosan-contaminated dust.

Other potential exposure pathways for infants in the 6 to 12 month old age group that are captured – and overestimated for the 6 to 12 month olds -- by the NHANES age groups 6-11 years old include:

- Brushing teeth with triclosan-treated tooth paste;
- Washing hands with triclosan-treated antibacterial soap;
- Exposure to impregnated fabrics and textiles such as clothing/sportswear, blankets, mattresses, tooth brush bristles, etc. that may be treated with triclosan;
- Exposure to impregnated polymers and plastics such as food contact surfaces (e.g., cutting boards, conveyor belts, counter and table tops).

Table 5.3 presents the aggregate risks for the 6 to 12 month old age group. The aggregate risks presented represent the high-end of exposure that may co-occur from the various EPA and FDA-regulated triclosan products. The risk results of the 6-11 year old NHANES age group are used in conjunction with infant-specific exposure activities. The 6-11 year old age group represents exposures to all of the potential EPA-registered uses such as textiles and fabrics; plastic products; as well as FDA-regulated soaps and toothpaste. Clearly, including exposures to the FDA-regulated soaps and toothpaste for 6-11 year olds is a conservative assessment of exposure from these products to 6 to 12 month olds. Future refinements to the infant aggregate should focus on this portion of the total exposure.

The aggregate risks for infants 6 to 12 months old have been estimated by combining the mean NHANES distribution with the infant-specific bounding risks. The aggregate MOE from the measured mean of the 6-11 year old NHANES subjects combined with the bounding risks from nursing, object-to-mouth, and hand-to-mouth indicate a long-term MOE of 390. The 99th percentile of the NHANES dose (when using the 95% urine volume to estimate the 99th percentile dose) is combined with the infant-specific bounding risks and indicates a long-term MOE of 290.

Table 5.3. Aggregate Exposure and Risks for Infants 6 to 12 Months.

Scenario	Risk (MOE)			Representative Products
	Mean	99th%	Bounding	
NHANES 6-11 year olds	12,000	1,100	NA	Exposures inclusive of all triclosan-treated products that co-occur in the real world for 6-11 year olds (excludes infant-specific activities)
Nursing	NA	NA	6,000	Infants nursing (contaminated breast milk) from mothers exposed to triclosan-treated products that co-occur in the real world
Object-to-mouth	NA	NA	430	Wide range of triclosan-treated products such as toys that may be mouthed by infants
Hand-to-mouth	NA	NA	6.7E+6	Infants mouthing hands that have been contaminated by triclosan residues in house dust
Aggregate [a] (Total MOE)	390[b] (mean + bounding)	290[c] (99th + bounding)	NA	Total exposure of a 6-11 year old plus infant-specific activity exposures

(a) Aggregate (Total MOE) = $1/((1/MOE_{NHANES}) + (1/MOE_{Nursing}) + (1/MOE_{Object}) + (1/MOE_{HTM}))$

(b) Mean Aggregate = Sum of the mean NHANES MOEs plus the bounding MOE estimates from nursing, object-to-mouth, and hand-to-mouth.

(c) 99th%tile Aggregate = Sum of the 99th%tile NHANES MOEs plus the bounding MOE estimates from nursing, object-to-mouth, and hand-to-mouth.

5.2.3 Dermal Irritation

The potential for dermal irritation to occur from incidental dermal exposures from products treated at low concentrations of triclosan are expected to be minimal. The lack of incident data for irritation confirms this assumption.

The localized dermal irritation effects tested at the concentrated product (i.e., 99 percent triclosan) occurs at levels lower than the NOAEL of 100 ug/cm^2. EPA applies a 10x uncertainty factor for risk assessment purposes. Plastic articles are treated at a use dilution of 0.5 percent triclosan. Only a fraction of triclosan in impregnated articles would be available on the surface. Furthermore, only a fraction of the triclosan on the surface would be transferred to a localized skin area for irritation to occur. For illustrative purposes, the film thickness of a fluid on the hands is 1.75 mg/cm^2, which was extracted from the document entitled, *"A Laboratory Method to Determine the Retention of Liquids on the Surface of Hands"* (Cinalli, 1992). The film thickness is based on a machinist immersing both hands in metalworking fluid and then partially cleaning hands with a rag. Clearly this is an exaggerated estimate of exposure compared to dermal contact of triclosan-impregnated articles. This type of a screening-level approach indicates that 1.75 mg/cm^2 x 1000 ug/mg unit conversion x 0.005 triclosan application rate is 8.75 ug/cm^2. This conservative estimate does not indicate a dermal irritation concern. Additional residue transfer assumptions for impregnated articles up to 2 percent could be determined for similar screening-level assessments but are not warranted based on the above discussions.

5.2.4 Dermal Systemic

There is the potential for dermal-specific route of exposure to adults and children contacting impregnated textiles and fabrics such as clothing items and mattresses. The contribution of dermal exposure to the aggregate exposure is represented in the NHANES data. Nonetheless, a post-application screening-level clothing assessment to represent exposure to treated textiles and fabrics is provided. The route-specific dermal toxicological endpoint for the intermediate-term exposure duration is used to represent all textile uses. Long-term duration was not assessed because transferable triclosan residues from treated textiles and fabrics are not expected to be available continuously at the levels used in this screening-level assessment.

6.0 CUMULATIVE RISK

FQPA (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

A cumulative risk assessment for triclosan was not performed. The point has been raised in the public comment phase of the preliminary risk assessment that the chemical triclocarban should be included in a cumulative risk assessment for triclosan based on the co-occurrence of these chemicals in the environment and the structural similarity of these two chemicals. Examination of the chemical structure of triclocarban shows that it is in a different chemical class (hydroxyphenylurea) than triclosan (hydroxyphenylether). Furthermore, there is not necessarily a relationship between the mechanism of antimicrobial activity and mechanism of toxicity in mammals. There is currently insufficient evidence to suggest that these two chemicals share a common mechanism of toxicity with respect to toxic effects in mammals and that a cumulative assessment should be conducted.

7.0 OCCUPATIONAL EXPOSURE AND RISK

A complete explanation of the occupational exposure and risk assessment can be found in the supporting disciplinary chapter entitled Triclosan: Occupational and Residential Exposure Assessment Summary information is provided in this section.

The exposure scenarios assessed for representative uses of triclosan selected by EPA are shown in Table 7.1. The table also shows the maximum application rate associated with the representative use and the appropriate EPA Registration number for the product label. It should be noted that for the calculation of application rates in which 8.34 lb/gal is noted, the product is assumed to have the density of water because no product-specific density is available.

The occupational handler scenarios included in Table 7.1 were assessed to determine inhalation exposures. The general assumptions and equations that were used to calculate occupational handler inhalation risks are provided in Section 1.2 of the Occupational and Residential Exposure Chapter. The majority of the scenarios were assessed using CMA data and Equations 1-3. However, for the occupational scenarios in which CMA data were insufficient, other data and methods were applied.

Triclosan dermal irritation exposures and risks were not estimated for occupational handler exposures. Instead, dermal irritation exposures and risks will be mitigated using default personal protective equipment requirements based on the toxicity of the end-use product.

Table 7.1. Representative Exposure Scenarios Associated with Occupational Exposures to Triclosan				
Representative Use	Method of Application	Exposure Scenario	Example Registration #	Application Rate
Commercial/Industrial/Institutional Premises (Use Category III)				
HVAC coil applications	Airless sprayer	ST/IT Handler: Inhalation	82523-1	6.1E-4 lb ai/10 ft^2 (0.85 pints/10 ft^2 x 1 gal/8 pts x 8.34 lb/gal x 0.69% ai)
Painting (commercial painters)	Paint brush, Airless sprayer	ST/IT Handler: Inhalation	42182-1	0.1 lb ai/gallon [up to 1% product x 99% ai x 10 lb/gal paint density = 0.099 lb ai/gallon of paint]
Material Preservatives (Use Category VII)				
Paint	Liquid pour, Powder	ST/IT Handler: inhalation	42182-1	0.1 lb ai/gallon [up to 1% product x 99% ai x 10 lb/gal paint density = 0.099 lb ai/gallon of paint]
Industrial processes and water systems (Use Category VIII)				
Pulp and Paper	Metered pump	ST/IT Handler: Inhalation	70404-5	2% ai by weight of paper product (2% product by weight x 99% ai for paper mulch) Note : other labels for paper and paper board have lower rates, 42182-1 and 3090-165)

The resulting inhalation exposures and MOEs for the representative occupational handler scenarios are presented in Table 6.2. The calculated MOEs were above the target MOE of 100 for all scenarios, except for the commercial painters (both by brush and airless sprayer).

Table 7.2. Short- and Intermediate-Term Inhalation and Intermediate-Term Dermal Risks Associated with Occupational Handlers									
Exposure Scenario	Method of Application	Unit Exposure (mg/lb a.i.)		Application Rate	Quantity Handled/ Treated per day	Daily Dose (mg/kg/day)[a]		MOE[b] (Target MOE = 100)	
		Inhalation	Dermal			Inhalation	Dermal	Inhalation	Dermal
Commercial, Institutional and Industrial Premises and Equipment (Use Site Category III)									
HVAC	Airless sprayer	0.83	38	6.1E-4 lb ai/10ft^2	Large building 1000 ft^2	0.00072	0.033	4,500	1,200
Painting (commercial)	Paint brush	0.26	180	0.1 lb ai/gal	5 gallons	0.002	1.3	1,600	31
	Airless sprayer	0.83	38		50 gallons	0.059	2.7	54	1
Material Preservatives (Use Site Category VII)									
Paint (manufacturing process)	Liquid pour	0.00346	0.135 (gloves)	0.99% ai	20,000 lbs	0.0098	0.38	330	110
	Liquid pump	0.000403	0.00629 (gloves)		200,000 lbs	0.011	0.18	290	220
Industrial Processes and Water Systems (Use Site Category VIII)									
Pulp and Paper	Metering pump	0.000403	0.00629 (gloves)	2% ai	500 tons	Require closed loading systems to mitigate the exposure/risk			

a Daily dose (mg/kg/day) = [unit exposure (mg/lb a.i.) x absorption factor (1 for inhalation and 1 for dermal) x application rate x quantity treated / Body weight (70 kg).

b MOE = NOAEL (mg/kg/day) / Daily Dose [Where inhalation LOAEL = 3.21 mg/kg/day for all inhalation exposure durations and the IT dermal NOAEL is 40 mg/kg/day from a dermal route-specific study]. Target MOE = 100.

7.1 Occupational Post-application Exposures

Occupational post-application dermal and inhalation exposures are assumed to be negligible based on the use patterns.

7.2 Data Limitations/Uncertainties

There are several data limitations and uncertainties associated with the occupational handler and post application exposure assessments as noted in the occupational and residential exposure chapter. These are reproduced here and include:

- Surrogate dermal and inhalation unit exposure values were taken from the proprietary Chemical Manufacturers Association (CMA) antimicrobial exposure study (USEPA, 1999: DP Barcode D247642) or from the Pesticide Handler Exposure Database (USEPA, 1998). Since the CMA data are of poor quality, the Agency requires that confirmatory data be submitted to support the occupational scenarios assessed in this document.

- The quantities handled/treated were estimated based on information from various sources, including HED's Standard Operating Procedures (SOPs) for Residential

Exposure Assessments (USEPA, 2000 and 2001), and personal communication with experts. The individuals contacted have experience in these operations and their estimates are believed to be the best available without undertaking a statistical survey of the uses. In certain cases, no standard values were available for some scenarios. Assumptions for these scenarios were based on AD estimates and could be further refined from input from registrants.

8.0 ENVIRONMENTAL RISK

8.1 Ecological Hazard

The toxicity endpoints presented below are based on the results of ecotoxicity studies submitted to EPA to meet the Agency's data requirements for the uses of triclosan.

A. Toxicity to Terrestrial Animals

(1) Birds, Acute

The results of three acute oral toxicity studies, submitted for triclosan, are provided in the following table:

Species	Chemical, % Active Ingredient (a.i.) Tested	Endpoint (mg/kg)	Toxicity Category	Satisfies Guidelines/ Comments	Reference (MRID No.)
Mallard duck (*Anas platyrhynchos*)	Triclosan 99.7%	LD_{50} = >2150 NOAEL = 2150	Relatively nontoxic	Yes (core) - 14-day test duration - 19 weeks of age	430226-03
Bobwhite quail (*Colinus virginianus*)	**Triclosan 99.7%**	LD_{50} = 825 NOAEL = <147	Slightly toxic	Yes (core) - 14-day test duration - 21 weeks of age	430226-02
Bobwhite quail (*Colinus virginianus*)	**Triclosan 3.89%**	LD_{50} = >2000 NOAEL = N.R.	Relatively nontoxic	Yes (core for a formulated product)	410089-10

These three acceptable acute oral toxicity studies indicate that triclosan is slightly toxic to relatively nontoxic to birds on an acute oral basis. The guideline requirement OPPTS 850.2100/(71-1) is satisfied.

(2) Birds, Subacute

This testing was required for triclosan. The results of two subacute dietary toxicity studies, submitted for triclosan, are provided in the following table:

Species	Chemical, % Active Ingredient (a.i.) Tested	Endpoint (ppm)	Toxicity Category	Satisfies Guidelines/ Comments	Reference (MRID No.)
Bobwhite quail (*Colinus virginianus)*	Triclosan 99.7%	LC_{50} (diet) = >5000 NOAEC = 1250	Relatively nontoxic	Yes (core) - 8-day test duration - 13 days of age	430226-04
Bobwhite quail (*Colinus virginianus)*	Triclosan 3.89%	LC_{50} (diet) = >5000 NOAEC = N.R.	Relatively nontoxic	Yes (core for formulated product) - 8-day test duration - 7-10 days of age	410089-11

The results of these two acceptable studies indicate that triclosan is relatively nontoxic to avian species through subacute dietary exposure. These studies fulfill guideline requirement OPPTS 850.2100/ (71-2a – Bobwhite quail/71-2b – Mallard duck).

B. Toxicity to Aquatic Animals

The Agency requested that aquatic toxicity studies be conducted with triclosan since, under typical use conditions, it may be introduced into the aquatic environment.

(1) Freshwater Fish, Acute

In order to establish the acute toxicity of triclosan to freshwater fish, the Agency requires freshwater fish toxicity studies using the TGAI. The preferred test species are rainbow trout (a coldwater fish) and bluegill sunfish (a warm water fish). The results of 5 freshwater fish acute studies submitted for triclosan are presented in the following table:

Species	Chemical, % Active Ingredient (a.i.) Tested	Endpoint (mg/L)	Toxicity Category	Satisfies Guidelines/ Comments	Reference (MRID No.)
Rainbow Trout (*Oncorhynchus mykiss)*	Triclosan 99.3%	LC_{50} = 0.288 NOAEC = 0.100	Highly toxic	Yes (core) - 96-hr test duration - static test system	439693-01
Fathead minnow (*Pimephales promelas*)	Triclosan 99.7%	LC_{50} = 0.26 LOEC = 0.18 NOAEC = 0.10	Highly toxic	No (supplemental) - 96-hr test duration - static test system - nominal concentrations not verified	430460-01
Bluegill sunfish (*Lepomis macrochirus)*	Triclosan 3.89%	LC50 = 37.2 NOAEC = N.R.	Slightly toxic	Yes (core for formulated product) - 96-hr test duration - static test system	410089-13
Rainbow Trout (*Oncorhynchus mykiss)*	Triclosan 3.89%	LC_{50} = 23.4 NOAEC = N.R.	Slightly toxic	Yes (core for formulated product) - 96-hr test duration - static test system	410089-12

Freshwater acute toxicity tests indicate that triclosan is highly toxic to slightly toxic to fish on an acute basis. These studies fulfill guideline requirement OPPTS 850.1075 (72-1a&b). Because acute toxicity to fish is <1.0 mg/L, the environmental hazard section of triclosan labels must state: "This pesticide is toxic to fish."

(2) Freshwater Invertebrates, Acute

The results of the two acute studies submitted for triclosan are provided in the following table:

Species	Chemical, % Active Ingredient (a.i.) Tested	Endpoint (mg/L)	Toxicity Category	Satisfies Guidelines/ Comments	Reference (MRID No.)
Waterflea (*Daphnia magna)*	Triclosan 99.7%	EC_{50} = 0.39 NOAEC = 0.10 (a.i.)	Highly toxic	No (supplemental) - 48-hr test duration	430460-02

Species	Chemical, % Active Ingredient (a.i.) Tested	Endpoint (mg/L)	Toxicity Category	Satisfies Guidelines/ Comments	Reference (MRID No.)
				- static test system - nominal concentrations not verified	
Waterflea (*Daphnia magna)*	Triclosan 3.89%	LC_{50} = 0.42 NOAEC = N.R.	Highly toxic	No (supplemental) - 48-hr test duration - static test system - lack of pH and DO measurements and formulated product used	410089-14
Waterflea (*Daphnia magna)*					423221-02

The results of these studies indicate that triclosan is highly toxic to freshwater invertebrates. These studies **do not** fulfill guideline requirement OPPTS 850.1010 (72.2a). Because the acute aquatic invertebrate toxicity values are < 1.0 mg/L, the environmental hazard section of triclosan labels must state: "This pesticide is toxic to aquatic invertebrates."

(3) Estuarine and Marine Organisms, Acute

Acute toxicity testing with estuarine and marine organisms using the TGAI is required when the end-use product is intended for direct application to the marine/estuarine environment or effluent containing the active ingredient is expected to reach this environment. The preferred fish test species is the sheepshead minnow. The preferred invertebrate test species are mysid shrimp and eastern oysters. At this time this testing is not required for triclosan, but is dependent upon the results of environmental fate data which may be required. (See triclosan environmental fate chapter and comments above on potential data requirements). No studies have been submitted to fulfill these data requirements (OPPTS 850.1075/(72-3a), OPPTS 850.1035/(72-3c) and OPPTS 850.1025/(72-3b)).

(4) Aquatic Organisms, Chronic

Chronic toxicity testing (fish early life stage and aquatic invertebrate life cycle) is required for pesticides when certain conditions of use and environmental fate apply. The preferred freshwater fish test species is the fathead minnow. The preferred freshwater invertebrate is *Daphnia magna*. At this time this testing is not required for triclosan, but is dependent upon the results of environmental fate data which may be required. (See triclosan environmental fate chapter and comments above on potential data requirements).
The results of one toxicity study submitted for triclosan is presented in the following table:

Species	Chemical, % Active Ingredient (a.i.) Tested	Endpoint (mg/L)	Satisfies Guidelines/ Comments	Reference (MRID No.)
Waterflea (*Daphnia magna*)	Triclosan % purity unknown	LOEC = <0.1388 NOAEC = N.R.	No (supplemental) - 21-day test duration **- static renewal test system** - growth not measured as a chronic endpoint - % a.i. not given - raw data missing	437407-01

Species	Chemical, % Active Ingredient (a.i.) Tested	Endpoint (mg/L)	Satisfies Guidelines/ Comments	Reference (MRID No.)
			- concentration analysis insufficient	

No fathead minnow study has been submitted. The study on the waterflea does not fulfill the guideline requirement for a chronic aquatic invertebrate study (OPPTS 850.1300).

C. Toxicity to Plants

Non-target plant phytotoxicity testing is required for pesticides when certain conditions of use and environmental fate apply. At this time this testing is not required for triclosan, but is dependent upon the results of environmental fate data which may be required. (See triclosan environmental fate chapter and comments above on potential data requirements). However, testing has been conducted with triclosan on several aquatic plant species. Testing is normally conducted with one species of aquatic vascular plant (*Lemna gibba*) and four species of algae: (1) freshwater green alga, *Selenastrum capricornutum,* (2) marine diatom, *Skeletonema costatum,* (3) freshwater diatom, *Navicula pelliculosa,* and (4) bluegreen cyanobacteria, *Anabaena flos-aquae.* The rooted aquatic macrophyte rice (*Oryza sativa*) is also tested in seedling emergence and vegetative vigor tests.

Four studies that evaluate the toxicity of triclosan to freshwater aquatic plants have been submitted. Results of these studies are presented in the following table:

Species	Chemical, % Active Ingredient (a.i.) Tested	Endpoint (mg/L)	Satisfies Guidelines/ Comments	Reference (MRID No.)
Marine Diatom (*Skeletonema costatum*)	Triclosan 99.5%	EC_{50} = >0.066 NOEC = 0.0126	Yes (core) - 96-hour test duration - static test system	444228-01
Freshwater Diatom (*Navicula pelliculosa*)	Triclosan 99.5%	EC_{50} = 0.016 NOEC = 0.005	Yes (core) - 96-hour test duration - static test system	444228-01
Bluegreen Cyanobacteria (*Anabaena*	Triclosan 99.5%	EC_{50} = 0.0012 NOEC = N.R.	Yes (core) - 96-hour test duration	444228-01

Species	Chemical, % Active Ingredient (a.i.) Tested	Endpoint (mg/L)	Satisfies Guidelines/ Comments	Reference (MRID No.)
flos-aquae)			- static test system	
Duckweed (*Lemna gibba*)	Triclosan 99.5%	EC_{50} = >0.0625 NOEC = 0.0125	Yes (core) - 7-day test duration - static test system	444228-01

The guideline requirement for an algal toxicity test (850.5400, 123-2) is partially fulfilled. One additional algal toxicity test under 850.5400 is outstanding: a test with the freshwater green alga, *Selenastrum capricornutum*. The other non-target aquatic plant toxicity requirement, floating freshwater aquatic macrophyte duckweed (*Lemna gibba*) – guideline 850.4400 - is satisfied. Studies on the rooted freshwater macrophyte rice (*Oryza sativa*) – 850.4225 and 850.4250 (2 tests on seedling emergence and vegetative vigor) -- have not been submitted.

8.2 Environmental fate and Transport

Triclosan [5-chloro-2-(2,4-dichlorophenoxy)phenol] is a white crystalline powder with low solubility in water (12 ppm). Triclosan is hydrolytically stable under abiotic and buffered conditions over the pH 4-9 range based on data from a preliminary test at 50°C. Photolytically, triclosan degrades rapidly under continuous irradiation from artificial light at 25°C in a pH 7 aqueous solution, with a calculated aqueous photolytic half-life of 41 minutes. One major transformation product has been identified, DCP (2,4-dichlorophenol), which was a maximum of 93.8-96.6% of the applied triclosan at 240 minutes post-treatment.

In soil, triclosan is expected to be immobile based on an estimated K_{oc} of 9,200. Triclosan is not expected to volatilize from soil (moist or dry) or water surfaces based on an estimated Henry's Law constant of 1.5×10^{-7} atm-m^3/mole. Triclosan exists partially in the dissociated form in the environment based on a pKa of 7.9, and anions do not generally adsorb more strongly to organic carbon and clay than their neutral counterparts. In aquatic environments, triclosan is expected to adsorb to suspended solids and sediments and may bioaccumulate (K_{ow} 4.76), posing a concern for aquatic organisms. There is a low to moderate potential for bioconcentration in aquatic organisms based on a BCF range of 2.7 to 90.

Hydrolysis is not expected to be an important environmental fate process due to the stability of triclosan in the presence of strong acids and bases. However, triclosan is susceptible to degradation via aqueous photolysis, with a half-life of <1 hour under abiotic conditions, and up to 10 days in lake water. An atmospheric half-life of 8 hours has also been estimated based on the reaction of triclosan with photochemically produced hydroxyl radicals. Additionally, triclosan may be susceptible to biodegradation based on the presence of methyl-triclosan following wastewater treatment.

Of the published literature studies on the occurrence of triclosan in waste water treatment plants, treatment plant efficiency, and open water measurements of triclosan, the majority suggest that aerobic biodegradation is one of the major and most efficient biodegradation pathways (70-80%) through which triclosan and its by-products are removed from the aquatic environment, with actual efficiencies ranging from 53-99% (Kanda *et al*., 2003) in activated sludge plants, and trickle down filtration ranging from 58-86% (McAvoy *et al*., 2002). Another pathway of removing triclosan from water in wastewater treatment plants is through the sorption of triclosan and associated by-products to particles and sludge (10-15%) because of the chemical's medium to high hydrophobicity. Benchtop fate testing of triclosan found that 1.5-4.5% was sorbed to activated sludge and 81-92% was biodegraded (Federle *et al*., 2002).

8.3 Environmental Exposure and Risk

The ecotoxicity test values (measurement endpoints) used in the acute and chronic risk quotients are derived from required studies. Examples of ecotoxicity values derived from short-term laboratory studies that assess acute effects are: (1) LC_{50} (fish and birds), (2) LD_{50} (birds and mammals), (3) EC_{50} (aquatic plants and aquatic invertebrates) and (4) EC_{25} (terrestrial plants). Examples of toxicity test effect levels derived from the results of long-term laboratory studies that assess chronic effects are: (1) LOAEC (birds, fish, and aquatic invertebrates), and (2) NOAEC (birds, fish and aquatic invertebrates). For birds and mammals, the NOAEC generally is used as the ecotoxicity test value in assessing chronic effects, although other values may be used when justified. However, the NOAEC is used if the measurement endpoint is production of offspring or survival.

Risk Presumptions for Terrestrial Animals

Risk Presumption	RQ	LOC
Birds and Wild Mammals		
Acute Risk	EEC[1]/LC50 or LD50/sqft[2] or LD50/day[3]	0.5
Acute Restricted Use	EEC/LC50 or LD50/sqft or LD50/day (or LD50 < 50 mg/kg)	0.2
Acute Endangered Species	EEC/LC50 or LD50/sqft or LD50/day	0.1
Chronic Risk	EEC/NOAEC	1

[1] abbreviation for Estimated Environmental Concentration (ppm) on avian/mammalian food items

[2] $\frac{mg/ft^2}{LD50 * wt. of bird}$ [3] $\frac{mg\ of\ toxicant\ consumed/day}{LD50 * wt. of bird}$

Risk Presumptions for Aquatic Animals

Risk Presumption	RQ	LOC
Acute Risk	EEC[1]/LC50 or EC50	0.5
Acute Restricted Use	EEC/LC50 or EC50	0.1
Acute Endangered Species	EEC/LC50 or EC50	0.05
Chronic Risk	EEC/MATC[2] or NOAEC	1

[1] EEC = (ppm or ppb) in water
[2] MATC = maximum allowable toxicant concentration

Risk Presumptions for Plants

Risk Presumption	RQ	LOC
Terrestrial and Semi-Aquatic Plants		
Acute Risk	EEC/EC25	1
Acute Endangered Species	EEC/EC05 or NOAEC	1
Aquatic Plants		
Acute Risk	EEC[1]/EC50	1
Acute Endangered Species	EEC/EC05 or NOAEC	1

1 EEC = (ppb/ppm) in water

Triclosan was found in approximately 36 US streams (Klopin et al., 2002), where effluent from activated sludge waste water treatment plants, trickle down filtration, and sewage overflow are thought to contribute to the occurrence of triclosan in open water. For this study, the U.S. Geological Survey surveyed a network of 139 streams across 30 states during 1999 and 2000. The selection of sampling sites was biased toward streams susceptible to contamination (i.e. downstream of intense urbanization and livestock production). The median concentration of triclosan was 140 ng/L and the maximum concentration detected was 2300 ng/L (Klopin *et al*., 2002). Discharge into U.S. surface waters has resulted in other researchers finding triclosan from the low ng/L levels to a maximum of 2.3 µg/L (U.S. EPA, 2007).

From the toxicity tables in section I above, the highest toxicity in an acceptable fish study was achieved in a study on the rainbow trout (*Oncorhynchus mykiss*). The LC_{50} value obtained in this study was 0.288 mg/L (MRID 439693-01). There were no acceptable acute toxicity studies for freshwater invertebrates or estuarine and marine organisms nor were there any acceptable chronic toxicity studies available for aquatic organisms. Therefore, risk to these species cannot be assessed. The highest toxicity in an acceptable aquatic plant toxicity study was achieved in a study on the bluegreen cyanobacteria (*Anabaena flos-aquae*). The EC_{50} value obtained in this study was 0.0012 mg/L and no NOEC was reported (MRID 444228-01).

For aquatic animals the LOC ranges from 0.05 for endangered species to 1 for chronic risks. Comparing the maximum concentration of triclosan found in US streams (280 ng/L or 0.00028 mg/L) to the highest toxicity found in a fish acute study (0.288 mg/L), an RQ of 0.00097 is obtained. This is less than all LOCs for aquatic animals and therefore the potential for triclosan to cause adverse effects on fish is not high.

For aquatic plants the LOC is 1. Comparing the maximum concentration of triclosan found in US streams (2.3 µg/L or 0.0023 mg/L) to the highest toxicity found in aquatic plants (0.0012 mg/L), an RQ of 1.92 is obtained. This is higher than the LOC and therefore the potential for acute risk to aquatic plants from triclosan exists. An evaluation of the effects of triclosan on natural freshwater algae located above and below a wastewater treatment plant indicates that a concentration of 0.00015 mg/L caused a significant reduction in *Chlamydomonas sp*. (RQ of 15.33). This is considered supplemental data, but points to the need for further research on shifts in algal communities, reductions in biomass, and effects on higher trophic levels (Wilson et al., 2003). A meta-analysis of literature, plus exposure modeling were used to conduct a probabilistic assessment of triclosan. This analysis sheds light on the difficulties associated with relating laboratory data to field effects and concludes that additional studies may be needed to refine scientific knowledge of metabolites and degradates, bioaccumulation factors, endocrine-related effects, and community level impacts. The exposure models used in this study (GREAT-ER and PhATE) have not been peer reviewed by the Agency (Capdevielle et al., 2008).

The triclosan degradation product methyl triclosan was studied by the National Oceanic and Atmospheric Administration's (NOAA) Hollings Marine Laboratory to assess it's toxicity to the estuarine organisms grass shrimp (*Paleamonetes pugio*), bioluminescent bacterium (*Vibrio fischeri*), and the phytoplankton *Dunaliella tertiolecta*. Methyl triclosan

is believed to be more persistent in the environment that its parent and have a higher potential to bioaccumulate since it is more lipophilic. However, mechanisms of transformation (and subsequent uptake) if by microbes in the gut or in the seawater, are unclear (DeLorenzo et al, 2007). Uncertainties exist as to the potential for triclosan degradates to contribute to acute and/or chronic impacts on aquatic organisms and ecosystems.

Risk Quotients – Based On Consumer Environmental Modeling

For a full discussion of the assumptions, approaches, and techniques used in the Agency's consumer environmental modeling effort for triclosan, the reader is referred to the Appendix of the Triclosan Ecological Hazard and Environmental Risk Assessment Chapter entitled "**Estimates of Exposures and Risks To Aquatic Organisms From Releases of Triclosan to Surface Water as a Result of Uses Under EPA's Jurisdiction**" and the environmental fate chapter for triclosan. These documents discuss in detail how the Agency performed this modeling effort. The conclusions of this consumer environmental modeling are summarized here.

Consumer Environmental Modeling Results: As outlined in the Appendix, the Agency performed screening level environmental modeling and concluded that, if ***all of the triclosan produced annually for antimicrobial uses is released to surface water as a result of consumer uses***, then:[1]

- **Aquatic Animals**: Estimated concentrations of triclosan in surface water do not exceed concentrations of concern for acute risk presumptions for aquatic animals. (*See Appendix, Table 2*.)

- **Aquatic Animals**: Estimated concentrations of triclosan in surface water do not exceed concentrations of concern for endangered species risk presumptions for aquatic animals. (*See Appendix, Table 3*.)

- **Aquatic Vascular Plants**: Estimated concentrations of triclosan in surface water do not exceed concentrations of concern for endangered species risk presumptions for aquatic vascular plants (e.g., duckweed, *Lemna gibba*). (*See Appendix, Table 4*.)

- **Aquatic Non-Vascular Plants**: Estimated concentrations of triclosan in surface water do exceed concentrations of concern for acute risk presumptions for species that represent non-vascular freshwater plants (i.e., algae). The number of days of exceedance of the concentration of concern is 1 day for blue-green algae, 5 days for

1 As discussed in the revised triclosan environmental fate chapter, only acute concentrations of concern were evaluated for aquatic organisms since acceptable chronic aquatic data are not available. However, considering the low probability of triclosan being released into household wastewater and surface waters, EPA also concludes that chronic aquatic risks are unlikely from consumer uses of triclosan-treated plastic and textile items.

green algae, and 57 days for *Chlamydomonas sp.* (*See Appendix, Table 4*.)

Adjustments to Consumer Environmental Modeling Results: As indicated above, the Agency performed this environmental modeling in an effort to estimate:

(1) Concentrations of triclosan in surface water [from antimicrobial uses of triclosan (e.g., triclosan-treated plastic and textile items in households) to which aquatic organisms may be exposed as a result of potential releases of triclosan from these consumer uses; and

(2) Number of days per year that the concentration of triclosan in surface water exceeds the concentration of concern for aquatic organisms.

A critical assumption in this screening level, modeling analysis was that ***all of the triclosan produced annually for antimicrobial uses is released to surface water as a result of consumer uses***. That is, 100 % of all triclosan produced annually is released into household wastewater during washing and rinsing of products treated with triclosan as a materials preservative or as a functional component.

However, in an effort to check this 100 % release value used above for consumer scenarios, EPA reexamined available textile leaching data and determined that the 100 % assumption (for release of triclosan into household wastewater) is highly unlikely. Specifically, available data for textile leaching of triclosan indicate that triclosan leaches from a variety of fabrics in the range of 0.00 % to 0.55 %.[2]

8.4 Endangered Species Consideration

Section 7 of the Endangered Species Act, 16 U.S.C. Section 1536(a)(2), requires all federal agencies to consult with the National Marine Fisheries Service (NMFS) for marine and anadromous listed species, or the United States Fish and Wildlife Services (FWS) for listed wildlife and freshwater organisms, if they are proposing an "action" that may affect listed species or their designated habitat. Each federal agency is required under the Act to insure that any action they authorize, fund, or carry out is not likely to jeopardize the continued existence of a listed species or result in the destruction or adverse modification of designated critical habitat. To jeopardize the continued existence of a listed species means "to engage in an action that reasonably would be expected, directly or indirectly, to reduce appreciably the likelihood of both the survival and recovery of a listed species in the wild by reducing the reproduction, numbers, or distribution of the species." 50 CFR. § 402.02.

To facilitate compliance with the requirements of the Endangered Species Act subsection (a)(2) the Environmental Protection Agency, Office of Pesticide Programs has established procedures to evaluate whether a proposed registration action may directly or indirectly reduce appreciably the likelihood of both the survival and recovery of a listed species in the wild by reducing the reproduction, numbers, or distribution of any listed species (U.S. EPA

2 EPA assumes that leaching values for plastic are of the same magnitude as for textile products. Note that the Agency used the 0.55 % leaching value in its evaluation for children who may mouth (incidental oral ingestion) plastic items (e.g., toys).

2004). After the Agency's screening-level risk assessment is performed, if any of the Agency's Listed Species LOC Criteria are exceeded for either direct or indirect effects, a determination is made to identify if any listed or candidate species may co-occur in the area of the proposed pesticide use. If determined that listed or candidate species may be present in the proposed use areas, further biological assessment is undertaken. The extent to which listed species may be at risk then determines the need for the development of a more comprehensive consultation package as required by the Endangered Species Act.

For certain use categories, the Agency assumes there will be minimal environmental exposure, and only a minimal toxicity data set is required (Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs U.S. Environmental Protection Agency - Endangered and Threatened Species Effects Determinations, 1/23/04, Appendix A, Section IIB, pg.81). Chemicals in these categories therefore do not undergo a full screening-level risk assessment, and are considered to fall under a no effect determination.

A preliminary analysis indicates that there is a potential for triclosan use to overlap with listed species and that a more refined assessment is warranted, to include direct, indirect and habitat effects.[3] The more refined assessment should involve clear delineation of the action area associated with proposed use of triclosan and best available information on the temporal and spatial co-location of listed species with respect to the action area. This analysis has not been conducted for this assessment. **An endangered species effect determination will not be made at this time.**

9.0 INCIDENT REPORT ASSESSMENT

The Following databases were consulted for poisoning incidence data on OPP:

1) Office of Pesticides Programs (OPP) Incident Data System (IDS)
2) Poison Control Centers
3) California Department of Pesticide Regulations
4) National Pesticide Telecommunications Network (NTPT)
5) Published Scientific Literature on Incidences

9.1 OPP's Incident Data System (IDS)

There were no reported incidents from examination of this database.

9.2 Poison Control Center

There were no reported incidents from examination of this database

3 The Agency is making this statement because triclosan and triclosan transformation products are being detected in various environmental components (see triclosan environmental fate chapter).

9.3 California Data- 1982-through 2003.

There were no reported incidents from examination of this database

9.4 National Pesticide Telecommunications Network (NPTN)

There were no reported incidents from examination of this database

9.5 Hazardous Substances Data Bank (HSDB)

There were no reported incidents from examination of this database.

10.0 References

Ecotox REFERENCES

41008910. Terrell, Y. 1985. Acute Oral Toxicity Study of Issue Plus II; ID No. 88-472; Prepared by American Standards Biosciences Corp. for Diversey Wyandotte Corporation, Wyandotte, Michigan.

41008911. Terrell, Y. 1988. Avian Dietary Quaily (Litmus Test) of Issue Plus in Bobwhite Quail; Project No. 88-471; Prepared by American Standard Biosciences Corp. for Diversey Wyandotte Corporation, Wyandotte, Michigan.

41008912. Terrell, Y. 1988. The Acute Toxicity Bioassay of Issue Plus on Rainbow Trout; Project No. 88-474; Prepared by American Standard Biosciences Corp. for Diversey Wyandotte Corporation, Wyandotte, Michigan.

41008913. Terrell, Y. 1988. The Acute Toxicity Bioassay of Issue Plus on Bluegill Sunfish; Project No. 88-473; Prepared by American Standard Biosciences Corp. for Diversey Wyandotte Corporation, Wyandotte, Michigan.

41008914. Terrell, Y. 1988. Acute Toxicity of Issue Plus on *Daphnia magna*; Project No. 88-475; Prepared by American Standard Biosciences Corp. for Diversey Wyandotte Corporation, Wyandotte, Michigan.

42322101. Boettcher, J. 1990. Report on the Acute Toxicity (96h) of FAT 80, 023/Q to Zebrafish. Test No. G 069 04. Prepared by Ciba-Geigy, Ltd., D&C Product Ecotoxicology, Basel, Switzerland. Submitted by Ciba-Giegy Corporation, Greensboro, North Carolina.

42322102. Wuethrich, V. 1990. 48-Hour Acute Toxicity of FAT 80, 023/Q to *Daphnia magna* (OECD-Immobilization Test). Project No. 262923. Prepared by RCC Umweltchemie AG, Itingen, Switzerland. Submitted by Ciba-Giegy Corporation, Greensboro, North Carolina.

43022602. Pedersen, C.A. and B.R. Helsten. 1993. Triclosan (IRGASAN DP300®): 14-Day Acute Oral LD_{50} Study in Bobwhite Quail. Study performed by Bio-Life Associates, Ltd., Neillsville, Wisconsin. Laboratory Project No. 102-024-03. Submitted by CIBA-GEIGY Corporation, Greensboro, North Carolina.

43022603. Pedersen, C.A. and B.R. Helsten. 1993. Triclosan (IRGASAN DP300®): 14-Day Acute Oral LD_{50} Study in Mallard Ducks. Study performed by Bio-Life Associates, Ltd., Neillsville, Wisconsin. Laboratory Project No. 102-023-04. Submitted by CIBA-GEIGY Corporation, Greensboro, North Carolina.

43022604. Pedersen, C.A. and B.R. Helsten. 1993. Triclosan (IRGASAN DP300®): 8-Day Acute Dietary LC_{50} Study in Bobwhite Quail. Study performed by Bio-Life Associates, Ltd., Neillsville, Wisconsin. Laboratory Project No. 102-022-01. Submitted by CIBA-GEIGY Corporation, Greensboro, North Carolina.

43046001. Bowman, J.H. 1990. Acute Toxicity of D1063.01 (Triclosan: Irgasan DP300) to Fathead Minnow (*Pimephales promelas*). Laboratory Project ID No. 38655. Prepared by Analytical Bio-Chemistry Laboratories, Inc, Columbia, Missouri. Submitted jointly by Proctor and Gamble Company and Ciba-Geigy Corp.

43046002. Forbis, A.D. and J.G. Muckerman. 1990. Acute Toxicity of D1063.01 (Triclosan: Irgasan DP300) to *Daphnia magna*. Laboratory Project ID No. 38656. Prepared by Analytical Bio-Chemistry Laboratories, Inc, Columbia, Missouri. Submitted jointly by Proctor and Gamble Company and Ciba-Geigy Corp.

43740701. Wuethrich, V. 1990. Influence of FAT 80023/Q (Irgasan DP300) on Reproduction of *Daphnia magna*. Project No. 262934. Prepared by RCC Umweltchemie AG, Itingen, Switzerland. Submitted by Ciba-Giegy AG, Basel, Switzerland.

43969301. Sword, M.C. 1996. Static Acute Toxicity of Triclosan to Rainbow Trout. Study performed by ABC Laboratories, Inc., Columbia, Missouri. Laboratory Report No. 42997. Sponsored by CIBA Chemical Division, Greensboro, North Carolina.

44422801. Staveley, J.P. and T.L. Williams. 1997. Effects of Triclosan on the Growth and Reproduction of Aquatic Plants. Study performed by Carolina Ecotox, Inc., Durham, North Carolina. Laboratory Report ID: 21-02-1. Sponsored by Ciba-Geigy Corporation, Greensboro, North Carolina.

Federle, T.W., Kaiser, S.K., and Nuck, B.A. 2002. Fate and Effects of Triclosan in Activated Sludge. Environmental Toxicology and Chemistry/SETAC. 21(7): 1330-7.

Kanda, R., Griffin, P., and James, H.A., *et al*. 2003. Pharmaceutical and Personal Care Products in Sewage Treatment Works. Journal of Environmental Monitoring. 5(5): 823-30.

Klopin, D.W., Furlong, E.T., Meyer, M.T., *et al*. 2002. Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000: A National Reconnaissance. Environmental Science and Technology. 36(6): 1202-11.

McAvoy, D.C., Schatowitz, B., Martin, J., *et al*. 2002. Measurement Of Triclosan In Wastewater Treatment Systems. Environmental Toxicology and Chemistry. 21 (7): 1323-9.

Dietary REFERENCES

FDA, 2003, A Guidance For Industry: Preparations of food Contact Notifications and Food Additive Petitions for Food Contact Substances, Chemistry Recommendations. Final Guidance, April 2003. http://www.cfsan.fda.gov

FDA, 2003. Sanitizing Solutions: Chemistry Guidance for Food Additive Petitions, January 2003. Http://www.cfsan.fda.gov

An AD Memo by Tim McMahon to Jess Rowland, Executive Secretary for Agency's HIARC Committee, 1998.

Calculations reported by Bob Quick in an AD Memo by Bob Quick to Bob Brennis, 1998.

Environmental Fate REFERENCES

420279-08 Pointurier, R. 1990. Irgasan® DP 300 – Report on Hydrolysis as a Function of pH. Unpublished study performed and submitted by Ciba-Geigy Ltd., Basel, Switzerland.

430226-08 Spare, W. 1993. Aqueous Photolysis of Triclosan. Agrisearch Project No.: 12208. Unpublished study performed by Agrisearch Inc., Frederick, MD; and submitted by Ciba-Geigy Corporation, Greensboro, NC.

---------- The Estimation Programs Interface (EPI) Suite. Windows based suite of physical/chemical properties and environmental estimation models developed by the US EPA's Office of Prevention, Pesticides and Toxic substances (OPPTS) and Syracuse Research Institute (SRC). Physical properties of Triclosan. EPI Suite Summary (v3.12). http://www.epa.gov/opptintr/exposure/docs/EPISuitedl.htm

---------- Hazard Substances Data Bank (HSDB). A Database of the National Library of Medicine's TOXNET System. Triclosan: Environmental Fate and Exposure. http://toxnet.nlm.nih.gov

Agüera, A., Fernandez-Alba, A.R., Luis, P., et al. 2003. Evaluation Of Triclosan And Biphenylol In Marine Sediments And Urban Wastewaters By Pressurized Liquid Extraction And Solid Phase Extraction Followed By Gas Chromatography Mass Spectrometry And Liquid Chromatography Mass Spectrometry. Analytica Chimica Acta 480: 193-205.

Anderson, P.D., D'Aco, V.J., Shanahan, P., et al. 2004. Screening Analysis of Human Pharmaceutical Compounds in U.S. Surface Waters. Environmental Science and Technology. 38(3): 838-49.

Bendz, D., Paxeus, N.A., Ginn, .R., et al. 2005. Occurrence And Fate Of Pharmaceutically Active Compounds In The Environment, A Case Study: Hoje River In Sweden. Journal of Hazardous Materials. 122: 195-204.

Bester, K. 2003. Triclosan In A Sewage Treatment Process--Balances And Monitoring Data. Water Research. 37 (16): 3891-6.

Bester, K. 2005. Fate of Triclosan and Triclosan-Methyl in Sewage Treatment Plants and Surface Waters. Archives of Environmental Contamination and Toxicology. 49 (1): 9-17.

Boyd, G.R., Palmeri, J.M., Zhang, S., et al. 2004. Pharmaceuticals And Personal Care Products (PPCPs) And Endocrine Disrupting Chemicals (EDCs) In Stormwater Canals And Bayou St. John In New Orleans, Louisiana, USA. Science of the Total Environment. 333 : 137-48.

Boyd, G.R., Reemtsma, H., Grimm, D.A., et al. 2003. Pharmaceuticals And Personal Care Products (PPCPs) In Surface And Treated Waters Of Louisiana, USA And Ontario, Canada. Science of the Total Environment (Netherlands). 311 (1-3): 135-49.

Federle, T.W., Kaiser, S.K., and Nuck, B.A. 2002. Fate and Effects of Triclosan in Activated Sludge. Environmental Toxicology and Chemistry/SETAC. 21(7): 1330-7.

Federle, T.W. and E.L. Schwab. 2003. Triclosan Biodegradation in Wastewater Treatment Plant Effluent Diluted in Various River Wastes. Abstr. Gen. Meet Am Soc. Microbiol 103. p. 0-017.

Gatidou, G., Thomaidis, N.S., Stasinakis, A.S., et al. 2007. Simultaneous Determination Of The Endocrine Disrupting Compounds Nonylphenol, Nonylphenol Ethoxylates, Triclosan And Bisphenol A In Wastewater And Sewage Sludge By Gas Chromatography-Mass Spectrometry. Journal of Chromatography A. 1138: 32-41.

Gomez, M.J., Martinez Bueno, M.J., Lacorte, S., et al. 2007. Pilot Survey Monitoring Pharmaceuticals And Related Compounds In A Sewage Treatment Plant Located On The Mediterranean Coast. Chemosphere. 66 (6): 993-1002.

Hua, W., Bennett, E.R., Letcher, R.J. 2005. Triclosan In Waste And Surface Waters From The Upper Detroit River By Liquid Chromatography-Electrospray-Tandem Quadrupole Mass Spectrometry. Environment International. 31: 621-30.

Kanda, R., Griffin, P., and James, H.A., et al. 2003. Pharmaceutical and Personal Care Products in Sewage Treatment Works. Journal of Environmental Monitoring. 5(5): 823-30.

Kolpin, D.W., Furlong, E.T., Meyer, M.T., et al. 2002. Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams, 1999-2000: A National Reconnaissance. Environmental Science and Technology. 36(6): 1202-11.

Lee, H., and Peart, T.E. 2002. Organic Contaminants in Canadian Municipal Sewage Sludge. Part I. Toxic or Endocrine-disrupting Phenolic Compounds. Water Quality Research Journal of Canada. 37(4): 681-696.

Lee, H., Sarafin, K., and Peart, T.E., et al. 2003. Acidic Pharmaceuticals in Sewage: Methodology, Stability Test, Occurrence, and Removal from Ontario Samples. Water Quality Research Journal of Canada. 38(4): 667-682.

Lee, H., Peart, T.E., and Svoboda, M.L. 2005. Determination of Endocrine-Disrupting Phenols, Acidic Pharmaceuticals, and Personal-care Products in Sewage by Solid-phase Extraction and Gas Chromatography-Mass Spectrometry. Journal of Chromatography. 1094(1-2): 122-9.

Lindstrom, A., Buerge, I.J., Poiger, T., et al. 2002. Occurrence and environmental behavior of the bactericide triclosan and its methyl derivative in surface waters and in wastewater. Environmental Science Technology. 36: 2322-2329. Comment in Environmental Science Technolology. 36 (11): 228A-230A.

Loraine, G.A., Pettigrove, M.E. 2006. Seasonal Variations In Concentrations Of Pharmaceuticals And Personal Care Products In Drinking Water And Reclaimed Wastewater In Southern California. Environmental Science and Technology. 40(3): 687-95.

McAvoy, D.C., Schatowitz, B., Martin, J., et al. 2002. Measurement Of Triclosan In Wastewater Treatment Systems. Environmental Toxicology and Chemistry. 21 (7): 1323-9.

Mezcua, M., Gomez, M.J., Ferrer, I., et al. 2004. Evidence of 2,7/2,8-Dibenzodichloro-*p*-dioxin As A Photodegradation Product Of Triclosan In Water And Wastewater Samples. Analytica Chimica Acta. 524 (1-2): 241-247.

Morales, S., Canosa, P., and Rodriguez, I., et al. 2005. Microwave Assisted Extraction Followed by Gas Chromatography with Tandem Mass Spectrometry for the Determination of Triclosan and Two Related Chlorophenols in Sludge and Sediments. Journal of Chromatography. 1082: 128-35.

Nakada, N., Toshikatsu, T., and Hiroyuki, S., et al. 2006. Pharmaceutical Chemicals and Endocrine Disrupters in Municipal Wastewater in Tokyo and their Removal during Activated Sludge Treatment. Water Research. 40(17): 3297-303.

Paxeus, N., and Gryaab, K. 2004. Removal Of Selected Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Gemfibrozil, Carbamazepine, Beta-Blockers, Trimethoprim And Triclosan In Conventional Wastewater Treatment Plants In Five EU Countries And Their Discharge To The Aquatic Environment. Water Science and Technology. 50 (5): 253-60.

Sabaliunas, D., Webb, S.F., Hauk, A., et al. 2003. Environmental Fate Of Triclosan In The River Aire Basin, UK. Water Research (England). 37: 3145-54.

Samsoe-Petersen L.,Winther-Nielsen M., Madsen T. Fate and Effects of Triclosan. Environment Project No. 861. Copenhagen: Danish Environmental Protection Agency; 2003.

Shiraishi, H., Otsuki, A., and Fuwa, K. 1985. Identification Of Extractable Organic Chemicals In Sewage Effluent By Gas Chromatography/Mass Spectrometry. Biomedical Mass Spectrometry. 12 (2): 86-94.

Singer, H., Muller, S., Tixier, C., et al. 2002. Triclosan: Occurrence And Fate Of A Widely Used Biocide In The Aquatic Environment: Field Measurements In Wastewater Treatment Plants, Surface Waters, And Lake Sediments. Environmental Science and Technology. 36(23): 4998-5004.

Thomas, P.M., and Foster, G.D. 2004. Determination of Nonsteroidal Anti-inflammatory Drugs, Caffeine, and Triclosan in Wastewater by Gas Chromatography-Mass Spectrometry.2004. Journal of Environmental Science and Health. Part A, Toxic/Hazardous Substances & Environmental Engineering. 39(8): 1969-78.

Thomas, P.M., and Foster, G.D. 2005. Tracking Acidic Pharmaceuticals, Caffeine, And Triclosan Through The Wastewater Treatment Process. Environmental Toxicology and Chemistry. 24 (1): 25-30.

Thompson, A., Griffin, P., and Stuetz, R., et al. 2005. The Fate and Removal of Triclosan during Wastewater Treatment. Water Environment Research. 77(1):63-67.

Waltman, E.L., Venables, B.J., and Waller, W.T. 2006. Triclosan In A North Texas Wastewater Treatment Plant And The Influent And Effluent Of An Experimental Constructed Wetland. Environmental Toxicology and Chemistry. 25 (2): 367-72.

Wind, T., Werner, U., Jacob, M., et al. 2004. Environmental Concentrations Of Boron, LAS, EDTA, NTA and Triclosan Simulated with GREAT-ER in the river Itter. Chemosphere (England). 54: 1135-44.

Ying, G. and Kookana, R.S. 2007. Triclosan In Wastewaters And Biosolids From Australian Wastewater Treatment Plants. Environmental International. 33 (2): 199-205.

Toxicology REFERENCES

MRID 34335: Stierlin, H. (1968) “Percutaneous Absorption of GP 41 353 in the Rat and the Rabbit.” (Unpublished study; prepared by J.R. Geigy, AG, submitted by Ciba-Geigy Corp., Greens- boro, N.C.; CDL:000506-M)

MRID 43429: Stenger, E.G.; Scharer, (1963) “Local Effects on Rabbit's Eye.” (Unpublished study; prepared by J.R. Geigy, AG, Switzerland, submitted by Ciba-Geigy Corp., Greensboro, N.C.; CDL:108210-J)

MRID 96102: Burther, B.R.; Gordon, D.E. (1973) “Report to Ciba-Geigy Corporation: 90-day Subacute Oral Toxicity Study with Irgasan DP-300 in Beagle Dogs: IBT No. C1435.” (Unpublished study; prepared by Industrial Bio-Test Laboratories, Inc., submitted by Ciba-Geigy Corp., Greensboro, N.C.; CDL:008400-C)

MRID 100178/130187: Schoenig, G. (1967) “Report to Geigy Chemical Company: Acute Dermal Toxicity Study on CH 3565: IBT No. A5460.” (Unpublished study; prepared by

Industrial Bio-Test Laboratories, Inc., submitted by Ciba-Geigy Corp., Greensboro, N.C.; CDL:000503-D)

MRID 133545: Goldsmith, L. (1983) 90-Day Oral Toxicity Study in Rats with Fat 80'023/H: LBI Project No. 22188. Final Report. (Unpublished study received Dec. 23, 1983 under 100-502; submitted by Ciba-Geigy Corp.)

MRID 251773: Drake, J.C. & Buxtorf, A. (1976) 1 Year Oral Toxicity Study in Baboons with Compound FAT 80 023/A. Geigy Pharmaceuticals, Toxicology Department.

MRID 40623701: Morseth, S.L. (1988) "Two-Generation Reproduction Study in Rats with FAT 80'02390" Hazleton Laboratories America, Inc.

MRID 42027906: Study 1 - Yau, E.T. and Green, J.D. (1986) Fat 80'023 2 Year Oral Administration to Rats; Study 2 – Parkes, D.G. (1986) Determination of Fat 80'023 in Blood and Tissue Samples Taken During a Two-Year Chronic Oral Toxicity/Oncogenicity Study in Albino Rats (24-month Final Report). Ciba-Geigy Corporation.

MRID 42306902, 43310501: Duchosal F. and Ph. Thevenaz (1990) "4-Hour Acute Inhalation Toxicity Study with FAT 80'023/Q in Rats" Ciba-Geigy Ltd.

MRID 42306903: Sachsse, K.; Ullman, L. (1975) Skin Irritation in the Rabbits after Single Application of FAT 80'023/A. Unpublished Study Conducted by Ciba Geigy Ltd., Basel Switzerland. Project No. Siss 4719. Submitted to EPA by Chemical Division of Ciba Geigy Corp. (9/11/75).

MRID 43022605**:** Trutter, Janet A. (1993) "13-Week Subchronic Oral Toxicity Study of Triclosan in CD-1® Mice." Hazleton Washington, Inc.

MRID 43206501: Wnorowski, Gary. (1994) "Acute Toxicity Limit Test for Triclosan (Irgasan® DP 300) Product Safety Labs.

MRID 43206502: Wnorowski, G. (1994) Dermal Sensitization Test-Buehler Method for Triclosan (Irgasan® DP 300) Lot No. 5.2.0211.0. Product Safety Labs; Study No. 2635. Submitted to EPA by Ciba-Geigy Corp. Unpublished.

MRID 43328001: Trimmer, Gary W. (1994) "90-Day Subchronic Dermal Toxicity Study in the Rat with Satellite Group with Irgasan DP300 (MRD-92-399)" Exxon Biomedical Sciences, Inc.

MRID 43533301: Jones, E., Wilson, L.A. (1988) "Ames Metabolic Activation Test to Address the Potential Mutagenic Effect of Triclosan (Irgasan DP 300)" Huntingdon Research Center, Ltd. Cambridgeshire, England.

MRID 43740801: Heidemann, A. (1990) "Chromosome Aberration Assay in Chinese Hamster V79 Cells In Vitro with FAT 80'023/Q (Irgasan® DP 300); Cytotest Cell Research GMBH & Co. KG, Federal Republic of Germany; Study No. 179100. Unpublished.
MRID 43740802: Volkner, W. (1991) "Chromosome Aberration Assay in Bone Marrow Cells of the Rat with FAT 80'023/Q (Irgasan® DP300); Cytotest Cell Research GMBH & Co. KG, Federal Republic of Germany; Study No. 218305. Unpublished.

MRID 43817502, 43817503: Denning, H.J., Sliwa, S., and Willson, G.A. (1992) "Triclosan: Effects on Pregnancy and Post-Natal Development in Rats: Volume 1, Volume 2 and Appendices 1-17" Unilever Research, Colworth/ Welwyn Lab.

MRID 43820401, 43022607: Schroeder, R.E. et al. (1992) "A Segment II Teratology Study in Rabbits with Irgacare MP" Bio/dynamics Inc.

MRID 44389701: Eldrige, S. (1993) Cell Proliferation in Rodent Liver: (Triclosan): Final Report: Lab Project Number: 142. Unpublished study prepared by Pathology Associates, Inc. 14 p.

MRID 44389702: Molitor, E., Persohn, E., Thomas, H. "The Effect of FAT 80'023/Q (Irgasan DP 300) on Selected Biochemical Liver Parameters Following Subchronic Dietary Administration to Male and Female Mice. Ciba-Geigy Limited, Switzerland, Report CB 91/18, May 22, 1992.

MRID 44389703: Molitor, E.; Persohn, E. (1993) The Effects of FAT 80'023/Q (Irgasan DP 300) on Selected Biochemical and Morphological Liver Parameters Following Dietary Administration to Male Rats: Lab Project Number: CB 92/28. Unpublished study prepared by Ciba-Geigy Ltd. 70p.

MRID 44389704: Henderson, L.M., et al. (1988) An Assessment of the Mutagenic Potential of Triclosan Using the Mouse Lymphoma TK Locus Assay. Huntingdon Research Center Ltd., Huntingdon, Cambridgeshire, PE18 6ES, England. Study No. ULR 216/88644. Unpublished.

MRID 44389705: 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. Unpublished.

MRID 44389706: 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. Unpublished.

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

MRID 44389708: 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. Unpublished.

MRID 44389710: 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. Unpublished.

MRID 44874001, 44751101: Chambers, P.R. (1999) "Potential Tumorigenic and Chronic Toxicity Effects in Prolonged Dietary Administration to Hamsters." Huntingdon Life Sciences Ltd., Huntingdon, England. CBG 756/972896.

MRID 45307501, 45307502: Van Dijk, Dr. A. (1994) "^{14}C- Triclosan: Absorption, Distribution, Metabolism, and Elimination after Single/Repeated Oral and Intravenous Administration to Hamsters." RCC Umweltchemie AG. RCC Project No. 351707.

MRID 45307503: Van Dijk, Dr. A. (1995) "^{14}C- Triclosan: Absorption, Distribution, Metabolism, and Elimination after Single/Repeated Oral and Intravenous Administration to Mice." RCC Umweltchemie AG. RCC Project No. 337781.

Tox Record No. 001955, 001956 (1968)

Tox Record No. 001968 (1977)

Allmyr, M.; McLachlan, MS; Sandborgh-Englund, G.; and Adolfsson-Erici, M. 2006. Determination of Triclosan as Its Pentafluorobenzoyl Ester in Human Plasma and Milk Using Electron Capture Negative Ionization Mass Spectrometry. Anal. Chem. 2006, 78, 6542-6546.

Capen, C. Toxic Responses of the Endocrine System. In: Casarett and Doull's Toxicology: The Basic Science of Poisons, 5th ed., Curtis D. Klaassen, Ph.D., editor. McGraw-Hill.

Crofton, KM; Paul, KB; DeVito, PB; Hedgea, JH. 2007. Short-term in vivo exposure to the water contaminant triclosan: Evidence for disruption of thyroxine. Environmental Toxicology and Pharmacology 24: 194–197.

Flaherty, C.M. and S.I. Dodson. (2005). Effects of pharmaceuticals on Daphnia survival, growth, reproduction. MRID to be assigned. Chemosphere. 61: 200-207.

Hanioka, N. et. al. (1996) effect of 2,4,4'-Trichloro-2'-hydroxyphenyl Ether on Cytochrome P450 Enzymes in the Rat Liver. MRID to be added. Chemosphere. 34: 719-730.

Hovander, L. et. al. (2001). Identification of Hydroxylation PCB Metabolites and Other Phenolic Halogenated Pollutants in Human Blood Plasma. MRID to be added. Environmental Contamination and Toxicology. 42: 105-117.

Ishibashi, H.; Matsumura, N.; Hirano, M.; Matsuoka, M.; Shiratsuchi, H.; Ishibashi, Y.; Takao, Y.; and Arizono, K. 2004. Effects of triclosan on the early life stages and reproduction of medaka Oryzias latipes and induction of hepatic vitellogenin. Aquatic Toxicology 67:167–179

Matsumura, N.; Ishibashi, H.; Hirano, M.; Nagao, Watanabe N; Shiratsuchi, H; Kai, T; Nishimura, T.; Kashiwagi, A.. and Arizono, K. 2005. Effects of nonylphenol and triclosan on production of plasma vitellogenin and testosterone in male South African clawed frogs (Xenopus laevis).Biol. Pharm. Bull. 28: 1748–1751.

Palenske, N.M., Dzialowski, E.M (2005). Effects of the Environmental Contaminant Triclosan on the Physiology of Developing Xenopus Laevis Tadpoles. Integrative and Comparative Biology. 45(6): 1175. Published.

Tamura,H., Y. Ishimoto., T. Fujikawa et al. (2006). Use of Structural basis for androgen receptor agonists and Antagonists: Interaction of SPEED 98-listed chemicals and Related compounds with the androgen receptor based on an In vitro reporter gene assay and 3D-QSAR. MRID to be Assigned. Bioorganic & Medicinal Chemistry. 14:7160-7174.

Veldhoen, N; Skirrow, RC; Osachoff, H.; Wigmore, H; Clapson, DJ; Gunderson, MP; Aggelen, GV; Helbing, CC. (2006). The bactericidal agent triclosan modulates thyroid hormone-associated gene expression and disrupts postembryonic anuran development. Aquatic Toxicology 80: 217–227.

U.S. EPA 2008). T. E. Stoker and W. Setzer. The Endocrine Disrupting Effects of Triclosan, a common pharmaceutical and personal care product: Alteration of the Thyroid Axis Following a Peri-juvenile Exposure in the Male Wistar Rat. EPA/600/X-08/010.
Broker, P.C., Gray, V.M., Howell, A. (1988) "Analysis of Metaphase Chromosomes Obtained from CHO Cells Cultured *in vitro* and Treated with Triclosan." Huntingdon Research Center, Ltd. ULR 214/88731; Unilever Test #: KC880171. Unpublished.

Eldrige, S. (1995) Cell Proliferation in Rodent Liver. Study conducted by Pathology Associates, Inc. Submitted to EPA (no MRID). Unpublished.

San Sebastian, J.R., Morgan, J.M. (1993) "Rat Hepatocyte Primary Culture/DNA Repair Test on 39317" Pharmakon Research International, Inc. Pharmakon Study #: PH311-CP-001-93. Unpublished.

See, Norman A. (1996) Review and Evaluation of Pharmacology and Toxicology Data Division of Dermatologic and Dental Drug Products (HFD-540) Food and Drug Administration.

Human Exposure REFERENCES

Calafat AM, Ye X, Wong LY, Reidy JA, and Needham LL. 2007. Urinary Concentrations of Triclosan in the U.S. Population: 2003-2004. Environmental Health Perspectives. Dated December 7, 2007. Available online at http://dx.doi.org/

Cauosa (2007). Determination of Parabens and Triclosan in Indoor Dust Using Matrix Solid-Phase Dispersion and Gas Chromatography with Tandem Mass Spectrometry. Anal. Chem. 2007, 79, 1675-1681.

Cohen J. 2008. Computations of Human Triclosan Dose Based On NHANES Urine Concentrations. Memorandum from Dr. Jonathan Cohen, ICF International to Tim Leighton, David Miller, Philip Villaneuva, USEPA, dated March 6, 2008. Contract EP-W-06-091, WA 0-02, TAF CM 19.

Dayan AD. 2007. Risk assessment of triclosan [Irgasan] in human breast milk. Food and Chemical Toxicology 45 (2007) 125-129.

DOE. 1997. Energy Information Administration: Profile of Commercial Buildings in 1995. http://www.eia.doe.gov/emeu/cbecs/char95/profile.html

Freeman, N , Jimenez M, Reed KJ,Gurunathan S, Edwards RD, Roy A, Adgate JL, Pellizzari ED, Quackenboss J, Sexton K, Lioy PJ, 2001. Quantitative analysis of chilren's microactivity patterns: The Minnesota Children's Pesticide Exposure Study. Journal of Exposure Analysis and Environmental Epidemiology. 11(6): 501-509.

Geigy. 1981. *Geigy Scientific Tables, Volume 1. Units of measurement, body fluids, composition of the body, nutrition.* Eighth edition. (Edited by C. Lentner). CIBA-GEIGY.

Mage D.T., Allen R., Gondy G., Smith W., Barr D.B., Needham L.L. 2004. Estimating Pesticide Dose from Pesticide Exposure Data by Creatinine Correction in the Third National Health and Nutrition Examination Survey (NHANES-III). *J Exposure Anal Environ Epidemiol* 14:457-465.

Mage D.T., Allen, R.H., Kodali, A. 2007. Creatinine corrections for estimating children's and adult's pesticide intake doses in equilibrium with urinary pesticide and creatinine concentrations. *J Exposure Sci Environ Epidemiol* 1-9.

Sandborgh-Englund G, Adolfsson-Erici M, Odham G, and Ekstrand J. 2006. Pharmacokinetics of Triclosan Following Oral Ingestion in Humans. Journal of Toxicology and Environmental Health, Part A, 69:1861-1873, 2006.

Schafer, K.S,, Reeves, M., Spitzer, S., Kegley, S. E. 2004. Chemical Trespass: Pesticides in Our Bodies and Corporate Accountability. Pesticide Action Network North America. May 2004.

USEPA. 1996. Office of Research and Development, Descriptive Statistics Tables from a Detailed Analysis of the National Human Activity Pattern (NHAPS) Data; EPA/600/R-96/148, July 1996. Data Collection Period October 1992 - September 1994 .

USEPA. 1997. Exposure Factors Handbook. Volume I-II. Office of Research and Development. Washington, D.C. EPA/600/P-95/002Fa. August 1997.

USEPA. 1998. PHED Surrogate Exposure Guide. Estimates of Worker Exposure from the Pesticide Handler Exposure Database Version 1.1. Washington, DC: U.S. Environmental Protection Agency.

USEPA. 1999. Evaluation of Chemical Manufacturers Association Antimicrobial Exposure Assessment Study (Amended on 8 December 1992). Memorandum from Siroos Mostaghimi, PH.D., USEPA to Julie Fairfax, USEPA. Dated November, 4 1999. DP Barcode D247642.

USEPA. 2000. Residential SOPs. EPA Office of Pesticide Programs, Human Health Effects Division. Dated April 5, 2000.

USEPA. 2001. HED Science Advisory Council for Exposure. Policy Update, November 12. Recommended Revisions to the Standard Operating Procedures (SOPs) for Residential Exposure Assessment, February 22, 2001.

USEPA. 2002. CHILD-SPECIFIC EXPOSURE FACTORS HANDBOOK (INTERIM REPORT). USEPA EPA-600-P-00-002B. 01 Sep 2002. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington Office, Washington, DC, 448.

USEPA. 2005. Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants. Risk Assessment Forum, U.S. Environmental Protection Agency, November 2005. EPA/630/P-03/003F.

USEPA. 2007. 5-Chloro-2-(2,4-dichlorophenoxy)phenol (triclosan): Toxicology Chapter for the Reregistration Eligibility Decision (RED) document.

Product Chemistry References

42027901 LoMenzo, J. (1991) Irgasan DP 300: Product Identity and Composition. Unpublished study prepared by Ciba-Geigy Corp.

42027902 Basingthwaite, J. (1983) Irgasan DP 300: Batch Analysis and Analytical Methodology. Unpublished study prepared by Ciba-Geigy Ag.

42027904 Vogel, A. (1990) Irgasan 300 DP: Report on Melting Point/Melting Range. Unpublished study prepared by Ciba-Geigy Ltd.

43022601 Morrissey, M. (1993) Stability Determination of Irgasan DP 300 in the Presence of Metal: Final Report: Lab Project Number: HWI 6117-246. Unpublished study prepared by Hazleton Wisconsin, Inc.

43277801 Morrissey, M. (1994) Stability Determination of Irgasan DP300 Exposed to Metal Ions: Final Report: Lab Project Number: HWI 6117-261. Unpublished study prepared by Hazleton Wisconsin, Inc.

43277802 Schatowitz, B. (1990) Additional Data Required by the US EPA for the Results of the Analysis of Irgasan DP300 for Dioxins/Furans: Lab Project Number: 102290. Unpublished study prepared by Ciba-Geigy Ltd.

43533901 Schatowitz, B. (1995) Additional Data Required by the U.S. EPA for the Product Analysis of Irgasan DP 300: Lab Project Number: 11995. Unpublished study prepared by Ciba Research Services.