May 28, 2014

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RE: June 17–18, 2014 Meeting of NTP Board of Scientific Counselors – Comments Regarding NTP Research Concept for Triclocarban (TCC)

Dear Dr. White:

The American Cleaning Institute (ACI)[1] appreciates this opportunity to provide comments to the Board of Scientific Counselors for the National Toxicology Program on the Research Concept for Triclocarban[2] as part of their June 17-18, 2014 meeting. We offer the following comments organized by sections corresponding to those in the Research Concept paper.

1. Background and rationale

Use

The Research Concept states: *Triclocarban was nominated for toxicological evaluation based on its extensive use, high potential for human exposure, and potential endocrine activity*

Comment:

While we understand that TCC may also be used as a preservative in some cosmetics, we believe its primary use in the US is as an antibacterial active ingredient in bar soap. Over the past decade, the market penetration of antimicrobial bar soaps has decreased from approximately 30% to 15% of total bar soap sales with TCC being the primary active ingredient used. Based on national retail sales data for 2011 we obtained from IRI,[3] we estimate total sales of antibacterial bar soap of 75 million pound. Additionally the concentration of TCC in most bar soap has decreased from 0.6 to 0.3%. Consequently, we estimate the current market volume of TCC used

[1] ACI is the trade association representing the $30 billion U.S. cleaning products market. 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. ACI and its members are dedicated to improving health and the quality of life through sustainable cleaning products and practices. ACI's mission is to support the sustainability of the cleaning product and oleochemical industries through research, education, outreach and science-based advocacy.

[2] http://ntp.niehs.nih.gov/ntp/about_ntp/bsc/2014/june/triclocarban_concept_508.pdf

[3] http://www.iriworldwide.com/

in the US for antibacterial bar soap is approximately 225,000 pound. The combination of these factors has resulted in a significant decrease in human exposure over the past decade.

The potential for endocrine activity associated with TCC has been shown in cellular systems with little relevance for consumer exposure. Additionally, the effect on a pathway may not result in a toxicological effect or disease. The toxicological endpoint for endocrine activities include reproductive effects, fertility, developmental effects. Results from traditional safety studies with triclocarban have not raised any concerns on these endpoints.

The Research Concept states: *TCC production volumes in 2002 were between 1 and 10 million pounds, but listed as less than 500,000 pounds in 2006; however, estimates, based on the amount of TCC entering a water treatment plant, suggests higher rates of TCC usage.*

Comment:

As noted above, the annual use volumes of TCC in antibacterial bar soap has decreased over the past decade. While we understand that TCC may also be used as a preservative in some cosmetics, we believe its primary use in the US is as an antibacterial active ingredient in bar soap. Consequently, we believe that current annual TCC use volume is much lower than the 500,000 pounds reported in 2006, on the order of 225,000 pounds.

The annual use volume estimates based on the amount of TCC entering a water treatment plant based on the study from Halden and Paull (2005)[4] was based on grab samples taken on three occasions in 2002-2004 when the use concentration and sales of antibacterial soap were much higher.

<u>Exposure</u>

The Research Concept states: *The primary routes of exposure for products containing TCC are dermal (through the use of skin care products) and oral (direct consumption of marine life exposed to TCC and residues left on tools for food handling).*

Comment:

The primary route of exposure is the dermal route. The comment regarding TCC exposure from direct consumption of marine life and from residues left on tools for food handling is highly speculative and without scientific basis. It is true that some personal care product (PCP) ingredients have been detected in marine sediments;[5] however, we are not aware of studies reporting TCC in marine fish consumed by humans. The mobility of TCC in biosolids and sediments is strongly retarded,[6] therefore it is very unlikely that TCC will be available for uptake

[4] Halden, R. U. and Paull, D. H. 2005. Co-occurrence of triclocarban and triclosan in U.S. water resources. *Environ Sci Technol* 39, 1420-1426, doi:15819193.

[5] Chen, F. Analysis of pharmaceuticals and personal care products in marine sediment and biota using liquid chromatrography-tandem mass spectrometry. SETAC annual meeting, Long Beach, CA (November 11-15, 2012)

[6] Agyin-Birikorang et al. 2010. Retention-release characteristics of triclocarban and triclosan in biosolids, soils, and biosolids-amended soils. *Env. Tox. & Chem*. 29, 1-9, doi:10.1002/etc.251

by fish. In fact, in 2009 a national pilot study in the US failed to detect PCP ingredients (e.g. triclosan) in edible fish filets[7].

The Research Concept states: *Additionally, it has been detected at low levels in human urine samples (maximum levels of 2.5 and 1.8 ug/g creatinine in Danish women and children and 3.85 ng/mL in males and females in Atlanta, GA).*

Comment:

According to the Second Report on Human Biomonitoring of Environmental Chemicals in Canada,[8] the urine of all Canadian Health Measures Survey cycle 2 (2009–2011) participants aged 3 to 79 years was analyzed for TCC. The results for 96.23% of the 2,549 samples were below the limit of detection of 1 μg/L.

Likewise, recently presented unpublished monitoring data of urinary triclocarban concentrations from 181 African American women sampled in 2007-2009 found triclocarban undetected at a limit of detection of 1 ug/L but using a more sensitive method, the researchers measured a median concentration of 0.2 ug/L triclocarban in urine.[9]

The Research Concept states: *Additional experiments demonstrated that showering with a commercially available soap containing 0.6% triclocarban lead to an absorption rate of 0.6%. Studies in rats and mice washed with soap containing TCC have shown that <2% of the applied dose remained in the skin and that dermal absorption is dose-dependent, but not time-dependent.*

Comments:

The consumer exposure model for "showering" was developed to artificially increase TCC absorption through the skin but does not represent consumer habits for showering with a bar soap. In the referenced study (Schebb et al. 2012), the individuals took a shower, rubbing soap throughout the whole body and let the foam stand for 15 min prior to wash off. Typical showering habits include an average *total* shower time of 10 minutes and the foam is rinsed off the body almost immediately.

In addition, since the study was conducted, the referenced consumer bar soap has reduced the TCC level from 0.6% to 0.3%.

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[7] Ramirez et al. 2009. Occurrence of pharmaceutical and personal care products in fish: Results of a national pilot study in the United States. *Env. Tox. & Chem*. 28(12), 2587-2597.

[8] http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/chms-ecms-cycle2/index-eng.php.

[9] L. Geer, B. Pycke, R. Halden. 2013. Analysis of Maternal Urine, Amniotic Fluid and Cord Blood to Explore Fetal Exposure to Endocrine Disrupting Compounds and Adverse Health Outcomes. Presented at the Society of Environmental Toxicology and Chemistry North America 34th Annual Meeting, Nashville, Tennessee, 17–21 November 2013. View presentation at: http://setac.sclivelearningcenter.com/index.aspx?PID=9484&SID=187028.

The Research Concept states: *Studies in rats and mice washed with soap containing TCC have shown that <2% of the applied dose remained in the skin and that dermal absorption is dose-dependent, but not time-dependent.*

Comment:

The amount of TCC deposited in the skin of a clipped rat and hairless mouse was 1.5 and 1.1% of the applied dose, respectively. It was concluded that the greater deposition of TCC onto rat skin was likely due to the presence of greater amount of hair. The 1.1% deposition in the hairless mouse was suggested to better predict the deposition of TCC on human skin.[10] In this study the soap contained 1.5% [^{14}C]TCC. Currently soaps contain 0.3% TCC (5X lower) which would suggest a much lower deposition rate.

In the rat, the absorption of TCC through non-occluded skin is much lower than occluded-skin conditions and depends on the concentration applied.[11] The authors of this study concluded that the rat skin is between four and seven times more permeable to TCC than human skin.[11] Therefore in a real world scenario, current *lower* TTC concentrations applied to *non-occluded human skin* would be anticipated to be lower.

The percent of TCC dermally absorbed has been reported to be 0.39% of the amount applied with a soap in a showering experiment.[12] In this study subjects took a single shower with a soap containing 2% TCC. It is anticipated that the absorption would be lower with a soap containing 0.3% TCC.

Recent assessments

The Research Concept states: *TCC has been assessed in a number of in vitro assays as part of the NTP's Tox21 High Throughput Screening Program (HTS), where it was classified as mitochondrial toxicant; estrogen receptor and farnesoid-X-receptor antagonist; and aryl hydrocarbon receptor, p53, and antioxidative response element agonist.*

Additionally, it has been shown to increase testosterone regulated gene expression in castrated male rats, resulting in a significant size increase in all male sex accessory organs. These data suggest that the bioactivity of endogenous hormones may be amplified by exposure to products containing sufficient levels of TCC.

Comments:

The positive results using in vitro assays are difficult to extrapolate directly to whole body dosages. For example, Ahn et al.[13] evaluated the *in vitro* biological activity of TCC in a battery

[10] Demetrulias, J., Corbin, N. & North-Root, H. (1984). The hairless mouse as a model for quantitating skin deposition of 3,4,4'-trichlorocarbanilide in bar soap. Toxicol Lett 22, 241-248, doi:6474514

[11] Howes, D. and Black, J.G. 1976. Percutaneous absorption of triclocarban in rat and man. Toxicology, 6(1):67-76

[12] Scharpf, L. G., Jr.; Hill, I. D.; Maibach, H. I. Percutaneous penetration and disposition of triclocarban in man: Body showering. Arch. Environ. Health 1975, 30 (1), 7–14

[13] Ahn K.C., Zhao B., Chen J., Cherednichenko G., Sanmarti E., Denison M., Lasley B., Pessah I., Kultz D., Chang D., Gee S., and Hammock B. (2008). In vitro biological activities of the antimicrobials triclocarban, its analogues, and triclosan in bioassay screens: receptor-based bioassay screens. Env. Health. Perspect. 116(9), 1203-1210.

of *in vitro* cellular system screening tools (AhR, ER, AR and RyR bioassays) in recombinant rat hepatoma (liver cancer) cells, human ovarian cancer cells, and skeletal myotube primary cultures from mice. The study reported that in the presence of estrogen or testosterone, TCC enhanced the actions of these hormones.

The cell cultures were exposed to TCC concentrations ranging from 1 to 10 µM; while *in vitro* exposures are difficult to extrapolate directly to whole body dosages, by rough estimation the cell cultures received an approximate dose of 100-1000 µg/kg-body weight/day. By comparison, a bar soap user would get an estimated systemic average dose on the order of 0.0035 and 0.035 mg/kg bw/day.[14]

The Research Concept states: *Currently, there is limited in vivo toxicological data to adequately characterize the possible endocrine actions and human health effects of TCC; however, from the available data, there is evidence that TCC has effects on the reproductive, immune, and hepatic systems.*

Comments:

TCC has a low order of toxicity to mammalians based on a variety of acute, subchronic and chronic toxicity studies. The toxicological endpoints referenced above were included in traditional safety studies submitted to government agencies including EPA under the HPV Chemical Challenge Program and are publicly available.[15]

Effects on the reproductive system

Reproductive effects were found with extremely highly doses of TCC administered by a non-relevant route of exposure. Two-year bioassays were conducted with rats for carcinogenic and reproductive endpoints after the oral administration of TCC. Rats exposed to 1000 mg/kg/day for 30 days showed no adverse effects. The No-Observed-Effect-Level (NOEL) was established at 25 mg/kg/day after some testicular degeneration was found at 75 mg/kg/day in the 24 month-oral study. Another study (Nolen and Dierchman, 1979)[16] reported some reproductive effects of a 2:1 mixture of TCC and 3-trifluoromethyl-4,4'-dichlorocarbanilide. However, reproductive studies with TCC alone did not find any effects.

Effects on the immune system

The 3 generational study referenced in the Research Concept where organs weights of adult rats (liver, kidney, spleen) were observed used high doses of TCC (23 – 280 mg/kg/d). The high doses (> 50 mg/kg/d) resulted in these effects. In F3 weanlings, the lower spleen and liver weights were observed at TCC greater than 95 mg/kg/d. By comparison, humans may get exposed to TCC concentrations lower than 1 mg/kg/day.[14]

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[14] TRICLOCARBAN (CASRN 101-20-2). (3,4,4'-Trichlorocarbanilide). Potential Designated Chemical. May 24, 2010 Meeting of Scientific Guidance Panel (SGP). Biomonitoring California. http://biomonitoring.ca.gov/events/biomonitoring-california-scientific-guidance-panel-meeting-may-2010.

[15] http://www.epa.gov/hpv/pubs/summaries/tricloca/c14186tc.htm.

[16] Nolen, G. and T. Dierchman, 1979. Reproduction and teratogenic studies of a 2:1 mixture of 3,4,4'-trichlorocarbanilide and 3-trifluoromethyl-4,4'-dichlorocarbanilide in rats and rabbits.*Toxicol Appl Pharmacol* 51:417-25.

The EU SCCP reviewed a chronic 2-year toxicity study where statistically significant changes in the spleen weight was observed; however, because no microscopic changes were found, it was concluded that changes may not have been biologically significant.[17]

Hepatic effects

The hepatic effects were observed in the 3 generational study described above where high doses of TCC were used. The EU SCCP that reviewed the chronic 2-year toxicity study with statistical changes in the liver weight, also determined that there were no microscopic changes and the effect might not have been biological significant.[17]

Another chronic feeding toxicity study found no gross, biochemical, hematological, central nervous system or histopathological effects related to TCC.[18]

2. Key Issues:

The Research Concept states: *Available toxicological data and published literature suggest that Triclocarban may have, or may amplify, endocrine activity and given that most endocrine endpoints have not been thoroughly evaluated, an assessment of potential endocrine actions (after oral administration), in the developing animal would be essential for a complete evaluation of the compound.*

The majority of the experiments regarding endocrine activity have been conducted with *in vitro* systems and have little relevance for consumer exposure. In a Hershberger assay on castrated rats, TCC did not affect body weight and did not affect weights of androgen-sensitive tissues such as seminal vesicles, glans penis, Cowper's glands and levator ani/bulbocavernous muscles, but increased the absolute liver and ventral prostate weights.[19] The effects of TCC are observed in the presence of added androgen testosterone suggesting the action of testosterone is enhanced. The relevance of these results are unknown.

We agree that an assessment of potential endocrine actions in the developing animal would be essential for a complete evaluation.

The Research Concept states: *Additionally, determining if there is a critical window of developmental exposure for these effects, if there are target organ toxicities (e.g. reproductive organs, thyroid, liver, and kidneys), and including a characterization of potential immune-related toxicities will provide a more comprehensive evaluation.*

Comments:

A review of toxicological data previously submitted to EPA, including studies referencing target organ toxicities, did not raise any concerns. The Environmental Defense Fund (EDF) reviewed and confirmed TCC's safety based on the mammalian toxicity data. EDF concluded that TCC

[17] Scientific Committee on Consumer Products. Opinion on Triclocarban. SCCP/0851/04

[18] Wright et al. (1975). Pharmacokinetic and toxicological studies with triclocarban. Toxicol. Appl. Pharm. 33, 171.

[19] Chen, J., Ahn, K.C., Gee, N.A., Ahmed, M.I., Duleba, A.J., Zhao, L., Gee, S.J. Hammock, B.D. and Lasley, B.L. (2008). Triclocarban enhances testosterone action: a new type of endocrine disruptor?. *Endocrinology*, 149(3): 1173-1179

has low acute toxicity, is negative in genetic toxicity tests and is also negative for carcinogenesis in a 2-year bioassay in rats.[15] EDF also agreed that there are few or no apparent effects observed in the well-conducted reproductive and developmental toxicity studies that were performed.

In addition, TCC has been reviewed for safety globally. The European Union Scientific Committee on Consumer Products (SCCP) concluded in 2005 that the use of Triclocarban for non-preservative purposes in cosmetic rinse-off hand and body care products up to a maximum concentration of 1.5% does not pose a direct risk to the health of the consumer. Moreover, TCC is approved as a preservative for cosmetics with a maximum permissible concentration of 0.2% under the European Union Cosmetic Products Directive (EU Directive 76/768/EEC). TCC is approved for use as an antimicrobial in cosmetic products in Switzerland at a maximum use concentration of 0.2%, (Annex 2, Swiss Cosmetic Product Regulation). TCC is also listed in the Japanese Cosmetic Standard as an approved preservative for cosmetic products with a maximum use concentration of 0.3% for leave-on cosmetics and no specified upper limit for rinse-off cosmetics.

3. Specific Aims

The Research Concept states:

- *Characterize the dose-response effects of oral exposure to TCC on target organ systems with a focus on reproductive, developmental, hepatic, and renal endpoints in the developing animal.*
- *Determine potential immune related toxicities after oral administration of TCC.*
- *Additional studies (e.g. carcinogenicity) will be included, as needed.*

Comment:

The oral exposure is not typical and has little relevance to consumers. From existing traditional studies authoritative bodies around the world have concluded that low risk for carcinogenicity exist.

In addition, FDA recently reviewed the safety profile of active ingredients used in consumer antiseptic products.[20] For TCC, FDA reviewed 2-yr oral carcinogenicity data from the manufacturer where the NOAEL in the rat was determined 25 mg/kg/day. The oral carcinogenicity study was considered adequate and showed that TCC does not pose a risk of cancer after repeated oral administration.

4. Proposed Approach

The Research Concept states:
Phase 2:
In vivo toxicity oral evaluation of TCC in rodents:

- *Subchronic oral including perinatal exposure window to assess potential for reproductive and developmental toxicities.*
- *Developmental immunotoxicology evaluation.*
- *Adult oral exposure 90-day toxicity study.*

[20] FDA Tentative Final Monograph on Consumer Antiseptics. http://www.reginfo.gov/public/servlet/ForwardServlet?SearchTarget=RegReview&textfield=0910-AF69

Comments:

Oral exposure should represent a worst-case exposure. If decided to proceed, data should be available to extrapolate to the dermal route. A request to repeat the study via the dermal route would be unfounded.

The TCC doses proposed for Phase 2 should be carefully selected to represent consumer exposure under realistic scenarios. As summarized in the EU SCCP report,[17] the signs of systemic toxicity were observed in the adult generations at dose levels above 50 mg/kg but adverse effects for reproductive and developmental toxicity were observed above 280 mg/kg. These doses are extremely high compared to consumer exposure levels.

We do not have comments on Phase 1 or Phase 3 of the Proposed Approach.

5. Significance and Expected Outcome:

The Research Concept states: *Triclocarban's widespread use in a number of consumer products and presence in the environment and aquatic organisms suggests that a more comprehensive understanding of its hazards is required. Therefore, a complete evaluation of potential endocrine activity and toxicities is expected to address data gaps for a chemical that appears to target hepatic, immune, reproductive, and developmental endpoints.*

Comment:

As we stated above, previous estimates of the market penetration for antibacterial bar soap, the primary use of triclocarban, and the use rate were much higher than current conditions. There is a substantial body of data available from which to characterize the hazards and potential risks to triclocarban. A number of authoritative bodies around the world have characterized those hazards and risks, and have set the conditions of safe use of triclocarban. There may some studies which are appropriate for filling gaps in the data but the proposed research program seems to go beyond what is called for given the level of use and what is currently known about the compound.

We appreciate your consideration of our comments. If you have any question regarding our submission, please feel free to contact me by phone at 202-662-2516 or by e-mail at pdeleo@cleaninginstitute.org.

Sincerely,
[Redacted]

Paul C. DeLeo, Ph.D.
Associate Vice President, Environmental Safety