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Application of the Navigation Guide systematic review methodology to the evidence for developmental and reproductive toxicity of triclosan

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ABSTRACT

Background: There are reports of developmental and reproductive health effects associated with the widely used biocide triclosan.
Objective: Apply the Navigation Guide systematic review methodology to answer the question: Does exposure to triclosan have adverse effects on human development or reproduction?
Methods: We applied the first 3 steps of the Navigation Guide methodology: 1) Specify a study question, 2) Select the evidence, and 3) Rate quality and strength of the evidence. We developed a protocol, conducted a comprehensive search of the literature, and identified relevant studies using pre-specified criteria. We assessed the number and type of all relevant studies. We evaluated each included study for risk of bias and rated the quality and strength of the evidence for the selected outcomes. We conducted a meta-analysis on a subset of suitable data.
Results: We found 4282 potentially relevant records, and 81 records met our inclusion criteria. Of the more than 100 endpoints identified by our search, we focused our evaluation on hormone concentration outcomes, which had the largest human and non-human mammalian data set. Three human studies and 8 studies conducted in rats reported thyroxine levels as outcomes. The rat data were amenable to meta-analysis. Because only one of the human thyroxine studies quantified exposure, we did not conduct a meta-analysis of the human data. Through meta-analysis of the data for rats, we estimated for prenatal exposure a 0.09% (95% CI: −0.20, 0.02) reduction in thyroxine concentration per mg triclosan/kg-bw in fetal and young rats compared to control. For postnatal exposure we estimated a 0.31% (95% CI: −0.38, −0.23) reduction in thyroxine per mg triclosan/kg-bw, also compared to control. Overall, we found low to moderate risk of bias across the human studies and moderate to high risk of bias across the non-human studies, and assigned a "moderate/low" quality rating to the body of evidence for human thyroid hormone alterations and a "moderate" quality rating to the body of evidence for non-human thyroid hormone alterations.
Conclusion: Based on this application of the Navigation Guide systematic review methodology, we concluded that there was "sufficient" non-human evidence and "inadequate" human evidence of an association between triclosan exposure and thyroxine concentrations, and consequently, triclosan is "possibly toxic" to reproductive and developmental health. Thyroid hormone disruption is an upstream indicator of developmental toxicity. Additional endpoints may be identified as being of equal or greater concern as other data are developed or evaluated.

1. Introduction

Integration of the available scientific evidence to reach a strength-of-evidence conclusion about chemical toxicity is fundamental to developing hazard assessments for regulatory action, clinical guidelines, and safer alternatives to toxic chemicals. To this end, the Navigation Guide systematic review methodology was developed by a working group in 2009 to provide a transparent, reproducible framework to evaluate the quality and strength of evidence about the relationship between

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environmental exposures and reproductive and developmental health (Woodruff and Sutton, 2011). Beginning in 2011, the National Toxicology Program (NTP) undertook a complementary effort to develop a framework for systematic reviews in environmental health (Rooney et al., 2014). In 2014 two reports by the National Academy of Sciences found that such methods of evidence integration reflect the approach that the U.S. Environmental Protection Agency (U.S. EPA) should adopt to determine whether environmental chemicals are harmful to human health (National Research Council, 2014a; National Research Council, 2014b). A report from the UK similarly recommended uptake of systematic methods of evidence integration by relevant European Union agencies, to increase transparency and decrease bias in regulatory rulemaking (Whaley, 2013). Since 2012, the NTP has been actively building the tools, expertise, and other infrastructure that will facilitate increased utilization of systematic review methodologies (Rooney et al., 2014; National Toxicology Program, 2015). The U.S. EPA has proposed steps to begin to incorporate principles of systematic review into its Integrated Risk Information System (IRIS) process (U.S. Environmental Protection Agency, 2014; The National Academies, 2012). A 2014 case study applying the Navigation Guide methodology to evaluate the human and non-human evidence of perfluorooctanoic acid (PFOA) on fetal growth demonstrated how the efforts under development by the NTP and consideration by the U.S. EPA are achievable (Koustas et al., 2014; Johnson et al., 2014; Lam et al., 2014; Woodruff and Sutton, 2014). The present case study was intended as part of ongoing proof-of-concept and an opportunity for the California Office of Environmental Health Hazard Assessment (OEHHA) to explore the Navigation Guide methodology on a broader range of outcomes. This systematic review evaluates the evidence for the effects of exposure to the widely-used biocide triclosan on endpoints of developmental and/or male or female reproductive toxicity.

Triclosan, or 2,4,4′-trichloro-2′-hydroxydiphenyl ether, is a synthetic, broad-spectrum anti-microbial agent developed over 50 years ago and introduced as a surgical scrub (Cooney, 2010). In 2013, there were 2000 antimicrobial consumer products, including soaps and other personal care products, dental products, clothing, paints, plastics and children's toys (Halden, 2014). A 2000 survey found that 76% of U.S. liquid soaps and 29% of bar soaps contained triclosan or an alternative antimicrobial triclocarban (Perencevich et al., 2001).

The FDA has the authority to regulate triclosan when used in personal care products and medical devices. As the FDA has not finalized its 1974 draft topical antimicrobial drug products Over-the-Counter Drug Monograph, triclosan is currently unregulated in personal care products (U.S. Food and Drug Administration, 2013). With intent to finalize the Monograph, the FDA proposed a new rule in 2013 that would require manufacturers to provide safety data and data that demonstrates the clinical benefit of using antibacterial soaps over plain soap and water (U.S. Food and Drug Administration, 2013). Pesticidal uses of triclosan come under the regulatory authority of U.S. EPA (U.S. EPA, 2015).

Exposure to triclosan is widespread in the U.S. population (Adolfsson-Erici et al., 2002; Calafat et al., 2008; Wilding et al., 2009; Wolff et al., 2007). There is also growing concern over triclosan's possible effects on public health, including direct health effects, e.g., skin irritation (Robertshaw and Leppard, 2007; Schena et al., 2008), endocrine disruption and associated reproductive effects as observed in animal experiments (Foran et al., 2000; Matsumura et al., 2005; Veldhoen et al., 2007; Stoker et al., 2010) and human studies (Wolff et al., 2010; Chen et al., 2013; Koeppe et al., 2013), and indirect effects, i.e., antibiotic resistance (Aiello et al., 2007).

This is the first systematic review of the human and animal evidence linking exposure to triclosan to adverse reproductive or developmental health endpoints. Past reviews of triclosan were expert-based narrative reviews, not systematic reviews, and/or primarily focused on assessing the risk of using personal care products containing triclosan, using exposure estimates based on certain concentrations of triclosan in the products (Rodricks et al., 2010; SCCS. Scientific Committee on Consumer Safety, 2011; Witorsch, 2014). In contrast, we did not estimate exposure or assess risk in the present review; we evaluated the evidence of the chemical's toxicity (i.e., hazard).

Based on the presence of triclosan in wide-ranging consumer products, the environment, and humans, and potential for human health effects, we applied the Navigation Guide systematic review methodology to evaluate the strength of the evidence relating triclosan exposure to developmental or reproductive health effects.

2. Methods

The Navigation Guide is based on best practices in evaluation of clinical evidence and adapts the evidence-based medicine methodology developed by Cochrane and the Grading of Recommendations Assessment Development and Evaluation (GRADE), tested and evaluated since the 1990s (Guyatt et al., 2011; Balshem et al., 2011).We assembled a team of reviewers with expertise in toxicology, epidemiology, environmental health, biology, statistics and systematic review, and developed a pre-specified protocol for conducting the systematic review (Johnson et al., 2013). Each of the protocol steps are described below and the protocol is available at http://prhe.ucsf.edu/prhe/pdfs/Triclosan%20Protocol.pdf.

2.1. Specify the study question

Our objective was to answer the question: "Does exposure to triclosan have adverse effects on human development or reproduction?" We developed a "Participants," "Exposure," "Comparator" and "Outcomes" (PECO) statement, which is used as an aid to developing a strategy for answering the study question (Higgins and Green, 2011). Our PECO statement was:

2.1.1. Participants

Humans or animals (whole organism studied during the reproductive or developmental time period, tissue, organ, cell line or components), or computer models of humans or animals.

2.1.2. Exposure

For developmental effects, we included one or more exposures to triclosan, by any route, which occurred during the following periods: pre-conception (exposure of either or both parents or, if relevant, preceding generations), prenatal (exposure of pregnant female and/or directly of fetus), or postnatal (until the time of sexual maturation).

For reproductive effects, we include one or more exposures to triclosan at any time preceding assessment of reproductive outcome.

2.1.3. Comparators

Comparable populations or subjects (human, non-human, tissues, organs, cell lines or components) exposed to vehicle-only treatment or lower levels of triclosan than the more highly exposed subjects.

2.1.4. Outcomes

Reproductive effects: alterations in hormone levels; effects on male or female gametes (production, maturation, or transport), fertility, fecundity, estrous cycles, menstrual cycles, endocrine function, sexual behavior, gestation, parturition, lactation, age at puberty or reproductive senescence or menopause; pregnancy complications; increased pregnancy wastage; or alterations in size, morphology, or function of reproductive organs.

Developmental effects: fetal loss or resorption, stillbirth, neonatal or subsequent mortality, alterations in sex ratio, altered fetal or postnatal growth, structural malformations and variations, altered gestation length, functional deficits such as alterations in behavior, and morbidity. In addition to effects of prenatal exposure during all or any part of gestation, developmental toxicity can result from: 1) pre-conception exposure of parental or previous generations causing genetic mutation or