
June 16, 2014

Colleen Rogers
Center for Drug Evaluation and Research
Food and Drug Administration
Building 22, Room 5411
10903 New Hampshire Avenue
Silver Spring, MD 20993

**Re: Proposed Rule: Proposed Amendment of the Tentative Final Monograph, Federal Register, Vol. 78, No. 242, Tuesday, December 17, 2013.**

**Docket identification (ID) number: FDA-1975-N-0012**

**Regulatory Information Number: 0910-AF69**

Dear Ms. Rogers:

The American Cleaning Institute (ACI)[1] appreciates this opportunity to provide comments on the proposed rule to amend the 1994 tentative final monograph (the 1994 TFM) for over-the-counter (OTC) antiseptic drug products to establish conditions under which OTC consumer antiseptic products intended for use with water (referred to throughout as consumer antiseptic washes) are generally recognized as safe and effective.

ACI has a specific interest in triclosan (TCS) within the proposed rule since our members produce consumer antiseptic wash products containing triclosan and manufacture triclosan. Triclosan-containing consumer antiseptic wash products play a beneficial role in the daily hygiene routines of millions of people throughout the U.S. and worldwide. They have been and are used safely and effectively in homes, hospitals, schools and workplaces every single day. Furthermore, triclosan and products containing it are regulated by a number of governmental bodies around the world and have a long track record of human and environmental safety which is supported by a multitude of science-based, transparent risk analyses.

ACI members are concerned that FDA has not appropriately assessed the safety data that are available prior to proposing that additional safety data are necessary to support the safety of triclosan for this use. According to the agency's proposed rule, triclosan is the most studied

[1] ACI is a trade association representing the $30 billion U.S. cleaning products industry. ACI members include the formulators of soaps, detergents, and general cleaning products used in household, commercial, industrial and institutional settings; companies that supply ingredients and finished packaging for these products; and oleochemical producers.

active ingredient for OTC antiseptic use for both safety and efficacy. FDA, however, neglected a substantial amount of relevant information beyond what is reported in the notice. Studies related to the safety and efficacy of ticlosan are cited and described in these comments.

The following summarizes our response to the points raised in the proposed rule and the attachment provides detailed comments on these points.

1. The extensive triclosan database on absorption, distribution, metabolism and excretion (ADME) has demonstrated similarities in absorption, distribution, metabolism (ADM) between species as well as differences in excretion. This is especially relevant in that hamster data is sufficiently similar to human data, therefore, justifying extrapolation with minimal allometric scaling. These data remove the necessity of additional testing. Metabolism is similar following oral and dermal exposures.
2. *In vivo* carcinogenicity studies in three species (hamster, rat, mouse) additionally supported by extensive *in vitro* and *in vivo* mutagenicity studies demonstrate that triclosan is not a carcinogen based on assessments by both FDA and EPA.
3. Based on the above information, the ongoing dermal carcinogenicity study is not necessary. Concern about triclosan dermal photolysis to "dioxins" does not take into consideration that the most likely photolysis product, 2,8-dichlorobenzodioxin, is considered toxicologically inert based on the recognized toxicology equivalence factor (TEF) concept.
4. Extensive *in vivo* studies demonstrate that triclosan exhibits reproductive no observable effect levels (NOELs) that provide a wide margin of safety to humans under existing use conditions.
5. The existing database of *in vitro*, *in vivo* animal and human studies does not support a conclusion that triclosan causes hormonal effects in humans at actual relevant exposure concentrations. The reports of high throughput screening and animal studies showing thyroid or other hormonal activity demonstrated both effect and no-effect levels as expected in adequately designed studies. Extrapolation of these findings, based on dose and relevance of effect, provides a wide margin of safety to humans.
6. The clinical evaluation of actual real-life antimicrobial (antiseptic) resistance has conclusively demonstrated no relevant association between triclosan exposure and microbial resistance to antibiotics.
7. The proposed new FDA standard of demonstrating efficacy by use of clinical population studies is inherently flawed. It requires an infection/disease reduction standard that is not necessary. As long as FDA accepts that antimicrobials (antiseptics) have been adequately shown to have the ability to decrease bacterial (or other relevant organisms) populations, it can control usage by limiting claims. The new standard assumes a claim that would be the exception rather than the rule. Only those wishing this exception would have to meet the clinical population standard. This differentiation would allow FDA to meet their standards for efficacy and safety within a reasonable timeline. Triclosan has demonstrated both *in vitro* and *in vivo* efficacy utilizing formulations that have

demonstrated infection control in clinical situations and dermal bacterial reduction in consumer settings.

Regarding efficacy testing, FDA should reconsider the new efficacy testing requirements presented in its proposed rule, which are unprecedented. Given the significance of the proposed change to the testing requirements for Consumer Antiseptics and the lack of precedent for this action, FDA should withdraw the proposed rule and reissue it as an Advance Notice of Proposed Rulemaking (ANPR) to give industry and other stakeholders an opportunity to engage with FDA on the generally recognized as effective (GRAE) testing requirements for the active ingredients and surrogate endpoint testing of final formulations.

FDA's efficacy requirements are unjustified by the risk-benefit analysis. Typically, reassessments of benefits and risks are prompted by a safety signal, such as the appearance of a particular sign, symptom, or symptom-complex. However, there has been no demonstration of a scientifically confirmed risk associated with the usage of consumer antiseptic products. There is only speculation around potential risks associated with endocrine disruption and antimicrobial resistance, without consideration of the full weight of evidence or a properly conducted risk assessment. This reliance on speculation to justify unparalleled testing requirements is unwarranted and is not justified on a scientific basis. Furthermore, the FDA does not appear to have considered the potential risks for having an increase in infection(s), including food-borne illness(es), among consumers by their not having access to antibacterial product formulations. This is consistent with FDA's failure to make public their assessment of a safety risk in accordance with accepted transparent scientific principles recognized by the FDA.

FDA's proposed clinical trial requirements are unrealistic and infeasible. We believe that the testing of active ingredients for efficacy, rather than a formulation, is unnecessary and counter to the positions taken by FDA during the lifetime of this monograph as well as other monographs. To this end, we ask that FDA clearly differentiate between active ingredient and final formulation requirements as well as consider simulation testing and surrogate endpoints which are more reasonable than testing for reduced infection rate.

ACI urges FDA to revise its proposed *in vitro* testing methods. We recommend that FDA require MIC/MLC testing of active ingredients on the ATCC reference strains described in the proposed rule to determine the spectrum of antibacterial activity. ACI urges the agency to adopt American Society for Testing and Materials (ASTM) Method E2783 (Standard Test Method for Assessment of Antimicrobial Activity for Water Miscible Compounds Using a Time-Kill Procedure) as the standard for conducting the Time-Kill testing for speed of antimicrobial effect for evaluation of formulated antiseptics. We request, however, that FDA reconsider the performance criteria, which are more demanding than the performance abilities of approved healthcare antiseptic products and likely the unformulated active ingredients.

Recognizing that the use of standardized test methods is critical for regulatory testing and approval to assure consistency, FDA should adopt, as appropriate, established and accepted methodology to support the surrogate endpoint efficacy testing for finished antiseptic formulations, such as the following ASTM methods: E1174 - Standard Method for the Evaluation of Health Care Handwash Formulation, E2783 - Standard Test Method for Assessment of Antimicrobial Activity for Water Miscible Compounds Using a Time-Kill

Procedure, and E2784 - Standard Test Method for Evaluation of the Effectiveness of Handwash Formulations Using the Paper Towel (Palmar) Method of Hand Contamination.

In summary, the available toxicological information provides no evidence for data gaps or gives cause for concern under typical use conditions of triclosan in consumer antiseptic wash products. After a transparent and scientific evaluation of existing data in accordance with established principles, we expect FDA will find that the triclosan database, in association with more recently published information, is sufficient for demonstrating the safety and efficacy of triclosan.

ACI can provide copies of the cited studies and reports upon request. Please contact me if you have any questions on these comments or would like to discuss them.

Sincerely,

Richard Sedlak
Executive Vice President, Technical & International Affairs

**American Cleaning Institute (ACI) comments on:**

**Proposed Rule: Proposed Amendment of the Tentative Final Monograph, Federal Register, Vol. 78, No. 242, Tuesday, December 17, 2013**

This document presents the American Cleaning Institute's (ACI) detailed comments on the proposed rule,[1] along with citations to supporting studies and reports, addressing the use of triclosan (2,4,4'-trichloro-2'-hydroxy-diphenylether) as an antimicrobial ingredient in consumer antiseptic wash products.

The following summarizes our response to the proposed rule followed by specific comments and details:

- Triclosan Absorption, Distribution, Metabolism, and Excretion (ADME): This extensive database has demonstrated similarities in ADM between species as well as differences in excretion. A wealth of data exist that reveal the toxicokinetics of triclosan in several species, including humans. Based on similarities in distribution, metabolism, and excretion between humans and hamsters, this database allows for the determination that the hamster is the most relevant species for human risk assessment.
- Carcinogenicity: Extensive *in vivo* studies (in hamster, rat, and mouse) demonstrate that triclosan is not a carcinogen based on assessments by both FDA and EPA. This is further supported by *in vitro* and *in vivo* mutagenicity studies. The ongoing dermal carcinogenicity study is not necessary. Concern about triclosan dermal photolysis to "dioxins" does not take into consideration that the most likely photolysis product, 2,8-dichlorobenzodioxin, is considered toxicologically inert based on the recognized toxicology equivalence factor (TEF) concept
- DART: Extensive *in vivo* studies demonstrate that triclosan exhibits No Observed Effect Levels (NOELs) that provide a wide margin of safety to humans under existing use conditions.
- Hormonal Effects*:* The existing database of *in vitro*, *in vivo* animal and human studies does not support a conclusion that triclosan causes hormonal effects in humans at actual relevant exposure concentrations. The reports of high throughput screening and animal studies showing thyroid or other hormonal activity demonstrated both effect and no-effect levels as expected in adequately designed studies. Extrapolation of these findings, based on dose and relevance of effect, provides a wide margin of safety to humans.

[1] Safety and Effectiveness of Consumer Antiseptics; Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Proposed Amendment of the Tentative Final Monograph; Reopening of Administrative Record, 78 Fed. Reg. 76,444 (Dec. 17, 2013)

- Antimicrobial resistance: The clinical evaluation of actual real-life antimicrobial (antiseptic) resistance has conclusively demonstrated no relevant association between triclosan exposure and microbial resistance to antibiotics.
- Triclosan-containing Antibacterial Wash Products are Efficacious: The proposed new FDA standard of demonstrating efficacy by use of clinical population studies is inherently flawed. It requires an infection/disease reduction standard that is not necessary. As long as FDA accepts that antimicrobials (antiseptics) have been adequately shown to have the ability to decrease bacterial (or other relevant organisms) populations, they can control usage by limiting claims. The new standard assumes a claim that would be the exception rather than the rule. Only those wishing this exception would have to meet the clinical population standard. This differentiation would allow FDA to meet their standards for efficacy and safety within a reasonable timeline. Triclosan has demonstrated both *in vitro* and *in vivo* efficacy utilizing formulations that have demonstrated infection control in clinical situations and dermal bacterial reduction in consumer settings.

## I. Triclosan ADME Data

In the proposed rule, FDA states that "the animal ADME data are not adequate and additional pharmacokinetic data (e.g., AUC, Tmax, and Cmax) at steady-state levels continue to be necessary to bridge animal data to humans."[2] Moreover, FDA indicates additional data are needed "regarding the potential for formation of photodegradation products on human skin" and related effects.[3]

As reflected below, there is an extensive triclosan database on ADME, which has demonstrated similarities in ADM between species as well as differences in excretion. Of particular relevance, hamster data is sufficiently similar to human data, which justifies extrapolation with minimal allometric scaling. Moreover, metabolism is similar following oral and dermal exposures. ACI believes that the existence of this wealth of data removes the need for additional ADME testing. With respect to the issues around photodegradation, the most likely photolysis product, 2,8-dichlorobenzodioxin, is considered toxicologically inert based on the recognized toxicology equivalence factor (TEF) concept. Therefore, additional data evaluating photodegradation products on skin is not warranted.

### *Overall ADME Summary*

In the approach described below, the most suitable species for human risk assessment was determined based on a comparison of toxicokinetic data from humans and various animal species.

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[2] *Id.* at 76,468

[3] *Id.*

Oral absorption of triclosan is almost complete in all species tested (mice, rats, hamsters, guinea pigs, rabbits, dogs baboons, and rhesus monkeys) whereas dermal absorption for leave-on and rinse-off products following various study conditions is not more than 12%. The type and extent of washing regimens influences uptake, as does vehicle. Pharmacokinetic and distribution data suggest that enterohepatic circulation occurs in the rat and mouse, but appears to be absent in humans and hamsters.

All species tested so far exhibit complete metabolism of the parent compound to the glucuronide and sulfate conjugate. In a number of species, including the rat, the sulfate conjugate is predominant with the feces being the primary route of excretion. In hamsters and humans, the glucuronide conjugate predominates in urine which is the primary route of excretion of these two species. The elimination half-lives in hamsters and humans are similar (but different from those in the rat and mouse). Depending on the conditions, a metabolic shift towards the sulfate conjugate may occur in the plasma of both hamsters and humans. However, a shift to the glucuronide occurs before excretion in urine which is unique to these two species.

The fact that oral absorption, metabolism and excretion are comparable in hamsters and humans suggests that the hamster is the most relevant species for human risk assessment. Because of the similarities between hamsters and humans, allometric scaling is not warranted and a lower interspecies assessment factor can be justified in extrapolating from hamster data to the human situation.

*Oral Absorption*

Absorption following oral administration was rapid and almost complete in all rodent and non-rodent species tested with maximum plasma concentrations of free and conjugates (sulfate and/or glucuronide) being reached within 4 to 8 hours.[4,5,6,7,8,9,10,11,12] In humans, absorption can only be

[4] Ciba-Geigy (1995), 14C-Triclosan: absorption, distribution, metabolism and elimination after single/repeated oral and intravenous administration to mice, report number RCC Project 337781, 1 Mar 1995

[5] Colgate-Palmolive (1990), Pharmacokinetics of Triclosan in rats following a single oral administration, report number 8 Mar 1990

[6] Black, J.G. and D. Howes (1975), Percutaneous absorption of Triclosan from toilet preparations. J Soc Cosmet Chem,. 26: 205-215

[7] Siddiqui, W.H. and H.S. Buttar (1979), Pharmacokinetics of Triclosan in rat after intravenoius and intravaginal administration. J Environ Pathol Toxicol, 2(3): 861-871

[8] Ciba-Geigy (1994), 14C-Triclosan: absorption, distribution, metabolism and elimination after single/repeated oral and intravenous administration to hamsters, report number RCC Project 351707, 11 Nov 1994

[9] Ciba-Geigy (1976), Investigations of percutaneous absorption in the rat and the rabbit. GP 41 353 (Triclosan). report number B4/1976, 16 Jan 1976

[10] Ciba-Geigy (1972), Study of pharmacokinetics and metabolism in mouse, rat, rabbit and dog, report number 33/1972, 01 Dec 1972

[11] Ciba-Geigy (1978), Irgasan DP300 oral dose kinetic study in adult rhesus monkeys, 19 Oct 1978

[12] Colgate-Palmolive (1997), A pilot study to determine Triclosan plasma levels in humans following a single oral administration of Triclosan containing products

judged from excretion data and appeared almost complete following single or repeated oral dose administration (80% and 10% of the dose were eliminated via urine and feces, respectively[13]). Similar data are available for single oral dose administration, where 87% of the dose was recovered in the urine and 11% in the feces.[14] In rats and mice, two peak concentrations were detected following single or repeated dosing which is suggestive of enterohepatic circulation that leads to an enhanced local concentration of triclosan in the liver and GI tract.[15,16,17,18] This was substantiated by an intravenous study in mice that confirmed reabsorption of triclosan from the bile into the duodenum.[19] By contrast, pharmacokinetic or distribution data provide no evidence of this mechanism in hamsters and humans.[20,21,22]

*Dermal Absorption*

Several human *in vivo* and *in vitro* studies are available to assess the dermal characteristics of triclosan. *In vitro* studies using diffusion cells showed that absorption is limited and independent of the concentration used within the range of anticipated concentrations in consumer products. Dermal absorption (as calculated from the amounts of triclosan recovered in the dermis and epidermis layers) was 12%, 7.7% and 7.2% for a dishwashing (0.2%), deodorant (0.2%), and soap (0.02%, 10 min incubation)) formulation, respectively.[23,24,25] A study with human subjects

[13] Lücker, P.W., N. Wetzelsberger, and Y. Sturm (1990), Safety (Tolerance) and pharmacokinetics of Triclosan (TCS), report number 27419, 13 Aug 1990

[14] *Id.*

[15] Ciba-Geigy (1995), 14C-Triclosan: absorption, distribution, metabolism and elimination after single/repeated oral and intravenous administration to mice, report number RCC Project 337781, 1 Mar 1995

[16] Ciba-Geigy (1972), Study of pharmacokinetics and metabolism in mouse, rat, rabbit and dog, report number 33/1972, 01 Dec 1972

[17] Ciba-Geigy (1991), Concentration of Triclosan, Triclosan glucoronide and Triclosan sulfate in dog plasma, urine and faecal samples, report number 10 Jun 1991

[18] Unilever (1989), Toxicokinetics of Triclosan. Part 2. Fate of Triclosan in the C57 Mouse, report number Oct 1989

[19] Ciba-Geigy (1995), 14C-Triclosan: absorption, distribution, metabolism and elimination after single/repeated oral and intravenous administration to mice, report number RCC Project 337781, 1 Mar 1995

[20] Lücker, P.W., N. Wetzelsberger, and Y. Sturm (1990), Safety (Tolerance) and pharmacokinetics of Triclosan (TCS), report number 27419, 13 Aug 1990

[21] Ciba-Geigy (1994), 14C-Triclosan: absorption, distribution, metabolism and elimination after single/repeated oral and intravenous administration to hamsters, report number RCC Project 351707, 11 Nov 1994

[22] Unilever (1989), Toxicokinetics of [14C] Triclosan. Part 3. Fate of Triclosan in the Syrian hamster, Study reference No. AM86.04, ESL No. ESL 89 1034; IMIS No. 14-95-10-611, Oct 1989

[23] Ciba-Geigy (1998), *In vitro* human skin penetration and distribution of [14C] labelled Triclosan from dishwashing liquid, report number CSC/4e2/98, 8 Oct 1998

[24] Ciba-Geigy (1998), *In vitro* human skin penetration and distribution of [14C] labelled triclosan from a deodorant formulation, report number CSC/4e3/98, 8 Oct 1998

[25] Ciba-Geigy (1998), *In vitro* human skin penetration and distribution of [14C] labelled triclosan from a soap solution, report number CSC/4e4/98, 8 Oct 1998

who washed their hands with a soap formulation containing 1% triclosan over 21 days (5 washes/day, 30 sec treatment with soap) revealed delayed onset of detectable triclosan in plasma. Even at 21 days plasma levels were < 100 ppb, which makes it likely that hardly any dermal absorption occurs under realistic rinse-off conditions.[26] Other studies using a 1% soap bar with multiple daily washes and showering demonstrated significantly higher plasma levels.[27] This demonstrates the variability with respect to formulation and degree of usage. A recent *in vivo* study with human subjects who received a whole body dermal treatment with a triclosan-containing cream (2% triclosan) revealed that after 12 h, absorption was < 10% (mean: 5.9%).[28] Hence, 12% dermal absorption can be assumed as a worst case for leave-on products, whereas for rinse-off products the above mentioned study with a soap formulation and a 10 min incubation time represents the relevant worst case scenario at 7.2% absorption.

*Metabolism*

Triclosan is metabolized to the glucuronide and sulfate conjugates in all species examined. To date these include mice, rats, hamsters, dogs, rhesus monkeys, baboons and humans. The relative ratio of these metabolites differs between species: whereas the sulfate dominates in mice, rats and dogs, the glucuronide conjugate is the major metabolite in hamsters and humans.[29,30,31,32,33] The glucuronide/sulfate plasma patterns are consistent between hamsters and humans and can vary with dose. In addition, the glucuronide is the predominant conjugate in urine (60-87% in the hamster, ~100% in humans). No free parent triclosan was detected in plasma of either hamsters or humans indicating comparable metabolic patterns between the two species.

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[26] Ciba-Geigy (1973), Irgasan DP-300 and hexachlorophene content of plasma samples from the Hill Top Research, Inc. 21 days handwashing study, report number AEL project No. 73-019 and 73-034, 5 Oct 1973

[27] Chun Hong, H.S., Kurz, N.D., Wolf, T., De Salva, S.J. (1976), Chemical Analysis of Hexachlorophene (HCP), Tribromsalan (TBS), Triclosan (DP-300), Triclocarban (TCC) and Cloflucarban (CF3) in Tissues, Blood and Urine of Animals and Humans. Written for verbal presentation at the March 16, 1976 Meeting of the Society of Toxicology in Atlanta, Georgia

[28] Queckenberg C., Meins J., Wachall B., Doroshyenko O., Tomalik-Scharte D., Bastian B., Abdel-Tawab M., Fuhr U. (2010), Absorption, pharmacokinetics, and safety of triclosan after dermal administration. Antimicrob Agents Chemother. 54(1): 570-2

[29] Ciba-Geigy (1995), 14C-Triclosan: absorption, distribution, metabolism and elimination after single/repeated oral and intravenous administration to mice, report number RCC Project 337781, 1 Mar 1995

[30] Ciba-Geigy (1994), 14C-Triclosan: absorption, distribution, metabolism and elimination after single/repeated oral and intravenous administration to hamsters, report number RCC Project 351707, 11 Nov 1994

[31] Ciba-Geigy (1978), Irgasan DP300 oral dose kinetic study in adult rhesus monkeys, report number 19 Oct 1978

[32] Lücker, P.W., N. Wetzelsberger, and Y. Sturm (1990), Safety (Tolerance) and pharmacokinetics of Triclosan (TCS), report number 27419, 13 Aug 1990

[33] Ciba-Geigy (1991), Concentration of Triclosan, Triclosan glucoronide and Triclosan sulfate in dog plasma, urine and faecal samples, report number 10 Jun 1991

Metabolism to the glucuronide and sulfate conjugate was also demonstrated to occur in rat skin *in vitro* and *in vivo*.[34] Effects observed in animal studies following oral administration are not expected to occur following dermal exposure since critical plasma and/or tissue levels are not likely to be reached through this route.

*Excretion*

The primary route of excretion is the feces in mice (up to 89%) and rats (up to 84%) whereas in hamsters and humans it is the urine (up to 80% and 87%, respectively). The terminal elimination half-life was 9-12 (mice), 10-13 (rats) and 24-32 (hamsters) hours.[35,36,37,38,39,40,41,42] In humans, the terminal elimination half-life, when able to be determined, was around 20 hours.[43,44,45,46,47] This value is very similar to hamsters at a comparable oral dose. [48,49]

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[34] Moss, T., D. Howes, and F. M. Williams (2000), Percutaneous penetration and dermal metabolism of triclosan (2,4, 4'-trichloro-2'-hydroxydiphenyl ether). Food Chem Toxicol, 38(4): 361-70

[35] Ciba-Geigy (1995), 14C-Triclosan: absorption, distribution, metabolism and elimination after single/repeated oral and intravenous administration to mice, report number RCC Project 337781, 1 Mar 1995

[36] Colgate-Palmolive (1990), Pharmacokinetics of Triclosan in rats following a single oral administration, report number 8 Mar 1990

[37] Ciba-Geigy (1994), 14C-Triclosan: absorption, distribution, metabolism and elimination after single/repeated oral and intravenous administration to hamsters, report number RCC Project 351707, 11 Nov 1994

[38] Lücker, P.W., N. Wetzelsberger, and Y. Sturm (1990), Safety (Tolerance) and pharmacokinetics of Triclosan (TCS), report number 27419, 13 Aug 1990

[39] Unilever (1989), Toxicokinetics of Triclosan. Part 2. Fate of Triclosan in the C57 Mouse, report number Oct 1989

[40] Unilever (1989), Toxicokinetics of Triclosan. Part I. Fate of Triclosan in the Swiss-S Mouse, report number Project No. 47980, study reference No. AM86.04, ESL No., ESL 89 1015; IMIS No. 14-95-10-611, Jun 1989

[41] Unilever (1989), Toxicokinetics of [14C] Triclosan. Part 3. Fate of Triclosan in the Syrian hamster, Study reference No. AM86.04, ESL No. ESL 89 1034; IMIS No. 14-95-10-611, Oct 1989

[42] Chung Hong, H.S., et al. (1976),Chemical analysis of Hexachlorophene (HCP), Tribromsalan (TBS), Triclosan (DP-300), Triclocarban (TCC) and Cloflucarban (CF3) in tissues, blood and urine of animals and humans. Written for verbal presentation at the March 16, 1976 meeting of the Society of Toxicology in Atlanta, Georgia

[43] Colgate-Palmolive (1997), A pilot study to determine Triclosan plasma levels in humans following a single oral administration of Trilcosan containing products

[44] Lücker, P.W., N. Wetzelsberger, and Y. Sturm (1990), Safety (Tolerance) and pharmacokinetics of Triclosan (TCS), report number 27419, 13 Aug 1990

[45] Colgate-Palmolive (1997), A pilot study to determine triclosan plasma levels in children following a single oral administration of a Triclosan containing product.

[46] Sandborgh-Englund, G., et al. (2006), Pharmacokinetics of triclosan following oral ingestion in humans. J Toxicol Environ Health A, 69(20): 1861-73

[47] Allmyr, M., et al. (2009), Human exposure to triclosan via toothpaste does not change CYP3A4 activity or plasma concentrations of thyroid hormones. Basic Clin Pharmacol Toxicol, 105(5): 339-44

[48] Lücker, P.W., N. Wetzelsberger, and Y. Sturm (1990), Safety (Tolerance) and pharmacokinetics of Triclosan (TCS), report number 27419, 13 Aug 1990

*Relevant Dose Descriptor*

Several chronic studies are available that could serve as points of departure for a risk assessment. These include studies in mice, rats and hamsters.[50,51,52] The NOAELs for rat and hamster (40 mg/kg bw/d for rats, 75 mg/kg bw/d for hamsters) are of the same order of magnitude and most likely only differ due to differences in dose spacing. A NOAEL was not able to be established for the mouse, which has been attributed to a species-specific sensitivity.[53] This indicates that only minor toxicodynamic differences occur between relevant species in response to triclosan and, based on the previously mentioned findings, the hamster is considered to be the most relevant species for human risk assessment. This is further substantiated by the following:

A recent review compared all available animal data using a benchmark-dose approach and confirmed that the hamster, of all animals tested thus far, is the most sensitive species.[54] The benchmark-dose (BMD) based on renal nephropathy was calculated to be 150 mg/kg bw/d (data not published in Rodricks et al., 2010;[55] A. Shipp, co-author of the paper, personal communication).

As illustrated above, triclosan is rapidly and completely absorbed in both humans and hamsters with no evidence for the enterohepatic circulation found in rats and mice. The former two species share a similar metabolic rate and profile, with the same re-conjugation of the sulfate to a glucuronide conjugate in the kidney leading to a similar excretion pattern and elimination half-life in urine which makes it likely that effects seen in the hamster may also apply to humans.

*Bioaccumulation of Triclosan in the chronic hamster bioassay*

During the lifetime bioassay, blood samples were taken during week 53 and at termination (week 91) to assess the systemic exposure of male and female hamsters to triclosan. The mean plasma concentrations increased with increasing dose over the nominal dose range of 12.5 to 250 mg/kg bw/day.[56] Plasma concentrations appeared to increase by more than would be predicted from a linear relationship in males and females at the termination of the study. However, this was only

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[49] Unilever (1989), *Toxicokinetics of [14C] Triclosan. Part 3. Fate of Triclosan in the Syrian hamster,* report number Study reference No. AM86.04, ESL No. ESL 89 1034; IMIS No. 14-95-10-611, Oct 1989

[50] LSR, Pharmaco (1995), An 18-month oral oncogenicity study of triclosan in the mouse via dietary administration, final report, report number 93-2260, 22 Nov 1995

[51] Ciba-Geigy (1986), FAT 80'023 2-year oral administration to rats, report number MIN 833005, 28 Apr 1986

[52] Ciba-Geigy (1999), FAT 80'023/S. Potential tumorigenic and chronic toxicity effects in prolonged dietary administration to hamsters, report number CBG 756/972/972896, 30 Mar 1999

[53] Trutter, J.A. (1993) 13-week subchronic oral toxicity study of triclosan in CD-1 mice. HWA 483-287. Hazleton Washington Inc. 9200 Leesburg, Pike, Vienna, Virginia 22182. 28 Jan 1993

[54] Rodricks, J. V., et al. (2010), Triclosan: a critical review of the experimental data and development of margins of safety for consumer products. Crit Rev Toxicol, 40(5): 422-84

[55] *Id.*

[56] Ciba-Geigy (1999), FAT 80'023/S. Potential tumorigenic and chronic toxicity effects in prolonged dietary administration to hamsters, report number CBG 756/972/972896, 30 Mar 1999

statistically significant in males. These values are not indicative of bioaccumulation which would typically occur in fatty tissue. Toxicokinetic studies provided evidence of total recovery in feces and urine and a terminal elimination half-life of 24-32 h in hamsters, thus demonstrating the lack of bioaccumulation.[57] In humans, triclosan is completely recovered in feces and urine, so there is no indication for a deep compartment of high capacity, i.e. triclosan does not accumulate in the human body.[58]

*Photodegradation*

Photodegradation of triclosan in aqueous solutions yields the 2,8-dichlorodibenzodioxin as an intermediate of the degradation pathway. However, even under laboratory conditions this reaction occurs only with a yield of 3-12%.[59] The high yield of 12% is only reached under basic pH conditions with no relevance to human skin and only in an ideal laboratory situation. The 2,8-dichlorodibenzodioxin is itself subject to further and rapid photodegradation and, thus, hardly available to exert a toxic effect.[60] No evidence exists that triclosan metabolism *in vivo* leads to formation of any dioxin. The degree and positioning of chlorination determines the toxicity of dibenzodioxins. TCDD, considered the most toxic of the dioxin family, was used as a benchmark. Scientifically based toxicology equivalence factors (TEFs) relative to TCDD have been established. On this basis, 2,8-DCDD, the dioxin metabolite of triclosan in question, has been evaluated and found to be up to 100,000-times less toxic than TCDD and, therefore, considered toxicologically inert.

## II. New Triclosan Findings and Relevance for Assessment of Triclosan

In the proposed rule, FDA cites to a recent study performed by Cherednichenko et al.[61] evaluating the effects of triclosan on muscle function in mice and fish, and asks for "comment on what these findings tell us about triclosan's potential impact on human health and the submission of additional data on this subject."[62]

This study has several deficiencies that make it inappropriate to use the findings to evaluate human risk of triclosan. Specifically, exposure route used in the study is not relevant to the human exposure situation, the plasma levels of mice and humans were not equivalent, and the identified neurotoxic effects have not, to date, been seen in any species tested with oral, dermal

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[57] Ciba-Geigy (1994), 14C-Triclosan: absorption, distribution, metabolism and elimination after single/repeated oral and intravenous administration to hamsters, report number RCC Project 351707, 11 Nov 1994

[58] Lücker, P.W., N. Wetzelsberger, and Y. Sturm (1990), Safety (Tolerance) and pharmacokinetics of Triclosan (TCS), report number 27419, 13 Aug 1990

[59] Latch, D. E., et al. (2005), Aqueous photochemistry of triclosan: formation of 2,4-dichlorophenol, 2,8-dichlorodibenzo-p-dioxin, and oligomerization products. Environ Toxicol Chem, 24(3): 517-25

[60] *Id.*

[61] Cherednichenko, G., et al. (2012), Triclosan impairs excitation-contraction coupling and Ca2+ dynamics in striated muscle. Proc Natl Acad Sci U.S. a, 109(35): 14158-63

[62] 78 Fed. Reg. at 76,468

or inhalation exposure. Therefore, and as further discussed below, we believe that this study should not be considered by FDA for either evaluating triclosan safety or as a guide for additional studies.

*Route*

In the cited study, mice were exposed intraperitoneal (i.p.). This route of exposure is suitable to maximize toxic effects but is not relevant to the human exposure situation. Humans are exposed to triclosan primarily via the dermal route, and to a lesser extent via the oral route. Intraperitoneal administration circumvents physiologic barriers and mechanisms of detoxification which does not happen following oral and dermal exposures. In addition, the i.p. route also bypasses the metabolic first pass effect,[63,64] which explains why almost no unconjugated triclosan is detected in animal or human studies with relevant routes of exposure.

*Plasma Levels*

The authors of the cited study claim that plasma triclosan concentrations in mice parallel those in human studies following oral exposure. Mouse serum levels were in the low µM range (ca. 0.14, 0.23 and 0.31 µM for doses of 6.25, 12.5 and 25 mg/kg, respectively). However, single dose oral studies in the mouse[65] found concentrations were a factor of 170 higher at the 30 min sampling time at ca. 27 µM (parent equivalents) for the 2 mg/kg dose group. In the 200 mg/kg dose group, blood levels were as high as ~ 600 µM at the 30 min sampling time. In human studies with oral administration of triclosan capsules, a steady state concentration of ca. 1.40 µM was achieved with a dose of 15 mg/day (0.25 mg/kg for a 60 kg person). This total triclosan concentration consisted of conjugate (99%+) and parent triclosan (0.36%). Under normal use conditions during twice daily tooth brushing, total triclosan steady state levels reached 0.073 µM with (except for one subject) no detectable amounts of parent triclosan.[66] Hence, the triclosan administered to humans was almost completely metabolized whereas in the study by Cherednichenko et al., an amount of unmetabolized triclosan similar to the amount of total triclosan in some human studies was detected rendering the comparison physiologically inappropriate. The authors fail to explain that, although their lowest dose group was three times as high as the dose used in the oral mouse study, plasma levels were significantly lower (170-fold) with apparently only unconjugated triclosan present in the blood plasma.

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[63] Lücker, P.W., N. Wetzelsberger, and Y. Sturm (1990), Safety (Tolerance) and pharmacokinetics of Triclosan (TCS), report number 27419, 13 Aug 1990

[64] Lin, Y. J. (2000), Buccal absorption of triclosan following topical mouth rinse application. Am J Dent, 13(4): 215-7

[65] Ciba-Geigy (1995), 14C-Triclosan: Absorption, Distribution, Metabolism and Elimination after Single/Repeated Oral and Intravenous Administration to Mice.

[66] Colgate-Palmolive (1989), Steady-State Blood Levels of Triclosan (DP-300) following Dentifrice and Aqueous Solution Administration in 18 Normal Subjects.

*Effects*

Neurotoxic effects were not reported in any species tested to date with oral, dermal or inhalation exposure to triclosan. In fact, triclosan has been used as a negative control for neurotoxicity.[67] Historically, triclosan was required to be investigated for potential neurotoxic effects by FDA following the hexachlorophene tragedy over 40 years ago. A specific two-week neurotoxicity study in rats[68] designed to investigate this endpoint failed to show an effect at concentrations 4 times (100 mg/kg) those used by Cherednichenko et al. and revealed no specific neurotoxicity at concentrations up to 300 mg/kg. In addition, no pathological changes were found in the brain and in the peripheral nerves. Additional species have been administered triclosan for time periods extending up to lifetime exposure without evidence of neurotoxic or cardiac effects.

A long term oral mouse study is available that was conducted with triclosan up to 200 mg/kg daily exposure,[69] i.e. about 10-fold the amount used in the study cited above. The heart was not found to be a target organ after an 18 month exposure based on lack of any morphological or histopathological (tissue) changes indicative of an adverse effect.

It should be stressed that, of all species tested so far, the hamster represents the most relevant species when it comes to human risk assessment.[70,71,72,73,74,75] This is due to the high similarity in pharmacokinetic parameters between humans and hamsters. In hamsters, too, heart and neurotoxic effects were absent in subchronic and lifetime studies.[76,77]

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[67] Muth-Kohne, E., Wichmann, A. Delov, V. and Fenske, M. (2012) The classification of motor neuron defects in the zebrafish embryotoxicity test (ZFET) as an animal alternative approach to assess developmental neurotoxicity. Neurotoxicol Teratol 34(4): 413-24

[68] As cited in, Environmental Protection Agency (EPA) (2008b), Revised 5-Chloro-2-(2,4-dichlorophenoxy)phenol (Triclosan): Toxicology Chapter for the Reregistration Eligibility Decision (RED) Document. Case No 2340. EPA-HQ-OPP-2007-0513: Office of Prevention, Pesticides and Toxic Substances, May 14, 2008. http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2007-0513-0011

[69] Colgate-Palmolive (1995). An 18-month oral oncogenicity study of triclosan in the mouse via dietary administration, Report 93-2260, 22 Nov 1995

[70] Ciba-Geigy (1995), 14C-Triclosan: absorption, distribution, metabolism and elimination after single/repeated oral and intravenous administration to mice, report number RCC Project 337781, 1 Mar 1995

[71] Ciba-Geigy (1994), 14C-Triclosan: absorption, distribution, metabolism and elimination after single/repeated oral and intravenous administration to hamsters, report number RCC Project 351707, 11 Nov 1994

[72] Ciba-Geigy (1978), Irgasan DP300 oral dose kinetic study in adult rhesus monkeys, report number 19 Oct 1978

[73] Lücker, P.W., N. Wetzelsberger, and Y. Sturm (1990), Safety (Tolerance) and pharmacokinetics of Triclosan (TCS), report number 27419, 13 Aug 1990

[74] Ciba-Geigy (1991), Concentration of Triclosan, Triclosan glucoronide and Triclosan sulfate in dog plasma, urine and faecal samples, report number 10 Jun 1991

[75] Ciba-Geigy (1996), 14C-Triclosan: absorption, distribution, metabolism and elimination after single/repeated oral and intravenous administration to rats, report number RCC Project 341998, 17 Jul 1996

[76] Ciba-Geigy (1999), FAT 80'023/S. Potential tumorigenic and chronic toxicity effects in prolonged dietary administration to hamsters, report number CBG 756/972/972896, 30 Mar 1999

## III. Triclosan Carcinogenicity Data

FDA states in the proposed rule that a "long-term carcinogenicity study could be used to assess the relevance of the short-term dermal toxicity findings to a chronic use situation."[78]

As FDA indicates in the proposed rule, it nominated triclosan to the National Toxicology Program (NTP) for toxicological evaluation. In response, NTP is currently conducting a dermal carcinogenicity study. This is occurring despite the availability of oral carcinogenicity studies in three species which provided no evidence of a carcinogenic effect with relevance to humans.[79,80,81] Liver tumors observed in the mouse are thought to be a receptor-mediated, species-specific effect.[82] In addition, extensive *in vitro* and *in vivo* mutagenicity studies demonstrate that triclosan is not a carcinogen based on assessments by both FDA and EPA.

Therefore, based on the lack of carcinogenicity potential demonstrated in oral carcinogenicity studies in multiple species, the extensive battery of data demonstrating lack of mutagenicity, and the understanding of the potential degradation products on skin including their toxicolgical relevance, ACI strongly believes that the NTP dermal carcinogenicity study in progress is not necessary to characterize the dermal toxicity/carcinogenicity endpoint for triclosan use in consumer handwash products.

## IV. Triclosan Data on Hormonal Effects

FDA explains in the proposed rule that recent studies have demonstrated triclosan has effects on the thyroid, estrogen, and testosterone systems in several animal species, and that the "implications of these findings on human health, especially for children are still not well understood."[83] According to FDA, studies in juvenile animals "could address the consequences of short-term thyroid and reproductive finding on the fertility, growth, and development of triclosan-exposed litters."[84]

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[77] Ciba-Geigy (1994), 13 week oral toxicity (feeding) study with FAT 80'023/R in the hamster, report number RCC Project 356490, 27 Oct 1994

[78] 78 Fed. Reg. at 76,468

[79] LSR, Pharmaco (1995), An 18-month oral oncogenicity study of triclosan in the mouse via dietary administration., final report, report number 93-2260, 22 Nov 1995

[80] Ciba-Geigy (1986), FAT 80'023 2-year oral administration to rats, report number MIN 833005, 28 Apr 1986

[81] Ciba-Geigy (1999), FAT 80'023/S. Potential tumorigenic and chronic toxicity effects in prolonged dietary administration to hamsters, report number CBG 756/972/972896, 30 Mar 1999

[82] Rodricks, J. V., et al. (2010), Triclosan: a critical review of the experimental data and development of margins of safety for consumer products. Crit Rev Toxicol, 40(5): 422-84

[83] 78 Fed. Reg. at 76,468

[84] *Id.* at 76,469

ACI respectfully disagrees with FDA's position that the existing database is insufficient to adequately assess the potential risk of triclosan. The existing database of *in vitro*, *in vivo* animal and human studies does not support a conclusion that triclosan causes hormonal effects in humans at actual relevant exposure concentrations. The reports of high throughput screening and animal studies showing thyroid or other hormonal activity demonstrated both effect and no-effect levels as expected in adequately designed studies. Extrapolation of these findings, based on dose and relevance of effect, provides a wide margin of safety to humans. Therefore, ACI believes that no additional studies are warranted.

*Relevance of Published studies*

Studies in the public domain have shown an estrogenic, anti-estrogenic, anti-androgenic and androgenic potential of triclosan using *in vitro* cell lines and reporter assays at concentrations pushing the limits of solubility as well as exposure expectations. However, enticing for exploitation, these findings do not meet FDA's definition of a hormonally active compound – "substance that interferes with the production, release, transport, metabolism, binding, activity or elimination of natural hormones which results in a deviation from normal homeostasis, development or reproduction."

Kumar et al.[85] reported effects on androgen regulation with concomitant effects on testis, including weight and histopathological malformations. These effects were accompanied by reduced sperm density in the epididymis at doses as low as 20 mg/kg bw/day. Test material purity may not meet USP specifications. In contrast to Kumar's findings, several studies in the rat conducted as part of registration dossiers found no effect on the morphology of the testes or epididymis with doses up to ca. 300 mg/kg bw (90-day treatment, covering at least one spermatogenic cycle[86]) or up to ca. 150 mg/kg bw (two year treatment[87]). In addition, no effects on the testes or epididymis were observed in a two generation study.[88] Studies in other species such as the mouse, beagle dogs or baboons also found no effect on the gonads.[89,90,91,92,93] The

[85] Kumar, V., et al. (2009), Alteration of testicular steroidogenesis and histopathology of reproductive system in male rats treated with triclosan. Reprod Toxicol, 27(2): 177-85

[86] Ciba (2001), FAT 80'220/A: 13-week oral toxicity (gavage) study in the Wistar rat, report number RCC project number 762118, 30 Mar 2001

[87] Ciba-Geigy (1986), FAT 80'023 2-year oral administration to rats, report number MIN 833005, 28 Apr 1986

[88] Ciba-Geigy (1988), Two-generation reproduction study in rats FAT 80'023, report number HLA study No. 2386-100, 18 Mar 1988

[89] Colgate-Palmolive (1995). An 18-month oral oncogenicity study of triclosan in the mouse via dietary administration, Report 93-2260, 22 Nov 1995

[90] Ciba-Geigy (1970), 90 days oral toxicity study in Beagle dogs with CH 3565, report number 37/67/SL, 10 Jul 1970

[91] Ciba-Geigy (1975), 1 year oral toxicity study in Baboons with compound FAT 80 023/A (GP 41353, Triclosan), report number 169/75/SL, 28 Jul 1975

[92] Ciba-Geigy (1983), 90-day oral toxicity study in rats with FAT 80'023/H final report, report number LBI Project No. 22188, Oct 1983

incidence of regressed testes in the hamster lifetime bioassay is thought to be secondary to a treatment related decrement in body weight gain.[94] This is species-specific to the hamster as a seasonal breeder that has evolved certain mechanisms for the spontaneous regression of testicular tissue at times of the year when breeding is not possible.[95]

Conflicting results were obtained for effects on female reproductive organs. Stoker et al.[96] evaluated the estrogenic effects of triclosan *in vivo*, finding advanced vaginal opening and altered estradiol levels. This is contrasted by a study published in the same year[97] that found delayed vaginal opening at similar doses of triclosan in addition to other reproductive effects (lowered sex ratio, lowered pup body weights).

*Effects on testicular tissue in the hamster*

Hamsters showed significant morphological effects on and reduced numbers of spermatozoa and germ cells in both sub-chronic and chronic/carcinogenicity studies.[98,99] However, the hamsters in the high dose group from the chronic study had a very high mortality and a generally poor condition and in the short term hamster study the same effects on reproductive parameters were seen in all groups including the control. The hamster is a seasonal breeder that has evolved specific mechanisms to allow for delivery of offspring at times of the year that coincide with the greatest availability of foodstuffs. These mechanisms include the deliberate regression of testicular tissue. A comprehensive review on this subject has been published recently.[100]

*Male Fertility*

A recent report has shown morphological effects in the epididymis and testes and reduced daily sperm production and abnormal sperm morphology in Sprague-Dawley rats following oral

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[93] Ciba-Geigy (1993), Subchronic oral toxicity study of Triclosan in CD-1 mice, report number HWA 483-287, 28 Jan 1993

[94] Ciba-Geigy (1999), FAT 80'023/S. Potential tumorigenic and chronic toxicity effects in prolonged dietary administration to hamsters, report number CBG 756/972/972896, 30 Mar 1999

[95] Faber, Willem, (2009) Discussion of testicular lesions in the triclosan cancer bioassay conducted in hamsters and the time to conception data from the rat multigeneration study.

[96] Stoker, T. E., E. K. Gibson, and L. M. Zorrilla (2010) Triclosan exposure modulates estrogen-dependent responses in the female wistar rat. Toxicol Sci, 117(1): 45-53

[97] Rodriguez, P. E. and M. S. Sanchez (2010), Maternal exposure to triclosan impairs thyroid homeostasis and female pubertal development in Wistar rat offspring. J Toxicol Environ Health A, 73(24): 1678-88

[98] Ciba-Geigy (1999), FAT 80'023/S. Potential tumorigenic and chronic toxicity effects in prolonged dietary administration to hamsters, report number CBG 756/972/972896, 30 Mar 1999

[99] Ciba-Geigy (1994), 13 week oral toxicity (feeding) study with FAT 80'023/R in the hamster, report number RCC Project 356490, 27 Oct 1994

[100] Faber, Willem (2009), Discussion of testicular lesions in the triclosan cancer bioassay conducted in hamsters and the time to conception data from the rat multigeneration study.

administration of triclosan.[101] Another study reported effects on androgen regulation with concomitant effects on testis including weight and histopathological malformations.[102] These effects were accompanied by reduced sperm density in the epididymis at doses as low as 20 mg/kg bw/day. Both of these studies may have used triclosan of a purity less than that established by the United States Pharmacopeia (USP), which specifically limits levels of polychlorinated dibenzo-p-dioxins and -furans, amongst other criteria.

Numerous repeated dose studies with triclosan in several species with up to lifetime treatment[103,104,105,106,107,108,109] or over multiple generations[110] revealed no histopathological or weight changes in any of the above mentioned reproductive organs. Explanations for these differences can include quality of test material (USP grade or otherwise), rat strain differences and dosing (levels and form – diet, capsule, gavage). One possible conclusion is that the quality of triclosan used in the cited studies that were conducted according to internationally accepted guidelines does not cause these effects. The two generation study available with USP grade triclosan was conducted to a previous version of OECD guideline 416 that did not require the determination of sperm parameters.[111] This suggests that subtle changes in these parameters may have been missed due to the study design, especially because it was conducted with the hyperfertile rat. An evaluation by Mangelsdorf et al. (German Federal Institute for Occupational Safety and Health, BAuA) found a strong correlation between histopathology data, organ weights and male fertility. The authors concluded that these data from repeated dose studies may

[101] Lan, Z., et al. (2013), Triclosan exhibits a tendency to accumulate in the epididymis and shows sperm toxicity in male sprague-dawley rats. Environ Toxicol.

[102] Kumar, V., et al. (2009), Alteration of testicular steroidogenesis and histopathology of reproductive system in male rats treated with triclosan. Reprod Toxicol, 27(2): 177-85

[103] Ciba-Geigy (1986), FAT 80'023 2-year oral administration to rats, report number MIN 833005, 28 Apr 1986

[104] Colgate-Palmolive (1995). An 18-month oral oncogenicity study of triclosan in the mouse via dietary administration, Report 93-2260, 22 Nov 1995

[105] Ciba (1999), FAT 80'220/A: 28-day oral toxicity (Gavage) study in the Wistar rat, report number RCC project 712135, 13 Apr 1999

[106] Ciba (2001), FAT 80'220/A: 13-week oral toxicity (gavage) study in the Wistar rat, report number RCC project number 762118, 30 Mar 2001

[107] Ciba-Geigy (1970), 90 days oral toxicity study in Beagle dogs with CH 3565, report number 37/67/SL, 10 Jul 1970

[108] Ciba-Geigy (1975), 1 year oral toxicity study in Baboons with compound FAT 80 023/A (GP 41353, Triclosan), report number 169/75/SL, 28 Jul 1975

[109] Ciba-Geigy (1983), 90-day oral toxicity study in rats with FAT 80'023/H final report, report number LBI Project No. 22188, Oct 1983

[110] Ciba-Geigy (1988), Two-generation reproduction study in rats FAT 80'023, report number HLA study No. 2386-100, 18 Mar 1988

[111] *Id.*

be used to identify adverse effects on male reproduction.[112] Histopathology and organ weights taken from 90 day studies were in fact shown to be more sensitive than fertility parameters that were measured during multi-generation studies. It could also be shown that exposure for 4 weeks suffices for an assessment of male fertility, although 90 day studies have been regarded as superior in the past because they cover a complete cycle of spermatogenesis. If such a 28 day (or 90 day) study reveals neither significantly elevated testis or ovary weights nor histopathological alterations in those organs, the weight of the evidence is that effects on reproduction are also not expected.[113] A comparison of more than one hundred 90 day studies with two-generation studies that used the same test substance additionally showed that the No Observed Adverse Effect Level (NOAELs) differed by less than the variation limit of studies, i.e. a factor of two.[114] Therefore, the information gained from a two-generation study can be regarded as minimal if a 90 day study has been performed.

Effects on the weight and histopathology of the gonads of several species are absent in studies reviewed by several agencies worldwide, including the U.S. EPA.[115,116,117,118] In conclusion, however, although the present OECD guideline 416 requires fertility parameters that were not assessed during the two-generation study available, the already available data in several species are sufficient to assess the endpoint of 'male fertility.'

Weanling rats were treated with 0, 3, 30, 100, 200, or 300 mg/kg bw/d by oral gavage from postnatal day (PND) 23-53 by Zorilla et al.[119] Triclosan administration had no influence on growth or the onset of preputial separation and, despite a non-dose dependent decrease in serum testosterone in the 200 mg/kg bw dose group only, no effects were observed on androgen-dependent reproductive tissue weights.

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[112] Mangelsdorf, I., J. Buschmann, and B. Orthen (2003), Some aspects relating to the evaluation of the effects of chemicals on male fertility. Regul Toxicol Pharmacol, 37(3): 356-69

[113] Mangelsdorf, I; Buschmann, J (2002), Extrapolation from results of animal studies to humans for the endpoint male fertility, report number Fb 984

[114] Janer, G., et al. (2007), A retrospective analysis of the two-generation reproductive study versus the rat subchronic toxicity study. Reprod Toxicol, 24(1): 103-113

[115] Ciba-Geigy (1970), 90 days oral toxicity study in Beagle dogs with CH 3565, report number 37/67/SL, 10 Jul 1970

[116] Ciba-Geigy (1975), 1 year oral toxicity study in Baboons with compound FAT 80 023/A (GP 41353, Triclosan), report number 169/75/SL, 28 Jul 1975

[117] Ciba-Geigy (1983), 90-day oral toxicity study in rats with FAT 80'023/H final report, report number LBI Project No. 22188, Oct 1983

[118] Ciba-Geigy (1994), 90-day subchronic dermal toxicity study in the rat with satellite group with irgasan DP300 (MRD-92-399), report number 139910B, 14 Jul 1994

[119] Zorrilla, L. M., et al. (2009), The effects of triclosan on puberty and thyroid hormones in male Wistar rats. Toxicol Sci, 107(1): 56-64

*Effects on the Thyroid axis*

The overall weight of evidence, including the human study described below, supports the finding that exposure to triclosan through the use of personal care products, either orally or dermally, would not affect the thyroid hormone system in humans, nor cause any other hormonal disruption.

A review of the mammalian and human literature pertaining to potential endocrine disruptive effects of triclosan has recently been completed in which it has been concluded that TCS use through personal care products does not present a risk to humans of endocrine disruptive adverse health effects.[120]

Further supporting the position demonstrating that triclosan in personal care products does not act as an endocrine disruptor in humans is a study by Cullinan et al.[121] Use of a TCS-containing toothpaste by volunteers for 4 years did not affect thyroid function. This investigation was a placebo controlled clinical trial comparing the effects of 0.3% TCS toothpaste with placebo toothpaste on thyroid function in subjects with coronary heart disease over a 4-year period. Thyroid function was assessed by measuring thyroid stimulating hormone (TSH), free thyroxine (fT4), free triiodothyronine (fT3), antithyroglobulin antibody (anti-TGab), and antithyroid peroxidase antibody (TPOab). At 1 year, the authors reported that there were no differences between the TCS group and the placebo group on these thyroid parameters. At year 5, the authors noted that except for fT4, there were no group differences between the TCS and control group on thyroid measurements. Although the TCS group had a higher level of fT4 compared to the placebo group, the authors concluded that it was due to a reduction of fT4 in the placebo, and not due to changes of fT4 in the TCS group. In addition, the authors suggested that this difference was not clinically relevant because the fT4 concentrations remained within the laboratory reference range for both groups. Therefore, the authors stated that long term use of a TCS-containing toothpaste did not alter thyroid function. Since use of other triclosan-containing products were not controlled, this assessment is conservative. While blood levels were not determined, one can conservatively estimate the dose of triclosan based on standard tooth brushing practices. This is a conservative assessment as other potential sources of exposure (resulting from use of personal care products containing triclosan) may have been possible. Adult human exposure to triclosan from a single brushing would result in an estimated ingestion of 5% of 1.25 g of tooth paste containing 0.3% triclosan resulting in a daily intake of 0.0062 mg/kg of triclosan.

The potential of TCS to affect the endocrine system, with a focus on thyroid function, has been the subject of published studies over the last few years. Many of these short-term studies have been conducted in the rat animal model and evaluated the effects of TCS on total serum thyroid

[120] Witorsch, R.J. (2014), Critical Analysis of Endocrine Disruptive Activity of Triclosan and Its Relevance to Human Exposure Through the Use of Personal Care Products. Critical Reviews in Toxicology. 2014 June 4, 1-21

[121] Cullinan, M., Palmer, J.E., Carle, A.D., West, M.J., Seymour, G. J. (2012). Long term use of triclosan toothpaste and thyroid function. Science of the Total Environment. 416: 75-9

hormone concentrations.[122,123,124,125,126,127,128,129,130] While they indicate that TCS has the potential to decrease thyroxine ($T_4$), there was no observed consistent change in triiodothyronine ($T_3$) or thyroid stimulating hormone (TSH). It has been postulated that the reduction in $T_4$ may be initiated by a possible constitutive androstane receptor (CAR-) and/or pregnane X receptor (PXR-) mediated upregulation of hepatic enzymes.[131,132] This induction of hepatic enzymes may be mediated by TCS acting as a PPARα agonist, a mode of action that is not relevant to humans.[133] Based on these findings, it appears that at least some of the decrease in $T_4$ is due to TCS inducing the liver enzymes which metabolize $T_4$, as opposed to acting on the thyroid gland itself, making the occurrence of a human thyroid alteration even less likely.

*Triclosan and Thyroid Hormone Homeostasis*

ACI believes sufficient data exists to support that TCS does not elicit an adverse effect on the human thyroid. An adverse thyroid effect such as hypothyroidism has been defined by the

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[122] Crofton, K., Paul, K., DeVito, M., and Hedge, J. (2007). Short-term in vivo exposure to the water contaminant triclosan: Evidence for disruption of thyroxine. Environmental Toxicology and Pharmacology. 24: 194-197

[123] Paul, K., Hedge, J., DeVito, M., and Crofton, K. (2010a). Short-term exposure to triclosan decreases thyroxine in vivo via upregulation of hepatic catabolism in young Long-Evans rats. Toxicological Sciences. 113(2): 367-379

[124] Paul, K., Hedge, J., DeVito, M., and Crofton, K. (2010b). Developmental triclosan exposure decreases maternal and neonatal thyroxine in rats. Environmental Toxicology and Chemistry. 29(12): 2840-2844

[125] Paul, K., Hedge, J., Bansal, R., Zoeller, R.T., DeVito, M., and Crofton, K. (2012). Developmental triclosan exposure decreases maternal, fetal, and early neonatal thyroxine: a dynamic and kinetic evaluation of a putative mode-of-action. Toxicology. 300(1-3): 31-45

[126] Zorrilla, L., Gibson, E., Jeffay, S., Crofton, K., Setzer, W., Cooper, R., and Stoker, T. (2009). The effects of triclosan on puberty and thyroid hormones in male Wistar rats. Toxicological Sciences. 107(1): 56-6.

[127] Stoker, T., Gibson, E., Zorilla, L. (2010). Triclosan exposure modulates estrogen-dependent responses in the female Wistar rat. Toxicological Sciences. 117(1): 45-53

[128] Rodriguez, E. and Sanchez, M. (2010). Maternal exposure to triclosan impairs thyroid homeostasis and female pubertal development in Wistar rat offspring. Journal of Toxicology and Environmental Helath, Part A. 73: 1678-1688

[129] Fang, J., Vanlandingham, M., B., F.A., Juliar, B.E., Olson, G., Patton, R., Pearce, M.G., Harrouk, W. (2013). 13-week dermal toxicity of triclosan in B6C3F1 mice. Society of Toxicology Poster.

[130] Axelstad, M., Boberg, J., Vinggaard, A.M., Chistiansen, S., Hass, U. (2013). Triclosan exposure reduces thyroxine levels in pregnant and lactating rat dams and directly exposed offspring. Food and Chemical Toxicology. 59: 534-540

[131] Paul, K., Hedge, J., DeVito, M., and Crofton, K. (2010a). Short-term exposure to triclosan decreases thyroxine in vivo via upregulation of hepatic catabolism in young Long-Evans rats. Toxicological Sciences. 113(2): 367-379

[132] Paul, K., Hedge, J., Bansal, R., Zoeller, R.T., DeVito, M., and Crofton, K. (2012). Developmental triclosan exposure decreases maternal, fetal, and early neonatal thyroxine: a dynamic and kinetic evaluation of a putative mode-of-action. Toxicology. 300(1-3): 31-45

[133] Rodricks, J.V., Swenberg, J.A., Borzelleca, J.F., Maronpit, R.R., and Shipp, A.M. (2010). Triclosan: A critical review of the experimental data and development of margins of safety for consumer products. Critical Reviews in Toxicology. 1-63

American Thyroid Association as decreased free $T_4$ concentrations accompanied by increased serum TSH concentrations.[134] This combination has not been seen in any known rat studies, nor in several other species administered TCS for sub-chronic and chronic durations at doses comparable to those administered in the rat studies discussed above. It has been suggested that the use of thyroid weights and histology provide a better assessment of thyroid function because these endpoints are less sensitive to confounders such as stress and diurnal variations.[135] Numerous sub-chronic and chronic studies in various mammalian species (mice, rats, dogs, hamsters, and baboons) showed no evidence of thyroid enlargement or thyroid hyperplasia at doses of TCS as high as 900 mg/kg/day.[136] In addition, if a state of hypothyroidism were developed, it would also be expected to have adverse effects on reproduction and development. However, the findings from one- and two-generation reproductive and developmental studies conducted with TCS in mice, rats, hamsters, and rabbits found no adverse effects on reproduction and development.[137] For example, a two-generation study in rats revealed TCS had no effect on reproductive and developmental outcomes such as gonad development, sexual development, litter size, and body weight gain. In the absence of these effects, the lack of clear indicators of hypothyroid function in rats with TCS exposure suggests that decreases in $T_4$ may not be sufficient to cause overt hypothyroxinemia.

There is considerable evidence that humans are more resistant to changes in circulating thyroid hormones compared to rats. Humans have both robust compensatory feedback mechanisms and extensive binding capacity, both of which maintain thyroid hormone levels within a homeostatic range. For example, $T_4$ and $T_3$ bind to the binding protein transthyreitin (TRR) in rodents and thyroid binding globulin (TBG) in humans. The human TBG has a much higher binding affinity for $T_4$ and $T_3$ than that of rodent TRR, resulting in lower levels of free $T_4$ and $T_3$ and a less active and dynamic thyroid system in humans compared to rodents. Because of the robust nature of the human thyroid hormone system, humans are expected to be more resistant to perturbations in thyroid hormone levels than rodents.

This conclusion is reinforced by studies in humans where no changes in thyroid hormone levels were seen in humans receiving doses of TCS that are in the relevant range encountered from the use of consumer products. The study by Allmyr et al.[138] complements the Cullinan et al. study[139]

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[134] Surks, M.I., Chopra, I.J., Mariash, C.N., Nicoloff, J.T., Solomon, D.H. (1990). American Thyroid Association guidelines for use of laboratory tests in thyroid disorders. JAMA. 263(11): 1529-32

[135] DeVito M., Biegel L., Brouwer A., Brown S., Brucker-Davis F., Cheek A.O., Christensen R., Colborn T., Cooke P., Crissman J., Crofton K., Doerge D., Gray E., Hauser P., Hurley P., Kohn M., Lazar J., McMaster S., McClain M., McConnell E., Meier C., Miller R., Tietge J., Tyl R. (1999). Screening methods for thyroid hormone disruptors. Environ Health Perspect. 107: 407-415

[136] Rodricks, J.V., Swenberg, J.A., Borzelleca, J.F., Maronpit, R.R., and Shipp, A.M. (2010). Triclosan: A critical review of the experimental data and development of margins of safety for consumer products. Critical Reviews in Toxicology. 1-63

[137] *Id.*

[138] Allmyr, M., Panagiotidis, G., Sparve, E., Diczfalusy, U., and Sandborgh-Englund, G. (2009). Human Exposure to Triclosan via Toothpaste does not change CYP3A4 Activity or Plasma Concentrations of Thyroid Hormones. Basic and Clinical Pharmacology and Toxicology. 105(5): 339-344

in that the former found that an estimated exposure to 0.01 mg/kg/day of TCS for 2 weeks in human volunteers (5 men and 7 women) resulted in no changes in thyroid function. Therefore, both short-term and long-term use of TCS has been shown to not disrupt thyroid function in humans. The Cullinan et al. (2012) study population was not generalizable to the entire population for which triclosan-containing toothpaste products are labeled, such as pregnant women, women of child-bearing age, and children. A cross-sectional study using data obtained from the 2007-2008 National Health and Nutrition Examination Survey (NHANES) cycle examined the relationship between urinary TCS and serum endpoints of the thyroid system including free and total $T_3$ and $T_4$, thyroglobulin, and TSH.[140] This study assessed both male and female adolescents (ages 12-19; N = 185 and 171 for males and females, respectively) along with males and female adults (ages $\geq$ 20; N = 785 and 708 for males and females, respectively). The authors of this study reported a modest positive relationship between urinary TCS and serum total $T_3$ in adolescents without changes in any other indicator of thyroid functions. However, when the data was stratified according to gender, this association was not seen to be more prevalent in female vs. male adolescents. In addition, although there was a positive association between TCS and $T_3$, the levels of $T_3$ were within previously published reference values of $T_3$ in adolescents.[141] The positive association was modest and the authors acknowledged that it could have been due to residual confounding or chance. Moreover, an elevation of $T_3$ is not consistent with the animal data and does not have a plausible physiological explanation. Further, and significantly, no other association between urinary TCS and thyroid function endpoints was observed for adolescents or adults such as TSH and $T_4$ levels. Therefore, this study which is generalizable to a larger population, adds to the weight of evidence suggesting that TCS exposure is not associated with adverse thyroid dysfunction in humans.

The proposed adverse outcome pathway (AOP) for TCS induced hypothyroxinemia in rats has been suggested to be increased hepatic catabolism of thyroid hormones following interactions with the xenobiotic nuclear receptors (NRs), CAR and PXR.[142,143] Since this mechanism may be species-dependent, Paul et al.[144] further characterized this AOP using cell-based PXR and CAR

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[139] Cullinan, M., Palmer, J.E., Carle, A.D., West, M.J., Seymour, G. J. (2012). Long term use of triclosan toothpaste and thyroid function. Science of the Total Environment. 416: 75-9

[140] Koeppe, E.S., Ferguson, K.K., Colacino, J.A., Meeker, J.D. (2013). Relationship between urinary triclosan and paraben concentrations and serum thyroid measures in NHANES 2007–2008. Science of the Total Environment. 445-446: 299-305

[141] Kapelari, K., Kirchlechner, C., Hogler, W., Schweitzer, K., Virgolini, I., Moncayo, R. (2008). Pediatric reference intervals for thyroid hormone levels from birth to adulthood: a retrospective study. BMC Endocrine Disorders. 8: 1

[142] Paul, K., Hedge, J., DeVito, M., and Crofton, K. (2010a). Short-term exposure to triclosan decreases thyroxine in vivo via upregulation of hepatic catabolism in young Long-Evans rats. Toxicological Sciences. 113(2): 367-379

[143] Paul, K., Hedge, J., Bansal, R., Zoeller, R.T., DeVito, M., and Crofton, K. (2012). Developmental triclosan exposure decreases maternal, fetal, and early neonatal thyroxine: a dynamic and kinetic evaluation of a putative mode-of-action. Toxicology. 300(1-3): 31-45

[144] Paul, K.B., Thompson, J.T., Simmons, S.O., Vanden Heuvel, J.P., Crofton, K.M. (2013). Evidence for triclosan-induced activation of human and rodent xenobiotic nuclear receptors. Toxicology in Vitro. 27: 2049-2060

reporter assays for mice, rats, and humans.[145] Paul et al.[146] reported that TCS may interact with nuclear receptors (NRs) to regulate hepatic catabolism and down-stream thyroid hormone homeostasis in both rat and human models, through divergent pathways (with the CAR and PXR pathway being important to humans while the rodent CAR (rCAR) being more important for the rat). The authors discussed that while this study supported the proposed AOP, there is no literature to support that human exposure to TCS results in up-regulation of Phase I or Phase II enzymes or TCS-induced hypothyroxinemia. This study noted that an approximate lowest observed effect level for TCS activation of human PXR of 10 μM would approximate a 15 mg/kg/day human oral exposure. The authors noted that Rotroff et al.[147] published an estimated human oral exposure to TCS of 0.13 mg/kg/day (representing an estimated aggregate human oral exposure from food and drinking water sources for the most highly exposed group or subpopulation) and that an equivalent *in vivo* exposure in rats would not have elicited a decrease in thyroid hormone concentrations. The authors concluded that current human exposures to TCS are insufficient to activate human PXR and CAR and, therefore, are not likely to mediate downstream adverse outcomes related to thyroid hormone homeostasis.

*Neurodevelopment*

It is well understood that significant disruptions in thyroid function during pregnancy can cause neurological deficits in offspring.[148,149] However, potential neurodevelopmental effects in the offspring from maternal exposure to chemicals will only occur with sufficient hypothyroidism or hypothyroxinemia in the mother, such that maternal transfer of $T_4$ to the fetus is impaired. For example, even quite significant decreases in $T_4$ levels (55%) in the early postnatal period were not sufficient to alter synaptic transmission in the dentate gyrus of the hippocampus of rat pups.[150] A study by Axelstad et al.[151] showed that the UV-filter Octyl Methoxycinnamate

[145] Paul, K.B., Thompson, J.T., Simmons, S.O., Vanden Heuvel, J.P., Crofton, K.M. (2013). Evidence for triclosan-induced activation of human and rodent xenobiotic nuclear receptors. Toxicology in Vitro. 27: 2049-2060

[146] *Id.*

[147] Rotroff, D.M., Wetmore, B.A, Dix D.J., Ferguson, S.S., Clewell, H.J., Houck K.A., LeCluyse, E.L., Andersen, M.E., Judson, R.S., Smith, C.M., Sochaski, M.A., Kavlock, R.J., Boellmann, F., Martin, M.T., Reif, D.M., Wambaugh J.F., Thomas, R.S. (2010). Incorporation human dosimetry and exposure into high-throughput *in vitro* toxicity screening. Toxicological Sciences 117(2): 348-358

[148] Hartoft-Nielsen, M.L., Boas, M., Bliddal, S., Rasmussen, A.K., Main, K., Feldt-Rasmussen, U. (2011). Do Thyroid Disrupting Chemicals Influence Foetal Development during Pregnancy? Journal of Thyroid Research. Vol 2011,1-14

[149] Negro, R., Soldin, O.P., Obregon M.J., Stagnaro-Green A. (2011). Hypothyroxinemia and Pregnancy. Endocrine Practice. 17(3): 422-9

[150] Gilbert, M. E., Mundy, W. R., and Crofton, K. M. (2000). Spatial learning and long-term potentiation in the dentate gyrus of the hippocampus in animals developmentally exposed to Aroclor 1254. Toxicological Sciences. 57: 102-111

[151] Axelstad, M., Boberg, J., Hougaard, H.S., Christiansen, S., Jacobsen, P.R., Mandrup, K.R., Nellemann, C., Lund, S.P., Hass, U. (2011b). Effects of pre- and postnatal exposure to the UV-filter octyl methoxycinnamate (OMC) on the reproductive, auditory and neurological development of the rat offspring. Toxicology and Applied Pharmacology. 250: 278-290

(OMC) decreased $T_4$ in rat dams (96%) and male offspring (36%) without affecting behavior of the offspring. Moreover, the fungicide Mancozeb has been shown to induce a dose dependent decrease in $T_4$ in rat dams without affecting thyroid weights, histology, reproductive organ weights, or behavior in the offspring.[152] Therefore, Axelstad et al.[153] concluded that in rats, moderate maternal hypothyroxinemia during gestation does not necessarily lead to neurodevelopmental behavioral deficits in the rat offspring.

In compounds that do cause developmental neurotoxicity as a result of thyroid hormone disruption, observed neurodevelopmental deficits were accompanied or preceded by significant effects on the thyroid weight and histology, and decreases in litter size, pup survival, and pup body weight gain.[154,155] As reviewed by Rodricks et al.,[156] numerous sub-chronic and chronic studies in various mammalian species showed no evidence of thyroid enlargement, thyroid hyperplasia, or effects on reproduction and development after TCS exposure. For example, in sub-chronic studies where thyroid weights and/or histopathological evaluations were conducted, TCS did not produce effects on the thyroid at doses as high as 900 mg/kg/day. In addition, chronic studies in rats, mice, hamsters, and baboons showed no effects on thyroid weight or histopathology at doses of 150 mg/kg/day, 200 mg/kg/day, 250 mg/kg/day, and 300 mg/kg/day, respectively. Moreover, TCS did not cause reproductive or developmental effects as demonstrated in one- and two-generation reproductive and developmental studies conducted in mice, rats, hamsters, and rabbits. The absence of such effects suggests that TCS-induced developmental neurotoxicity in humans is not a concern.

A recent study by Axelstad et al.[157] evaluated the thyroid disrupting effects of TCS in rats. In the first experiment, pregnant rats were given TCS via gavage at doses of 75, 150, or 300 mg/kg/day throughout gestation and lactation (GD7-PND16). The study found that TCS decreased $T_4$ by 59%, 72%, and 72% in the three TCS groups, respectively. There was no reduction of $T_4$ in the offspring at the end of the lactation period. Due to the suspected influence of TCS on sex

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[152] Axelstad, M., Boberg, J., Nellemann, C., Kiersgaard, M., Jacobsen, P.R., Christiansen, S., Hougaard, H.S., Hass, U. (2011a). Exposure to the widely used fungicide mancozeb causes thyroid hormone disruption in the rat dams but no behavioral effects in the offspring. Toxicological Sciences. 120(2): 439-446

[153] *Id.*

[154] Brosvic, G.M., Taylor, J.N., Dihoff, R.E. (2002). Influences of early thyroid hormone manipulations: Delays in pup motor and exploratory behavior are evident in adult operant performance. Physiology & Behavior. 75(5): 697-715

[155] Noda, S., Muroi, T., Takakura, S., Sakamoto, S., Takatsuki, M., Yamasaki, K., Tateyama S., Yamaguchi, R. (2005). Preliminary evaluation of an in utero-lactation assay using 6-n-propyl-2-thiouracil. Developmental Toxicity. 79: 414-421

[156] Rodricks, J.V., Swenberg, J.A., Borzelleca, J.F., Maronpit, R.R., and Shipp, A.M. (2010). Triclosan: A critical review of the experimental data and development of margins of safety for consumer products. Critical Reviews in Toxicology. 1-63

[157] Axelstad, M., Boberg, J., Vinggaard, A.M., Chistiansen, S., Hass, U. (2013). Triclosan exposure reduces thyroxine levels in pregnant and lactating rat dams and directly exposed offspring. Food and Chemical Toxicology. 59: 534-540

hormones, this experiment also examined endpoints typically affected by anti-androgenic chemicals such as anogenital distance (AGD), nipple retention, prostate weight and prostate histology, and found no effect. Since the lack of effect on $T_4$ in the offspring could have been due to limited exposure through maternal milk, the authors conducted a second experiment where pups were directly given 50 or 150 mg/kg/day of TCS through direct oral exposure on postnatal days (PND) 3-16. The results showed that $T_4$ was reduced in the 16 day old offspring by 16% and 39%, respectively. Interestingly, the $T_4$ reductions seen in the dams were more pronounced than seen in the directly treated offspring (59-72% in dams compared to 16-39% in offspring). Since the proposed mechanism of action for the reduction in $T_4$ in rats is due to an increase in hepatic clearance, the authors hypothesized that the reduced activity of many phase II enzymes in neonatal rats may have decreased their capacity to metabolize and excrete $T_4$. This study also demonstrated that there was no thyroid weight, histology changes, and no general toxicity in the offspring, and no effect was demonstrated on gestation length, offspring weights, neonatal death, post implantation losses, and litter size. Therefore, the TCS-induced decrease in rodent $T_4$ represents a mild perturbation of the thyroid system, unlikely to produce adverse neurodevelopmental effects.

The American Thyroid Association defines hypothyroxinemia as a normal maternal TSH concentration in conjunction with free $T_4$ ($fT_4$) concentrations in the lower 5$^{th}$ and 10$^{th}$ percentile of the reference range.[158] Pop et al.[159] showed that infants who were born to women with the first trimester of $fT_4$ concentrations $\leq$ 10$^{th}$ percentile had developmental delays compared to women with higher $fT_4$ values. This was consistent with findings by Kooistra et al.[160] who reported that infants of women with $fT_4$ concentrations $\leq$ 10$^{th}$ percentile had lower scores in the Neonatal Behavioral Assessment Scale orientation index compared to infants born to mothers with $fT_4$ values between the 50$^{th}$ and 90$^{th}$ percentile. Similar to the animal studies, these studies indicate that a severe reduction in $T_4$ is needed to produce neurodevelopmental effects. Indeed, it has been suggested that a certain threshold in pregnant women with normal TSH levels must be reached before low concentrations of fT4 affect children's neurodevelopmental outcomes.[161,162] Furthermore, as previously discussed, triclosan has not been shown to exhibit neurotoxic effects.

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[158] Stagnaro-Green, A., Abalovich, M., Alexander, E., Azizi, F., Mestman, J., Negro, R., Nixon, A., Pearce, E.N., Soldin, O.P., Sullivan, S., Wiersinga, W. (2011). Guidelines of the American Thyroid Association from the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 21 (10): 1081-1125

[159] Pop, V.J, Kuijpens, J.L., van Baar, A.L., Verkerk, G., van Son, M.M., de Vijlder, J.J., Vulsma, T., Wiersinga, W.M., Drexhage, H.A., Vader, H.L., (1999). Low maternal free thyroxine concentration during early pregnancy are associated with impaired psychomotor development in infancy. Clin. Endocrinol. 50(2): 149-55

[160] Kooistra, L., Crawford, S., van Baar, A.L., Brouwers, E.P., Pop, V.J. (2006). Neonatal effects of maternal hypothyroxinemia during early pregnancy. Pediatrics. 117: 161-167

[161] Pop, V.J, Kuijpens, J.L., van Baar, A.L., Verkerk, G., van Son, M.M., de Vijlder, J.J., Vulsma, T., Wiersinga, W.M., Drexhage, H.A., Vader, H.L., (1999). Low maternal free thyroxine concentration during early pregnancy are associated with impaired psychomotor development in infancy. Clin. Endocrinol. 50(2): 149-55

[162] Henrichs, J., Bongers-Schokking, J.J., Schenk, J.J., Ghassabian, A., Schmidt, H.G., Visser, T.J., Hooijkaas, H., de Muinck Keizer-Schrama, S.M.P.F, Hofman, A., Jaddoe, V.V.W., Visser, W., Steegers, E.A.P., Verhulst, F.C., de

The lack of clear indicators of hypothyroid function in rats coupled with the sensitivity of rodents to thyroid hormone disturbances suggests that adverse effects of the thyroid system in humans are unlikely. Moreover, studies in humans have shown that $T_4$ levels are not affected by use of a TCS-containing toothpaste. In sensitive populations, such as pregnant women, at doses of TCS such as those encountered by brushing with a TCS-containing toothpaste, alterations in $T_4$ are unlikely to occur and consequently, neurobehavioral effects are unlikely to occur at doses relevant to potential human exposures.

*Margin of Safety*

To develop a margin of safety for triclosan related to the hazard of developmental neurotoxicity via thyroid effects, a conservative approach would be to compare human aggregate exposure from all triclosan-containing consumer products with a comparison to a No-Observed-Effect-Level (NOEL) for thyroid hormone (T4) decrease in the rat animal model. To determine an estimate of human triclosan exposure, Rodricks et al.[163] considered daily estimates for selected consumer products and also considered use of triclosan concentrations measured from urine samples collected from subjects participating in National Health and Nutrition Examination Survey (NHANES). When comparing these two potential sources of triclosan exposure the authors found that the estimates for daily triclosan exposure developed by determining the aggregate exposure through use of consumer products as intended was highly conservative (a higher daily triclosan value) compared to the exposure value derived from the NHANES participants (with comparison to the 95$^{th}$ percentile urinary concentrations from the NHANES cohort). The NHANES data set is based on actual measurements of triclosan in urine (regardless of source) and is not estimates of product usage. Therefore, the use of the NHANES data for development of margin of safety calculations is more reflective of the real world estimate of exposure to triclosan. Estimated daily triclosan intakes corresponding to the 95$^{th}$ percentile were used for this assessment. Also, the use of the 95$^{th}$ percentile of distribution of urinary triclosan levels in each of the populations considered (men, woman, and children) should provide a conservative estimate of the upper bound triclosan exposure, irrespective of source.

The combined exposure (daily triclosan intake) estimate reported by Rodricks et al.[164] based on urinary concentrations from NHANES (2003-2004) were 0.009, 0.007, and 0.004 mg/kg/day, for men, women, and children (age 6-11 years), respectively. For derivation of a margin of safety, one can compare the benchmark response of 20% reduction in T4 seen in rats following 31 day exposure to triclosan calculated by Zorrilla et al.[165] to be 7.23 mg/kg. Using this BMDL and

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Rijke, Y.B., Tiemeier, H. (2010). Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: The generation R study. J Clin Endocrinol Metab. 95(9): 4227-4234

[163] Rodricks, J.V., Swenberg, J.A., Borzelleca, J.F., Maronpit, R.R., and Shipp, A.M. (2010). Triclosan: A critical review of the experimental data and development of margins of safety for consumer products. Critical Reviews in Toxicology. 1-63

[164] *Id.*

[165] Zorrilla, L., Gibson, E., Jeffay, S., Crofton, K., Setzer, W., Cooper, R., and Stoker, T. (2009). The effects of triclosan on puberty and thyroid hormones in male Wistar rats. Toxicological Sciences. 107(1): 56-64

comparing it to the daily exposure parameter for humans described by Rodricks, one can calculate a Margin of Safety (MOS) of 803, 1032, and 1807 for men, women, and children, respectively. In addition, it is important to emphasize that this calculation is based on use of an animal model (rats) that is more prone to disturbances than humans and as described previously may therefore overestimate the potential for thyroid effects in humans further adding to the conservatism of the margin of safety calculations.

*Conclusion*

Overall, triclosan has been shown to alter $T_4$ levels in rats with no evidence that it induces adverse effects on rat thyroid function. A well-defined adverse outcome pathway (AOP) for human developmental neurotoxicity due to reduction in thyroid hormone has been established.[166,167,168,169] In addition, even the mild $T_4$ perturbation seen in rats is unlikely to occur in humans due to the considerable buffering capacity of the human thyroid hormone system. Moreover, levels of human exposures to triclosan from personal care products are insufficient to induce the molecular-initiating event needed to decrease $T_4$. This is consistent with the human studies demonstrating that triclosan did not have adverse effects on the thyroid system. A wide margin of safety exists between the elicitation of the hazard associated as the precursor to developmental neurotoxicity (reduction in thyroid hormone T4) and the exposures experienced by humans (using conservative estimates of exposure from all sources of triclosan).

In summary, the overall weight of evidence suggests the potential of thyroid related effects (including neurodevelopmental outcomes) in humans using triclosan containing personal care products is not likely.

## V. Triclosan and Antimicrobial Resistance

To date, the most thorough review of any potential antimicrobial resistance caused by triclosan has been conducted by the Scientific Committee on Consumer Safety (SCCS) in 2010. In 2010, the SCCS published the results of a comprehensive assessment of triclosan resistance by independent scientists based on the data available at that time.[170]

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[166] Kapelari, K., Kirchlechner, C., Hogler, W., Schweitzer, K., Virgolini, I., Moncayo, R. (2008). Pediatric reference intervals for thyroid hormone levels from birth to adulthood: a retrospective study. BMC Endocrine Disorders. 8: 1

[167] Paul, K., Hedge, J., DeVito, M., and Crofton, K. (2010a). Short-term exposure to triclosan decreases thyroxine in vivo via upregulation of hepatic catabolism in young Long-Evans rats. Toxicological Sciences. 113(2): 367-379

[168] Paul, K., Hedge, J., Bansal, R., Zoeller, R.T., DeVito, M., and Crofton, K. (2012). Developmental triclosan exposure decreases maternal, fetal, and early neonatal thyroxine: a dynamic and kinetic evaluation of a putative mode-of-action. Toxicology. 300(1-3): 31-45

[169] Paul, K.B., Thompson, J.T., Simmons, S.O., Vanden Heuvel, J.P., Crofton, K.M. (2013). Evidence for triclosan-induced activation of human and rodent xenobiotic nuclear receptors. Toxicology in Vitro. 27: 2049-2060

[170] Scientific Committee on Consumer Safety (2010), Opinion on triclosan Antimicrobial Resistance, report number SCCP/1251/09, 22 Jun 2010

The SCCS stated in this paper that *"bacterial resistance to biocide is not a new phenomenon and it has been reported since the 1950s"* and that *"To date, bacterial resistance has been described for all the biocides that have been investigated."*

Similar to the assessment of the SCCS, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) published a comprehensive assessment based on available scientific data and literature.[171]

There have been various reports on the development of resistance to triclosan under laboratory conditions. In the majority of these studies, bacteria were exposed to low concentrations of triclosan in order to select for strains with increased susceptibility to triclosan. The result of these studies is, in most cases, the development of strains with increased minimum inhibitory concentrations (MIC), so called "low-resistant" strains. These strains show increased tolerance to triclosan with MICs still at the ppm-level but can be efficiently killed by use concentrations of triclosan as they are typically used in skin wash formulations (0.3% to 1%). It is, in the meantime, commonly accepted within the scientific community that *in vitro* findings on biocide-resistant microorganisms from laboratories do not allow any conclusions to be drawn on the occurrence and relevance of resistance to biocides and the impact on cross-resistance to antibiotics under real-world conditions. Therefore, the assessment of the risk of biocides and cross-resistance between biocides and antibiotics needs to be done on the basis of *in-situ* and monitoring studies.

For triclosan, unlike most other biocides, there are a number of *in-situ* studies available. Most of the key studies, published before 2010, have been already used in the assessment by the SCCS in 2010.[172] Other in-situ studies have been published since 2010. All of these studies are described below:

**Ledder et al. (2006)** investigated acquired high-level triclosan resistance in a number of distinct environmental isolates and reported that a relatively small number of strains showed a decrease in triclosan susceptibility (*E. coli, Klebsiella oxytoca, Aranicola proteolyticus* and *S. maltophilia*) while the susceptibility of the remaining 35 species remained unchanged. They concluded that repeated exposures to triclosan did not systematically produce high-level triclosan resistance in all bacteria. Furthermore, among the strains with decreased susceptibility, there was no change in antibiotic susceptibility or susceptibility to other biocides. [173]

[171] Scientific Committee on Emerging and Newly Identified Health Risks (2010), Research strategy to address the knowledge gaps on the antimicrobial resistance effects of biocides, 27 Mar 2010

[172] Scientific Committee on Consumer Safety (2010), Opinion on triclosan Antimicrobial Resistance, report number SCCP/1251/09, 22 Jun 2010

[173] Ledder, R. G., et al. (2006), Effects of chronic triclosan exposure upon the antimicrobial susceptibility of 40 ex-situ environmental and human isolates. J Appl Microbiol, 100(5): 1132-40

**Cole et al. (2003)** collected 1238 isolates from the homes of users and non-users of antibacterial product and were unable to demonstrate any cross-resistance to antibiotic and antibacterial agents in target bacteria.[174]

**Sullivan et al. (2003)** studied the effect of triclosan in toothpaste on bacterial species from the oral flora of 9 human volunteers over a 14-day period. Triclosan usage contributed to a decrease in *lactobacilli* although this decrease had no clinical significance. Furthermore, the antibiotic susceptibility profile of the oral *streptococci* investigated did not change following the use of triclosan-containing toothpaste.[175]

**Aiello et al. (2004)** did not find any statistical significance between elevated triclosan MICs and antibiotic susceptibility in bacterial isolates taken from the hands of individuals using either antibacterial cleaning and hygiene products (including a 0.2%-containing hand soap) or non-antibacterial cleaning and hygiene products for a 1-year period.[176]

**Jones et al. (1988)** reported no change in the predominant plaque flora in 13 volunteers following the use of triclosan (2 g/L) for seven months. The authors did not observe any increase in triclosan MIC in these bacteria.[177]

**Walker et al. (1994)** found no changes in the microbial flora in 144 patients following the use of 3 g/L triclosan-containing toothpaste.[178]

**Lear et al. (2002)** isolated more than 100 strains with tolerance to chloroxylenol and triclosan from industrial sources and compared their minimum inhibitory concentrations (MICs) with those of culture collection (standard) strains. The authors found that high tolerances in terms of MIC were not reflected in terms of lethal effects. The study did not produce any evidence suggesting that the presence of residual biocide concentrations in the industrial environment promotes the emergence of bacterial tolerance for them.[179]

**Lear et al. (2006)** followed up from their 2002 study, using PCMX-tolerant strains (*Acinetobacter johnsonii* and *Citrobacter freundii*) and triclosan-tolerant strains (*Pseudomonas aeruginosa* and *Pseudomonas stutzeri*) to test for susceptibility against a panel of 14 antibiotics and other biocides (i.e., benzalkonium chloride, chlorhexidine and phenol). This study did not

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[174] Cole, E. C., et al. (2003), Investigation of antibiotic and antibacterial agent cross-resistance in target bacteria from homes of antibacterial product users and nonusers. J Appl Microbiol, 95(4): 664-76

[175] Sullivan, A., B. Wretlind, and C. E. Nord (2003), Will triclosan in toothpaste select for resistant oral *streptococci*? Clin Microbiol Infect, 9(4): 306-9

[176] Aiello, A. E., et al. (2004), Relationship between triclosan and susceptibilities of bacteria isolated from hands in the community. Antimicrob Agents Chemother, 48(8): 2973-9

[177] Jones RD, Jampani HB, Neman JL, Lee AS. (2000), Triclosan: a review of effectiveness and safety in health care settings. American Journal of Infection Control 28: 184-196

[178] Walker, C., et al. (1994), The effects of a 0.3% triclosan-containing dentifrice on the microbial composition of supragingival plaque. J Clin Periodontol, 21(5): 334-41

[179] Lear, J. C., et al. (2002), Chloroxylenol- and triclosan-tolerant bacteria from industrial sources. J Ind Microbiol Biotechnol, 29(5): 238-42

demonstrate relevant tolerance in practice to other biocides or cross-resistance to the antibiotics tested. Where some decreased susceptibility was demonstrated, strains were still clinically sensitive to antibiotics, and this appeared to be innate to the microorganisms.[180]

**McBain et al. (2003)** investigated the microflora of domestic drain biofilm ecosystems and the impact of short and long-term use of triclosan on the microflora. The bacteria were investigated on their susceptibility to four biocides, including triclosan and six antibiotics. The authors concluded from their results that the use of triclosan did not significantly affect the community profiles of susceptibility to the test biocides or antibiotics.[181]

**Lambert (2004)** analyzed data from the MIC study of 256 clinical isolates of methicillin-sensitive (MSSA) and methicillin-resistant *Staphylococcus aureus* (MRSA) and 111 clinical isolates of *Pseudomonas aeruginosa* against eight antimicrobial biocides and several clinically relevant antibiotics. Comparisons show that alterations in the mean susceptibility of *Staphylococcus aureus* to antimicrobial biocides have occurred between 1989 and 2000, but that these changes were mirrored in MSSA and MRSA, suggesting that methicillin resistance has little to do with these changes. Between 1989 and 2000 a sub-population of MRSA has acquired a higher resistance to biocides, but this has not altered the antibiotic susceptibility of that group. In both, *Staphylococcus aureus* and *Pseudomonas aeruginosa*, several correlations (both positive and negative) between antibiotics and antimicrobial biocides were found. The authors concluded that from the study results it is very difficult to support a hypothesis that increased biocide resistance causes increased antibiotic resistance in *Staphylococcus aureus* or *Pseudomonas aeruginosa*.[182]

**Aiello et al. (2005)** examined whether household use of antibacterial cleaning and hygiene products is an emerging risk factor for carriage of antimicrobial drug-resistant bacteria on hands of household members (study on 224 households with randomized use of antibacterial (including triclosan-containing product) or non-antibacterial cleaning and hygiene products for 1 year). Antibacterial product use did not lead to a significant increase in antimicrobial drug resistance after 1 year nor did it have an effect on bacterial susceptibility to triclosan.[183]

**Cole et al. (2011)** investigated more than 200 individuals which were grouped in i) frequent users of triclosan-containing wash products, ii) infrequent users of triclosan containing wash products and iii) users of non-antimicrobial wash products. The investigation of *Staphylococcus* isolates from users of antibacterial wash products and users of non-antibacterial products showed

[180] Lear, J.C., et al. (2006), Chloroxylenol- and triclosan-tolerant bacteria from industrial sources – susceptibility to antibiotics and other biocides. Int. Biodeter. Biodegr. 57: 51-6

[181] McBain, A. J., et al. (2003), Exposure of sink drain microcosms to triclosan: population dynamics and antimicrobial susceptibility. Appl Environ Microbiol, 69(9): 5433-42

[182] Lambert, R. J. (2004), Comparative analysis of antibiotic and antimicrobial biocide susceptibility data in clinical isolates of methicillin-sensitive Staphylococcus aureus, methicillin-resistant Staphylococcus aureus and Pseudomonas aeruginosa between 1989 and 2000. J Appl Microbiol, 97(4): 699-711

[183] Aiello, A. E., et al. (2005), Antibacterial cleaning products and drug resistance. Emerg Infect Dis, 11(10): 1565-70

a lack of antibiotic/antibacterial cross-resistance. The authors conclude that the study confirms other data showing the lack of evidence that the use of antibacterial wash products facilitates antibiotic resistance and antibiotic/antibacterial cross-resistance.[184]

**Copitch et al. (2010)** tested 428 isolates of *Salmonella* from human and animal sources that were screened for decreased susceptibility to triclosan. About 4% of the strains demonstrated decreased susceptibility to triclosan. Analysis of these isolates showed that the level of resistance to triclosan was generally low (triclosan MIC range 0.25-4 mg/L). The percentage of multiple drug resistant strains was higher in the group of low-level resistant strains compared to the group with lower MICs against triclosan. Whether the depression of multidrug resistance (MDR) efflux systems in the low-triclosan-resistant strains is a consequence of triclosan exposure in the environment or other substrates was not possible to determine. Moreover, the MICs of the resistant strains were in a range of 0.25 to 4 mg/l, which is far below typical concentrations of triclosan in hand wash products (0.3% to 1% triclosan), so that it can be expected that under realistic use conditions triclosan-containing wash products can efficiently control the resistant strains.[185]

**Ciusa et al. (2012)** investigated a large number of clinical *Staphylococcus* strains from various sources. They found a distribution of triclosan-sensitivity with the most resistant strains having MICs of up to 32 µg/ml. Tests of the resistant strains in a suspension test according to the European standard test EN 1276 showed that whereas the wild type strain *S. aureus* ATCC 6538 showed a kill rate of 5 log at 600 ppm triclosan, the most resistant strains showed a kill rate of 4 log at the same triclosan concentrations. As typical concentrations of triclosan in hand soaps are 0.3% to 1%, it can be expected that these strains do not survive under realistic use conditions.[186]

**Cullinan et al. (2014)** reported that the use of triclosan-containing toothpaste did not appear to lead to increase on the MIC of triclosan of oral bacterial isolates following a 5-year study. The study collected dental plaque samples from 40 volunteers in a randomized controlled trial. Study participants were randomly assigned to use triclosan (3000 µg/mL, n = 18) or placebo toothpaste (n = 12). The study found that at 3000 µg/mL triclosan, there was no growth of bacteria, and that the MICs for all isolates ranged from 125 to 1000 µg/mL in both groups. Species common to both groups had similar MICs.[187]

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[184] Cole, E. C., et al. (2011), Investigation of antibiotic and antibacterial susceptibility and resistance in Staphylococcus from the skin of users and non-users of antibacterial wash products in home environments. International Journal of Microbiology Research, 3(2): 90-96

[185] Copitch, J. L., R. N. Whitehead, and M. A. Webber (2010), Prevalence of decreased susceptibility to triclosan in Salmonella enterica isolates from animals and humans and association with multiple drug resistance. Int J Antimicrob Agents, 36(3): 247-51

[186] Ciusa, M. L., et al. (2012), A novel resistance mechanism to triclosan that suggests horizontal gene transfer and demonstrates a potential selective pressure for reduced biocide susceptibility in clinical strains of Staphylococcus aureus. Int J Antimicrob Agents, 40(3): 210-20

[187] Cullinan, M. P., et al. (2014), No evidence of triclosan-resistant bacteria following lont-term use of triclosan-containing toothpaste. J. Periodont. Res., 49: 220-25

**Morrisey et al. (2014)** conducted a comprehensive study, that included 3319 clinical isolates of a wide range of microorganisms (including *Staphylococcus aureus*, *Salmonella* spp., *Escherichia coli*, *Candida albicans*, *Klebsiella pneumonia*, *Enterobacter* spp., *Enterococcus faecium*, and *Enterococcus faecalis*), which aimed at establishing epidemiological cut-off values (ECOFFs) for a range of biocides (including triclosan).[188] The concept of ECOFFs is widely used in the antibiotic resistance area; it differs from clinical breakpoints as ECOFFs are not based on the likelihood of treatment failure to define resistance. Instead, ECOFFs are defined on the basis of the normal distribution of Minimum Inhibitory Concentrations (MICs) in a given bacterial species. All isolates which have MICs inside this distribution are considered as 'wild-type' (i.e. species with absence of acquired or mutational mechanisms of resistance), and those presenting MICs above this value are considered as resistant. This novel study applied this concept to establish MIC and Minimum Bactericidal Concentration (MBC) ECOFFs to facilitate future studies of biocide resistance and potential selection of antibiotic resistance by biocides in natural isolates. For triclosan, the study reported the highest MIC and MBC ECOFF values to be 32 mg/L (for *E. faecium*) and 128 mg/L (for *Salmonella* spp.), respectively. These values demonstrate that use concentrations of triclosan typically used in skin wash formulations (0.3% to 1%) would efficiently kill field (real-world) isolates. Moreover, the large panel of clinical isolates evaluated in this study represents a natural population likely to have been exposed to continued antimicrobial selective pressure.

In conclusion, laboratory data available show that bacteria can be trained to achieve a lower susceptibility to biocides such as triclosan (low-resistance to triclosan), but the majority of these low-resistant bacteria still show very low MICs magnitudes, below typical triclosan use concentrations, and have a high susceptibility in time kill studies at triclosan concentrations used in practice. Moreover, it has been stated by various authors that the translation of laboratory findings to clinical and environmental situations is difficult and should be viewed with caution as the fitness of *in vitro* generated resistant bacteria under real world conditions is doubted.[189]

Bacteria under clinical and environmental conditions are not exposed to well-defined laboratory conditions with low concentrations of biocides but to typical use concentrations of biocides in a complex formulation matrix with inherent antimicrobial activity (surfactants, chelating agents, solvents, etc.) at varying pH and temperature conditions providing additional stress on microorganisms and overall much less favorable conditions.[190]

The most helpful assessment of the risk of biocide resistance and cross-resistance to antibiotics are *in situ* studies and the work with clinical and environmental strains. From our analysis of

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[188] Morrisey, I., et al. (2014), Evaluation of epidemiological cut-off values indicates that biocide resistant subpopulations are uncommon in natural isolates of clinically relevant microorganisms. PLoS ONE, 9(1): e86669. doi:10.1371/journal.pone.0086669

[189] Russell, A. D. (2003), Biocide use and antibiotic resistance: the relevance of laboratory findings to clinical and environmental situations. Lancet Infect Dis, 3(12): 794-803

[190] Scientific Committee on Consumer Safety (2010), Opinion on triclosan Antimicrobial Resistance, report number SCCP/1251/09, 22 Jun 2010

such studies, we conclude that there is no proof of triclosan resistance or confirmation that triclosan/antibiotics cross-resistance is becoming a problem under real world conditions.

## VI. Triclosan-containing Antibacterial Wash Products are Efficacious

When using triclosan containing antibacterial wash products, a consumer and public benefit (i.e., reduced levels of pathogenic organisms) is provided compared to non-antibacterial wash products. The bacterial reduction from washing may be linked to reduced infections from pathogenic bacteria.

The use of antibacterial wash products for infection control in both clinical and non-clinical settings has been documented in the published literature. A summary of several pertinent studies and reports follows.

- The single infection control measure of changing a hand wash and bathing product to a 0.3% triclosan product was associated with the immediate termination of the acute phase of a Methicillin Resistant *Staphylococcus aureus* (MRSA) outbreak.[191]
- Following the introduction of a triclosan hand wash in a neonatal intensive care unit, there was a gradual elimination of MRSA in the unit, and lower antibiotic use and nosocomial infections were recorded.[192]
- It has been demonstrated that there is a much greater potential to reduce the acquisition and transmission of disease resulting from the handling of food through the use of an antibacterial hand wash compared to plain soap.[193]
- Antimicrobial hand soaps have been shown to provide a significantly greater bacterial reduction on the hands compared to plain soap. In addition, the transfer of bacteria to objects following washing with antimicrobial hand soap was significantly reduced compared to plain soap.[194]
- A 2005 meeting of the Nonprescription Drugs Advisory Committee (NDAC) recommended to the FDA that antibacterial hand wash products should demonstrate a reduction in infection when compared with non-antibacterial hand wash products. A summary of a scientific model and expert panel review of the model developed to demonstrate the effectiveness of antibacterial hand wash products versus non-

[191] Zafar AB et al. (1995. Use of 0.3 triclosan to eradicate an outbreak of MRSA in a neonatal nursery. Am. J. Infect. Control. 23: 200-208

[192] Webster J, et al. (1994), Elimination of methicillin resistant Staphylococcus aureus from a neonatal intensive care unit after hand washing with triclosan. J. Pediatr. Child Health. 30: 59–64

[193] Fischler GE, et al. (2007), Effect of hand wash agents on controlling the transmission of pathogenic bacteria from hands to food. J. Food Protect. 70: 2873-2877

[194] Fuls JL, et al. (2008), Alternative hand contamination technique to compare the activities of antimicrobial and non-antimicrobial soaps under different test conditions. Appl. Environ. Microbiol. 74: 3739-3744

antibacterial hand wash products has been published since the 2005 NDAC meeting.[195] The expert panel concluded that the model was a realistic test for the efficacy (demonstration of reduction in infection) of antibacterial hand wash products. Data from studies using this model were presented to FDA in November 2008 and formally submitted to the FDA under FDA docket number FDA-1980-N-0006.

- Based on the expert panel's recommendation a larger study was performed by an independent laboratory using the *Shigella* dose model. The study used 163 subjects to compare a spectrum of antimicrobial actives, (TCS, chlorhexidine gluconate, ethanol) vs. plain soap. The findings concluded that all three actives resulted in statistically significantly lower concentration of *Shigella* on the melon balls relative to the plain soap treatments. The data was then used in a quantitative microbial risk assessment which showed that the antibacterial treatments would result in significantly less cases of *Shigellosis* from $10^6$ *Shigella* per hand down to as low as 100 *Shigella* per hand.[196]

[195] Boyce JM, DuPont HL, Massaro J, Sack D, Schaffner DW (2012). An expert panel report of a proposed scientific model demonstrating the effectiveness of antibacterial hand wash products. American Journal of Infection Control 40: 742-9

[196] Schaffner DW, Bowman JP, English DJ, Fischler GE, Fuls JL, Krowka JF, Kruszewski FH. Quantitative Microbial Risk Assessment of Antibacterial Hand Hygiene Products on Risk of Shigellosis. 2014. Journal of Food Protection. 4: 528-690