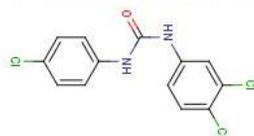


Triclocarban



Vicki Sutherland, PhD
National Institute of Environmental Health Sciences

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Antibacterial Overview:

- Triclocarban and Triclosan are residue producing antibacterial chemicals found in health & skincare products, (i.e. soaps, talc & deodorant)
 - Triclocarban - bar soaps
 - Triclosan - liquid soaps
- Triclosan use has expanded to include bonding to products (e.g. plastic kitchen tools, cutting boards, highchairs, toys, bedding and other fabrics)
- Triclosan and Triclocarban are both regulated as an over the counter drug by the FDA
 - FDA has requested additional efficacy and safety information
- Triclosan is currently under evaluation by the NTP due to its widespread commercial and personal use:
 - Dermal carcinogenicity study ongoing
 - Endocrine related health effects studies are in design



Triclocarban Nomination:

- Nominated by NIEHS for toxicological evaluation:
 - Use in consumer products
 - High level of human exposure
 - Potential for endocrine activity
- Aggregate production volumes:
 - 1998 - 0.5 and 1 million pounds
 - 2002 - 1 and 10 million pounds
 - 2006 - < 500,000 pounds

Triclocarban Routes of Exposure:

- **Dermal:** Use of products containing the compound (absorption across human skin is very low):
 - Bar soap concentrations range from 0.3 to 1.5%
 - Liquid soap concentrations 0.115 – 0.2%
 - Talc product concentrations range from 0.1 to 0.5%
 - No to low level skin and eye irritant
- **Oral:** Consumption of food contaminated with TCC either through direct consumption of marine life exposed to TCC or through handling food with hands or tools exposed to TCC
- **Inhalation:** production workers

Triclocarban Environmental Exposure:

- Triclocarban is among the most commonly detected organic wastewater contaminant¹
- Detected in rivers, streams, and wastewater treatment influent and effluent from multiple locations in the US^{2,3}
- Identified as persistent in water, soil, and sediment, but not bioaccumulative (although detected in a variety of marine life^{4,5})

1. Brausch and Rand 2011. Chemosphere 82:1518
2. HSDB (Hazardous Substances Data Bank). 2012. Triclocarban. HSDB No. 5009
3. Halden and Paull 2005 Environ Sci Technol, 39:1420
4. Ramaswamy, B. R. et al 2011. J Hazard Mater **192**:1739
5. U.S. EPA. 2014a. ECOTOX

Triclocarban Detection in Human Urine:

Location	Concentrations	
Denmark: ^{1,2}	<u>Mean Levels</u>	<u>Maximum Levels</u>
- Mothers	0.10 µg/g	2.5 µg/g
- Children	0.08 µg/g	1.8 µg/g
- Men		0.22 to 0.56 ng/mL
Atlanta, GA ³	3.85 ng/mL	
Athens, Greece ⁴	0.8 ng/mL	1.9 ng/mL

1. Frederiksen, et al., 2013. Int J Hyg Environ Health, 216:772

2. Lassen, et al., 2013. Environ Res, 126:164

3. Ye, X., et al., 2011. Toxicology, 286:69

4. Asimakopoulos, et al., 2013. Sci Total Environ, 470-471C:1243

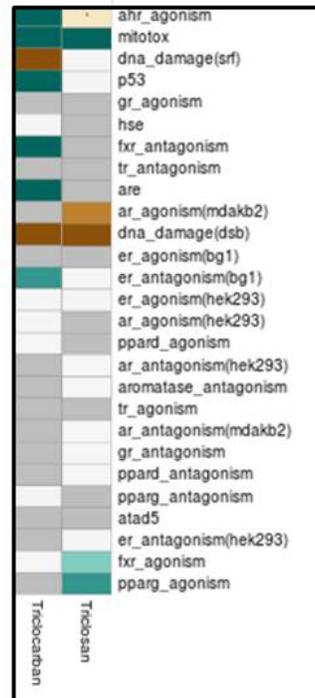
Triclocarban Dermal Toxicity:

- Humans:
 - ^{14}C TCC oral administration - 3.7 nmol/g plasma (maximal concentration)
 - Single & repeated dermal exposure - concentrations of < 25 – 167 ng/mL
 - Dermal TCC - 1.35% remained in skin
 - Showering with 0.6% TCC soap - absorption rate of 0.6%
- Rodents:
 - SD rats and hairless mice washed with soap containing ^{14}C TCC - < 2% remained in the skin
 - Dermal absorption is dose-dependent, but not time-dependent
- ADME/TK
 - TCC is moderately absorbed via oral route (depending on vehicle) and poor to moderately absorbed dermally

Tox21 High Throughput Screening data:

Triclocarban activity:

- Estrogen receptor and farnesoid-X-receptor antagonism
- Aryl hydrocarbon receptor, p53, and antioxidative response element agonism



Triclocarban Endocrine Activity:

- Increases gene expression regulated by testosterone:^{1,2}
 - TCC enhances testosterone-induced androgen receptor-mediated transcriptional activity *in vitro*
 - Amplification effect was noted *in vivo* when TCC was added to the diet of castrated male rats and all male sex accessory organs increased in size
 - Suggestions that it may also affect thyroid and estrogen hormones

The data suggest that the bioactivity of endogenous hormones may be amplified by exposure to products containing sufficient levels of TCC

1. Duleba, et al. 2011 Reproductive Sciences 18:119
2. Chen, J. 2008 Endocrinology, 149:1173

Triclocarban *in vivo* study data:

Study	Summary Results
Rat 30-day oral study ¹ <ul style="list-style-type: none">- 10 animals/sex- 500 & 1000 mg/kg- Gavage of 25% TCC	<ul style="list-style-type: none">• No effects noted for parameters measured• No endocrine evaluations (1960)
Rat 8-week in male ¹ <ul style="list-style-type: none">- 35 males/group- 25, 75, & 250 mg/kg- Diet	<ul style="list-style-type: none">• Lowered body weights and food consumption• No control group, no necropsy, no histopathology, no clinical chemistry
Rat 2-year oral study ¹ <ul style="list-style-type: none">- 20 animals/sex- 25, 75, & 250 mg/kg- Diet	<ul style="list-style-type: none">• Slightly lowered body weights and food consumption• Increase in organ weights (spleen, heart, testes, and liver)• Changes in clinical pathology parameters, including anemia

1. Summary Data - Studies submitted to Environmental Protection Agency (EPA)

Triclocarban *in vivo* study data:

Study	Summary Results
Rat 3 Generation study ¹ - 250,500, 1000 and 3000ppm - Diet	<ul style="list-style-type: none">• Changes in organ weights (spleen, liver, kidneys) and bone marrow• Decreases in the mean number of live births and pup weights for the F1 generation• Abnormalities (e.g., spina bifida) were noted in two offspring (1979)
Rat reproductive toxicity 2:1 diet mix TCC to TFC ²	<ul style="list-style-type: none">• Reductions in number of animals that conceived, number of pups born, number of pups surviving to weaning, and pup body weights
Rabbit Teratogenicity 2:1 oral mix TCC to TFC ²	<ul style="list-style-type: none">• Dose-related evidence of maternal toxicity, including weight losses, abortions, and deaths.

1. Summary Data - Studies submitted to Environmental Protection Agency (EPA)

2. Nolen G.A. and Dierckman T.A. 1979. Toxicol. Appl. Pharmacol. 51:417



Knowledge Gaps:

- Limited developmental and reproductive for public review
- Limited information on endocrine effects of TCC
- Limited chronic exposure data available for public review
- Limited chronic data in multiple species for public review
- Comprehensive ADME/TK profile
- No immunotoxicity, neurotoxicity data
- Limited carcinogenicity data



Challenges/Key Issues:

- Previous studies of limited utility for evaluation of endocrine-related effects
- Endocrine activity or amplification of endocrine activity
- Determine route of exposure
- Issues with *in vitro* assessments for antimicrobial agents
- Critical window of developmental exposure
- Specific organ toxicity
- Potential immune toxicity



Specific Aims and Approaches:

1. Characterize the dose-response effects of TCC exposure in both rat and mouse short-term and long-term studies:
 - Endocrine activity – reproductive and developmental evaluation
 - Target organ toxicities - focus on the hepatic and renal systems
2. Characterize ADME and TK profiles
 - Oral to dermal extrapolation
3. Determine if TCC has immunotoxic effects



Proposed Approach:

Phase 1:

In vivo toxicity evaluation of oral administration of TCC in rodents:

- Perinatal oral exposure dose range finding study in rats
- Short-term adult oral exposure toxicity study in mice
- ADME/TK characterization (strain, oral-to-dermal)



Proposed Approach:

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 in rats
- Developmental immunotoxicology evaluation
- Adult mouse 90-day toxicity study

Phase 3:

Additional studies, as needed



Significance and Outcome:

Triclocarban's use in consumer products and presence in the environment suggests that a more comprehensive understanding of its hazards is required:

- Evaluation of potential endocrine activity
- Characterize organ toxicities

Data will address data gaps for a chemical that appears to target hepatic, immune, reproductive, and developmental endpoints

Review questions:

1. Comment on the merit of the proposed project relative to the mission and goals of the NTP. The NTP's stated goals are to: Provide information on potentially hazardous substances to all stakeholders; Develop and validate improved testing methods; Strengthen the science base in toxicology; Coordinate toxicology testing programs across DHHS (<http://ntp.niehs.nih.gov/go/about>).
2. Comment on the clarity and validity of the rationale for the proposed project. Has the scope of the problem been adequately defined? Are the relevant knowledge gaps identified and clearly articulated?
3. Comment on the strategy and approach proposed to meet the stated objectives of the project. Are specific aims reasonable and clearly articulated? Is the scope of work proposed appropriate relative to the public health importance of the issue(s) under consideration? If not, what modifications do you recommend? Where steps to further refine the strategy and/or approach are proposed, are they appropriate?
4. There are challenges inherent to achieving the aims of any proposed project. Are the relevant challenges and/or key scientific issues identified and clearly articulated? Where approaches to overcome challenges are proposed, are they appropriate? Are you aware of other scientific issues that need to be considered?
5. Rate the overall significance and public health impact of this project as low, moderate, or high. Identify any elements of the proposed project that you feel are more important than others, and/or that have a higher likelihood of success at meeting pre-defined specific aims.
6. Provide any other comments you feel NTP staff should consider in developing this project.