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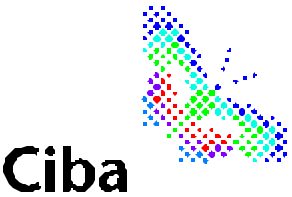

November 6th 2008

Dr. Barbara Shane
Executive Secretary for the NTP BSC
NTP Office of Liaison, Policy and Review
NIEHS
P.O. Box 12233-MD A3-01
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Dear Dr. Shane:

On Thursday, October 2nd 2008 the US Federal Register announced the scheduled meeting of the NTP Board of Scientific Counselors (NTP BSC) and requested comments on the recently nominated substances, the nomination rationale, and the preliminary study recommendations for these substances. In response to this request, Ciba Inc. is providing this letter and supporting documentation for consideration by the NTP BSC. It is our request that the NTP BSC recommends against accepting triclosan for testing under the NTP because Ciba has already been working cooperatively with FDA to support Category 1 classification of triclosan under the OTC monograph process. We intend to conduct the additional testing required for the Category 1 classification to meet data needs cited in the NTP Research proposal. We provide the following rationale in support of our request.

Ciba Inc. firmly believes that triclosan is safe and effective for its intended use as a nonprescription antibacterial ingredient in consumer products. The extensive database, collected over more than 40 years of study and real-world application, confirms that the ingredient is effective and safe for humans and the environment. The scientific data supporting the safety of triclosan stands clearly and consistently against misconceptions often presented in activist campaigns and the media. On the basis of this wealth of data triclosan is registered world-wide to support its use throughout the global market and has not been removed from the marketplace by regulatory restrictions in any country.

As a major manufacturer of triclosan, Ciba is committed to supporting this product. Ciba has supported the safety and efficacy of triclosan for FDA topical applications on various occasions since the last publication of the Tentative Final Monograph (TFM) for Health Care Antiseptic Drug Products on July 17, 1994. And, in fact, as described below, Ciba has actively pursued avenues of communication and agreements on filling and completing the regulatory requirements set forth by the FDA as described below.

The NTP Summary of Nomination information states that FDA has not taken any action on triclosan since its 2001 dermal carcinogenicity assessment of triclosan. It is important to note that since 2001, Ciba has provided FDA with several submissions that support the safety and efficacy of triclosan. Since these data are not mentioned or included in the NTP Summary of Nomination document, we are concerned that this information may not have been reviewed and that *the overall assessment is deficient.*

As such, it is imperative to note that on August 26, 2003[1], as part of the reopening of the administrative record on the Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Health Care Antiseptic Drug Products monograph (68 FR 32003, May 29, 2003), Ciba provided the FDA with a summary of all of the information submitted to the FDA Docket (No. 75N-183H) supporting the Category I safety and efficacy status of triclosan for topical concentrations of up to 1.0 percent. In this correspondence to FDA, it was reiterated that data supporting the safety of triclosan were previously submitted to FDA under two separate Citizen Petitions (CPs):one on September 13, 2001 and a second on February 11, 2002[2] (and addendum on February 13, 2002[3]). Included with the September 13, 2001[4] CP submission was a document titled *"Triclosan Industry Alliance Position Paper: Triclosan: Adequacy of Data to Support the Lack of Potential Dermal Carcinogenicity"* and three additional 14-day repeated dose dermal studies of triclosan in mice and rats. The February 13, 2002 CP submission included a human dermal pharmacokinetics study evaluating the percutaneous absorption of triclosan.

In the absence of any substantive comments from FDA regarding the safety studies submitted in support of triclosan, Ciba submitted 27 additional studies supporting the safety of triclosan for short and long-term topical application uses at concentrations (single or in combination) of up to 1.0 percent as part of the August 26, 2003[5] submission. Moreover, the letter also requested that FDA advise Ciba whether any further studies were necessary to support the safety of triclosan prior to the finalization of the monograph. Ciba did not receive a response from FDA.

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[1] www.fda.gov/ohrms/dockets/dailys/03/Sept03/090303/75n-0183h-c000085-01-vol170.pdf
[2] http://www.fda.gov/ohrms/dockets/dailys/02/Feb02/021202/75n-183h_cp00012_01_vol123.pdf
[3] http://www.fda.gov/ohrms/dockets/dailys/02/Feb02/021502/75n-183h_sup0005_01_vol125.pdf
[4] http://www.fda.gov/ohrms/dockets/dailys/01/Sep01/091701/cp00009.pdf
[5] www.fda.gov/ohrms/DOCKETS/dockets/75n0183h/75n-0183h-sup0013-10-Attachment-03-vol202.pdf

Given the lack of FDA response to these data submissions, in January 2006[6] Ciba requested an in-person meeting with FDA Office of Nonprescription Products staff to discuss any outstanding issues related to the safety of triclosan. In response to this request the FDA replied with the following statement, "We have considered your request and have concluded that a discussion of these topics would, at this time, be premature."[7] In light of this response from FDA, and the historical absence of clear discussions and conclusion for a way to closure, we find it fully surprising that instead the FDA nominated triclosan to the NTP for toxicological studies. Similarly, but with a different history behind a potential nomination rationale, we find the absence of an FDA nomination for other antimicrobial active ingredients lacking dermal carcinogenicity data to be inequitable.

We repeat here, that Ciba is committed to ensuring triclosan is and is perceived as a safe and effective antimicrobial substance suitable for oral and topical consumer products. This commitment brings us here to state our intention to conduct the testing required by FDA under the condition that we have proper guidance and discussion opportunities to ensure the perceived data gaps are closed and the NTP Research Concept has been satisfied to mutual agreement.

In our review of the rationale for testing triclosan and the proposed NTP Research Concept, we do not agree that dermal carcinogenicity testing of triclosan will give more certainty or clarity to the safety profile of triclosan for its topical and oral applications because our database of studies can be used to inform human health risk assessment for all routes of triclosan exposure from consumer products. Regardless, we consider the Agency demand for covering all testing categories as fulfilling their mandate and, as we have in the past as witnessed by our ongoing requests and submissions to FDA, can concede the need for this testing.

Further, while we find merit in the discussion of photosafety of topically applied triclosan, we know that triclosan on skin will respond differently to UV irradiation than will triclosan in aqueous environmental media such as wastewater receiving water bodies. We do not have, nor are we aware of other sources of sufficient empirical evidence to refute or support the action spectrum for triclosan on or in human skin; however, our extensive body of test results in animals and humans indicate an absence of phototoxicity and photosensitization responses to triclosan.

Additional discussion points we found in the Nomination Profile are presented in our appendices to this letter.

To conclude, Ciba presents in this letter to the NTP BSC our commitment to conducting in a reasonable timeframe the needed additional testing of triclosan as proposed in the NTP Research Concept; this will include the key studies identified but in animal models most

[6] http://www.fda.gov/ohrms/dockets/dockets/75n0183h/75n-0183h-sup0013-toc.htm
[7] Letter from FDA, Dr. Charles Ganley, Director, Office of Nonprescription Products, CDER, dated April 27, 2006 http://www.fda.gov/ohrms/dockets/dailys/06/may06/050206/050206.htm

representative of and relevant to human risk assessment. This is consistent with our previous interactions with FDA. Further, Ciba, as a responsible manufacturer of triclosan, is willing to conduct the necessary safety studies in our ongoing commitment to support the completion of the review and Category 1 classification of triclosan under the OTC monograph process. We feel that these studies will be applicable to the NTP review and we welcome the opportunity to discuss this option with both FDA and NTP.

Sincerely,
Ciba Inc.

[Redacted]

[Redacted]

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Appendix I

Comments on the NTP proposal and on the toxicology database available on triclosan

At this point, we make a brief review and comment to the published documentation supporting the nomination of triclosan. Many of the comments provided are taken from a propriety summary report of all of the available data on triclosan. This report can be provided, under confidential disclosure, to the members of the NTP BSC to support their full understanding of the robust triclosan dataset. In the meantime, key excerpts are herewith included.

Comments on Nomination Profile Summary Document for Triclosan

Comments are organized by sections corresponding to those in the nomination profile document.

a. Chemical Information: No comments

b. Exposure Potential:

Use

i. Triclosan is not and never has been authorized for use in household cleaning products. This statement should be removed.

ii. Triclosan is currently registered with the U.S. Environmental Protection Agency (EPA) under Federal Insecticide Fungicide and Rodenticide Act (FIFRA) as an antimicrobial for the protection of polymers/plastics and textiles. Triclosan is NOT an agricultural pesticide. It is NOT used on crops, it is NOT used on plants, it is NOT used to kill insects or nuisance rodents. It is a biocide and like other antimicrobials it can be used to control odor-causing and spoilage/deterioration micro-organisms on textile and textile fibers and can be added to polymers/plastics to protect the material against direct or indirect effects by microorganisms which could change the properties, appearance or odor of the finished articles.

Effectiveness/Efficacy:

i. Soaps: This review of studies is incomplete. The results of a study published in the prestigious, peer reviewed *Journal of Food Protection*, prove that not all hand soaps are alike in their performance. In fact, this first of a kind, real-world study showed that Antibacterial Foaming Hand Soap containing 0.45% triclosan helps protect people from significantly more illness-causing germs than ordinary soap.[8]

ii. Additionally information should also be included from the publication *Alternative hand contamination technique to compare the activities of antimicrobial and*

[8] Fischler GE, Fuls JL, Dail EW, Duran MH, Rodgers ND, and Waggoner AL. Effect of Hand Wash Agents on Controlling the Transmission of Pathogenic Bacteria from Hands to Food. (2007). Journal of Food Protection, Vol 70, No. 12, 2873-2877.

nonantimicrobial soaps under different test condition.[9] Appendix 2 summarizes the effectiveness/efficacy of triclosan.

c. Acute, Subchronic, and Chronic Toxicity:
Reproductive/developmental toxicity
Triclosan was not teratogenic nor a reproductive toxicant in a full complement of reproductive and developmental toxicity studies conducted in mice, rats, and rabbits. These data have been reviewed by both the US FDA and US EPA with no data gaps identified. Study reports are available upon request.

d. Absorption, Distribution, Metabolism, Elimination:
   i. Triclosan is metabolized to parent sulfate and parent glucuronide conjugate compounds in all species examined to date. The relative ratio of these conjugates differs among species.[10,11,12] This detail is of critical importance when selecting animal models for the evaluation of triclosan.
   ii. Data on the systemic (not dermal) metabolism of dermally-applied triclosan are available from a 90-day bathing study conducted in Rhesus monkeys and its accompanying pilot study[13,14] and show that triclosan is absorbed and metabolized to both glucuronide and sulfate conjugates following dermal application and that repeated dermal exposures to triclosan result in the formation of the sulfate conjugate of triclosan as the primary metabolite.
   iii. Dermal Metabolism: An *in vitro* diffusion skin cell model was used to assess the ability of the skin (rat and human) to metabolize triclosan applied using an ethanol:water (9:1) vehicle[15]. Glucuronidation and sulfation of triclosan were demonstrated to occur in this model (*i.e.*, the conjugates were found in the collecting reservoir following absorption through the skin), with the glucuronide being the primary metabolite at levels up to 1.4%. These findings were supported by *in vivo* studies with rats in which 0.4% and 1.5% of the parent glucuronide were reported to occur in the urine and skin, respectively, following the dermal application of triclosan [Moss *et al.*, 2000]. These data show that, triclosan is metabolized in the skin, primarily to glucuronide and sulfate conjugates, as well as other non-parent metabolites as it is in the liver.

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[9] Fuls JL, Rodgers ND, Fischler GE, Howard JM, Patel M, Weidner PL, Duran MH.(2008). *Alternative hand contamination technique to compare the activities of antimicrobial and nonantimicrobial soaps under different test conditions*. Appl Environ Microbiol Jun;74(12):3739-44.
[10] van Dijk, ^{14}C-Triclosan: Absorption, Distribution Metabolism and Elimination after Single/Repeated Oral and Intravenous Administration to Hamsters (RCC Project 351707). November 11 (1994).
[11] van Dijk, ^{14}C-Triclosan: Absorption, Distribution, Metabolism and Elimination after Single/Repeated Oral and Intravenous Administration to Mice (RCC project no. 337781). March 1, 1995.
[12] van Dijk, ^{14}C-Triclosan: Absorption, Distribution and Excretion (ADE) after Single Oral and Repeated Oral Administration to Male Rats (RCC Project 341998). July 7 (1996).
[13] Parkes et al., Pilot Study. Single-dose dermal absorption of triclosan in 3-day old Rhesus monkeys. Analyses of blood and soap samples. June 5 (1978).
[14] Hazleton Laboratories, Irgasan DP 300 90-day bathing study in newborn Rhesus monkeys. Final Analytical Report. April 26, (1979).
[15] Moss et al., Percutaneous penetration and dermal metabolism of triclosan (2,4,4'-trichloro-2'-hydroxydiphenyl ether). Food and Chemical Toxicology 38, 361-370 (2000).

iv. Routes of Excretion Following Dermal Applications of Triclosan: Excretion following dermal applications of triclosan showed that the fecal route predominated in rats, where triclosan was 70 to 90% excreted in the feces compared to 3 to 4% eliminated in the urine.[16] Comparable data showing primarily fecal excretion of triclosan regardless of the formulation of the dose were found in other rat studies.[17,18] In contrast to rats, rabbits exposed to triclosan in a dermally-applied solution or cream showed moderately greater urinary excretion compared to fecal elimination (47 to 53% *vs.* 38% of the applied triclosan solution excreted in the feces; 29 to 48% in urine *vs.* less than 2% in feces following the cream application).[19] Triclosan levels in the urine and feces of monkeys bathed daily from birth to 90 days with 15 mL of a soap solution containing triclosan (1 mg/mL) were found to range from 0.3 to 4.8 ppm in the urine and 0.1 to 10.5 ppm in the feces[20]. These data suggest that the fecal route may have dominated in the excretion of triclosan in these species. For the purposes of comparison, it should be noted that the primary route of excretion in humans exposed to triclosan *via* the dermal route is urinary. In summary, the primary route of excretion following dermal exposure to triclosan differs between species, with the fecal route predominating in the rat, but the urinary route predominating in the rabbit. Neither fecal nor urinary elimination appear to be strongly favored in the case of primates based on the available data.

v. Human Distribution. A total of over 30 pharmacokinetic studies investigating the absorption, metabolism and excretion of triclosan in humans have been reviewed. The pharmacokinetic parameters assessed for triclosan in humans include the C_{max}, the time required to reach T_{max}, the AUC values for plasma concentrations *versus* time, and the elimination half-life (t½) of plasma concentrations. In these studies, several different routes of administration, including oral exposure to triclosan-containing products (*e.g.*, toothpaste), oral ingestion of capsules, aqueous solutions, and dental slurries (*i.e.*, following brushing with triclosan-containing toothpaste), and percutaneous exposure (*in vivo* and *in vitro*) have been investigated. Overall, ingested triclosan is almost completely absorbed, whereas oral and percutaneous exposure to triclosan-containing products (*e.g.*, toothpaste, soap, cream, *etc.*) results in limited absorption. Following all routes of administration, absorbed triclosan is nearly totally converted to glucuronic and sulphuric acid conjugates (varied relative proportions), with only trace amounts of the parent compound detected in the plasma, and the predominant route of excretion for

[16] Ciba-Geigy, GP 41 353 (Triclosan): Investigations of Percutaneous Absorption in the Rat and the Rabbit. (1976).
[17] Hong *et al.*, Animal and Human Absorption Study with Triclosan and Triclocarbon. Meeting of the Society of Toxicology in Atlanta, Georgia (1976)
[18] Moss et al., Percutaneous penetration and dermal metabolism of triclosan (2,4,4'-trichloro-2'-hydroxydiphenyl ether). Food and Chemical Toxicology 38, 361-370 (2000).
[19] Ciba-Geigy, GP 41 353 (Triclosan): Investigations of Percutaneous Absorption in the Rat and the Rabbit. (1976).
[20] Hazleton Laboratories, Irgasan DP 300 90-day bathing study in newborn Rhesus monkeys. Final Analytical Report. April 26, (1979).

triclosan is the urine, with the majority of the compound appearing as the glucuronide conjugate.

vi. Relatively invariable plasma concentrations of triclosan provide evidence of a lack of bioaccumulation following dermal application in human studies. Plasma levels of total triclosan ranged between 85 and 101 ng/mL between Days 5 to 20 in males and 41 to 47 ng/mL in females over the same time period in which triclosan exposure occurred through the use of hand wash containing 1% triclosan[21]. These data suggest a balance between absorption and elimination and a lack of bioaccumulation following dermal absorption.

e. Genotoxicity and Mutagenicity:

We concur with the assessment that "preponderance of data suggests triclosan is not genotoxic or mutagenic compound."

f. Carcinogenicity:

The US EPA classified the chronic carcinogenicity study with hamsters as acceptable/ guideline and stated that it fulfilled the guideline requirement for a chronic carcinogenicity study. Therefore, it is not clear on what reference the following statement is based, "the adequacy of the reporting and completeness of the histopathology evaluation of the study was questionable by the pharmacology/toxicology reviewer who suggested that the sponsor provide the histopathology slides…." We are not aware of an official request from FDA to the Triclosan Industry Alliance for these slides, nor of an official FDA requested third party audit this study. It should be noted that the protocol for this study was submitted to the FDA's Carcinogen Assessment Committee for approval prior to study initiation. Communication regarding this exchange is available in FDA Docket 75N-0183H.

g. Reproductive and Developmental Toxicity

We concur with the assessment that, at this time, sufficient data exist on the effects of triclosan exposure on reproductive and developmental health. Nevertheless, Ciba is actively engaged in research to elucidate the validity or lack thereof of reports of endocrine disruptor activity associated with triclosan. This includes work in both amphibian and mammalian models evaluating developmental landmarks under endocrine regulation. These studies evaluate the potential effect, if any, of environmentally-relevant triclosan concentrations. The work completed with amphibians demonstrates that triclosan does not affect thyroid hormone regulated metamorphosis in *X. laevis*.[22,23,24]

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[21] Ciba Specialty Chemicals. A Pilot Study for the *In Vivo* Evaluation of the Percutaneous Absorption of Triclosan. Report No. CIBA-03-01-0131. January 17 (2002).)

[22] DJ Fort, JW Gorsuch, L Navarro, R. Peter, and JR Plautz, Triclosan and Anuran Metamorphosis: No Effect on Thyroid-Mediated Metamorphosis in *X. laevis*, Presented at SETAC Europe, Warsaw, Poland, May 25-29, 2008.

[23] DJ Fort, LT Navarro, R. Peter, J. Inauen, and JR Plautz. Triclosan and Thyroid-Mediated Metamorphosis in Anurans: Differentiating Growth Effects from Thyroid-Driven Metamorphosis, Presented at the PORS Meetings, UC-Davis, Davis, CA, October 1-2, 2008.

h. Environmental Fate and Aquatic Toxicity

We concur that there is insufficient data on the levels of triclosan degradation products on the skin that may form following photodecomposition, but question if this is even possible. The behaviour of UV irradiation applied to an aqueous mixture of triclosan will give a fully different action spectrum than when triclosan is applied topically in preparations or absorbed from oral products. It is well known that one cannot conclude that reaction sequences of a photodegradation determined in a solvent can be extrapolated to another solvent or to surface reactions. Thus, photodegradation of triclosan in aquatic systems can not be assumed to be representative of triclosan applied topically to skin.

For example it has been shown that photodegradation of TCS in water results in 2,8-dichlorodibenzo-p-dioxin as an intermediate[25,26]. Triclosan under UV-photostress in methanol shows as an impurity a hydroxy-dichloro-dibenzofuran and no 2,8-DCDD formation[27]. Therefore it is clear that different routes of degradation occur in solutions and in solid form. In addition, it is our understanding that there are no accepted standard tests available for solid-phase photodegradation studies

As another example, UV irradiation of triclosan in solution will lead to the formation of dichlorophenol at strong alkaline pH (>pH 10). It is well known that the organoleptic threshold for chlorophenol is quite low (the drinking water threshold to protect against malodor is 0.3 ug/L for dichlorophenols). If this were a common reaction on the skin, the odor alone would discourage the application of triclosan in personal care products.

It is clear that conditions under which triclosan is degraded, in the presence or absence of UV irradiation, are not attainable on the skins surface as they require either extreme temperatures or aggressive alkaline conditions.

In addition, data are also available from phototoxicity and photosensitization testing of triclosan in animals and humans indicating that triclosan is not phototoxic. Additionally, the results of tests conducted with triclosan in representative formulations indicate that no skin toxicity or adverse reactions with or without UV irradiation occur in the presence of triclosan.

i. Development of Resistance: No comments

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[24] DJ Fort, JW Gorsuch, LT Navarro, R. Peter, and JR Plautz**,** No Effect of Triclosan on Thyroid-Mediated Metamorphosis in *X. laevis*, Presented at SETAC NA, Tampa, FL, November 21-25, 2008

[25] Latch D.E., Packer J.L., Arnold W.A. McNeill K. (2003): Photochemical conversion of Triclosan to 2,8-dichlorodibenzo-p-dioxin in aqueous solution; J. Photochem.Photobiol.A 158; 63-66

[26] Latch D.E., Packer J.L., Stender B.L. Vanoverbeke J., Arnold W.A. and McNeill K. (2005): Aqueous Photochemistry of Triclosan: Formation of 2,4-Dichlorophenol, 2,8-Dichlorodibenzo-p-dioxin and oligomerization Products; Environment. Toxicol. & Chem. Vol 24 No. 3 517-525 (SETAC)

[27] Choudhry G.G., Webster G.R.B. (1987): Environmental Photochemistry of Polychlorinated Dibenzofurans and Dibenzo-p-dioxins - A Review; Toxicol. and Environ. Chem Vol. 14, 43-61

j. Regulatory Position and Recommended Studies

We believe that the safety of triclosan should be evaluated as a dermal drug and not as an industrial chemical. The existing triclosan database can be used to complete human health risk assessment for all routes of triclosan exposure from consumer products. It is unknown if new dermal carcinogenicity testing will give more certainty or clarity to the safety profile of triclosan for its topical and oral applications. We do find merit in the discussion of photosafety of topically applied triclosan, although we do not expect triclosan on skin to respond to UV irradiation like triclosan in aqueous environmental media. An extensive body of test results in animals and humans indicate an absence of phototoxicity and photosensitization responses to triclosan.

Comments on NTP Research Concept for Triclosan

The toxicology of triclosan has been thoroughly investigated in mice, rats, hamsters, guinea pigs, rabbits, dogs, monkeys, and baboons. Animal studies for triclosan have examined the full range of toxicological endpoints, including acute, repeated-dose, and sub-chronic toxicity; irritation; sensitization/photosensitization; reproductive and developmental toxicity; mutagenicity/ genotoxicity; and carcinogenicity. In addition, a number of pharmacokinetics and metabolism studies have provided data that contribute to the interpretation of the toxicology data. In addition to the animal toxicology data available, there is a considerable database of human data that has also been included in the toxicology/safety evaluation of triclosan. The human studies have examined the safety and tolerability of triclosan, as well as evaluating its potential irritation/corrosivity and sensitization effects, and its pharmacokinetics and metabolism. Both studies in healthy volunteers, and epidemiological evidence of safety and tolerability have been reviewed. As with the animal toxicology studies, the human safety data cover a number of routes of administration, including oral and dermal routes. Altogether, the number and types of toxicology and/or safety studies in the triclosan database are considered to be sufficient to evaluate the safety of this compound.

The metabolism of triclosan is similar between rodents and humans in the formation of glucuronide and sulfate conjugates. However, the relative extents to which glucuronide and sulfate conjugates of triclosan are formed vary with the type of dosing (single-dose *versus* repeated doses), and with species. The half-life of elimination is shortest in mice and rats (9 to 13 hours) and longest in hamsters (24 to 32 hours). The half-life of elimination of triclosan in humans ranges from 11 to 20 hours in humans. Data from studies that examined the excretion of triclosan have shown that hamsters, primates, and humans eliminate triclosan primarily *via* the urine, while excretion is primarily fecal in mice and rats. The mouse and rat also differ from hamsters in that triclosan appears to undergo enterohepatic circulation in the first 2 species, but not in the latter.

With regard to similarities between animal species to humans, based on pharmacokinetic data, the hamster may be considered the most representative of the animal models for comparison to the human, based on similarities in the patterns of metabolism (*e.g.*, the predominance of the glucuronide conjugate in plasma and urine) and excretion (urinary excretion predominating over

fecal excretion), and a longer half-life than in mice and rats (range of 9 to 13 hours in mice and rats, but 24 to 32 in hamsters and 11 to 20 in humans). In addition, there is a lack of evidence for enterohepatic circulation in hamsters, like humans, whereas evidence indicates the existence of this pathway in mice and rats.

Appropriate test species

Based on metabolism data (primarily glucuronidation) and elimination parameters (routes of elimination, $t_{1/2}$), the hamster is considered to be the most appropriate animal model for the assessment of human safety of triclosan. This information was used as the reasoning to select the hamster as the animal specie of choice to satisfy EPA guideline requirement under OPPTS 870.4300 (combined chronic toxicity/carcinogenicity). The oral (diet) chronic toxicity/oncogenicity study (MRID 44874001, FAT 80'023/S) in hamsters found no evidence of potential carcinogenicity at doses found adequate based on the observed systemic toxicity. We believe that this study should be considered acceptable to satisfy FDA requirements for chronic toxicity studies with rodents (as an animal specie of special use).

FDA also requires chronic toxicity studies in non-rodent species such as the dog, primate or pig. Pigs and minipigs have been used as experimental animals for a relatively long time, because many of their physiological characteristics are close to those of humans[28]. Studies have found that the minipig, like the domestic pig, is also good model for skin studies and have emerged as potential models of human dermatology and, in some aspects, may be superior to commonly used rat skin[29]. Minipigs are currently used as models to study the kinetics of absorption of topically applied drugs. Their skin has structural properties very similar to human skin, with skin from minipig ears and the back showing the highest level of esterase activity-similar to human breast skin used in *in vitro* absorption studies[30]. These results suggest that skin from the minipig back is an appropriate model for preclinical human skin studies. This supports the use of the minipig, with topical application to the back, as a model for the investigation of pharmacokinetics and metabolism of topically applied drugs[31,32].

The International Conference on Harmonization (ICH) guidance has also recommended 9-month chronic toxicity studies in non-rodents. FDA already considers 9-month studies in non-rodents acceptable for most drug development programs. We propose to work collaboratively with FDA to determine the testing conditions (e.g. range finding studies) to use the minipig as the

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[28] Green CJ (1979) *Animal Anaesthesia*. Laboratory Animals Ltd., London.

[29] Prusakiewicz JJ, Ackerman C, and Voorman R. (2006). Comparison of skin esterase activities from different species. Pharm Res. Jul;23(7):1517-1524.

[30] Jewell C, Prusakiewicz JJ, Ackerman C, Payne NA, Fate G, and Williams FM. (2007) The distriburtion of esterases in the skin of the minipig. Toxicol. Lett. Sep. 10;172(2):118-123.

[31] Jewell C, Ackerman C, Payne NA, Fate G, Voorman R., and Williams FM. (2007). Specificity of procaine and ester hydrolysis by human, minipig, and rat skin and liver. Drug Metab Dispos. Nov;35(11):2015-2022.

[32] Jewell C, Prusakiewicz JJ, Ackerman C, Payne NA, Fate G, Voorman R, and Williams FM. (2007). Hydrolysis of a series of parabens by skin microsomes and cytosol from human and minipigs and in whole skin in short-term culture. Toxicol Appl Pharm. Dec 1; 225(2):221-228.

animal specie in a 9-month chronic/dermal carcinogenicity study to satisfy FDA requirements for the evaluation of triclosan.

We welcome the opportunity to further discuss the details of the robust data set available on triclosan and thank you for considering our comments and requests.

Appendix 2
Effectiveness/Efficacy

The benefit from the use of an antibacterial soap lies primarily in the ability to reduce potentially pathogenic bacteria on the skin to a greater degree than can be achieved from washing with plain soap. This difference, or lack thereof is often cited as either the reason for or against their use.

For example, Larson (2004) conducted a recent study in this area. However, this study was inconclusive for the following reasons: (1) it involved multiple interventions such as hygiene promotion and education, visits by study personnel, etc. which may have affected outcome; (2) there was no determination as to whether topical antimicrobial products reduced transient flora more effectively than plain soap; and (3) targeted hygiene (a risk-based approach to target certain high risk situations), which is crucial in reducing transmission of infectious microbes, was not considered in the study.

In reviewing such studies, it is important to note that several prominent hygiene experts, have recognized the benefits of antimicrobial consumer products and have suggested several specific instances and indications when these products are beneficial to the general public (Larson and Rotter, 1990; Keswick et al., 1996; Larson, 2001, Luby, 2002, Luby, et al., 2005). The most notable of these recommendations, also echoed by other experts, was made by Larson (2004) and states that there is indeed a need and place for topical antimicrobial products in the home and that their use and indications should be reflective of their benefits.

Additionally experts have also stated that definitive, classical, prospective, randomized and controlled clinical trials typically used to assess therapeutic benefits are not considered practical in measuring prophylactic benefits of antimicrobial products (Larson 1995).

Two new studies not cited by the FDA (Fischler et al., 2007; Fuls et al., 2008) evaluated the comparative effectiveness of hand washing regimens with antibacterial and non-antibacterial soaps.

Fischler (2007) found that following a single 15 or 30 second hand wash with a soap containing 0.46% triclosan a significantly greater reduction of transient bacteria was achieved compared to plain soap. In addition, the numbers of bacteria subsequently transferred to a food item was reduced to a far greater degree following an antibacterial hand wash, than from the use of plain soap. The levels of bacteria either remaining on the hands, or found on the food were compared to dose response data for the organisms. It was concluded that the there was a greater risk of disease acquisition after using plain soap compared to the antibacterial soap.

Fuls (2008) similarly demonstrated the superiority of a triclosan containing hand soap compared to plain soap at reducing transient bacteria when wash time and soap volumes were standardized.

It has also been shown that the product formulation can play a significant role in the effectiveness of antibacterial ingredients, particularly triclosan (Taylor, et al., 2004).
The biocidal activity of triclosan is dependant on percent saturation and saturation solubility. In high surfactant solutions the efficacy of triclosan can be significantly reduced due to its being highly partitioned in a micellar phase of the surfactant. It is possible to produce highly effective antibacterial soaps containing relatively low (<0.5%) levels of triclosan through careful formula development.

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