April 8, 2011

Timothy F. McMahon
Office of Pesticide Programs (OPP)
Regulatory Public Docket (7502P)
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460–0001

Re: Petition for a Ban on Triclosan, Federal Register, Vol. 75, No. 235, Wednesday, December 8, 2010.

Docket identification (ID) number: EPA–HQ–OPP–2010–0548

Dear Dr. McMahon:

The American Cleaning Institute (ACI) appreciates this opportunity to provide comments on a petition submitted by Beyond Pesticides and Food & Water Watch (hereafter referred to as ''the petitioners'') to the Environmental Protection Agency (hereafter referred to as ''EPA'' or ''the Agency''), asking EPA to use its authority under various statutes to ban triclosan. ACI is a trade association representing the $30 billion U.S. cleaning products industry. 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 members have an interest in the petition since our members utilize triclosan in personal care and hand hygiene products regulated by FDA. These products play a beneficial role in the daily hygiene routines of millions of people throughout the U.S. and worldwide. They have been and are used safely and effectively in homes, hospitals, and workplaces every single day. Furthermore, triclosan and products containing it are regulated by a number of governmental bodies around the world and have a long track record of human and environmental safety which is supported by a multitude of scientifically based transparent risk analyses.

ACI members take exception to the Beyond Pesticides and Food & Water Watch petition for the following reasons:

- First and foremost, ACI points to the very comprehensive review of triclosan recently completed by the EPA during the development of the Re-registration Eligibility Decision (RED) (September 2008). The RED included an evaluation of all routes of human exposure (both those regulated by the EPA and those regulated by the FDA). As part of the RED process, EPA utilized data from the National Center for Health Statistics (NCHS) National Health and Nutrition Examination Survey (NHANES) database in order to reach its findings

and conclusions. Comprehensive reviews were conducted by similar regulatory agencies (e.g., Australia, European Union). Additional reviews have been conducted by expert panels and are published in the scientific literature;

- Second, ACI points out that in the U.S., this ingredient is regulated by the FDA or the EPA, depending upon the intended product use and associated claims. The petitioners have erroneously implied in the presentation of their petition that the EPA has authority to regulate products regulated by FDA (e.g., hand hygiene products, toothpaste). EPA's focus must remain on products over which it has statutory authority to regulate, and ignore the petitioners' information and requests for relief related to FDA-regulated products;
- Third, the petitioners based their request for a ban on a variety of claims as well as statutory mandates. The petitioners' position is deficient in many ways. Primary amongst these is their failure to demonstrate the actual existence of significant risks or harm to human health and the environment that were missed or ignored by the EPA during the course of the Agency's due diligence process while producing the RED document on triclosan. This would be a minimal necessity for a ban under regulatory requirements. The petitioners contend "that the scientific evidence and the legal authorities are so substantial as to require suspension of the registered uses of triclosan pending agency deliberations regarding cancellation." However, nowhere do they provide actual data refuting the EPA RED evaluation nor do they demonstrate that damage to humans and the environment is imminent and/or substantial; and
- Finally, the petitioners have relied on scientific bias, failed to present new relevant research that could impact EPA's findings, and appear to rely on an uninformed view of the established re-registration process. The petitioners have neither demonstrated nor proven their contention that triclosan "poses an actual and imminent threat to human health and the environment." In their own words, "contact with sufficient quantities of triclosan" is an important factor for "specific threats," "potential destruction" and becoming "vulnerable." Further, EPA has made a commitment to expedite another RED review in 2013, a full 10 years ahead of its previously planned schedule under FIFRA. The petitioners have not presented any basis for further accelerating EPA's review. On the basis of that lack of demonstration, combined with the evidence presented in these comments, EPA should deny this petition and the RED process should be allowed to proceed at its intended pace.

The following summarizes our response to the scientific points raised in this citizen petition and the attachment provides detailed comments on points made by the petitioners.

- **Endocrine Disruption**

  Based on extensive studies relevant to understanding the potential for triclosan to cause endocrine disruption in humans and aquatic animals, triclosan is not a cause of endocrine related effects at environmentally relevant concentrations. Further, extensive *in vivo* studies demonstrate that triclosan is not causing reproductive or cancer effects.

- **Bacterial Resistance**

  Recognizing the uncertainty and variability in laboratory data, evaluation of potential antimicrobial resistance should be related to *in situ* use of triclosan. *In situ* studies

conclusively demonstrate no association between triclosan exposure and microbial resistance to antibiotics.

- **Biomonitoring**

  Assessments of the potential impacts of triclosan found in human body fluids and tissues demonstrate, in concert with the assessment conducted as part of the EPA RED, that the use of triclosan in various products does not increase risks of harm, including for infants, children, and workers.

- **Ecosystems, Drinking Water and Food**

  Triclosan and its degradates do not pose a risk to aquatic or terrestrial environments, nor do they pose a threat of accumulation in drinking water or food.

- **Efficacy**

  The efficacy of triclosan has been demonstrated to the EPA for the products the Agency regulates. The petitioners present no information that draws into question EPA's conclusions. Although not regulated by EPA, the petitioners present views on the efficacy of antibacterial hand wash products that are not supportable by the weight of evidence. Antibacterial hand wash products containing triclosan, which are regulated by FDA as Over-the-Counter (OTC) drug products, provide a public health benefit by reducing or eliminating pathogenic bacteria on the skin to a significantly greater degree than plain soap and water. The use of antibacterial hand wash products containing triclosan for infection control in both clinical and non-clinical settings has been documented in the published literature.

- **Decisions Regarding Triclosan**

  Many government organizations and other groups have reviewed the triclosan database and agree that insufficient information exists to demonstrate that triclosan harms human health. They neither rejected nor banned triclosan but rather decided that setting safe and effective concentration levels was appropriate.

The citizen petition to the EPA requesting a ban on triclosan has uniformly failed to provide an acceptable basis for such a ban in each major area of claims - endocrine disruption, bacterial resistance, presence in the body, wastewater treatment, toxicity (including degradate toxicity) and ecosystem impact. The EPA should summarily reject this petition as inadequate, insufficient and lacking in merit.

Please contact me if you have any questions on these comments or would like to discuss them.

Sincerely,

Richard Sedlak
Senior Vice President
Technical & International Affairs

American Cleaning Institute (ACI) comments on:

Petition for a Ban on Triclosan, Federal Register, Vol. 75, No. 235, Wednesday, December 8, 2010: Docket identification (ID) number EPA–HQ–OPP–2010–0548

The petitioners, Food & Water Watch and Beyond Pesticides, have submitted a Citizen Petition to the United States Environmental Protection Agency (USEPA) requesting a ban on the use of triclosan (2,4,4'-trichloro-2'-hydroxy-diphenylether), an antimicrobial ingredient. This document presents the American Cleaning Institute's (ACI) detailed comments on the petition, along with citations to supporting studies and reports.

I. Environmental Laws and the Administrator's Authority to Take Action to Protect Public Health and Safety and the Environment

A. *Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA)*

1. Regulatory Jurisdiction of EPA and FDA

As noted in EPA's *Federal Register* notice, triclosan is an antimicrobial substance used in a variety of antimicrobial pesticide, hand hygiene, toothpaste, and consumer products. EPA regulates antimicrobial pesticides under the statutory authority of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The premarket approval requirements for antimicrobial pesticides require special tests to ensure efficacy and to determine human and ecological risks (U.S. EPA, 2011).

Antimicrobial pesticide products are categorized as either "public health" or "non-public health" products, depending on the specific claims made on a product label. Registrants of public health antimicrobial pesticide products must submit efficacy data to support their application for registration or amendments to add public health claims, whereas registrants of non-public health antimicrobial pesticide products are required to generate efficacy data but not submit those data, unless EPA requests that the data be submitted on a case-by-case basis. Pesticide registration and reregistration requires a complete scientific analysis in order to show that a pesticide or pesticide product can be used without causing unreasonable adverse effects to human health or the environment. EPA is responsible for the development and issuance of Reregistration Eligibility Decision Documents (REDs) for all pesticide chemicals. The RED document formally presents the Agency's evaluation of the data base supporting the reregistration of a pesticide (including conclusions regarding which uses are eligible for reregistration under specific conditions and requirements) (U.S. EPA, 2008a). EPA issued the RED for triclosan, including the required human health and environmental risk assessments and risk management decisions, in September 2008 (USEPA, 2008a).

Antimicrobial substances used in or on living animals or humans are subject to the Federal Food, Drug, and Cosmetic Act (FFDCA). Personal care products containing triclosan (e.g., antibacterial soaps, toothpastes, and some cosmetics) are regulated by the U.S. Food and Drug Administration (FDA). FDA has stated that insufficient evidence exists to demonstrate that triclosan harms human health. FDA has also announced that it is currently in the process of reviewing all of the available evidence on triclosan's safety and plans to issue a proposed rule for

Consumer Antiseptic Drug Products, which includes antimicrobial soaps and antiseptic handwashes that are intended for daily use by the public, in the spring of 2011 (U.S. FDA, 2010). Given that FDA has primary jurisdiction over these types of products and has already announced that it will be reviewing the safety of triclosan under a public rulemaking covering Consumer Antiseptic Drug Products in the spring of 2011, there is no need for EPA to take further action under this petition.

Some antimicrobial products are also subject to both FIFRA and FFDCA (i.e., dual jurisdiction products) because they involve direct or indirect food uses, or use on food contact surfaces. However, it is important to note that all exposures, including those resulting from EPA-registered products as well as from products outside EPA's regulatory jurisdiction (e.g., products regulated by FDA), were considered in EPA's exposure evaluation under the triclosan RED in 2008.

The petitioners claim that both EPA and the FDA have concurrent regulatory jurisdiction over certain substances and uses and cite a number of examples, as follows: sanitizers for food contact surfaces; microbiocides in packaging coming into contact with food; antimicrobial agents used on medical devices; and substances used to control microorganisms in cane sugar and beet sugar mills. However, the only situation among those cited where EPA has regulatory authority under FFDCA is in the area of sanitizers for food contact surfaces (specifically, food-contact substances intended to exert an ongoing antimicrobial effect on a semi-permanent or permanent food-contact surface, other than the surface of food packaging). Going further, in this instance of use, triclosan is not listed for use as a sanitizer for food contact surfaces. EPA should recognize the overstatements made by the petitioners and respond with a clarification for the public record as to which products it actually does regulate.

2. EPA Regulation

The EPA RED evaluation of the triclosan database met the Agency's mandate using established scientific principles and determined that triclosan met the requirements for re-registration pending satisfactory completion of certain additional studies. This process is continual and evolving as new data and concerns are raised. The petitioners have ignored the established registration process. The Agency should continue to fulfill its mandate under FIFRA and the RED process should be allowed to proceed at its intended pace.

3. EPA should deny the relief under FIFRA requested in the petition

Whenever the EPA bans or restricts chemical substances, they are held to a standard of relying on evidence of definitive human and/or environmental adverse effects. Petitioners should be held to the same requirements and provide actual evidence of damage to human health, safety and the environment. In this case, the petitioners have not provided any new, compelling information that supports their contention that "the magnitude of the health threat posed by triclosan" necessitates that EPA cancel and suspend this substance in such a restricted manner that it takes precedence over all other active pesticide ingredients.

B. *Clean Water Act*

1. Objectives, Structure and Relevant Legal Provisions

The Federal Water Pollution Control Act (Clean Water Act (CWA)) establishes the basic structure for regulating discharges of pollutants into the waters of the United States and regulating quality standards for surface waters. The CWA provides EPA with the authority to set effluent limits on an industry-wide (technology-based) basis and on a water-quality basis that ensures protection of the receiving water. Effluent guidelines are national standards that are developed by EPA on an industry-by-industry basis, and are intended to represent the greatest pollutant reductions that are economically achievable for an industry.

To develop these technology-based regulations, EPA must first gather information on the industry's practices; characteristics of discharges (e.g., storm water flows and pollutants); technologies or practices used to prevent or treat the discharge; and economic characteristics. EPA must then identify the best available technology that is economically achievable for that industry in order to set regulatory requirements based on the performance of that technology. The effluent guidelines do not require facilities to install the particular technology identified by EPA; however, the regulations do require facilities to achieve the regulatory standards which were developed based on a particular model technology. The standards are then incorporated into National Pollutant Discharge Elimination System (NPDES) permits issued by States and EPA regional offices.

a) Technology-Based Regulation

When Congress passed the CWA, it specifically mandated a “technology-based” implementation program requesting that all national permits would require “best available treatment technology”. The biological treatment component of a municipal treatment plant is termed secondary treatment and is usually preceded by simple settling (primary treatment). Secondary treatment standards are established by EPA for publicly owned treatment works (POTWs) and reflect the performance of secondary wastewater treatment plants. These technology-based regulations apply to all municipal wastewater treatment plants and represent the minimum level of effluent quality attainable by secondary treatment, as reflected in terms of 5-day biochemical oxygen demand (BOD5) and total suspended solids (TSS) removal.

The secondary treatment standards also provide for special considerations regarding combined sewers, industrial wastes, waste stabilization ponds, and less concentrated influent wastewater for combined and separate sewers. In addition, the secondary treatment standards also provide alternative standards established on a case-by-case basis for treatment facilities considered equivalent to secondary treatment (trickling filters and waste stabilization ponds).

At the time the CWA was passed, wastewater treatment plants (WWTPs) were considered adequate if “secondary treatment” processes removed 85% of conventional wastewater constituents. Currently, however, WWTP’s are more efficient and >95% removals can be achieved, mostly attributed to aerobic biodegradation. In the case of triclosan, a removal rate of >97% is often reported for activated sludge (AS) plants (Thompson et al., 2005; McAvoy et al., 2002). This efficient removal rate results in very small levels of triclosan in the effluent, which are further reduced by in-stream sorption, biodegradation, and photodegradation resulting in

levels not considered an environmental hazard. Furthermore, the PEC/PNEC ratio for triclosan under even the highest likely exposures which could occur immediately downstream of the WWTP discharge point has been calculated to be less than 1.0 suggesting that risks to aquatic species are low (Capdevielle et al., 2007).

b) Health-Based Water Quality Regulation; Toxic Pollutants

NPDES permits may include discharge limits based on federal or state/tribe water quality criteria or standards that were designed to protect designated uses of surface waters, such as supporting aquatic life or recreation. These standards, unlike the technological standards, generally do not take into account technological feasibility or costs. Water quality criteria and standards vary from state to state (also tribe to tribe) and site to site, depending on the use classification of the receiving body of water. Most states/tribes follow EPA guidelines that propose aquatic life and human health criteria for many of the priority pollutants.

Criteria for aquatic life are based on national priority and addresses acute and chronic effects endpoints, survival, growth, reproduction, and development. One approach for doing this is via the use of different animal taxa (8 families for freshwater acute criterion and 3 families for fresh water chronic criterion). This approach is designed to protect the vast majority of aquatic animal species (e.g. 5^{th} percentile of tested aquatic species).

Criteria for the protection of human health are based on the potential adverse effects associated with human exposure. Human health criteria are based on Maximum Contaminant Levels (MCL) for waterbodies designated for public water supply. An MCL is the maximum concentration of a chemical allowed in drinking water systems. MCLs are set close to the MCL goals (MCLGs), which is the level below which there is no known or expected risk to health (Health Goal). If fish ingestion is important, the water quality criteria value should be based on fish consumption. Therefore, the MCLG (used as MCL as well) is the dose thought to provide protection against adverse effects including a margin of safety (MOS). The potential adverse effects considered for MCLGs are cancer and non-cancer effects.

For chemicals that do not cause cancer, an MCLG is established by first converting the safe dose (RfD) to a water concentration. Then this number is divided by five based on the assumption that exposure to the chemical through drinking water represents only one-fifth of the possible exposure to this substance. Other sources of exposure may be air, soil, and food. The EPA sets the MCLG at zero for chemicals believed to cause cancer (known or probable human carcinogens). Triclosan has not been determined to cause cancer and safe exposure levels have been determined through the RED process**.**

EPA continuously reviews its priority contaminants (Contaminant Candidate List) to determine whether or not to regulate these chemicals. Triclosan was nominated for the most recent priority list (CCL3), but a further screening review did not identify issues requiring it to be listed (see page 9). EPA also publishes methodologies to derive criteria based on the consumption of freshwater or estuarine fish. The biocentration factor (BCF) is determinant in developing this value. Triclosan does not bio-accumulate in food-chains because it is conjugated and excreted by animals via basic metabolism. If a constant inflow occurs, a steady concentration will be present in body fluids. These steady state concentrations cannot be interpreted as accumulation

and there is no triclosan remaining some time after cessation of intake. It is known that triclosan does not concentrate in the edible parts of fish. Thus, even though triclosan has been detected in fish bile from animals exposed to sewage treatment outflows or river sediment, it does not build up in the food chain.

c) Pretreatment of Toxic Pollutants

POTWs collect wastewater from domestic (e.g., homes) and non-domestic (e.g., commercial buildings, industrial facilities) users, and transport it via a series of pipes to the treatment plant. The General Pretreatment Regulations establish responsibilities of Federal, State, and local government, industry and the public to implement Pretreatment Standards to control pollutants from the industrial users which may pass through or interfere with POTW treatment processes or which may contaminate sewage sludge. Section 40 CFR 403.5 (b) lists specific characteristics for prohibitions for chemicals that should not be introduced into a POTW. Triclosan does not meet these criteria.

d) Regulation of Biosolids

The use or disposal of sewage sludge is currently subject to some Federal regulation. The CWA requires municipalities to clean their wastewater prior to discharging it. Wastewater treatment generates sludge which in turn must either be disposed of or used. Sludge management begins with sludge generation and continues through sludge processing and ultimate disposal. Section 405(e) of the CWA requires any person that uses or disposes of sewage sludge generated by a treatment works to comply with part 503 standards. The final part 503 rule is designed to be self-implementing and, therefore, clearly describes how the requirements apply to persons using or disposing of sewage sludge. When sewage sludge or sewage sludge products are sold or given away to the general public, sewage sludge must generally meet higher standards of quality. Triclosan is intrinsically-bound when present in sludge (biosolids-borne), suggesting minimal mobility and minimal plant and groundwater contamination (O'Connor, 2009). It, therefore, presents minimal threats to the environment.

2. EPA should deny the relief under CWA requested in the petition

The petitioners provide their interpretations of what the objectives, structure and relevant legal provisions are under the Clean Water Act. Included within this discourse is the statement that effluent limitations "shall be set at that level which the Administrator determines provides an ample margin of safety." Nowhere have the petitioners stated that triclosan or any of its presumed degradates (2,4-dichlorophenol, methyl triclosan, chloroform, 2,8-dichlorodioxin) exceed existing effluent limitations. If this is the case, the petitioners have not established their presumption of damage to "the chemical and biological integrity of the nation's waterways."

However, triclosan has been shown, in laboratory studies, to have a selective activity on certain biota. The EPA is addressing this and other relevant issues as part of the normal re-registration process. In fact, the petitioners, while acknowledging the presence of triclosan in the waterways, have not established a "serious threat."

The petitioners also state that according to scientific studies, triclosan in waterways transforms (93.8-96.6%) to 2,4-dichlorophenol (2,4-DCP). Recently, the presence of 2,4-DCP has been reported to form when triclosan reacts with singlet oxygen in a pH dependent reaction which is a

non-dominant photolysis reaction. The dominant photolysis reaction is a direct photo-initiated loss process. This mechanism occurs when triclosan is continuously irradiated with artificial light. Canosa et al. (2005) reported triclosan conversion up to 8.8% at 15 min and pH 7.3, but at pH 8.3 the conversion is only 1% at 5 min and 5% at 15 minutes. In addition, the reaction occurred at a chlorine concentration of 0.4 mg/L. Therefore, while 2,4-DCP may potentially arise as a result of the reaction of triclosan-containing products with residual chlorine in wastewater (used to disinfect treated effluent), such levels are expected to be extremely low and are not likely to present any meaningful risks.

C. *Safe Drinking Water Act*

1. Objectives, Structure and Relevant Legal Provisions

Under the Safe Drinking Water Act (SDWA), EPA sets legal limits on the levels of certain contaminants in drinking water. EPA has drinking water regulations for more than 90 contaminants. SDWA includes a process that EPA must follow to identify and list unregulated contaminants (called the Contaminant Candidate List or CCL), which may require a national drinking water regulation in the future. SDWA section 1412(b)(1) requires that in the development of the CCL, EPA consider specific data sources and include the scientific community. EPA must evaluate substances identified in section 101(14) of the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980 and substances registered as pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). SDWA also requires the Agency to consider the National Contaminant Occurrence Database established under section 1445(g) of SDWA.

The SDWA directs the Agency to consult with the scientific community, including the Science Advisory Board (SAB). In addition, it directs the Agency to consider the health effects and occurrence information for unregulated contaminants to identify those contaminants that present the greatest public health concern related to exposure from drinking water.

SDWA section 1412(b)(1) also requires EPA to determine whether to regulate at least five contaminants from the CCL every five years. SDWA specifies that EPA shall regulate a contaminant if the Administrator determines that:

- The contaminant may have an adverse effect on the health of persons;
- The contaminant is known to occur, or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and
- In the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

EPA developed a multi-step approach to select contaminants for the third CCL (CCL 3), which includes the following key steps:

1. The identification of a broad universe of potential drinking water contaminants (CCL 3 Universe);

2. A screening process that uses straightforward screening criteria, based on a contaminant's potential to occur in public water systems and thereby pose a potential public health concern, to narrow the universe of contaminants to a Preliminary-CCL (PCCL); and
3. A structured classification process (e.g., a prototype classification algorithm model) that objectively compares data and information as a tool and is evaluated along with expert judgment to develop a CCL from the PCCL.

EPA uses this list of unregulated contaminants to prioritize research and data collection efforts that help them to determine whether or not they should regulate a specific contaminant. Although triclosan was nominated to be included by Natural Resources Defense Council (NRDC) and New York Department of Health and it was included in the Draft and Final Universe List (117 and 131 chemicals, respectively), the screening process did not identify a concern to progress triclosan to the preliminary PCCL. As a result, triclosan is not included in the final CCL3 list of contaminants.

2. EPA should deny the relief under SDWA requested in the petition

The petitioners have not provided any scientifically credible evidence indicating triclosan contaminates drinking water at levels that threaten human health and the environment. Therefore, EPA should not consider any action against triclosan under the SDWA.

D. *Endangered Species Act*

1. Objectives, Structure and Relevant Legal Provisions

The Endangered Species Act (ESA) is intended to protect and promote the recovery of animals and plants that are in danger of becoming extinct and the habitats upon which they depend.

The ESA is administered by the Fish and Wildlife Service (FWS), in the Department of the Interior, and NOAA's National Marine Fisheries Service (NOAA Fisheries Service), in the Department of Commerce. NOAA Fisheries Service manages mostly marine and anadromous fish species, and the FWS manages the remainder of the listed species, mostly terrestrial and freshwater species. Anadromous fish are born in fresh water, migrate to the ocean to grow into adults, and then return to fresh water to spawn. Marine fish spend their entire life in salt water. Through the Listing Program, FWS and NOAA Fisheries Service determine whether to add a species to the Federal lists of endangered and threatened wildlife and plants. Once listed, a species is afforded the full range of protections available under the ESA, including prohibitions on killing, harming, or otherwise "taking" a species.

The EPA Office of Pesticide Programs has established procedures to evaluate whether a proposed registration action may directly or indirectly reduce appreciably the likelihood of both the survival and recovery of a listed species in the wild by reducing the reproduction, numbers, or distribution of any listed species (U.S. EPA 2004). Risks to birds, fish, invertebrates, mammals and plants are routinely assessed and used in EPA's determinations of whether a pesticide may be licensed for use in the United States. EPA's core pesticide risk assessment and regulatory processes ensure that protections are in place for all populations of non-target species. Because endangered species may need specific protection, EPA has developed risk assessment procedures to determine whether individuals of a listed species have the potential to be harmed by a pesticide and, if so, what specific protections may be appropriate. After the Agency's

screening-level risk assessment is performed, if any of the Agency's Listed Species Levels of Concern (LOC) Criteria are exceeded for either direct or indirect effects, a determination is made to identify if any listed or candidate species may co-occur in the area of the proposed pesticide use. If determined that listed or candidate species may be present in the proposed use areas, further biological assessment is undertaken. The extent to which listed species may be at risk then determines the need for the development of a more comprehensive consultation package as required by the Endangered Species Act.

2. EPA should deny the relief under ESA requested in the petition

The petitioners have not provided any credible scientific evidence suggesting that triclosan creates potential jeopardy for listed threatened and endangered species, or that it may destroy or adversely modify designated critical habitats. Therefore, EPA should not consider any action against triclosan under the ESA.

II. Statement of Scientific Grounds for Denial of Petition

The EPA should summarily reject this petition as inadequate, insufficient and lacking in merit for the following reasons:

- EPA has already completed the human health and environmental risk assessments for triclosan and determined the eligibility of triclosan's use as an antimicrobial pesticide ingredient for use in public health and non-public health treated articles as part of its reregistration eligibility and risk management decisions (Re-registration Eligibility Decision - RED) in September of 2008 (U.S. EPA, 2008a). The RED included an evaluation of all routes of human exposure (both those regulated by the EPA and those regulated by the Food and Drug Administration (FDA)). As part of the RED process, EPA utilized data from the National Center for Health Statistics (NCHS) National Health and Nutrition Examination Survey (NHANES) database in order to reach its findings and conclusions;
- Triclosan is regulated by the FDA or the EPA, depending upon the intended product use and associated claims. The petitioners have erroneously implied in the presentation of their petition that the EPA has authority to regulate products regulated by FDA (e.g., hand hygiene products, toothpaste). FDA has recently announced that it is currently in the process of reviewing all of the available evidence on triclosan's safety and plans to issue a proposed rule for Consumer Antiseptic Drug Products, which includes antimicrobial soaps and antiseptic handwashes, to the public in the Spring of 2011 (U.S. FDA, 2010). EPA's focus must remain on products over which it has statutory authority to regulate, and ignore the petitioners' information and requests for relief related to FDA-regulated products;
- The petitioners have failed to demonstrate the actual existence of significant risks or harm to human health and the environment that were missed or ignored by the EPA during the course of the Agency's due diligence process while producing the RED document on triclosan. This would be a minimal necessity for a ban under regulatory requirements. The petitioners also contend "that the scientific evidence and the legal authorities are so substantial as to require suspension of the registered uses of triclosan pending agency deliberations regarding cancellation." However, nowhere do they provide actual data refuting the EPA RED

evaluation nor do they demonstrate that damage to humans and the environment is imminent and/or substantial; and

- The citizen petition to the EPA requesting a ban on triclosan has uniformly failed to provide an acceptable basis for such a ban in each of their major scientific claims - endocrine disruption, bacterial resistance, biomonitoring, wastewater treatment, toxicity (including degradate toxicity) and ecosystem impact.

The following summarizes our response to the scientific points raised in the petition followed by specific comments and details on points made by the petitioners.

- Endocrine Disruption - Based on extensive studies relevant to understanding the potential for triclosan to cause endocrine disruption in humans and aquatic animals, triclosan is not a cause of endocrine-related effects at environmentally relevant concentrations. Further, extensive *in vivo* studies demonstrate that triclosan is not causing reproductive or cancer effects.
- Bacterial Resistance - Recognizing the uncertainty and variability in laboratory data, evaluation of potential antimicrobial resistance should be related to *in situ* use of triclosan. *In situ* studies conclusively demonstrate no association between triclosan exposure and microbial resistance to antibiotics.
- Biomonitoring - Assessments of the potential impacts of triclosan found in human body fluids and tissues demonstrate, in concert with the assessment conducted as part of the EPA RED, that the use of triclosan in various products does not increase risks of harm, including for infants, children, and workers.
- Ecosystems - Drinking Water and Food - Triclosan and its degradates do not pose a risk to aquatic or terrestrial environments, nor do they pose a threat of accumulation in drinking water or food.
- Efficacy - The efficacy of triclosan has been demonstrated to the EPA for the products the Agency regulates. The petitioners present no information that draws into question EPA's conclusions. Although not regulated by EPA, the petitioners present views on the efficacy of antibacterial hand wash products that are not supportable by the weight of evidence. Antibacterial hand wash products containing triclosan regulated by FDA as Over-the-Counter (OTC) drug products provide a public health benefit by reducing or eliminating pathogenic bacteria on the skin to a significantly greater degree than plain soap and water. The use of antibacterial hand wash products containing triclosan for infection control in both clinical and non-clinical settings has been documented in the published literature.
- Decisions Regarding Triclosan - Many government organizations and other groups have reviewed the triclosan database and agree that insufficient information exists to demonstrate that triclosan harms human health. They neither rejected nor banned triclosan but rather decided that setting safe and effective concentration levels was appropriate.

Overall Reviews

Triclosan has been extensively studied over the past forty plus years in clinical trials and other studies in human volunteers, and in experimental animals in which all aspects of potential toxicity have been evaluated. This vast body of literature and the potential that the use of triclosan in consumer products could result in adverse impacts on the health of users has been reviewed in considerable detail by the EPA during the RED process. In addition, a recent review (Rodricks et al., 2010) evaluated exposure to triclosan in two ways: 1) product-based estimates, i.e., known or assumed triclosan levels in selected consumer products combined with known or assumed usage patterns for each product evaluated; and, 2) biomonitoring-based estimates, i.e., actual upper bound triclosan levels in humans reported in data gathered by the Centers for Disease Control (CDC) as part of their on-going NHANES project. The conclusion reached was that exposure to triclosan in consumer products was not expected to result in adverse health effects in either children or adults who use these products as intended. Further, estimates of margins of safety (MOS) were significantly greater when based on actual levels of triclosan measured in a large, diverse U.S. population (biomonitoring-based estimates) than when based on hypothetical exposure scenarios (product-based estimates).

The Cosmetic Ingredient Review (CIR) Expert Panel recently issued a final report concluding that triclosan is safe for use in cosmetic products at the present concentrations described in the final safety assessment (Cosmetic Ingredient Review, 2010). Though focused on products not regulated by EPA, the CIR Expert Panel reviewed the overall toxicological database of triclosan in reaching its conclusion and found that the available safety data across a wide variety of studies support a conclusion that triclosan may be used safely in a variety of products. There were several areas of special consideration that are relevant to EPA's deliberations on triclosan, including:

- Triclosan as currently used does not pose a concern for endocrine disruption in humans.
- On the basis of the weight of evidence with respect to bacterial resistance and triclosan for in-use situations, triclosan as a potential contributor to bacterial resistance is not a concern.
- Levels of triclosan in human populations remain low and at levels that are not a concern.
- Triclosan is not a human carcinogen.

Similar conclusions were reached in comprehensive reviews that were also conducted by Australia and the European Union (National Industrial Chemicals Notification and Assessment Scheme (NICNAS, 2008; SCCP, 2009). Additional studies evaluating environmental concerns have established that actual levels of triclosan found in the environment do not adversely affect aquatic residents (Reiss et al., 2002; Orvos, 2002).

A. *Triclosan Does Not Result in Endocrine Disruption*

The issue of endocrine disruption has, is and will be the subject of extensive evaluation by a multitude of interested parties, including the EPA. In this particular case, however, innuendo rules the petition since a potential result is translated into "serious threats to thyroid and other organ functions and it can also influence the development of cancer." In fact, a recent

investigation evaluating the anti-cancer properties of triclosan found that it exhibited anti-proliferative properties in the MCF-7 breast cancer cell line at a concentration of 100 ug/ml (Vandhana et al., 2010). The petitioners have neither provided any scientific data that refutes the conclusions reached by the EPA nor utilized the vast scientific literature that does not support their position. Furthermore, they have failed to evaluate their own references in a manner conducive to transparency and sound science. The information presented on endocrine disruption in their petition does not support a ban on triclosan in EPA-regulated products.

The following is a summary of relevant studies and assessments pertinent to triclosan and endocrine disruption.

The petitioners ignore the basic principle of animal toxicology studies, namely to administer a range of dose levels repetitively or continuously over specified time periods in order to determine a continuum leading from no-effect to effect responses. Finding this continuum indicates a successful study since a risk assessment process can then utilize these and other results in order to determine an exposure level that would be "safe" to the greatest number of people. EPA did this as part of the RED process and it does not appear that any of the data cited by the petitioners would materially change the existing conclusions. Additional studies specifically designed to evaluate reproductive effects in different animal species are adequately described in the EPA RED section on toxicology. While they did not measure hormone levels specifically, clear no-effect levels were demonstrated.

Several studies in the open literature point to an endocrine disrupting effect of triclosan. However, these publications are partially contradictory and used almost exclusively a grade of triclosan that is not representative of what is used in common practice. For example, they used a grade of triclosan not tested analytically for impurities such as dibenzo-p-dioxins and dibenzofuranes or demonstrated to have levels of these impurities that would meet USP requirements. Triclosan that would meet the current USP standard for these impurities has been used in a 2-generation study in the rat (Ciba-Geigy, 1988) and teratogenicity studies in three species (mouse (Ciba-Geigy, 1992a), rat (Ciba-Geigy, 1992b) and rabbit (Piekacz, 1978)) in which there were no findings of any effects on fertility or the offspring. An ongoing CRADA (cooperative research and development agreement) of the U.S. EPA investigating the effect of USP quality triclosan on thyroid hormone homeostasis found a depression of T4 levels in male weanling rats upon exposure to triclosan which had no effect on the onset of puberty (Zorilla, 2009).

A number of recent studies deal further with thyroid and androgenic effects as well as metabolic enzyme induction (Chen et al., 2007; Fort et al., 2010a; Jacobs et al., 2005; Kumar et al., 2008; Paul et al., 2010; Stoker et al., 2010) and demonstrate effect and no-effect dose levels. In fact, Stoker et al. (2010) found that the lowest concentration showing an effect (either on estrogen or thyroid hormone responses) are 10-40 times higher than the highest levels reported in human plasma.

A recent study performed by the U.S. EPA in female weanling rats was designed to elucidate the mechanism of action of triclosan on thyroid hormone homeostasis (Paul et al., 2010). The Paul et al. study confirmed the effect on T4 found in male rats and found evidence for upregulation of hepatic catabolism. Furthermore, the researchers demonstrated that the highest triclosan dose

administered had initial effects on serum thyroxine which were no longer evident as the study progressed. In making their claims, the petitioners appeared to assume that the rat is equivalent to humans with respect to thyroid activity. This is clearly not the case since the rat is more sensitive to changes in thyroid homeostasis compared to man due to a missing T4 binding protein with concomitant shorter T4 plasma half-life. The data in weanling rats combined with the 2-generation and teratology studies suggest that effects on thyroid hormone homeostasis are below a threshold effect and can be viewed as adaptive. The data in weanling rats were nevertheless used in a risk assessment performed by the U.S. EPA (Paul et al., 2010). The Agency calculated a Bench Mark Dose Level (BMDL) of 65.6 mg/kg/d for a 20% decrease in T4. The human infant daily oral exposure was estimated by the U.S. EPA to be 0.005 mg/kg/d based on triclosan levels found in breast milk (Paul et al., 2010). Thus, this level provides a margin of exposure in breast milk of ~13,000 fold.

Studies in the literature have also pointed to effects of triclosan on the thyroid hormone mediated frog metamorphosis. Several studies on amphibian metamorphosis (on both *Xenophus laevis* (Fort et al., 2010a) and *Silurana tropicalis* (Fort et al., 2010b)) and fish reproduction (on fathead minnow (Fort et al., 2010c)) have been conducted in order to address this concern (Ciba Corporation, 2008; Ciba Specialty Chemicals Corporation, 2007; Fort et al., 2010c). All studies conducted were carried out according to GLP and in accordance to available and internationally accepted testing guidelines (e.g., U.S. EPA, ASTM) using USP-grade triclosan as test material. Overall, there was no evidence that triclosan has an endocrine disrupting effect in either amphibians or fish being exposed to environmentally relevant triclosan concentrations.

1. Triclosan Does Not Cause Breast Cancer

Specific tumor cell lines (MCF-7 and mouse mammary) have been utilized to study the influence of triclosan on cell proliferation and response to estrogen/androgen stimulation. Vandhana et al. (2010) found anti-proliferative properties at a concentration of 100 ug/ml while Gee et al. (2007) found increased growth at 1 uM. However, Gee et al. (2007) also demonstrated that triclosan can inhibit the growth stimulation of the above cell lines by testosterone and 17-beta estradiol. Concentrations varied greatly between these two *in vitro* studies and clearly cannot be extrapolated to an *in vivo* human breast cancer risk.

Gee et al. (2007) describe the *in vitro* ability of triclosan to displace estrogen and testosterone from their respective receptors and stimulate the growth of tumor cell lines. The authors believe that this is indicative of triclosan's ability to cause breast cancer. Although in vitro assays are a simple means of screening for candidates for further testing, they also yield a higher number of false positive results. Neither estrogenic nor androgenic effects have manifested themselves in any *in vivo* studies conducted in up to three species using triclosan that would meet current USP standards. Importantly, reproductive and developmental studies reported no effects on fertility or the pups (Ciba-Geigy, 1992a, b; Colgate-Palmolive, 1992). This indicates that the *in vitro* results have little if any relevance to the *in vivo* situation. The reason for this discrepancy may have to do with complete metabolism of triclosan to the glucoronide conjugate, likely eliminating the ability of the molecule to bind receptors, followed by rapid excretion as shown by several animal and human volunteer studies (Parkes, 1978; van Dijk, 1994, 1995, 1996; Lücker, 1990). Metabolism leading to comparable metabolic profiles was observed following both dermal

(Moss, 2000) and oral (Hohensee, 1991; Parkes, 1978; van Dijk, 1994, 1995, 1996) treatment. In addition, a recent study with human subjects who received a whole body dermal treatment with a triclosan-containing cream (2% triclosan) revealed that after 12 h, absorption was <10% (mean: 5.9%) (Queckenberg, 2010). This value is comparable to absorption values following rinse-off scenarios (Ciba Specialty Chemicals 1998a, b, c) which indicates that time is not a relevant factor in the context of dermal penetration.

In the absence of any supportive indicators in the toxicology database utilized by EPA in preparing the RED (which included genotoxicity, carcinogenicity and reproductive/developmental toxicity studies, amongst others), including negative results in the standard battery of genotoxicity tests (Pharmakon, 1993; Henderson, 1988a, b; Riach, 1988; Brooker, 1988), it is unlikely that exposure to triclosan is linked to neoplastic changes in the breast and hence these studies do not support a conclusion that triclosan causes breast cancer.

B. *Triclosan Does Not Contribute to Bacterial Resistance*

One aspect of the petitioners' claims, and a focus of our responses, is the unsubstantiated concern regarding the development of antimicrobial and antibiotic resistance. The Petitioners claim that the "wide-spread use" of triclosan has led to the "development of" or "results in" or "provokes" or "causes" not only resistance to triclosan in bacteria but also "creates" resistance in bacteria to "other, including unrelated antimicrobials and antibiotics (cross-resistance or co-resistance)", thereby, posing "significant health risks" to unsuspecting users.

These arguments are based on Levy (2001) and Yazdankhah et al. (2006). However, these investigators used the words "potential" or "possible" to preface their cautionary statements about triclosan use and bacterial resistance. Neither study included relevant clinical data to substantiate their speculation regarding potential health risks from the use of triclosan. Laboratory experiments may provide an adequate screen to initially identify resistant microorganisms (or organisms demonstrating decreased sensitivity) or potential mechanisms of that resistance. However, a direct correlation between these *in vitro* results with those obtained from investigations with human volunteers that are clinically relevant has not been demonstrated (Yazdankhah et al. 2006; Scientific Committee on Consumer Products (SCCP), 2010). The basis of relying on laboratory data to predict clinical or *in* situ responses is questionable (SCCP, 2010; Russell, 2003).

In addition to over-interpreting the statements made in these review articles, the petitioners failed to review the relevant primary literature available on this subject. This literature includes both laboratory and actual clinical studies demonstrating overwhelmingly that triclosan usage and exposure does not lead to widespread bacterial/antibiotic resistance. As discussed in the following sections, there have been no studies in the scientific literature demonstrating that in-home use of triclosan-containing products have led to bacterial resistance to antibiotics or other antimicrobials.

Furthermore, there are existing programs within the U.S. that are used to track antimicrobial resistance. These include the National Nosocomial Infections Surveillance (NNIS) program and the Interagency Task Force on Antimicrobial Resistance (NNIS, 2004; CDC, 2004). The NNIS is a joint program that has been in place since 1970 between the Centers for Disease Control and

Prevention (CDC) and 315 acute care hospitals. These programs have not provided any real world evidence that antimicrobials can select for antibiotic resistant bacteria.

The following is a summary of the studies relevant to understanding resistance and evidence showing that triclosan does not cause antibiotic resistant bacteria.

- McMurry et al. (1998) and Heath et al. (1998) used *Escherchia coli*, and identified specific genes (*fab* 1) and (*inhA*), as targets for triclosan at subleathal concentrations. Mutants without one of these genes are likely to be resistant to triclosan. In addition McMurry, identified the over expression of genes that regulate the efflux pumps, such as *marA* and *arcAB*, in bacterial strains that are resistant to triclosan. Triclosan has not caused either of these intrinsic genetic differences and is highly unlikely to cause mutational changes in key regulatory genes. Therefore, it has not *caused* the production of microbial resistance either to itself or to other antimicrobial or antibiotic agents.
- Rodricks et al. (2010) reviewed the mutagenicity and genotoxicity potential of triclosan. They reported that triclosan has been tested in an extensive battery of *in vitro* and *in vivo* assays that evaluated the full range of potential for mutagenicity or genotoxicity in prokaryotic and eukaryotic systems. Neither triclosan nor its metabolites were shown to be either a mutagen or a genotoxicant, which would be required for the types of acquired mutational changes mentioned above. Therefore, it must be concluded that triclosan is not causing genetic changes that result in resistance and, further, it cannot be concluded that triclosan is causally associated with the development of bacterial resistance.
- The reliability of *E. coli* to be a representative model of biocide resistance in multiple species that may be encountered in clinical or *in situ* setting has been questioned by a number of studies.
    - Bailey et al. (2009) reported differing response mechanisms by *E. coli* and *S. enteric.* Cottell et al. (2009) noted *E. coli* demonstrated more susceptibility after triclosan exposure to aminoglycoside antibiotics than *Staphlococcus aureus* and *Acinetobacter johnsonii*. Gomez Escalada (2003) noted a two-fold increase in triclosan resistance in *E. coli* (as measured by MIC response), with no corresponding decrease in the efficacy of triclosan.
    - Both McBain et al. (2004) and Ledder et al. (2006) reported “massive decreases” in susceptibility with *E.coli* and *Klebsiella oxytoca*, without corresponding decreases in triclosan susceptibility in other bacterial species.
    - Bailey et al. (2009) concluded, “*E. coli*, often offered as a paradigm for the *Enterobacteriaceae* when exploring the effects of antimicrobial agents, responds quite differently to triclosan compared with at least one other member of the same taxonomic family.”
    - Ledder et al. (2006) concluded that reduced sensitivity to triclosan in ordinarily highly susceptible bacteria is limited.

- McBain et al. (2004) likewise concluded that if unsubstantiated reports of triclosan susceptibility and studies of *E. coli* are precluded, few studies have reported changes in bacterial triclosan susceptibility.
- In the laboratory setting with serial passage of various bacteria, in particular *E.coli*, exposed continuously to sub-lethal concentrations of triclosan, pre-existing resistant organisms may proliferate. However, results in laboratory settings, as described below, have not been shown to correlate with clinical observations and have methodological issues that limit their interpretation as to causality.

In situ studies have not demonstrated an association with triclosan use and antibiotic resistance. The potential for triclosan to induce bacterial resistance has been well-studied *in situ* in a variety of studies in clinical (Davies et al., 2004), environmental (Ledder et al., 2006; McBain et al., 2004), and household (Aiello et al., 2004; Cole et al., 2003; Jones et al.,2000; Sullivan et al., 2003; Walker et al., 1994) settings. The results from comprehensive *in situ* studies refute the laboratory studies, failing to demonstrate the same association observed in the laboratory studies. In addition, Ledder et al. (2006) indicated that among strains with decreased susceptibility to triclosan, there was *no change* in antibiotic resistance, and also reported that triclosan tolerance in normally highly susceptible bacteria was restricted to several enteric bacteria. The *in situ* studies provide sufficient data to draw a conclusion that the use of triclosan does not lead to an increased incidence of either antibiotic or microbial resistance.

While there are not current specific guidelines for the conduct of *in situ* studies to investigate antimicrobial resistance, the Scientific Committee on Emerging and Newly Identified Health Hazards has proposed a list of technical requirements to ensure usability of the results (SCENIHR, 2010). These *in situ* studies form a robust data set that encompasses the key characteristics suggested by SCENIHR (2010). The findings indicate:

- In Davies et al. (2004), 16 random-designed, blinded studies were evaluated using meta-analysis. These studies were comprised of over 1,000 persons who participated for at least six months in clinical trials performed in the United States, Thailand, Sweden, Spain, China, Norway and the Dominican Republic. The results of these studies were internally consistent and demonstrated that triclosan significantly improved plaque control and gingival health, an indirect measure of the lack of development of microbial resistance.
- In Cole et al. (2003), no increases in antibacterial or cross-resistance to antibiotics in target bacteria were found in over 1200 isolates randomly collected from environmental or clinical samples in the homes of antibacterial product users compared to that seen in households that did not use antibacterial products. Approximately 50 gram positive and gram negative target bacteria were evaluated in tests conducted in both the United States and the United Kingdom. The authors stated that there was a lack of correlation between antibiotic resistance in target potential human pathogens and their resistance to triclosan. There was no significant difference found in the level of antibiotic resistance between the users and non-users. The results also showed no evidence of cross-resistance between antibiotics and

biocides in either the users or non-users. The non-user group did, however, have a significantly greater number of potentially pathogenic organisms present. Cole et al. stated, "this information [absence of antibiotic resistance] runs counter to the recent speculative claim that antibacterial-containing antiseptics and disinfectants can contribute to the selection and propagation of drug-resistant bacteria in the home environment." The authors also supported the use of triclosan in the home to reduce potential pathogen exposure.

- Aiello et al. (2004) did not report any significant correlation between triclosan MICs and susceptibility to antibiotics among several target species isolated from the hands of individuals in a community setting. Hand cultures were obtained from individuals randomized to using or not using antibacterial products for one year prior to the test (baseline) and evaluated after another year of continuous use of these products. Aiello et al. (2004) examined the triclosan and antibiotic susceptibility of staphylococci and Gram-negative bacteria isolated from the hands of individuals in a community setting. Triclosan-containing or non-antimicrobial soaps were provided to the study population for one year. There was no statistically significant association between triclosan MICs and susceptibility to the antibiotics tested. This could indicate that such a correlation does not exist.
- Aiello et al. (2005) examined whether household use of antibacterial cleaning and hygiene products is an emerging risk factor for the carriage of antimicrobial drug-resistant bacteria on the hands of household members. Over two hundred households were randomized to the use of antibacterial or non-antibacterial cleaning and hygiene products for one (1) year, including the use of a handwashing soap containing 0.2% triclosan. The authors conclude that the use of antibacterial products did not lead to a significant increase in antimicrobial drug resistance nor was there an effect on bacterial susceptibility to triclosan.
- Studies by Sullivan et al. (2003), Jones et al. (2000) and Walker et al. (1994) reported similar and consistent findings in groups of volunteers who used triclosan-containing toothpaste for 14 days to 7 months. The Walker et al. (1994) study consisted of 144 volunteers who participated in this randomized, double-blind analysis for 6 months.
- Lear et al. (2002) examined over 100 isolates from triclosan and para-chlorometa-xylenol (PCMX) manufacturing sites. The minimum inhibitory concentrations (MICs) of these isolates were compared with equivalent culture collection strains. They concluded that there was no evidence that the residual levels of biocides in the factory environment had led to changes in susceptibility. This study looked at sites where there was the greatest expectation of finding resistant strains, and none were found. Based on this finding, it would be unexpected to find resistant strains where exposure to these biocides is more casual, *i.e.*, in homes. In reviewing this study Gilbert and McBain (2002) concluded that any changes seen in the flora were due to clonal expansion of pre-existing resistant but less competitive species.
- Marshall et al. (2003) compared the incidence of bacteria, including antibiotic resistant bacteria, in the homes of users and non-users of antibacterial agents. The

authors concluded that high frequencies of antibiotic-resistant bacteria occurred in the home environment of both groups. However, there were no significant differences in the overall titers of bacteria, potential pathogens, or frequencies of antibiotic resistance in a single-time analysis of homes whether using or not using antibacterial-containing products.

- Lambert (2004) analyzed MIC data from a study of 256 clinical isolates of *Staphylococcus aureus* [169 methicillin-sensitive *Staphylococcus aureus* (MSSA) and 87 methicillin-resistant *Staphylococcus aureus* (MRSA)] and 111 clinical isolates of *Pseudomonas aeruginosa* against eight antimicrobial biocides and several clinically relevant antibiotics. Between 1989 and 2000, a subpopulation of MRSA had acquired a higher resistance to biocides, but this had not altered the antibiotic susceptibility of that group. These strains were surveyed for their susceptibility to a wider group of biocides and antibiotics. Numerous correlations were shown between the MICs of antibiotics and biocides. However, many of these correlations were negative, *i.e.*, an increase in MIC of a particular biocide was correlated with a decrease in the mean MIC of a particular antibiotic. Advanced statistical investigation using the method of principal component analysis grouped, in general, the antibiotics and the biocides separately. The groupings appeared to reflect the mode of action of the antimicrobials. In many cases the groupings showed little interaction, suggesting that little cross resistance exists between antibiotics and biocides.

- Fan et al. (2002) studied the inherent variation in MIC of clinical isolates of *S. aureus*. All of the isolates studied were within the MIC bounds of what would be considered susceptible. These levels are also well within the normal range of susceptibility of *S. aureus* to triclosan. Strains with higher MICs were shown to have elevated levels of ACP reductase (Fab I enzyme) as compared to strains with lower MICs. This study shows one mechanism whereby there is natural variation in the MICs of varying strains of *S. aureus.* In some cases a decreased susceptibility to an antimicrobial is linked to a decrease in susceptibility to an antibiotic. However, there are also examples where decreased susceptibility to an antimicrobial can increase the susceptibility to an antibiotic. In other cases there is no such correlation proven, *e.g.*, populations of MRSA are as equally sensitive to triclosan as are MSSA.

- A number of expert reviews by Russell (2003; 2004) and Gilbert (Gilbert *et al*, 2002; Gilbert and McBain, 2002) 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. No convincing evidence has been found to support the contention that triclosan usage has resulted in the clinical development of antibiotic-resistant Gram-negative bacteria, antibiotic-resistant cocci or isoniazid-resistant *M. tuberculosis*.

- Goodfellow et al. (2003) reviewed the safety and efficacy of triclosan and concluded that the use of triclosan in cosmetic and over-the-counter drug products was safe and not expected to select for antimicrobial resistant bacteria. Furthermore, Kampf and

Kramer (2004) reviewed the epidemiologic background of hand hygiene and evaluated the most important agents for scrubs and rubs. The authors concluded that triclosan has a low potential for acquired bacterial resistance. They also state that no acquired resistance has been reported to date for ethanol, isopropanol, or n-propanol. This is consistent with the biocidal action of alcohol, *i.e.*, cell membrane disruption and protein denaturation and the fact that an extensive literature search failed to reveal any citation of acquired microbial resistance to alcohol antisepsis.

- Finally, the European Commission's Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP (2002) reviewed the safety of triclosan and concluded that there was no convincing evidence that triclosan poses a risk to humans and the environment by inducing or transmitting antibacterial resistance. A second review in 2006 also indicated that there was no evidence of clinical resistance and cross-resistance occurring from the use of triclosan in cosmetic products (SCCP, 2006). Since then, there do not appear to be any compelling reasons or scientific data to support different conclusions regarding the potential for triclosan to induce or transmit antibacterial resistance. In fact, there are several studies that provide support for a lack of antibacterial resistance *in situ* (Cole et al., 2003; Jones, 2000; Ledder et al., 2006; McBain et al., 2004; Sullivan et al., 2003).

In summary, given the uncertainty and variability in laboratory data, evaluation of potential antimicrobial resistance should be based on *in situ* use of triclosan. There is no evidence in real world situations such as the home, food manufacturing, and industrial environments, outside the laboratory that antimicrobials can select for antibiotic resistant bacteria. The *in situ* studies conclusively indicate no association between triclosan exposure and microbial resistance to antibiotics. The petitioners have not proven their claim that triclosan poses "significant health risks" to unsuspecting users and a ban cannot be based on the speculation of bacterial resistance.

C. *Triclosan is Not Bioaccumulative and Its Presence in the Body Does Not Indicate that Triclosan Is Causing Harm*

Several human *in vivo* and *in vitro* studies are available to assess the dermal penetration potential of triclosan. *In vitro* studies using diffusion cells showed that absorption is limited and independent of the concentration used within the range of anticipated concentrations in consumer products. Dermal absorption (as calculated from the amounts of triclosan recovered in the dermis and epidermis layers) was 12%, 7.7% and 7.2% for dishwashing (0.2% triclosan), deodorant (0.2% triclosan), and soap (0.02% triclosan, 10 min incubation)) formulations, respectively (Ciba Specialty Chemicals Inc., 1998a, b, c). A study with human subjects who washed their hands with a soap formulation containing 1% triclosan over 21 days (5 washes/day, 30 sec treatment with soap) revealed delayed onset of detectable triclosan in plasma and even at 21 days, plasma levels were <100 ppb, which makes it likely that hardly any dermal absorption occurs under realistic rinse-off conditions (Spitzer, 1973). A recent *in vivo* study with human subjects who received a whole body dermal treatment with a triclosan-containing cream (2% triclosan) revealed that after 12 h, absorption was <10% (mean: 5.9%) (Queckenberg, 2010). Hence, 10% dermal absorption can be assumed as a worst case for leave-on products whereas for rinse-off products, the above mentioned study with a soap formulation and a 10 min incubation time

represents the relevant worst case scenario at 7.2% absorption. In addition, based on the available studies, dermal absorption seems independent of the incubation time for leave-on products.

A study that determined steady-state pharmacokinetics in humans following treatment with up to 30 mg triclosan for 30 days has been conducted (Lücker, 1990). Triclosan was nearly completely recovered in feces and urine which gave no indication for a deep compartment of high capacity. This was confirmed by the rapid restitution of the plasma concentrations to baseline values after the last dosage. The mass balance in the steady state was nearly complete and the dominant half-life was below 10 h which indicates that daily exposure to triclosan will not lead to accumulation.

However, the mere presence of a chemical in the body is not "immense and dangerous" by itself. Nor does it raise "concerns about a multitude of threats to humans." The EPA mandate is to ensure that sufficient toxicology testing has been, or is to be, done that would allow assessment of safe levels of exposure to both the general population and subgroups that may be more sensitive. The RED process that was recently completed by the Agency is an ongoing one but the petitioners ignored the large body of data reviewed by EPA to date. Furthermore, the petitioners' reference to "scientific studies of its activity in blood, urine and breast milk" is inaccurate since the studies they cite measured presence, which is not equivalent to activity.

The petitioners take the position that "triclosan is bio-accumulative and poses an immense body burden." We agree that triclosan detection is widespread due to its usage pattern, ability to be absorbed and availability of analytical methods capable of detecting its presence in the parts per billion (ppb) range. However, its ability to be absorbed has to be combined with the body's capability of readily and rapidly changing it to forms able to be easily excreted. The existing toxicology database utilized by the EPA, containing many studies comparing and evaluating the fate of triclosan in many species, including man, when used in conjunction with the NHANES findings and accepted procedures of risk assessment such as effect/no-effect levels and safety factors, provided a sound basis for the conclusion reached by the Agency to re-register triclosan provided the risk mitigation and data requirements outlined in the RED were implemented (U.S. EPA, 2008).

The petitioners contend that "the presence of triclosan in the human body imposes an immense and dangerous body burden. This presence raises concerns about a multitude of threats to humans." However, the studies cited to support this contention fail to do so because the petitioners confuse presence in blood, urine and breast milk with biologic activity. Furthermore, these citations fail to indicate that triclosan is "bio-accumulative in fatty tissues." In fact, they indicate that "triclosan is...prone to phase 2 metabolism...resulting in a short plasma half-life" "as is true for other non-persistent chemicals" and "chronic accumulation of triclosan in humans has not been shown" because "triclosan appears to be readily absorbed from the GI tract and has a rapid turnover in humans." The citizen petition ignores recent articles that actually assessed whether the presence of triclosan in the body is dangerous. These assessments demonstrated, in concert with those conducted as part of the EPA RED, that: triclosan in breast milk does not pose a risk to babies; triclosan in drinking water does not present a risk to human health; and repetitive triclosan usage in toothpaste does not alter drug metabolism or affect thyroid hormone

levels in humans. The petitioners have failed to provide support for their contention that the level of triclosan in the body is dangerous and a threat to humans. Therefore, a ban cannot be justified on the basis of this information.

1. Infants and Children Are Not Especially Vulnerable to Triclosan

The concept of triclosan potentially presenting an increased risk to infants and children due to their greater vulnerability does not hold true when the principles of sound science are applied. The EPA calculated exposure to these groups using accepted practices and did not find an increased risk. When combining this methodology with the known metabolic pathways available to infants and children (glucuronidation and/or sulfation), which are also used by the body to safely handle triclosan, the risk likelihood from everyday exposure, planned or not, becomes even more minute. The Agency considered these exposures in its decision to re-register triclosan (U.S. EPA, 2008a).

2. The Petitioners' Claim that Triclosan Poses Health Risks for Health Care Professionals is Not Supported by the Evidence

Health care professional hand washes containing triclosan are regulated by FDA. The use of such products is essential for infection control in clinical settings where the risk of exposure to pathogenic bacteria is high within a population that includes many individuals with weakened immune systems and an increased risk for serious infections. At this time, FDA and other federal agencies agree that insufficient evidence exists to demonstrate that the use of triclosan in hand hygiene and topical antiseptic drug products harms human health (U.S. FDA, 2010).

3. Triclosan Usage Does Not Pose Unmanageable Risks for the Skin

Triclosan is a skin irritant at concentrations above 5% when tested in primary skin irritation assays (Ciba-Geigy, 1975). However, the petitioners' comments on health risks to the skin are not relevant because they ignored the use conditions for triclosan-containing products. Several studies in human volunteers confirmed that repeated patch tests with Triclosan concentrations typically used in commercial products did not produce skin irritation (Barkvoll, 1994). Moreover, even a high concentration of triclosan (2%), which is even higher than that typically used in professional surgical scrubs, has a low irritation potential (Bendig, 1990). Subchronic dermal toxicity studies (90 day treatment) in rats (Trimmer, 1994), dogs (Dorner, 1973) and monkeys (Hazleton, 1979) revealed no treatment related adverse effects except for dermal irritation, as expected.

Several studies have been conducted to assess the photosensitizing properties of triclosan. The most extensive study with 745 subjects that exposed individuals to 2% triclosan in petrolatum revealed only 2 positive cases (0.27%) (Wennersten, 1984). In a modified Draize test, photosensitization was not observed in 187 subjects exposed to up to 20% Triclosan during induction and 1% during the challenge phase of the study (Marzulli, 1973). A third study was conducted at 2.5% triclosan applied to skin for 1 hour or at 10% triclosan during the induction phase, both followed by irradiation to assess phototoxicity and photosensitization, respectively (Kligman, 1969). There was no evidence for phototoxicity or photosensitization. Hence, it seems

unlikely that triclosan will produce phototoxicity or photosensitization in human skin at concentration levels typically found in consumer products.

D. *Triclosan is Largely Removed from Wastewater and Sludge, and Does Not Result in Food Contamination*

The petitioners discuss the fate of triclosan in the environment, including its removal from wastewater and sludge, degradation to other chemicals, and algal toxicity. Triclosan, along with many other chemicals used by consumers for a variety of reasons, finds its way down household drains into wastewater treatment facilities (WWTF).

These WWTFs remove components of their input to varying degrees depending on many factors. The WWTF outputs thereby have a varied content. Specific information is essential to determining the impact these output components could have on the environment and its inhabitants. With respect to triclosan, this could include environmental concentration, nature of existing habitat and susceptibility of habitat members, amongst others. Through the RED process, the EPA put into motion the steps necessary to obtain the missing information they need to adequately determine environmental risk. This process, in the case of triclosan, is ongoing for environmental modeling and monitoring required to support re-registration of triclosan. The petitioners indicate that EPA "shifted the responsibility for this (and control over) to applicants for re-registration at a later date," but the Agency rightly puts the responsibility on the registrant(s). The protocol design, interpretation and other related activities have to be approved by the EPA before the registrant can proceed. Again, the emphasis is on sound science and transparency. Petitioners believe that when the EPA has "uncertainty about ecological exposure and risk" they should apply the precautionary principle, "that is, in the face of credible evidence of health and environmental threats, a regulatory agency must not allow continued use of a suspect substance until scientific study and evidence clearly demonstrate the safety of that substance." This principle, if consistently applied, would require EPA to ban any pesticide reviewed via the RED process and found to require more data. Furthermore, application of this principle requires “credible evidence of health and environmental threats.” The petitioners have not supplied any such “credible evidence.”

With respect to the biodegradation of triclosan within WWTF-processes and the directly connected aquatic environment, several literature studies clearly indicate that triclosan will dissipate within the WWTF-process by both biotic and abiotic processes. In fact, aerobic degradation can be regarded as the major and most efficient biodegradation pathway (70 – 80 %) for triclosan and its by-products with respect to the removal from the aquatic environment (EPA 2008b). In detail, WWTF removal efficiencies ranged from 53 – 99 % and from 58 – 86 % within activated sludge plants and trickling filters, respectively (Kanda et al., 2003, McAvoy et al., 2002). Another pathway of removing triclosan within STP-processes is based on abiotic adsorption processes to particles and sludge (10 – 15 %) (see EPA, 2008b and NICNAS, 2008 for summaries).

Both biodegradation and adsorption have been further investigated within an activated sludge test showing primary biodegradation rates above 94 % and complete biotic mineralization down to CO_2 or incorporation into biomass of 81 – 92 %. Corresponding adsorption rates ranged from 1.5 – 4.5 % (Federle et al., 2002).

The overall elimination rate of triclosan and its by-products within WWTF-processes ranged from about 55 to 100 % based on both laboratory and field experiments indicating that triclosan is not persistent in the aquatic environment. A study carried out to evaluate the potential risk of triclosan found in both the aquatic and the terrestrial environment clearly demonstrates that there is no environmental risk present in either compartment (Reiss et al., 2002, 2007).

Based on these recent results, an accumulation of triclosan in drinking water or food is unlikely and, therefore, food contamination due to triclosan is not to be expected.

E. *Major Degradates are Not Persistent nor Do They Cause Harm*

Laboratory and field studies demonstrate that photodegradation is another pathway of triclosan removal in the aquatic environment, with 2,4-dichlorophenol as the relevant degradation product (Ciba, 1993). 2,4-Dichlorophenol, however, is a non-persistent substance that is rapidly subjected to further degradation (both abiotic and biotic).

Further, triclosan interaction with chlorine does not create harmful conditions. The petitioners claim that "wastewater contamination by triclosan is a serious health issue", "it may be transformed into dioxin and chloroform when exposed to sunlight under certain conditions, thus creating the threat of cancer development" and "triclosan can be highly toxic to different types of algae, thus creating .... potential destruction of larger ecosystem balance."

Reliable research results show that triclosan does not interact with chlorine under usual conditions of product use such as teeth-brushing (Hao, 2007) or under normal household or municipal activities such as cleaning with hypochlorite sanitation products and wastewater treatment (Heidler, 2007). The recent publication by Fiss et al. (2007), claimed that chlorine interacted with triclosan to form chloroform or dioxins under normal household hygiene situations. Closer examination and analysis of the publication and discussion with the author revealed a number of irregularities, including exaggerated experimental conditions, non-representative product use times, and reported generation of chloroform with products that did not contain triclosan. Furthermore, the amount of chloroform generated under assumed worst-case conditions was 10 to 250 times below the level regarded by the U.S. EPA as safe for drinking water (0.01 mg/kg/day, or ~250 mg/year, U.S. EPA IRIS database, oral RfD). A subsequent publication by the authors clarified the issues (Fiss, 2008).

F. *Triclosan Does Not Pose a Risk of Harm to Algae or Cause Ecological Damage*

Triclosan, under controlled laboratory conditions, has a greater toxicity toward certain green algae than to fish and other aquatic organisms. No evidence has been presented that this translates into destruction of actual ecosystems. However, the petitioners ignored their own references indicating that triclosan, at the average concentration found in U.S. streams, did not significantly alter algal biomass yields. In addition, an aquatic risk assessment, independent of the EPA RED process, conducted following established guidelines, was available to them, but ignored. This assessment found that existing maximal triclosan water concentrations would not damage aquatic communities below WWTF effluents.

As noted earlier in these comments, criteria for aquatic life are developed based on national priority and address acute and chronic effects endpoints, survival, growth, reproduction, and development. One approach for doing this is via the use of different animal taxa (8 families for

freshwater acute criterion and 3 families for fresh water chronic criterion), which is designed to protect the vast majority of aquatic animal species (e.g. 5th percentile of tested aquatic species). This approach was followed by Capdevielle et al. (2007) to construct a species sensitivity distribution (SSD) to estimate a Predicted Non-Effect Concentration (PNEC) for triclosan. The SSD analysis was based on published chronic toxicity data for 14 aquatic species which ranged from 0.53 µg/L for *Scenedesmus* (algae) to 290 µg/L for *Oryzias* (fish). Chronic toxicity data was used because it is a worst-case scenario when compared to acute toxicity values which ranged from 1.4 µg/L for *Scenedesmus* to 3,000 µg/L for *Chironomus*. The resulting chronic PNEC (HC5,50 value) was 1.55 µg/L. In the U.S., the predicted environmental concentration (PEC) for triclosan using worst-case scenario conditions (zero in-stream removal and low flow conditions) is 850 ng/L. Therefore, a PEC/PNEC is less than unity, indicating low risks for environmental effects.

Both an environmental and a terrestrial risk assessment on triclosan have been carried out, clearly demonstrating that triclosan under its current applications poses no risk to the aquatic or the terrestrial environment (Reiss et al., 2002, 2007).

G. *Triclosan-containing Antibacterial Hand Wash Products are Efficacious*

Triclosan is regulated by the FDA or the EPA, depending upon the product usage and claims. The petitioners have erroneously implied in the presentation of their petition that the EPA has authority to regulate products regulated by FDA (e.g., hand hygiene products). EPA does not have the regulatory authority to regulate antibacterial hand wash products containing triclosan. Antibacterial hand wash products containing triclosan are regulated by the U.S. FDA as Over-the-Counter (OTC) drug products under the Topical Antimicrobial Drug Products for OTC Human Use; Tentative Final Monograph (TFM) for Health-Care Antiseptic Drug Products (59 Fed. Reg. 31402, June 17, 1994). EPA's focus must remain on products over which it has statutory authority to regulate, and ignore the petitioners' information and requests for relief related to FDA-regulated products. However, it can be noted that FDA has recently announced that it will be reviewing the safety of triclosan and antibacterial consumer products under a proposed rule covering Consumer Antiseptic Drug Product in the spring of 2011. Therefore there is no need for EPA to take further action.

When using triclosan containing antibacterial hand wash products, a consumer and public benefit (i.e., reduced infection) is provided compared to non-antibacterial hand wash products. Antibacterial hand washes provide a public health benefit by reducing or eliminating pathogenic bacteria on the skin, including specifically transient pathogens, to a significantly greater degree than plain soap and water. The bacterial reduction from hand washing is linked to reduced infection from pathogenic bacteria.

The use of antibacterial hand wash products for infection control in both clinical and non-clinical settings has been documented in the published literature. A summary of several pertinent studies and reports follows.

- The single infection control measure of changing a hand wash and bathing product to a 0.3% triclosan product was associated with the immediate termination of the acute

phase of an Methicillin Resistant *Staphylococcus aureus* (MRSA) outbreak (Zafar et al., 1995).

- Following the introduction of a triclosan hand wash in a neonatal intensive care unit, there was a gradual elimination of MRSA in the unit, and lower antibiotic use and nosocomial infections were recorded (Webster et al., 1994).
- It has been demonstrated that there is a much greater potential to reduce the acquisition and transmission of disease resulting from the handling of food through the use of an antibacterial hand wash compared to plain soap (Fischler et al., 2007).
- Antimicrobial hand soaps have been shown to provide a significantly greater bacterial reduction on the hands compared to plain soap. In addition, the transfer of bacteria to objects following washing with antimicrobial hand soap was significantly reduced compared to plain soap (Fuls et al., 2008).
- A 2005 meeting of the Nonprescription Drugs Advisory Committee (NDAC) recommended to the FDA that antibacterial hand wash products should demonstrate a reduction in infection when compared with non-antibacterial hand wash products. A summary of a scientific model and expert panel review of the model developed to demonstrate the effectiveness of antibacterial hand wash products versus non-antibacterial hand wash products has been published since the 2005 NDAC meeting. The expert panel concluded that the model was a realistic test for the efficacy (demonstration of reduction in infection) of antibacterial hand wash products. Data from studies using this model were presented to FDA in November 2008 and formally submitted to the FDA under FDA docket number FDA-1980-N-0006. The data from the studies that used the new scientific model to demonstrate the benefit of antibacterial wash products compared with plain soap are currently in preparation for publication in a peer-reviewed journal (Kruszewski and Krowka, 2011).

H. *Organizational Decisions Related to Triclosan Usage*

1. Corporate Strategic Business Decisions Related to Triclosan

In 2009, a strategic business decision was taken by Ciba Specialty Chemicals, Inc. (now BASF) to re-focus sales of triclosan exclusively in the markets of personal hygiene, medical devices and health care. This change in strategy was formally communicated to the U.S. Environmental Protection Agency, the EU Biocides Product Directive Member State Rapporteur EPA Denmark (three product type applications were withdrawn, one product type is still undergoing approval under the scheme), and to the European Food Safety Authority and was not related to safety concerns. Triclosan continues to be regulated by FDA and other European authorities for use in personal hygiene, health care and medical device products. USP grade triclosan continues to be manufactured and/or sold for EPA-registered uses.

2. Decisions of Other Governmental Entities about Triclosan

a) European Commission, Scientific Committee on Consumer Products

The use of triclosan in relevant consumer products is controlled within Europe by strict European Law. There are currently two directives which are or will be regulating the use of Triclosan within the European Union:

- The use of triclosan in cosmetics and personal care ingredients is regulated according to the European Cosmetics Regulation (EC/1223/2009) (European Parliament and Council of the European Union, 2009).
- The use of triclosan as a biocidal ingredient will be regulated by the Biocidal Product Directive (98/8/EC), once it is included in the Annex I listing.

In 2009, the SCCS reconfirmed the safety of triclosan for use in certain personal care products. Additional data were submitted to the Committee and are currently being evaluated to enable expanded usage of triclosan in all personal care products without the listed restrictions. It is expected that the findings will be published in early 2011.

The review of triclosan as an active substance under the Biocidal Products Directive (BPD) is currently on-going in Europe. The Rapporteur Member State is Denmark. A draft assessment report is expected to be available in the first quarter of 2011. Once the report has been circulated to all European Member States, the process is expected to take up to another 18 months before a recommendation for Annex I listing is finalised.

b) California Environmental Protection Agency, Office of Environmental Health Hazard Assessment (OEHHA)

A public meeting of the Proposition 65 Carcinogen Identification Committee (CIC) was held on May 29, 2009 by the California Environmental Protection Agency, Office of Environmental Health Hazard Assessment (OEHHA) to identify whether triclosan was a candidate chemical for possible listing under Proposition 65. At that meeting, California's Office of Environmental Health Hazard Assessment (OEHHA) reviewed the extensive safety data set available on triclosan and decided to place triclosan in the lowest priority category for possible preparation of material to support its Hazard Identification (California Office of Environmental Health Hazard Assessment (OEHHA), 2009).

c) British Royal Commission on Environmental Pollution

This commission was originally formed in 1970 to advise the Queen, government, Parliament and the public on environmental issues. The publication from the British Royal Commission (RCEP) referenced by the petitioners was published in 2003. The Commission was recently disbanded. In this report, the comments refer to a general statement on a class of chemicals. It does not refer to triclosan explicitly and nowhere in the report is triclosan named. Thus, it does not contain any new information relevant to EPA's decision on the RED.

3. Decisions of Professional Associations

a) American Medical Association

While these types of products do not fall under EPA's jurisdiction, the American Medical Association's (AMA) 2000 opinion regarding antimicrobial resistance and the use of common antimicrobials as ingredients in consumer products (American Medical Association, 2000) was based on a limited amount of research and speculation. As summarized in comments elsewhere in this document, a comprehensive review of the scientific literature indicates that there is no evidence in real world situations such as the home, food manufacturing, and industrial environments, outside the laboratory that antimicrobials can select for antibiotic resistant bacteria. The *in situ* studies conclusively indicate no association between triclosan exposure and microbial resistance to antibiotics.

Furthermore, according to the federal Centers for Disease Control and Prevention, doctors write 50 million unnecessary prescriptions for antibiotics each year. It is this over-prescription of drugs -- and their misuse by patients -- that are the key reasons for the emergence of antibiotic resistance.

b) Canadian Medical Association

The petitioners cite a resolution by the Canadian Medical Association (CMA) calling for the Canadian federal government to ban the sale of household antibacterial products due to the risk of bacterial resistance. CMA's opinion is based on laboratory studies of antimicrobial resistance (Canadian Medical Association, 2010), which were noted earlier in these comments to be subject to uncertainty and variability such that potential antimicrobial resistance is best understood on the basis of *in situ* studies. CMA recognized this by stating, "It should be noted, however, that while resistance has been observed in laboratory studies, resistance has not been observed at the population level (household) studies." As summarized above, *in situ* studies conclusively indicate no association between triclosan exposure and microbial resistance to antibiotics.

a) Physicians for Social Responsibility

The 2009 report of the Physicians for Social Responsibility cited by the petitioners reports that studies demonstrate that health care professionals are exposed to triclosan through the workplace or in their personal lives. However, the study report states that the levels of triclosan found in the urine of the participants "mirrors" CDC's findings from the general population http://www.psr.org/assets/pdfs/hazardous-chemicals-in-health-care.pdf. This information suggests that there is no special consideration needed with regard to exposures of health care professionals and, therefore, as demonstrated earlier in these comments, the level of triclosan found in the urine is consistent with levels shown to be safe.

4. Decisions of Expert Reviews

a) Cosmetic Ingredient Review Expert Panel

On December 14, 2010 the CIR Expert Panel voted to issue a final report that triclosan is safe for use in cosmetic products at the concentrations presently used (Cosmetic Ingredient Review, 2010; Personal Care Products Council, 2010). The CIR Expert Panel reviewed the overall toxicological database of triclosan in reaching its conclusion and found that the available safety

data across a wide variety of studies support a conclusion that triclosan may be used safely in a variety of cosmetic products. There were several areas of special consideration as follows:

Endocrine Disruption

The Expert Panel concluded that triclosan did not present a concern for use by humans. Although some studies showed effects, these studies were generally conducted using cell cultures or animal models which don't well predict the human response. The Panel also considered in vivo reproductive and developmental toxicology studies where no disturbances of the endocrine system are reported with triclosan exposure, and concluded that triclosan as used does not pose a concern for endocrine disruption in humans.

Bacterial Resistance

The CIR Expert Panel considered the weight of evidence with respect to bacterial resistance and triclosan for in-use situations and found that it was not a concern. The CIR Expert Panel noted that although bacterial strains with resistance to triclosan can be developed in vitro, this phenomenon has not been seen in surveillance studies of organisms in real life use situations.

Levels of Triclosan in the Body

The CIR Expert Panel reviewed information that indicates that levels of triclosan in the body remain low in human populations and CIR did not consider this to be an issue of concern. Triclosan absorption through the skin is consistently low, with studies finding that blood levels increase immediately after application and were proportional to dose applied. Absorption via the oral route would be nearly complete. Because triclosan is metabolized and both glucoronide and sulfate conjugates occur in vivo in humans, the majority of circulating triclosan is in conjugated form, ready for excretion.

Impurities and Degradates

The CIR Expert Panel addressed impurities identified in the production of triclosan and found them not to be an issue of concern. Impurities data do indicate low levels of dioxins may be present but that limits on the levels of dioxin compounds in triclosan have been established by the United States Pharmacopeial Convention, showing that the technology exists to produce triclosan with minimal levels of dioxins. Accordingly, the Panel expects that dioxins in triclosan supplied for use in cosmetics will be as low as reasonably achievable and no greater than 1 ìg/g (1 ppm).

The Panel concluded that photodegradation of triclosan to dioxin would not take place under normal use and practices for cosmetic products. Available data suggest that photodegradation to produce dioxin takes place at 254 nm, a wavelength of light from the sun that does not reach the earth's surface. Accordingly, in normal use, triclosan would not photodegrade to produce dioxin.

Carcinogenicity

The CIR Expert Panel reviewed a number of life-time triclosan studies with respect to carcinogenicity and found that the weight of evidence supports a conclusion that triclosan is not a human carcinogen.

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