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Via Next Day Courier

Central Document Room
Food and Drug Administration
DHHS/FDA/CDER/ONP
5901-B Ammendale Road
Beltsville, MD 20705 – 1266
301-796-2060

Re: FDA OTC Docket No.: 75N-183H

Ciba Specialty Chemicals 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 35 years of study and real-world application data, confirms that the ingredient is effective and safe for humans and the environment. Nevertheless, it is recognized that nearly nine years have passed since the prior conclusions put forth by the FDA that the proliferation of triclosan-containing products was not a concern and that decreased susceptibility to antiseptics and the development of resistance to antibiotics from consumer antiseptics was not a concern. As a result, on September 15, 2005 a meeting notice was published in the Federal Register with the agenda identified as a discussion on the benefits and risks of antiseptic products marketed for consumer use (e.g., antibacterial hand-washes and body-washes). The discussion was to include topics such as the efficacy of antiseptics intended for use by consumers and potential risks to the individual and the general population from using these products. The background material was available the day before the meeting.

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75N-183H

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In light of the short duration the FDA background topics were available, the limited description of the meetings intended focus (i.e. triclosan) in the Federal Register notice, and the absence of an Industry Liaison Representative during the panel meeting, several subject areas involving triclosan were subject to an unbalanced discussion. As such, we appreciate the opportunity to address the topics raised during discussions at the October 20, 2005 Non-prescription Drug Advisory Committee (NDAC) meeting for the Consumer Antiseptic Handwash category and to amend the record[1] of this meeting.

Global Regulatory Status and Human Health Safety

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. A review of triclosan was completed in 2002 by both the EU Scientific Steering Committee (SSC)[2] and the Scientific Committee for Cosmetics and Non-Food Products (SCCNFP)[3]. They concluded that use of triclosan in cosmetics is safe and there was no need for setting new limits on its usage level with regard to potential bacterial resistance to triclosan. In 2004 the Swedish Medical Products Agency completed a review of cosmetic and hygiene ingredients, including triclosan, and concluded that there is no reason to propose banning or restricting the use of triclosan. More recently, an evaluation of the literature to date (2002-2005) has concluded that "in all of the environmental surveys published to date, no evidence of increasing resistance to triclosan has been shown."[4,5]

In the United States, the safety of triclosan has been extensively evaluated by the US FDA and US EPA. It is the subject of both an approved NDA[6] (for dentifrices) and approved medical device 510K's[7] (sutures and dentifrices) as well as approved for use in several antimicrobial applications under the authority of the EPA[8]. Triclosan has a robust data set including nonclinical and clinical studies,

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[1] Appendix 1: Corrections to Misstatements on Triclosan made during the 20 October NDAC Panel Meeting.
[2] Attachment 1: SCC Opinion
[3] Attachment 2: SCCNFP Opinion
[4] Appendix 2: Review on Bacterial Resistance and Triclosan to 2002
[5] Appendix 3: Literature Review on Bacterial Resistance and Triclosan between 2002 and 2005.
[6] Colgate Total (NDA #020231)
[7] Ethicon, Inc. COATED VICRYL® PLUS ANTIMICROBIAL (POLYGLACTIN 910) SUTURE (510K # K022715) and Dentsply NUPRO® T Prophylaxis Paste with Fluoride and Triclosan (510K # K983966
[8] EPA Registration Numbers: 70404-2, 70404-4, and 70404-5

as well as chronic oral carcinogenicity bioassays. The pharmacokinetics and metabolism of triclosan have been studied in both animals and humans. In addition to the good tolerability and safety data based upon consumer use data, evidence of triclosan's good clinical safety profile was found in 5 clinical studies with greater than 3,000 subjects that used triclosan-containing dentifrice for 12 weeks to 3 years.[9] Triclosan was reported to be well-tolerated in the studies, and there were no overt toxicities, or patterns of toxicities, that could be attributed to triclosan. As the dentifrices tested in the studies contained levels of triclosan comparable to currently-used commercial products, these data show that exposure to triclosan through the use of triclosan-containing personal-care products or via any secondary routes is not expected to result in any safety concerns. All of these data have been previously submitted to the OTC Docket 75N-0183H.[10]

As reported in the studies submitted, triclosan is well absorbed following oral ingestion (up to 98% of the dose). However, under normal conditions of toothpaste use (*i.e.*, expectoration and rinsing) or following percutaneous application of several different personal care products, there is only limited absorption (approximately 5 to 10% of the dose *via* either of these routes of administration). Based on plasma levels and percentage of dose absorbed, it is clear that low exposures to triclosan occur following either toothpaste use or soap/hand-wash use and that, with repeated exposures using either route, low steady-state levels of triclosan are reached after approximately 7 to 10 days.

Regardless of the formulation administered, only trace amounts of the parent compound are detected in the plasma following exposure to triclosan-containing products. Due to a pronounced first-pass effect[11], there is near total conversion of absorbed triclosan to glucuronic and sulfuric acid conjugates. Following ingestion, percutaneous application, or intravenous administration of triclosan, the predominant route of excretion is the urine, in which triclosan is present as the glucuronide conjugate. In contrast, triclosan excreted in the feces is present as the free unchanged compound. Pharmacokinetic data, in particular, AUC values after single or repeated oral exposures (*e.g.*, after toothpaste use), as well as plasma levels after dermal (soap application) exposures, indicate a lack of evidence of bioaccumulation of triclosan.

Based on these data it is unclear why information presented at the request of the FDA implied that triclosan was not well studied. "For personal care products that are labeled topical antiseptics, we study whether they absorb through the skin. We don't study, you know, what happens if you eat large quantities of them, for

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[9] Beiswanger and Tuohy, 1990. Analysis of blood plasma samples for free triclosan, triclosan-glucuronide, triclosan sulfate and total triclosan from subjects using a triclosan dentifrice or a dentifrice, bar soap and deodorant. OHRI Study #89-A-111. October 17, 1990. (Submitted to OTC Docket # 75-N-0183H on August 25, 2003)

[10] Attachment 3: Letter dated August 26, 2003 summarizing all documents submitted by Ciba Specialty Chemicals to OTC Docket 75N-183H in support of triclosan.

[11] Definition: First-pass effect, biotransformation of a substance in the liver after absorption from the intestine and before it reaches the systemic circulation.

example, because nobody is expected to eat the soap bar," as stated by Dr. Rolf Halden (a voting member of the NDAC panel and FDA invited speaker).[12]

Environmental Safety of Triclosan

> "We will also be talking about a category of risk that is not normally considered or not usually considered, is not part of a discussion at an advisory committee, but we are going to be touching on potential societal risks associated with the consumer antiseptics." (Dr. Susan Johnson, FDA)[13]

Although not normally considered a part of the discussion by NDAC, the environmental risks of antimicrobials, namely triclosan and triclocarban were discussed. Unfortunately, this topic was not disclosed in advance of the meeting and thus there was not sufficient time for the robust data set assessing the environmental health and safety of triclosan to be submitted and reviewed by the FDA and NDAC panel members. However, it should be noted that in October of 2000 Ciba reviewed data on triclosan with US EPA's Antimicrobials Division and in November of 2000, Ciba submitted existing safety information related to triclosan to the Interagency Testing Committee (ITC), a committee which includes FDA representation. This data call-in included environmental data such as biodegradation and ecological endpoints. Attached is a copy of the environmental information that was submitted to the EPA in 2000.[14] In response to this data call-in and review by ITC, triclosan was determined to satisfy the DEBITS criteria (Degradation Effects Bioconcentration Information Testing Strategies) listed in the 45th ITC Report published in the Federal Register of December 1, 2000 (65 FR 75544) (FRL-6399-5)[15]. As a result, ITC did not request any additional information on triclosan.

Triclosan does not pose a demonstrable risk to the environment and it does not accumulate in the environment. Triclosan is predominantly used in personal care applications, and after use, triclosan is discharged into the wastewater system. The substance is almost completely removed from the wastewater via biodegradation or sorption with only trace amounts detectable in the effluent water. Multiple waste water treatment plants (WWTP) studies show biodegradation of more than 94% with 4% sludge adsorption.[16] Effluents released into rivers may con-

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[12] Official transcripts, NDAC Meeting, Thursday October 20, 2005 http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4184T1.pdf

[13] Official transcripts, NDAC Meeting, Thursday October 20, 2005 http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4184T1.pdf

[14] Attachment 4: Summaries of Environmental Data Submitted for the ITC

[15] Attachment 5: Federal Register of December 1, 2000 (65 FR 75544)

[16] Federle et al. 2002; McAvoy et al. 2002; Singer et al. 2002

tain very small amounts of triclosan, where either biological or photolytic processes further degrade it within a few hours. Sludges containing adsorbed triclosan are either burned, degrading triclosan, deposited, or land-applied with rates of 21.8 % on agricultural soils (data for the USA[17]), where triclosan is biodegraded within days without harm to terrestrial organisms.[18]

For the USA, based on the data from McAvoy et al. (2002) taking the mix of WWTP facility-types into account, we conservatively expect around 5000 kg triclosan reaching agricultural soils from the 1.18 million (mio) metric tons sludge applied annually. A mass balance based on these data is attached in Appendix 5. This mass balance, based on all current data, safely excludes any risk to humans from secondary exposure to triclosan from any environmental route.

A number of environmental monitoring studies have been conducted in the USA and Europe, reporting approximate triclosan concentration ranges of 0.09 to 0.70 µg/L in effluent and <0.005 to 0.13 µg/L in surface waters.[19] Acute toxicity values range from 1 to 440 µg/L with mono-cellular algae being by far the most sensitive aquatic species. Chronic toxicity values range from 0.60 to 200 µg/L, with algae, again, being far more sensitive than invertebrates, fish and higher plants[20]. Laboratory studies have shown that triclosan is toxic to some mono-cellular algae species, having a tendency to stop algal growth and reproduction. However, since it is not present in streams at relevant concentrations during normal conditions (due to dilution at outflow), the concentrations are safely below the NOEC (no observed effect concentration), even for algae. Additionally, it has been demonstrated that organic substances like humic acid usually present in surface waters will increase the NOEC by a factor 3 due to an association to triclosan (Appendix 4, reference 26).

Orvos et al. (2002) showed that the toxic effect on small algae is a reversible inhibition of growth of the algae population. It has been shown that growth recommences and population size is re-established after algae are transferred into a triclosan free media.

A multispecies statistical model based on chronic data was used to estimate a PNEC (HC5[21]; log-logistic distribution) of 0.72 µg/L. The approach is supported by the EU TGD and the US-EPA and represents a more realistic threshold of effect than a single species value. Based on surface water concentrations and the updated PNEC, triclosan is not expected to impact aquatic ecosystems.[22]

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[17] Data based on EPA National Sewage Sludge and Needs Survey, 1988, EPA Biosolids Technology Fact-sheet, EPA 832-F-00-064

[18] Appendix 4: Summaries of Studies and Papers

[19] Sabaliunas et al. 2003, Thomas & Foster, 2005, Morall et al. 2004 ; Wind et al. 2004 ; Singer et al. 2002, Monitoring project UK Environment Agency, ongoing, unpublished data

[20] Orvos et al. 2002

[21] Ahlers J. and Martin, S. 2003; HC5, hazardous concentration 95% percentile

[22] Capdevielle, M, Van Egmond, R., Versteeg, D., and Hofmann-Kamensky, M., Triclosan in the Aquatic Environment: A Risk Assessment Revision, SETAC 2006: Abstract.

Reiss et al. (2002) evaluated the risk for the aquatic compartment and concluded that there is no reason for concern for all species, with the only exception of mono-cellular algae in low water conditions near outlet pipes of WWTP. However, even for the worst cases, margins of safety remained above 1 (1.3) at discharge point in very rare low flow conditions. It can be expected that a very limited and reversible growth inhibition effect can occur around discharge points, however, since algae are floating by and dissipation will lead to lower concentration, this presents no immediate concern.

Morall et al. (2004) showed a reduction in concentration at the same rates as organic matter (BOD[23]) in a US river over an 8 km stretch. The reduction in triclosan concentration from a single source WWTP outlet in this stretch was >75% and mainly due to photo- and biodegradation and to a much lesser extent to particle sorption and settling.

Bacterial Resistance and Triclosan

Surveillance studies searching for triclosan-resistant bacteria in the triclosan factory, in clinical settings, in the home, on the skin or in the oral cavity of users of triclosan have not found any such organisms[24]. Furthermore, considering the long history of use of triclosan (over thirty (30) years), it is highly likely that if bacteria were going to develop triclosan resistance, such bacteria would already be evident in the environments where triclosan-containing products have been repeatedly used. In all of the environmental surveys published to date, no evidence of increasing resistance to triclosan has been shown. The studies also indicate that intrinsically resistant species do not out-compete susceptible strains in biocide-treated environments.

As a comparison: When Penicillin was introduced as a routine antibiotic in the 1940s, immediately within weeks, resistant bacterial strains were noticed.

Laboratory studies have shown some cross-resistance to antibiotics and other biocides in some laboratory-derived mutants of *E. coli,* pseudomonads, and staphylococci. However, there is growing evidence that the generation of such mutants is strain specific and that these mutations do not appear to occur in all species. In fact there have been a number of reported failures by researchers trying to develop triclosan-resistant strains[25]. Additionally, such mutations are frequently lost when triclosan is removed from the media, suggesting that there is no competitive advantage to the organism to conserve that mutation. It is clear

[23] Definition: BOD, Biological Oxygen Demand as measure of organic matter decay
[24] Appendices 2 and 3
[25] McBain et al. 2004

that the natural environment provides many challenges to bacteria including a search for nutrients, appropriate conditions for growth, and competition with other organisms that are not duplicated in laboratory experiments.

The scientific data published since 2002 and discussed in the review (see Appendix 4 for literature cited) has demonstrated that

- Further work has been done and progress has been made to elucidate the many mechanisms of action of triclosan including membrane destabilization, inhibition of fatty acid synthesis, efflux mechanisms, and formation of biofilms;
- A number of additional studies have shown the safety, efficacy, and benefit of triclosan in oral care and skin care products;
- Laboratory studies continue to demonstrate that bacterial strains with increased tolerance to triclosan can be developed in the laboratory by selecting mutants based on growth in the presence of either sub-inhibitory concentrations of triclosan or supra-inhibitory concentrations of triclosan;
- A number of surveillance studies have been conducted looking for organisms with decreased susceptibility to triclosan in natural environments where there has been repeated exposure to triclosan. There was no evidence of shifts in populations or development of resistance to triclosan in any of these studies. Nor was there any evidence of a correlation of resistance between triclosan-tolerant strains and antibiotic resistant strains; and
- A number of expert reviews have concluded, that while cross-resistance to biocides and antibiotics can be demonstrated in the laboratory using pure cultures, it does not necessarily equate to the development of such resistance in the natural or clinical environment where complex, multispecies biofilms predominate, that the use of triclosan in cosmetic and over-the-counter drug products was safe and not expected to select for antimicrobial resistant bacteria, and that triclosan has a low potential for acquired bacterial resistance.

Despite the absence of evidence showing the development of decreased bacterial sensitivity to triclosan (in environments where there has been exposure to this antimicrobial), researchers and reviewers of this subject area recommend continued monitoring. Industry acknowledges this and fully supports continued study in the area of biocide use. The consumer benefits strongly support the continued availability of triclosan to our consumers in the hygiene products where it is currently used.

The evidence presented to date supports the 2002 conclusion of the SCC and the SCCNFP that triclosan does not pose a risk to humans or to the environment by inducing or transmitting antibacterial resistance under current conditions of use.

Conclusions

Triclosan, in the approved uses, poses no risk to man or the environment.

We understand that both safety and efficacy considerations are used to evaluate a substance for Category 1 status in the monograph process. Based on the outcome of the meeting in October 2005, plans for the conduct of efficacy studies by the CTFA/SDA Industry Coalition are in progress. As these plans mature, Ciba Specialty Chemicals would like confirmation from the agency that there are no outstanding data gaps in the specific areas of human health or environmental impact that may require additional review or study. It is very important to ascertain if there are any outstanding items that must be addressed before Industry-sponsored efficacy studies commence.

As a major manufacturer of triclosan, Ciba Specialty Chemicals is committed to supporting this material in the OTC Monograph process and wants to move forward with obtaining Category 1 status for triclosan. In light of the comments and quantity of information provided in this communication, we request an in-person meeting with FDA ONP staff to discuss any outstanding issues related to the safety of triclosan.

Yours truly,
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