

NTP Research Concept: Triclocarban

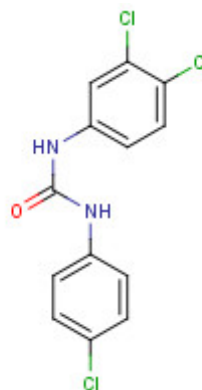
Project Leader

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Background and Rationale

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Triclocarban (TCC) was nominated by the National Institutes of Environmental Health Sciences (NIEHS) to the National Toxicology Program (NTP) for toxicological evaluation based on its extensive use, high potential for human exposure, and potential endocrine activity. TCC is utilized as an agent to disinfect surfaces and eliminate potentially harmful bacteria by inhibiting the enoyl-acyl carrier protein reductase (ENR) enzyme and thereby preventing the bacteria from manufacturing fatty acids for building cell membranes. It is primarily used in soaps and lotions. 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.¹



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). It is one of the most commonly detected organic wastewater contaminants² and has been found in rivers, streams, and wastewater influent. TCC is persistent in the environment, slightly persistent in the aquatic environment, and toxic to fish and potentially other aquatic organisms (<http://www.pbtprofiler.net/ChemDetails.asp?l=0>). 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).^{3,4}

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 (http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=7547&loc=ec_rcs). 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.

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. Rats administered TCC via diet exhibited a significant reduction in the number of animals that conceived, numbers of pups born to those that did conceive, number of pups that survived until weaning, and in pup body weight at weaning. Rabbits orally exposed to TCC during gestation had dose related weight losses, abortions, and death. In a 3 generational study in both male and female rats, decreases in organ weights (liver, kidney, spleen) were noted for adults. The mean number of live pups at birth was lower than controls in the F1 generation of the high dose group, and decreases in spleen, liver, and kidney weights were observed in the second F3 weanlings at the middle and/or high dose.

Human oral and dermal absorption studies have been performed and blood levels of TCC ranged from below the detection limit (10-25 ng/mL) to 167 ng/mL.^{5,6,7} Additional experiments demonstrated that showering with a commercially available soap containing 0.6% triclocarban lead to an absorption rate of 0.6%.⁸ Studies in rats and mice washed with soap containing ¹⁴C-TCC have shown that <2% of the applied dose remained in the skin and that dermal absorption is dose-dependent, but not time-dependent.^{5,9} The majority of TCC is found in bile with lower levels in the liver and kidneys.¹⁰

Assessments of chronic toxicity, immunotoxicity, reproductive, developmental, and carcinogenic evaluations have not been performed or are very limited in nature.

Key Issues

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. 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.

Specific Aims

- 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.

Proposed Approach

Phase 1

2

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

- Perinatal oral exposure dose range finding study
- Short-term adult oral exposure toxicity study

ADME/TK characterization in rodents: oral and intravenous exposure.

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.

Phase 3

Additional studies, as needed.

Significance and Expected Outcome

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.

References

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