CONTAMINANTS OF EMERGING CONCERN

Contaminant Guidebook
Contaminants of Emerging Concern
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Institute for Environmental Solutions

Contaminant Guidebook
A comprehensive and objective review of Contaminants of Emerging Concern.
Institute for Environmental Solutions

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I. Introduction

The Institute:
The Institute for Environmental Solutions (IES) is an independent nonprofit organization founded in 2004 in Denver, CO. IES engages stakeholders to deliver technically sound solutions to complex environmental and health problems -- without unwanted side effects. Our focus is on environmental threats to air and water quality, as well as the global climate. Other concerns include energy consumption and environmental stewardship in local communities. IES tackles these issues with the help of its institute associates, volunteers, graduate interns, the Board of Directors, and informed stakeholders.

The CEC Project:
IES is currently evaluating and addressing the dangers that contaminants of emerging concern (CECs) pose to public health and the environment. CECs are chemicals commonly used on farms, in industry, and in our homes. Commercial products, including lotions, sunscreens, and detergents, contain CECs. There is growing scientific evidence that many CECs function as endocrine-disrupting compounds (EDCs). EDCs are capable of altering normal hormonal functions of the endocrine system in the body, causing changes in cellular development that may lead to reproductive abnormalities or cancer. CECs have been shown to persist in the environment and wastewater treatment does not effectively remove them. Recent developments in chemical analysis have allowed scientists to detect the presence of CECs in our water resources. Scientists do not yet have adequate scientific data to determine exactly what level of exposure may be harmful to humans, but significant evidence exists to suggest high potential for toxicity.

The Guidebook:
The Contaminant Guidebook is intended to serve as a reference document containing collected data and secondary research on targeted contaminants. It is designed to be continually updated and expanded under a consistent format and freely distributed. Our goal is to provide comprehensive and accurate data on targeted contaminants and to do so without limiting applicability or audience. Contaminants are targeted based on their ability to be detected and analyzed, and the possibility of reducing prevalence by inducing behavior change in users. Their rate of occurrence, fate, and consequences to human and ecological health are poorly understood, but suspected to be adverse. Contaminants will also be targeted based on an evaluation of their relative toxicity, abundance, government regulation or lack thereof, current scientific findings, and level of public awareness.

IES encourages feedback and open communication. Additional resources and contact information can be found at the IES website (www.i4es.org).

II. Contaminants

A. ALKYLPHENOL SURFACTANTS - NONYLPHENOL AND OCTYLPHENOL

1. Overview

Alkylphenol surfactants (here represented by nonylphenol and octylphenol, two of the most common examples) are a class of widely used surfactants, or 'surface-active' agents. This means they are capable of reducing the surface tension present in a liquid, between two liquids, or in a liquid-solid interface. They are nonionic molecules, consisting of both a hydrophilic head and hydrophobic tail, which allows effective action as detergents, wetting agents, emulsifiers, foaming agents, and dispersants. They typically form following the breakdown of alkylphenol ethoxylates. Currently, these chemicals and their ethoxylated precursors are used in an array of settings, including laboratory detergents, household detergents (outside of Europe, where they have been deemed harmful), pesticides, paints, household cleaning and cosmetic products, contraceptive spermacide, and industrial wool and metal processing solutions.

These chemicals pose a threat to both human health and the environment due to their ability to mimic natural hormones (particularly estradiol/estrogen) coupled with their widespread use and persistence. While wastewater treatment plants are capable of effective removal of alkylphenol ethoxylates, these chemicals do not degrade naturally or efficiently in the environment, meaning that the broken down metabolites (nonylphenol from the original nonylphenol ethoxylate, octylphenol from the original octylphenol ethoxylate, and so on) are smaller, more persistent, and more toxic to downstream organisms. Additionally, removal of alkylphenol ethoxylates by wastewater treatment plants has not yet been mandated or regulated.

While few studies have examined a direct effect on human populations, there is an increasing body of data showing adverse effects on aquatic life. In fish, males were shown to have reduced testicular size and sperm production, while also producing female egg yolk proteins. Similar effects have been seen in rats. Human biomonitoring studies have shown the widespread presence of nonylphenol in breastmilk, umbilical cord blood, and urine samples. As a result of these studies, the EPA has recently considered extensive regulation, monitoring, and evaluation policies.

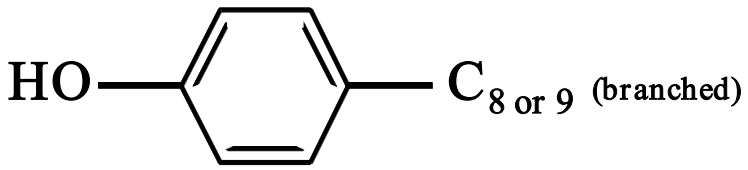
2. Introduction

Nonylphenol ($C_{15}H_{24}O$) and octylphenol ($C_{14}H_{22}O$) result from the degradation of alkylphenol ethoxylates (APEs), which are one of the most widely used classes of surfactants for making domestic detergents, pesticide formulations, and industrial products. Specific uses include detergents, wetting agents, dispersants, emulsifiers, solubilizers, and foaming agents. Primary degradation of APEs to more persistent shorter chain APEs and alkylphenols, such as nonylphenol, occurs in wastewater treatment plants, where they are ultimately released into the environment (Staples et al., 1998). Although the potential for nonylphenol degradation in the environment appears to be enhanced in highly oxygenated stream sediments, this chemical has been widely reported in aquatic systems.

Industrial applications, such as resin, plastic and elastomer manufacturing, paper and pulp production, textiles, and crop protection chemicals, account for the majority of APE useage (55%). Cleaners and detergents, both industrial and institutional, comprise approximately 30% of total APE use, with household and personal care products accounting for the remaining 15% (Staples et al., 1998). Alkylphenol ethoxylates derived from nonylphenol (NP), are called nonylphenol ethoxylates (NPEs), and comprise about 80% of the total market volume. Alkylphenol ethoxylates derived from octylphenol (OP), called octylphenol ethoxylates (OPEs), make up about 15 to 20% of the total APE market. Other APEs including dodecylphenol ethoxylates and dinonylphenol ethoxylates account for most of the remaining market volume. The widespread production and use of APEs in industrial activity and in household products leads to their discharge to treatment plants and the discharge of their degradation by-products into the environment. Degradation of APEs in wastewater treatment plants or in the environment generates more persistent shorter-chain APEs and alkylphenols (APs), such as nonylphenol (NP), octylphenol (OP) and AP mono- to triethoxylates (NPE1, NPE2 and NPE3). There is concern that APE metabolites (NP, OP, NPE1–3) can mimic natural hormones (particularly estradiol), and that the levels present in the environment may be sufficient to disrupt endocrine function in wildlife and humans. While much of the subsequent data is based on nonylphenol-oriented studies, the similar structure, function, and purpose of octylphenol suggests a high level of correlation.

3. Environment and Exposure

Figure 1 - General structure of an alkylphenol surfactant.



APEs make up the world's second largest group of surfactants in terms of production (following linear alkylbenzene sulfonates) and have been used widely in the industry for about 50 years (Pianoforte, 2012, Ying, 2002). Concern has increased recently regarding use of APEs due to both the relative environmental stability of the NP, OP, NPE1–3 metabolites and the estogenicity of these metabolites in aquatic organisms, inlcuding fish. To assess their environmental risk, it is necessary to understand the behavior and fate of APEs in the environment (Ying, 2002). Behavior and fate are strongly influenced by the degradation and sorption of these substances following their release into the environment. APEs discharged to modern sewage treatment plants generally undergo aerobic activated sludge treatment that routinely removes about 95 to 99% or more of the APE (Staples et al., 1998). Small amounts of various intermediate breakdown products of the parent APE, including the alkylphenol, alkylphenol ether carboxylates (APECs) and 1- or 2-mol APEs have been observed following treatment. While the parent material discharged to sewage treatment or to the environment may be a high-mole ethoxylate (EO, chain lengths up to several dozen), degradation proceeds rapidly, thereby exposing aquatic organisms to potentially a number of possible breakdown products prior to their ultimate conversion to CO_2 and water (Staples et al., 1998). As with many chemicals, the biodegradation of APEs under cold, nutrient-poor, and anaerobic conditions is expected to be slower, and the intermediate breakdown products formed may differ from those produced aerobically, including the formation of greater amounts of the alkylphenol (Staples et al., 1998, 2001).

Ecological receptors have the potential for significant exposure to NP and NPE for two reasons: 1) facilities that manufacture products containing NP or NPEs are discharging them into surface waters; and 2) NP and NPEs tend to partition to sediments and accumulate. Plants, fish, and both freshwater and saltwater invertebrates are sensitive to these chemicals and have demonstrated toxicity to it in varying degrees. EPA's Office of Water has derived freshwater and saltwater water quality criteria (WQC) for NP. The acute and chronic WQC for freshwater species are 28 μg/L and 6.6 μg/L, respectively. The acute and chronic WQC for saltwater species are 7 μg/L and 1.7 μg/L, respectively (EPA, 2005). A range of surface water and sediment levels of NP and NPEs have been measured in US waters. APEs are widely used as industrial laundry detergents and frequently found in wastewater and sewage treatment plant effluents (Ying et al. 2002). Surface waters near 11 different industrial discharges ranged in concentration of NP from 2 to 1617 μg/L. Surface water and sediments measured in the Great Lakes contained NP concentrations from 0.01 to 0.92 μg/L for water and 37 μg/g to 300 μg/g for sediments. Surface water samples collected along the Ohio River measured for total NPEs ranged from 0.13 to 1.0 μg/L for water, from 250 to 1020 μg/g for sediments, and from 32 to 920 μg/g for carp, a bottom dwelling fish. Some of the measured surface water concentrations particularly those near industrial discharges exceed the WQC for freshwater species living in the water column. NP and NPEs in the freshwater and saltwater ecosystems have the potential for ecological effects on all trophic levels of aquatic species exposed to them (EPA, 2005).
Toxicity curves for APEs appear to be steep. A slight increase in test concentration can change the organism response from no effects to significant effects. Differences between an LC50 and an LC0 or no-observed-effect concentration (NOEC) were observed to be small for several species tested with NP; hence, the toxicity curves were steep. A recent study reported NP 96-h LC50s and 96-h NOECs of 128 versus 84.5 mg/L, 221 versus 88.1 mg/L, and 209 versus 120 mg/L for fathead minnows, rainbow trout, and bluegill sunfish, respectively (Spehar et al, 2010).

A series of studies between the EU, Canada, and EPA found similar toxicological effects. The available acute and chronic toxicity data of NP to aquatic organisms indicates NP is highly toxic to fish, aquatic invertebrates, and aquatic plants. The 28-day no observed effect concentration (NOEC) of 4-nonylphenol for fish ranges from 0.05 to 0.07 mg/L and the 28-day lowest observed effect concentration (LOEC) ranges from 0.12 to 0.19 mg/L. A 33-day NOEC for fish is 0.007 mg/L and the 33-day LOEC is 0.014 mg/L. The 21-day NOEC for aquatic invertebrates ranges from 0.10 to 0.24 mg/L (EPA, 2010; EU, 2002).
For NPEs, toxicity to aquatic organisms tends to decrease with increasing degree of ethoxylation. For example, acute toxicity to killifish was 1.4 mg/L, 3 mg/L, 5.4 mg/L, 12 mg/L and 110 mg/L for NP, NP1EO (i.e., NPE with one ethoxylate group), NP6.4EO (i.e., NPE mixture with an average of 6.4 ethoxylate groups), NP9EO and NP16.6EO, respectively (EPA, 2005).
Environment Canada, based on a comprehensive analysis of available toxicity data for NP and NPEs, developed Toxic Equivalency Factors (TEFs) for NP and NPEs, as follows: NP =1; NP1EO and NP2EO =0.5 (i.e., half as toxic as NP); NP3EO to NP8EO also = 0.5 (a conservative estimate because of inadequate data); NP9EO and greater = 0.005 (i.e., 100 times less toxic than NP) (EPA 2010).

4. Human Health and Exposure

Alkylphenols were first found to be estrogenic in the 1930s, but more recent research has highlighted the implications of these effects. The growth of cultured human breast cancer cells is

negatively affected by nonylphenol at concentrations as low as 1 μM (220 μg/L), or concentrations of octylphenol as low as 0.1 μM (20 μg/L) (Warhurst, 1995).

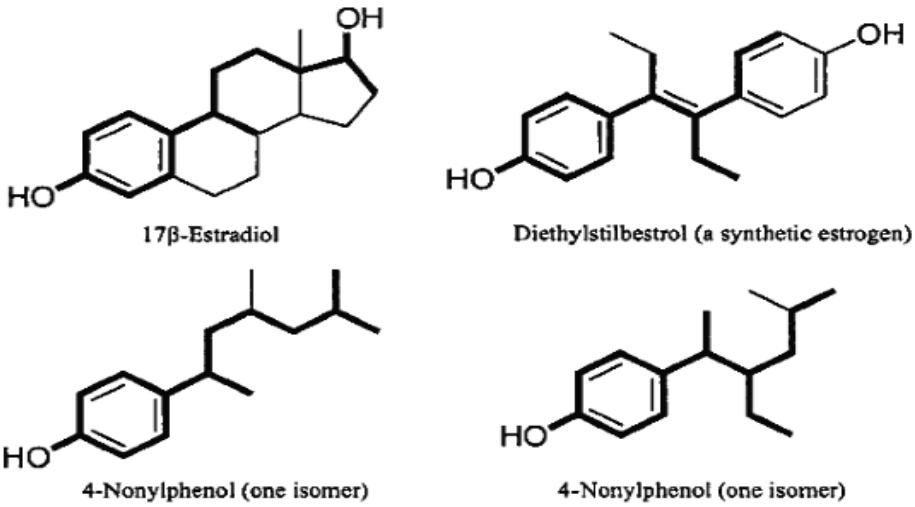


Figure 1. Structural similarities between two NPE metabolites and 17-b-Estradiol (a human estrogen) and Diethylstilbestrol (Montgomery-Brown, Reinhard 2003).

NP's acute (oral and dermal) toxicity is low. NP is highly irritating and corrosive to the skin and eye, but does not have significant skin sensitizing potential. NOAELs (No Observed Adverse Effect Levels) and LOAELs (Lowest Observed Adverse Effect Levels) for systemic toxicity (based on body weight or body weight gain) in repeat dose rat oral toxicity studies range from 13 to 100 mg/kg-bw/day and from 43 to 400 mg/kg-bw/day, respectively (EPA, 2010). NOAELs and LOAELs in rat for reproductive toxicity (based on decreases in epididymal sperm density or testicular sperm head counts, increases in estrous cycle length, and decreases in ovarian weights) range from 13 to19 mg/kg-bw/day, and from 43 to 64 mg/kg-bw/day, respectively. Developmental rat NOAELs and LOAELs for offspring (based on accelerated vaginal opening in pups) range approximately from 13 to 19 mg/kg-bw/day and from 43 to 64 mg/kg-bw/day, respectively. Developmental NOAELs and LOAELs for rat maternal toxicity (based on decreased terminal body weights) range from 13 to 19 mg/kg-bw/day and from 43 to 64 mg/kg-bw/day, respectively (EPA, 2010). NP is not mutagenic in the Ames assay, *in vitro* chromosomal aberration assay, or *in vivo* micronucleus assay. There are no data on its carcinogenic potential (EPA, 2010).

General population exposure to NP (either directly or as a metabolite of NPE) has been confirmed by biomonitoring data from breast milk, umbilical cord blood and urine (EPA, 2010). The maximum level of NP found in the breast milk was 56.3 μg/L, leading to an estimated maximum dose for an infant of 3.9 μg /kg/day. Exposure is a result of the presence of NP and NPEs in detergents, cleaners, agricultural and indoor pesticides, food packaging and cosmetics. These are potentially products of concern for women and children. For example, small children crawling on floors would be exposed to NPEs and NP in floor and carpet cleaners (EPA, 2010). There are potential children's health concerns related to NP and NPEs. NP exposure over several generations has been observed to cause slight changes in the estrous cycle length, timing of vaginal opening, ovarian weight, and sperm/spermatid count in laboratory animals (EU, 2002). NP exposure over several generations has been observed to cause slight but statistically significant changes in the estrous cycle length, timing of vaginal opening, ovarian weight, and sperm/spermatid count in laboratory animals beginning in 30-100 mg/kg/d dose groups (EU,

2002; Chapin et al., 1999). These findings are consistent with the observation that NP has estrogenic activity (EU, 2002), but a mode of action analysis has not been conducted. Data on children's exposure are limited, though children may have greater exposure to NP and NPEs because they consume more food, drink more water, and breathe more air per pound than adults.

5. Regulatory Status

NP compounds are not currently regulated under the Federal Clean Water Act, but in 2004 the EPA proposed draft water quality criteria for NP "designed to protect aquatic organisms." The EPA's draft criteria are divided into freshwater and saltwater criteria, as NP is more toxic to organisms in saltwater (EPA, 2010). For freshwater, the draft criterion for short-term exposure to NP is 27.9 parts per billion, and the criterion for long-term exposure is 5.9 parts per billion. For saltwater, the draft criterion for short-term exposure is 6.7 parts per billion, and the criterion for long-term exposure is 1.5 parts per billion (EPA, 2010).
Environment Canada has also established a concern level for NP (and NPEs, as expressed in NP Toxic Equivalency (TEQ) units) of 0.7 μg/L for indefinitely chronic exposures (EPA, 2005). The long-chain NPEs, while less "PBT" (Persistent, Bioaccumulative, and Toxic), are also highly toxic and degrade to the more toxic and persistent short forms of NPEs and NP in the environment (EPA, 2010). Internationally, Canada and the EU have acted to regulate NP and NPEs (Canada and the European Union have banned the use of NPEs in detergents, as NP compounds are toxic and their use "may have an immediate or long-term harmful effect on the environment or its biological diversity"), and the United Nations Environment Programme (an international organization tasked with coordinating United Nations environmental activities and assisting developing countries in creating environmentally-sound policies and practices) has identified NP as a chemical of global concern in its Regionally-based Assessment of Persistent Toxic Substances (EPA, 2010).

6. Alternatives

Use of APEs in US household settings has largely been phased out by the combined efforts of the EPA and detergent manufacturers, and is completely phased out in the EU (Warhurst, 1995). However, should they be present in a household product, they are likely listed as 'nonionic surfactants' (Cardona, 2011).

The simplest substitution for the use of NPEs is to use other APEs. NPEs are just one category of the numerous APEs available commercially, and other APEs may also be utilized for many of the same commercial products, including emulsifiers, dispersants, and surfactants. The main alternatives for NPEs are the linear and branched alcohol ethoxylates (AE's) (which are less toxic, readily biodegradable, and do not display estrogenic properties), glucose-based carbohydrate derivatives such as alkylpolyglucoside, glucamides, and glucamine oxides (EPA, 2010). Some surfactants may substitute for specific applications only, for instance, silicon surfactants are used in production of polyurethane foam while napthalene condensates are used in photofinishing solutions. In other cases, NPE can be replaced with a surfactant blend of alternative nonionics, or a blend that includes anionic or amphoteric surfactants. Market acceptance of these alternatives depends on a number of factors, including cost and performance in the intended use. Many of these alternatives are less persistent and break down to chemicals which are less toxic than NP and may be deemed safer substitutes for NPEs by EPA (EPA, 2010).

7. Conclusion

APEs are one of the most widely used surfactants in the world. Their metabolites (NP, OP, NPE1–3) are ubiquitous in the environment because of their wide use patterns and the widespread lack of adequate wastewater treatment (Ying, 2002). These compounds have been detected in air, water, sediment, soil and biota at differing levels in different parts of the world. Physicochemical properties indicate that APE metabolites are hydrophobic substances, and as such, they tend to bioaccumulate in lipids of organisms in the environment. They also have relatively high coefficients for adsorption onto sediment and soil (Ahel, 1994).

Although APEs can be highly treatable in conventional biological treatment facilities, effluent from wastewater treatment plants is still one of the major sources of APs and APEs due to incomplete removal and degradation of these surfactants. The concentrations of these APE metabolites varies among different treatment plants depending on the plant design and efficiency (Ying, 2002).

APEs and APE metabolites degrade much faster in the water column than in sediment. Aerobic conditions facilitate easier further biotransformation of APE metabolites than anaerobic conditions (Ying, 2002, Adams, 1996). Degradation of APEs in sediments needs to be further studied under aerobic and anaerobic conditions. Although APs have been reported to accumulate in several aquatic species, including aquatic plants, algae, fish and mussels, there is little research on the uptake of APEs and their degradation products by both plants and domestic animals.

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B. BHA – BUTYLATED HYDROXYANISOLE

1. Overview

BHA, or Butylated Hydroxyanisole, is a phenolic compound whose primary use is as a food additive (labeled E320), to play the role of preservative. Its main interest is to prevent food from becoming rancid. Baked and fried foods are the most common products in which BHA is added, since its properties are active much longer in food cooked this way. Butylated hydroxyanisole is also listed as an active ingredient in medicine, cosmetics and pesticides.
Studies have been conducted throughout the past decades to assess the threat that BHA can pose to the environment and human health. As for now, no dramatic effect has been recorded in humans, but several studies have pointed out morphological, toxic and carcinogenic effects on different wildlife species. It has also been showed that BHA is present at high concentration in urban water sources and that removal of BHA in wastewater treatment could be made more efficient. Calculations have been performed to estimate the daily amount of BHA intake in humans, and the results have been compared to the toxicity levels established from experiments with rats. Even though this average daily intake does not appear to reach critical levels, those calculations did not take into account the amount of BHA that is still present in drinking water. According to recent studies, more scientists tend to think that BHA poses a threat to the environment and human health in the long term, because they show long-term exposure to BHA is optimum for to increase the spread of its noxious properties.
BHA levels are regulated in the USA, and depend of the kind of product they are used in. BHA is generally considered as safe when its content does not exceed 0.02% by weight of the food's total fat or oil content. The European Food Safety Authority (EFSA) and Canada also came to the conclusion that BHA does not pose a threat for human health; however the State of California listed it as a carcinogen and BHA is banned in Japan.

2. Introduction

a. Relevance and importance

BHA stands for Butylated Hydroxyanisole, a chemical compound that belongs to the Phenol group. Due to the high preservative capacity of phenolic compounds, BHA is mostly used as an preservative in foods, and is also known as the food additive E320.

This phenolic compound is released into the environment via different routes. The major source comes from the consumption of BHA containing products in everyday life. It is also released from industrial sites that manufacture BHA products. An analysis conducted in Italy found that BHA, among other phenolic compounds, presented high concentrations in the Po river (Davi and Gnudi, 1999). That study also established that BHA concentrations tend to be correlated with the occurrence of spring and summer seasons, when maintenance treatments of industrial facilities take place and when BHA products are the most used to take care of houses and gardens. According to a USGS survey (Sprague and Battaglin, 2004), contaminants of emerging concern such as BHA are usually found at higher concentrations near industrial effluents and in urban streams. When treated in a wastewater treatment plant, conventional treatment processes do not completely remove BHA and other contaminants. The Water Environment Research Foundation rated the removal of BHA as poor by treatment plants (WERF, 2008). Recent studies have however pointed out alternative treatments that would remove BHA more effectively, either with enzyme based polymerization using organo-clays (Saka et al, 2008) or via UV photolysis with the addition of a green oxidant (Lau, 2007).

Studies have been conducted to assess the potential risks posed by BHA, both on the environment and human health. These studies revealed that the sensitivity to BHA depends of the animal species, as animals with a forestomach are more likely to develop tumors and cancers from the absorption of BHA (EFSA, 2011). A study from Armstrong and Wattenberg (1985) showed that BHA as more detrimental effects at longer exposure and higher dosages.

b. Physical data

Butylated Hydroxyanisole ($C_{11}H_{16}O_2$) is made from two isomers, called 2-tert-butyl-4-methoxyphenol and 3-tert-butyl-4-methoxyphenol. Its general structure is presented by Figure 1.

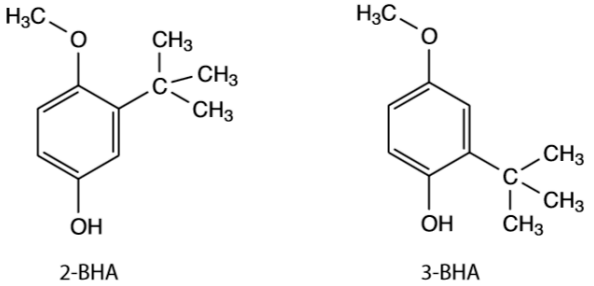

Figure 1. General structure of BHA (2-tert-butyl-4-methoxyphenol on the left and 3-tert-butyl-4-methoxyphenol on the right).

BHA presents itself as a yellowish or waxy solid. It is insoluble in water, and is volatile at 302ºF to 338ºF. It is readily lost from thermal processes that generate steam (Warner et al, 1986). One property of BHA that shows its preservative qualities is its preferential reaction with oxygen. In food, oxygen will react with BHA rather than with fats or oils, which prevent them from oxidization and thus from spoiling.

c. Uses

Due to its preservative properties, BHA is mostly used as a food additive to delay deterioration of flavors and odors, and to prevent fats from becoming rancid. It can be found mainly in baked foods and foods fried in animal oils, since it is stable at high temperatures and it can remain active in foods cooked this way (Environment Canada, Health Canada, 2010). It also appears in the ingredients of salad dressings, ready-to-eat cereals, dehydrated potato products, food and beverage mixes, snack food, confectionery, and chewing-gums (Environment Canada, Health Canada, 2010). Its properties extend its use to food packages as well, where it acts as stabilizer in some plastics that will be in direct contact with food. Apart from the food industry, its properties are used in medicine as it can also play the role of antimicrobial preservative. Some cosmetics can contain BHA too: it stabilizes oils and paraffin; and it is mostly used in deodorants, shampoos and body lotions. It may also be found in pesticides, fungicides, and insecticides.

3. <u>Environment and Exposure</u>

a. Environmental and ecological fate

Physical and chemical properties of BHA suggest that it will reside primarily in soil and water, depending where it has been released (Env. Canada, Health Canada, 2010). Models from this report indicate that BHA tends to biodegrade at a rate of half of its quantity over 6 months in water and soil, which is considered as not persistent.

The potential for bioaccumulation has been tested through recent experiments with salmon (NIFES, 2007). The results showed that BHA would be eliminated after 2 weeks, meaning that it is rapidly eliminated from the fish organism and thus presents a low potential for bioaccumulation. The Canadian government (Env. Canada, Health Canada, 2010) has run models to determine the bioaccumulation potential of BHA. The results of these models indicated that the bioaccumulation potential for BHA is low.

b. Wildlife effects

Morphological effects have been investigated by Jos et al (2004) on various life species, and adverse effects have been reported on each species studied. BHA inhibited the bioluminescence of a bacteria, the growth of unicellular algae, and generated morphological alterations in some cells of a salmon species. Xiangping et al (2009) also led an experiment with an alga to determine the toxicity potential of BHA. BHA turned out to alter the growth of the alga, and decreased its concentration of chlorophyll *a*.

The potential of BHA for carcinogenicity have been mainly studied with rats and mice. A study led on mice showed that the adjunction of BHA in their diet, in addition to two other chemicals, could enhance the occurrence of turmorigenesis when added to the first chemical, and inhibited it in the other case (Chung et al, 1986). Another study revealed that rats suffer from lesions in their forestomach after ingestion of a BHA diet, and that forestomachs of hamsters were also damaged by this diet (Altman et al, 1986). This work also established that guinea-pigs did not suffer the same side effects, which could be attributed to their lack of forestomach. Jeong et al (2005) assessed the toxicity of BHA on reproductive systems with rats. They observed that reproductive systems were underdeveloped and suffered weak dysfunction; the rats showed changes in testosterone levels, sex organ weight and early sexual maturation.

Those studies seem to indicate that the sensibility to BHA depends of the wildlife species, as animals with a forestomach are more likely to develop tumors and cancers from the absorption of BHA. They also tend to show that the organisms the most affected by BHA are the ones that live at the base of every ecosystem and food chain.

4. Human Health and Exposure

a. Exposure and biomonitoring

The main sources of exposure for humans are linked to the consumption of BHA containing products: ingestion, inhalation or dermal contact with foods, medicine or cosmetics. Regarding the experiments conducted on rats and mice and the results associated, the EFSA stated that a daily intake of BHA 1.0 mg/kg bw/day presents no risks for human health (2011). However, this report indicates that different models have been tested to estimate the likely average intake of BHA, and some results turned out to be above that threshold. In the meantime, estimations for the UK adult population presents the following results: the mean dietary exposure ranges from 0.1 mg/kg bw/day to 0.14 mg/kg bw/day, which is below the EFSA standards even for high level consumers of BHA. They also reported that in the UK, the exposure to BHA came mainly from these products: soups (14%), sauces and seasonings (13%), fine bakery wares (33%), and breakfast cereals (20%). In addition to the consumption of BHA containing products, exposure to BHA can come from other sources and has not been integrated into the above estimations. For example, some industrial workers are more likely to be exposed to BHA. People working in industries manufacturing BHA containing products and people working in fast food services are

daily exposed to BHA (NIH, 2011). Drinking water is another source of BHA consumption. Soliman et al (2007) carried a water analysis that pointed out that surface waters used as raw drinking water sources contained BHA, as well as some groundwaters.
A recent study conducted on a molecule similar to BHA, called BHT (butylated hydrotoluene), suggests that BHT would be eliminated by 50% via urine in the first 24 hours (Laningan and Yamarik, 2002). The fact that BHT has a low bioaccumulation potential would tend to suggests that BHA would not has a high bioaccumulation potential. The same conclusion was reached by Jobling et al (1995), stating that BHA may concentrate in human bodies, but at a low degree.

b. Health effects

Few studies have been conducted to assess the carcinogenicity of BHA in humans. A panel of volunteers (both men and woman) followed a BHA diet in 2000 (Botterweck et al). No increase of risk at standards levels of dietary intake of BHA had been observed. From this result and the fact that cancer or tumor had developed only in animals with a forestomach, it has been concluded that carcinogenicity is not a likely risk for humans (Env. Canada, Health Canada, 2010; EFSA, 2011). However, Sarafian et al (2002) tested the effect of BHA along with the consumption of marijuana via experiments with culture of tumor cells. It revealed that BHA, combined with the exposure to marijuana, may enhance damaging health effects in the lung, as significantly more necrosis was observed on cells in which both THC (a marijuana compound) and BHA were added.

BHA can also be the source of unwanted and disagreeable secondary effects. In 1990, Goodman et al. followed patients suffering from chronic urticarial, commonly known as hives. While the symptoms lessened after an appropriate treatment, they returned when patients were given a BHA diet. The conclusion of the BHA diet coincided with the strongest presence of the urticarial symptoms, which supports the possibility that BHA enhances urticaria.

5. Regulatory Status

a. United States

BHA is regulated by the FDA, and BHA content levels depend on the product. The FDA considers that safe BHA levels corresponds to 0.02% or less by weight of the food's total fat or oil content. However the California State listed BHA as a carcinogen after carcinomas were detected in animals during scientific experiments (CalEPA, 2012), and labels warning that BHA may cause cancer are required for BHA containing products.

b. Canada

Regulations in Canada (Env. Canada, Health Canada, 2010) stipulate that daily intake of BHA should not exceed 0.5 mg/kg body weight (kg-bw). The production of BHA is limited to 100kg per year; however it has been reported that between 100 and 1000kg were imported in the country in 2006 and it is estimated that the quantity of BHA used the same year stands between 1000 and 10000kg. The ministers of Health and Environment concluded that BHA does not present a threat for human health and the environment, since it did not match the standards for persistence and bioaccumulation. They also state that BHA cannot be defined as toxic by their criteria.

c. European Union

The Panel on Food Additives and Nutrient Sources added to Food (ANS) (EFSA, 2011) determined a threshold for daily intake of BHA. It is based on the same scientific background as the Canadian regulation; however the maximum permitted levels had been set at of 1.0 mg/kg body weight (kg-bw). Since tumors and carcinomas had been until now only observed in animals

with a forestomach, it is not considered as dangerous for humans. BHA can be used in food but its content should not represent more than 25% of processed foods. It is not authorized in beverages.

d. Japan

Japan banned the use of BHA in 1958 in food. Regular controls are made on imported food, and products are discarded when BHA is found in the product contents (Japan Ministry of Health, Labour and Welfare, 2007). It is against Japanese law to import products containing BHA or other banned chemicals.

6. Alternatives

Different alternatives to the use of BHA have been found, and one of them is pepper. Chemical constituents of peppers had been studied by Nakatani et al, 1986. Their study stated that one of the natural phenolic amides from the genus Piper had significant preservative qualities, as high as the synthetic preservative BHA. Microalgae preservative capacities have been investigated by Li et al (2007), and one of the microalgae could be a rich source of natural preservatives.

7. Conclusion

BHA is a common food additive, as well as a common ingredient in medicine and cosmetics. It has been proved that BHA has adverse effect on wildlife, at different levels: bacteria, algae, and plants are the organisms that are affected the most from BHA exposure as it had a direct impact on their growth. With animals, BHA can generate different reactions; tumors have been observed with animals with a forestomach, alteration of the reproductive system and morphological repercussions had been reported with other species. Although no such effects have been observed with humans, it has been noticed that unwanted and unpleasant side effects can develop due to the consumption of BHA, and that its combination with other substances may promote lung damage.

Regulations on BHA differ from one country to another, as it is permitted in foods in the United States, Canada and the European Union, but banned in Japan. However each government imposes limits to the content of BHA in foods and other products.

Some of the content is repeated a few too many times but overall the document is complete and compelling. This article argues that BHA is not a serious danger to humans but has more serious consequences for certain other organisms. Increased BHA targeting during wastewater treatment would decrease the chemical's effect on the environment but avoiding using these products would also be a helpful preventative action. You may need to add a little bit about how BHA interacts with organism cells.

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C. BPA – BISPEHNOL A

1. Overview

Bisphenol A (BPA) is a high production volume chemical used in the manufacturing of plastics and resins [2]. It is used in industrial chemicals to make polycarbonate plastics and epoxy resins. Those plastics and resins are used in aluminum beverage cans, canned foods, plastic food containers, water bottles, plastic beverage containers and plastic food wrap. Additionally, BPA is used in thermal paper (including receipts, mailing labels, event tickets) as well as in dental sealants and fillings. As an additive to plastic, BPA strengthens and hardens plastic and provides a wide temperature resistance [1]. The Food and Drug Administration (FDA) is currently the regulatory agency for BPA in food and beverage containers. In 2012, the FDA banned the use of BPA in baby bottles and children's sippy cups, as BPA is suspected to cause developmental abnormalities [4]. Additionally, BPA is detectable in 95% of Americans [10]. While more research is still needed, there are potential human health risks that are present through the consumption of BPA. The best alternative to BPA is to consume products that have not been packaged in BPA-containing materials, such as glass. In the case of thermal paper, opt to have receipts and event tickets e-mailed.

2. Introduction

a. Relevance and Importance

BPA strengthens and hardens plastics, provides temperature resistance between -40 to 145°C, and provides transparency and resistance to acids and oils [1]. The presence of BPA allows plastics to be stronger and harder.

b. Physical Structure

BPA (2,2-bis(4hydroxyphenyl)propane)) has a chemical formula of $C_{15}H_{16}O_2$. It is a "white solid with a mild phenolic odor" [4]. The structure of BPA consists of two phenol rings connected by a methyl bridge and two methyl functional groups attached to the bridge [1].

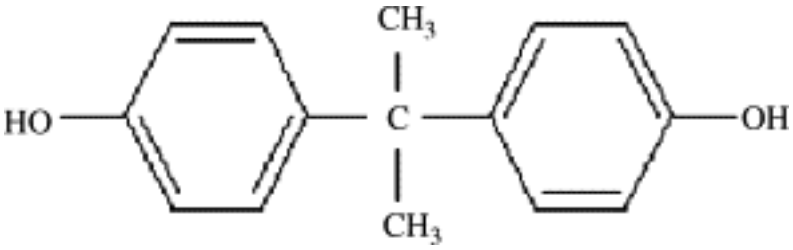

Figure 1: The chemical structure of BPA [1].

c. Uses

BPA is used in plastic food containers, plastic food wrap, water bottles, eyeglass lenses, compact discs (CDs) and tooth sealants [10]. Canned foods and beverages often contain BPA-containing plastic linings [1] Furthermore, BPA is found in thermal paper, the paper used for receipts,

mailing labels and event tickets. A thin coat of leuco dye and phenolic developer (in many cases BPA) are present on the printing paper. As the paper moves through the printer, the dye and developer react under heat and pressure to create visible color [12].

3. Environment and Exposure

a. Presence in the Environment

BPA has been found in water, air and soil. Due to wastewater treatment facilities' not targeting BPA and its inability to remove all of BPA, it can end up in surface water and can permeate into groundwater. BPA can also enter the water through leaching at manufacturing sites [1]. Its solubility in water is 120-300μg/ml [1]. The concentrations found in the air are significantly less than that found in water [1]. Inhalation of high levels of BPA is generally rare, but studies suggest those that epoxy resin sprayers had higher urinary BPA levels [1] (is the sentence complete or is there a verb missing?). BPA from water can be absorbed and stored in the soil at greater amounts than that stored in water. The half-life of BPA in soil is less than three days [1]. There is a low bioaccumulation potential and rapid biodegradation is observed for BPA in the environment [11].

b. Transport into the Environment

BPA enters the environment primarily through the manufacturing process of plastics and epoxy resins. Direct releases from manufacturing and processing facilities discharge BPA into the environment, including water, air and soil [4].

c. Toxicity to Aquatic Plants and Organisms

Freshwater fish are the most sensitive to BPA, but endocrine-related effects were found in fish, aquatic invertebrates, amphibians, and reptiles [11]. The toxicity range for BPA in freshwater and marine organisms is 1-10μg/mL [1]. Once it is introduced into water, BPA will degrade with the presence of bacteria. In freshwater, BPA degradation occurs 3-5 days after release [1]. However, BPA is more persistent in marine water, lasting up to 30 days [11]. Although BPA biodegradation occurs, BPA concentrations are still observed in aquatic organisms. A study conducted in 2006 reveals that a BPA concentration of just .01-.33 in surface water fish contained 2-75 ng/g dry weight in the liver and 1-11 ng/g dry weight in muscle [1].

4. Human Health and Exposure

a. BPA exposure and intake

Humans are exposed to BPA primarily through the consumption of food or beverages packaged with BPA-containing materials. The amount of BPA migration into food products is largely dependent on heating time and the temperature during the manufacturing process; storage time plays a smaller role in BPA migration [1]. Additionally, consuming fish that contain bioaccumulation of BPA in their tissues can be a cause for human exposure to BPA. Those who work in the manufacturing of BPA and cashiers can experience dermal irritation caused by BPA.

BPA is detectable in 95% of Americans, with the highest levels occurring in children and infants [10]. Children and infants often have the highest levels because the body weight to food consumption ratio is the greatest [10]. Also, children and infants tend to place their toys, often plastic and BPA-containing, in their mouths.

b. Toxicokinetics and Metabolism

Most BPA ingested by humans is released from the body through urine. However, the absorbed BPA is metabolized into bisphenol a glucuronide and enters the blood stream [4]. After it has entered the blood stream, the metabolized BPA is distributed throughout the body and can be distributed to fetal fluids, milk, the liver and cord blood [4].

c. Carcinogenicity

Exposure to BPA displays endocrine activity and estrogenic properties [5]. BPA is likely to cause increases in hematopoietic system based on animal studies [5]. Exposure to BPA early in life can lead to predisposition to pre-neoplastic lesions in mammary gland and prostate gland tissues [5]. Prenatal BPA exposure led to increased effects of symptoms in mice associated with breast cancer risk [5]. BPA exposure may promote tumor progression and reduce time to recurrence between advanced prostate cancers with androgen receptor mutations [5].

d. Genotoxicity

BPA is not a mutagen and does not induce cell transformation. Additionally, it is not likely to be a genotoxic hazard to humans [3].

e. Reproductive Effects

Human studies suggest that BPA can cause hormonal changes [4]. Research conducted on laboratory animals suggests that BPA causes both male and female reproductive toxicity. BPA can cause delayed vaginal opening in females and delayed preputial separation in males [4].

f. Developmental Effects

Laboratory animal studies have shown that low doses of BPA can cause neural and behavioral effects related to sexual dimorphism [4]. A high-dose exposure to BPA can lead to increased fetal death, reductions in fetal weight, and reduction in weight during postnatal life [4].

g. Neurotoxicity

Studies utilizing laboratory rats and mice reveal that low doses of BPA during development led to adverse effects on brain structure, function and behavior [11].

h. Endocrine Activity

BPA can bind to estrogen receptors alpha and beta effecting endocrine organs, including the thyroid [11]. Additionally, BPA can have inhibitory effects on androgenic activity of DHT [11].

i. Dermal Irritation

Case reports from humans and studies conducted on animals conclude that prolonged exposure to BPA can cause mild skin irritation [8]. However, it is not clear whether BPA dermal absorption occurs and leads to other potential health hazards [8].

5. <u>Regulatory Status</u>

a. United States

The FDA controls the use of BPA in food and drink products. In 2012, the use of BPA in baby bottle and children's sippy cups was banned. There are no additional regulation or limitation regarding the amount of BPA permitted in food and drink products [10]. The US EPA and the European Food Safety Authority (EFSA) set the reference dose/tolerable daily intake (TDI) of BPA at 50μg/kg/day [10].

b. European Union

BPA is prohibited in the manufacturing of polycarbonate infant bottles [6]. Since February 2012, BPA has been under review to re-evaluate its effects on human health. The EU, in comparison to the US has a more conservative TDI of 10μg/kg/day [6].

c. Canada

In 2010, Canada was the first country to declare BPA toxic [7]. Canada has already outlawed BPA's use in baby bottle and it is suspected that the use of BPA in beverage bottles and possibly canned foods will be prohibited [7]. Canada has adopted a "precautionary approach" toward BPA [11].

6. Alternatives

The easiest way to prevent BPA exposure is to avoid products packaged in BPA-containing materials. For food containers, elect food that is packaged in glass, polypropylene, polyethersulfone, PVC, polyamide, silicone, or Tritan copolyster [3]. Muir Glen, Eden Foods, Edward & Son, Trader Joe's, Vital Choice, Wild Planet Foods, Oregon's Choice Gourmet, and Eco Fish offer all or some food packaged in BPA-free containers [9]. To avoid BPA exposure from thermal paper, choose to have receipts and event tickets e-mailed so they can be printed at home.

7. Conclusion

BPA is a substance added to plastic to strengthen, harden, and provide temperature resistance. BPA enters the environment through direct releases from manufacturing and processing plants that leaches into the soil or is released into water. While more research is still needed, BPA has been shown to have adverse effects on human health. The most critical time to avoid BPA is during development. Canada has taken a precautionary approach to BPA regulation and the EFSA has elected to review recent BPA studies regarding adverse human health effects. To avoid BPA exposure, select foods and beverages that are not packaged in BPA-containing materials.

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D. DEET – DIETHYLMETATOLUAMIDE

1. Overview

DEET is the abbreviated term used for the chemical ***N,N*-Diethyl-*meta*-toluamide**, one of the most common active ingredients in insect repellents. DEET is used in commercially produced insect repellent sprays, wipes and lotions. This compound is used for protection against ticks, mosquitoes, chiggers and other biting insects, but is not an insecticide (does not kill target organisms).

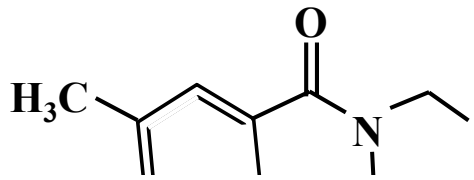
2. Introduction

a. Relevance and Importance

The chemical compound N,N-Diethyl-meta-toluamide, more commonly referred to as DEET, is the active ingredient in a wide array of insect repellent products. Originally developed by the U.S. Army in 1946 for use by military personnel in areas infested with insects, DEET comes in multiple forms including lotions, pressurized liquids, and impregnated materials. Annual US production (including imports) of N,N-Diethyl-meta-toluamide ranges from 2.6-4.4 million pounds, and DEET consumption rates make it one of the most popular active ingredients in insect repellents. Due to high production and use, concern has been raised over the toxicity and environmental impact of DEET-containing products, even as early as the 1980's [1]. It is a commonly held belief that greater concentrations of DEET repel more insects.

Figure 1.

Structure of N,N-Diethyl-meta-toluamide (DEET).



b. Physical Data

At normal conditions, N,N-Diethyl-meta-toluamide appears as a colorless, odorless liquid which is insoluble in water. It belongs to a group of chemicals known as organic amides and imides, and is created from converting *m*-toluic acid to acyl chloride and allowing it to react with diethylamine. The chemical structure of DEET is fairly stable; it does not react with strong acids, strong bases or hydrolyzing agents, and it does not quickly degrade in sunlight [2].

c. Uses

Current estimations by the United States Environmental Protection Agency (EPA) indicate that approximately 30% of the US population applies DEET every year. DEET use occurs in households, workplaces and within military settings. It is applied to household surfaces, clothing, human skin, directly on pets and on pet living/sleeping quarters. Concentrations of DEET products range from 4-100% [1].

3. Environment and Exposure

a. Environmental and Ecological Fate

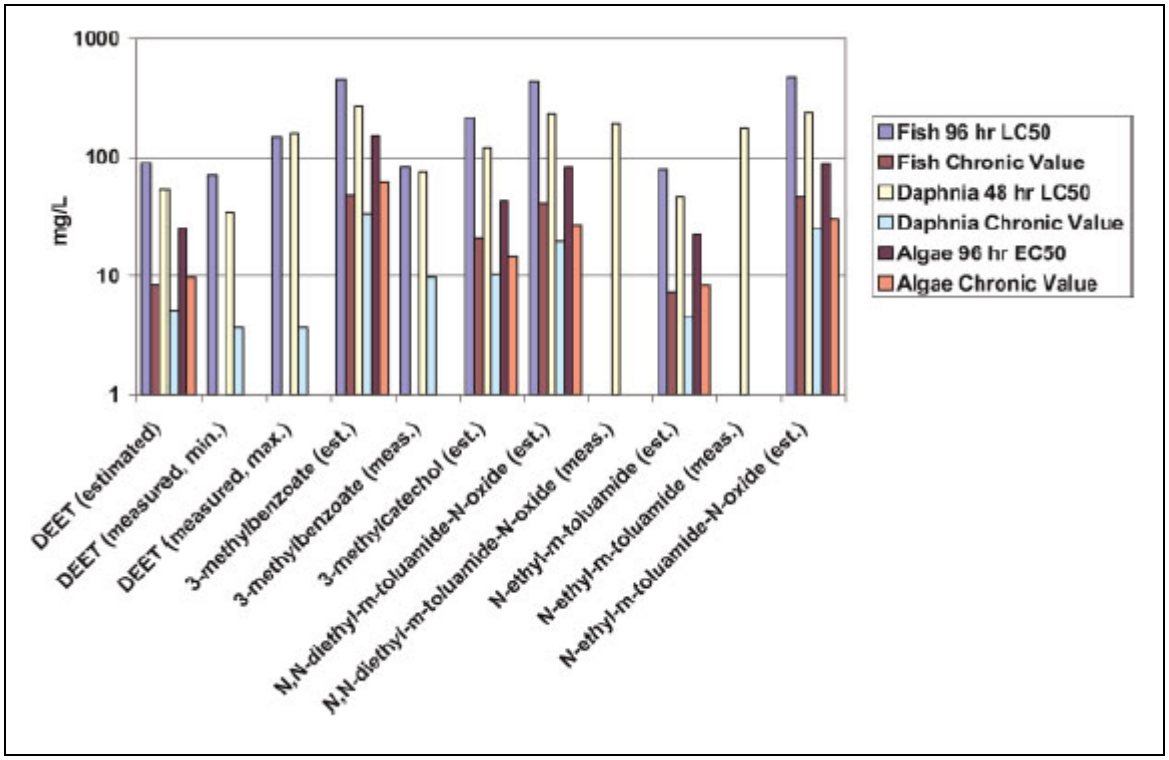
N,N-Diethyl-meta-toluamide is stable in aqueous solutions and not prone to hydrolization or breakdown in direct sunlight. Due to its widespread use, general stability and variable toxicity, concern over DEET's persistence in the environment has sparked investigation into the

prevalence of N,N-Diethyl-meta-toluamide in various environs. DEET has been detected in many non-target screenings such as river water and seawater, and is expected to enter these waterways primarily through communal sewage treatment plant effluents and to a much smaller extent through deposition into the atmosphere. In a study conducted by Weigel, et al (2001), DEET was measured at the part per trillion level (1.1-1.6 ng/L) in twelve of fifteen samples taken from the North Sea. Distribution patterns of DEET in this study indicated higher concentration gradients near the inlets of several major rivers, and declining concentrations as mixing occurred toward the more open waters of the North Sea [3].

b. **Wildlife Effects**

DEET has been shown to be slightly toxic to birds, fish and aquatic invertebrates, although at levels below 200 ppb (200 µg/L) it is not expected to be harmful to these species (if not harmful, why is it toxic?) [1]. Specific aquatic toxicity for target organisms and/or outcomes are not well understood from typical ambient exposure level to DEET, but in a study conducted by Aronson, et al (2011) levels of this compound were detected in ambient sampling and compared to the LC50 value for fish, *Daphnia magna* (freshwater flea) and algae [4]. As indicated in Figure 2, the chronic exposure levels did not approach the LC50 values for each species. Interestingly, these chronic values are higher than previously thought and indicate potential for bioaccumulation or perhaps increasing use patterns resulting in higher ambient concentrations of DEET.

Figure 2. Chronic exposure levels and acute toxicity values of DEET in three species.



Multiple laboratory studies have investigated the effects of DEET on a variety of species including lab rats, hamsters, mice and dogs. These studies typically investigate renal outcomes, carcinogenicity, and general behavioral/morphological changes. The dose (thousands of ppm) utilized in these studies is not representative of anticipated ambient exposure to DEET in the

normal environment. As such, these studies will not be discussed at length here. Of note however, are the renal impacts and potential for carcinogenicity of N,N-Diethyl-meta-toluamide in several studies. While the dose levels were exceptionally high, it is important to remember the mechanism through which DEET take its action on the target organism, particularly in the studies where the exposure route was ingestion (as opposed to injection), which would typically be the exposure route of concern for ambient DEET exposure [1].

4. Human Health Effects and Exposure

a. Exposure and Biomonitoring

Uptake of and exposure to DEET in non-normal use settings, such as from ingestion of drinking water containing detectable levels of DEET, have not been thoroughly investigated in the human population. Under normal use patterns (topical application of DEET to the skin or clothes) in vivo human studies have indicated 9-56% absorption of the applied dose, with ~~only~~ approximately 50% excretion of the absorbed dose in urine. In this same study, storage of DEET in the skin and fatty tissues of the volunteer cohort were also reported. Irritation of the skin was reported in multiple exposed individuals, although the mutagenicity and toxicity information gathered from this study was non-conclusive due to the small population [5].

b. Health Effects

The health implications from DEET exposure have been questioned in recent years as increasing use of the compound have resulted in identification of DEET in the atmosphere and in ambient waterways [6]. Specific negative health outcomes to date have been limited to a small number of deaths associated with direct ingestion of DEET. Additionally, a few deaths were reported from use of DEET containing products and dermal application. Two cases of psychological effects in humans have been reported from sub-chronic exposure to DEET, although in both cases the use patterns were not consistent with the recommended use on the product labels. The majority of acute and chronic health outcomes from DEET use in humans stems from its widespread use in military personnel [7]. Several cases of skin irritation have been reported in military personnel, and have always been associated with the antecubital fossa (sensitive area of the inner, or pit of the elbow) and repeated use of the product [8].

5. Regulatory Status

a. US Environmental Protection Agency and Food and Drug Administration

DEET has been approved for commercial use as an insecticide by the US Environmental Protection Agency at concentrations ranging from 4-100%. Recent regulatory developments in Canada permit the use of DEET as an active ingredient in bug repellents up to concentrations of 30%. Use of DEET as an insect repellent is allowed by the European Union, but the concentration is not specified [1].

6. Alternatives

Picaridin and the oil from lemon eucalyptus are two proposed (and approved by the US Centers for Disease Control & Prevention) alternatives as insect repellents. Picardin is synthetic in nature, and is in wide use throughout Europe. It has received the lowest and second lowest toxicity rankings by the US EPA for dermal application and for ingestion, respectively. PMD (*para*-Menthane-3,8-diol) is a plant-based derivative of the Australian lemon-scented gum tree, and the only natural repellent approved by the Centers for Disease Control & Prevention [9].

7. Conclusion

Based on the widespread use pattern of N,N-Diethyl-meta-toluamide as a common and effective insect repellent, there is understandable concern over its impacts in the environment and to human health. Evidence exists demonstrating that DEET has negative health outcomes in both animal and human studies. These findings are typically based on non-normal use patterns such as high doses in animal studies and intentional ingestion by humans. Additionally, little evidence exists regarding the complete lifecycle of DEET, from use to deposition in open waterways. Further research on the movement of DEET from residential use patterns to downstream water sources will allow scientists to determine what health impacts may arise from these lower level, ambient exposures in both aquatic species and in the human body.

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E. PARABENS

1. Overview

Parabens are a group of chemical compounds commonly utilized in the commercial manufacturing industry as preservatives in products such as food, drugs and cosmetics. Appearing as small colorless crystals or a fine, white powder, parabens are highly soluble in water and are therefore used frequently as antimicrobial agents (preserving against microbial growth). They have no taste, are odorless and come in a variety of chemical forms, the most common being methylparaben, ethylparaben, propylparaben and butylparaben. Parabens are permitted by the Food and Drug Administration (FDA) as a food additive, at levels of 0.1% (Soni, Carabin et al. 2005), and the United States Environmental Protection Agency (USEPA) currently only regulates butylparaben under the Toxic Substances Control Act (TSCA). Based on lacking regulation of these compounds as well as their widespread application, investigations have been conducted to determine their impact to health in humans and the environment. Water quality studies found parabens in wastewater effluent (Lee, Peart et al. 2005; Canosa, Rodríguez et al. 2006), and animal studies show that parabens negatively affect organ health (specifically, the ovaries, thyroid and adrenal glands) in rats, dogs and mice (Vo, Yoo et al. 2010). Most recently, use of paraben-containing personal care products has been implicated with human breast cancer cell production (Darbre and Harvey 2008). Additionally, a national study of human urine in the United States resulted in methyl- and propyl-paraben being present in >92% of the sample population (Calafat, Kuklenyik et al. 2005). A lack of scientific data on the specific pathways of paraben activity in human and ecological systems, continues to raise concern over their widespread use and introduction into the environment (Routledge, Parker et al. 1998; Ye, Bishop et al. 2006). Given the overuse of parabens in personal care products, and the potential for more naturally occurring alternatives, informed individuals can make the choice to avoid these products.

2. Introduction

a. Relevance and Importance

Parabens are a group of chemical compounds commonly used in the commercial manufacturing industry as preservatives in products such as food, drugs and cosmetics. Their importance as preservatives stems from their usefulness as antimicrobial agents, particularly against molds and yeasts (Soni, Burdock et al. 2001). These widely used preservatives are esters of p-hydroxybenzoic acid, and come in multiple forms including methylparaben, propylparaben and butylparaben. In order to increase the effectiveness of parabens, manufacturing companies frequently use multiple paraben compounds in one product. The current rate of production for paraben compounds is unclear, but these chemicals can be found in thousands of household products. Their introduction into the environment is primarily through household use of paraben-containing products which enter the environment through wastewater (Masten 2005). Parabens have recently been reported as having potential adverse effects to the reproductive systems of male rodents. Additionally, there is some indication that paraben compounds may have estrogenic activity in experimental cell and animal models. Due to lacking scientific data on the specific pathways of paraben activity in human and ecological systems, concern persists over their widespread use and introduction into the environment (Routledge, Parker et al. 1998; Ye, Bishop et al. 2006).

b. Physical Data

Parabens are produced when p-hydroxybenzoic acid is mixed with certain kinds of alcohols. Shown in Figure 1 is the general structure of a paraben compound, where 'R' denotes an alkyl group (carbon atoms bound to only hydrogen atoms or other carbon atoms). Each variation of paraben (methyl-, butyl-, propyl-paraben) retains a unique Chemical Abstracts Service Number (CAS Number), and exhibits unique chemical qualities. Parabens as a group are generally non-volatile and stable across a range of pH, have virtually no taste or odor, and are relatively soluble in water. The antimicrobial effectiveness of a paraben increases as the number of carbon atoms in the alkyl group increases (methyl=1, ethyl=2, propyl=3, etc.), while the solubility decreases with increasing number of carbon atoms in the alkyl group. For this reason, methyl- and propyl-paraben are the most commonly used configurations for the antimicrobial preservation of household products (Soni, Burdock et al. 2001).

c. Uses

Appearing as small colorless crystals or a fine, white powder, parabens are highly soluble in water and are therefore used frequently as preservatives (antimicrobial agents) in cosmetics, toiletries, food and pharmaceuticals. The range of uses for these compounds is such that a fully inclusive list in this document would be impractical. Examples include deodorants, eye makeup, shampoos/conditioners, face wash, beer, frozen foods, contraceptives, cough syrups and ingestible pills (Soni, Taylor et al. 2002). Methylparaben and propylparaben are the most commonly used parabens in today's market with as much as 48% of cosmetics and personal care products containing one or both of these compounds (Masten 2005). Concentrations of parabens range from 0.03% up to 1.0% depending on the paraben(s) used, the intended product (i.e. food versus cosmetics) and the country of production (Soni, Carabin et al. 2005).

3. Environment and Exposure

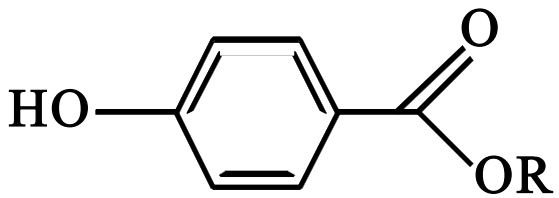
a. Environmental and Ecological Fate

Introduction of paraben compounds into the environment is thought to occur primarily through household use of paraben-containing products and their subsequent transportation into open waterways through wastewater from bathing/showering, urine excretion and cleaning. Few studies have been conducted to determine the transport and fate of paraben compounds in the environment (Peck 2006). However, it has been shown that chemically intact paraben compounds can be extracted from wastewater effluent (Lee, Peart et al. 2005; Canosa, Rodríguez et al. 2006).

b. Wildlife Effects

Due to concerns regarding paraben impacts to human health, many animal models have been utilized to determine the estrogenic and carcinogenic nature of parabens in living systems (Soni, Carabin et al. 2005; Peck 2006). In early studies regarding the absorption of parabens in living systems, it was determined that absorption of these compounds occurs in the gastrointestinal tract within rats, dogs, rabbits and cats. After absorption the compounds are hydrolyzed to p-Hydroxybenzoate or excreted as the parent compound in urine. No major accumulation of paraben compounds in the body occurred in these studies (SCOGS 1972).

Figure a-1 General structure of a paraben compound, where 'R' denotes an alkyl group.



i. Developmental

Lipophilic acids (such as parabens) inhibit the growth of mammalian cells in tissue culture studies. These effects in mammalian cells are similar to the desired effect of paraben use in personal care products, to limit the growth of unwanted bacteria (Ginsburg, Salomon et al. 1973). Further investigation of these interactions by Vo et al (2010) produced morphological changes to multiple organs in female rats treated orally with a range of paraben compounds. Specifically, methylparaben and isobutylparaben were shown to adversely affect organ weights of the ovaries, thyroid and adrenal glands, kidneys, and livers in the study population (Vo, Yoo et al. 2010). Findings raise concern regarding the long term exposure to paraben compounds, particularly during crucial developmental stages.

ii. Reproductive

In order to clarify the activity of paraben compounds in living animal systems, Routledge et al (1998) examined the ability of four common parabens (methyl-, ethyl-, butyl- and propyl-paraben) to mimic estrogenic activity in live female rats. Results indicated a weak ability (100,000 times less potent) for the paraben molecules to activate the estrogen receptor and induce a response in place of naturally occurring estrogen. When ingested orally, these compounds affected no estrogenic response. The results gathered by Routledge et al were seen when paraben compounds were administered intravenously, clarifying the importance of the route of exposure when examining chemicals of emerging concern (Routledge, Parker et al. 1998). Stemming from the findings of Routledge et al (1998), Oishi (2002) examined the extent of estrogenic activity of parabens (specifically, butylparaben) in male rats. Findings detail that consumption of butylparaben at levels within normal anticipated consumption (0.0%-1.0%) yielded an adverse dose-response relationship between butylparaben levels and late stage spermatogenesis. While it was not clear the exact mechanism of this action, the results of this study highlight the importance of further investigation as to the reproductive impacts paraben compounds may have in living systems (Oishi 2002).

iii. Immunotoxic

A wide range of estrogenic compounds have been shown to elicit immunologic responses *in vivo* and *in vitro*. Based on the limited estrogenicity of parabens (Routledge, Parker et al. 1998), there is concern that these 'environmental estrogens' may impact immunologic activities in living organisms. In a review study of multiple environmental estrogens, Sattar (2000) highlighted findings from a range of studies indicating the immune system as a likely target for these chemicals. Mechanistic evidence is limited however and human data is almost non-existent, resulting in many unanswered questions regarding the importance of compounds like parabens to immunotoxic responses (Sattar 2000).

iv. Genotoxic

Genotoxic effects of the many parabens used in personal care products are primarily limited to the reproductive effects shown by Routledge (1998) and Oishi (2002).

4. <u>Human Health Effects and Exposure</u>

a. Exposure and Biomonitoring

Human exposure to paraben compounds occurs through use of these products via dermal absorption, ingestion of paraben-containing products in drinking water, and inhalation. Dermal absorption rates vary between individual as does metabolic processing of the parent paraben compound once inside the human body (El Hussein, Muret et al. 2007). Once in the human body, parabens are either hydrolyzed to p-Hydroxybenzoate or secreted into the urine as the parent paraben compound. Because hydrolyzation converts any paraben into p-

Hydroxybenzoate, use of p-Hydroxybenzoate alone as a biomarker of paraben exposure has been determined to be insufficient (Ye, Bishop et al. 2006). For this reason, in a recent study comprised of subjects from the National Health and Nutrition Examination Survey (NHANES), sampling of human urine was completed in an effort to detect both the parent compounds, and the metabolites of paraben compounds within the US population. The biomonitoring data demonstrated detectable concentrations of methyl- and propyl-paraben in >92% of the sample population and concentrations of ethyl- and butyl-paraben in ~50% of the sample population. Concentrations in these samples ranged from <0.1 μg/L (which is just above the detection limit) >63 μg/L, depending on the paraben class analyzed. Variations in concentrations and whether or not parabens were detected between ages, ethnicity and gender are thought to reflect lifestyle differences resulting in exposure to paraben compounds (Calafat, Kuklenyik et al. 2005).

b. Health Effects

Human health data regarding toxic or potentially toxic substances are understandably limited, and consist primarily of human tissue studies or instances where exposure was accidental or occupational in nature. This applies to paraben compounds as well, where current knowledge has been derived from cell tissue analyses (Darbre, Aljarrah et al. 2004; Masten 2005; Soni, Carabin et al. 2005).

i. Developmental

Impact to human health and to development from exposure to paraben compounds is not well demonstrated. Primary action from parabens stems from their slightly estrogenic (Routledge, Parker et al. 1998) and potentially antiandrogenic effect (Satoh, Nonaka et al. 2005). While findings in animal studies and human tissue indicate morphologic alteration of multiple organs (Vo, Yoo et al. 2010), proper data is not available to verify this occurrence in humans.

ii. Reproductive

Estrogenic and antiandrogenic effects from parabens have been demonstrated in a variety of study designs both *in vivo* and *in vitro*. Causal pathways for these interactions are as of yet undefined and the specific mechanism for this action is only theorized. With regard to estrogenic effects of parabens, linkage of paraben concentrations to human breast cancer incidence is the closest science has come to a causal demonstration of negative health effects from parabens. The antiandrogenic effects of parabens shown in animal models have been demonstrated *in vitro* within human tissue. Again, these findings do not fully indicate the biological pathways through which parabens exert their effect, but do indicate that human health impacts can be seen from personal care product use (Darbre and Harvey 2008).

iii. Immunotoxic

Examination of the importance of estrogens in the propagation and/or treatment of immunologically mediated disease yielded recommendations to avoid estrogen therapy for certain types of these diseases (Cutolo and Straub 2009). This has lead to concern over the impact of environmental estrogens (such as parabens) to immunotoxicity in humans. A recent (currently accepted but unpublished) review article summarizes the possibility of adverse effects to autoimmunity. While parabens specifically have not been shown to directly impact human health through immunotoxicity, animal studies and human cell tissue studies indicate this is certainly a possibility (Chighizola and Meroni Unpublished).

iv. Genotoxic

Genotoxicity of paraben compounds in human tissue has been roundly accepted through demonstration of DNA damage via Comet assays. While this activity was demonstrated only in tissue cultures, the impact of paraben activity to mammary or to other human tissue remains unclear (Darbre and Harvey 2008; Tayama, Nakagawa et al. 2008). Detection of un-metabolized

paraben compounds in human breast cancer tissue opened the door to consideration of these chemicals in the causal pathway of human breast cancer. Prior to these studies, it was thought that paraben compounds were primarily excreted through urine and did not accumulate in human tissue (Ye, Bishop et al. 2006). Recovery of the parent compounds of parabens in human breast tumors (Darbre, Aljarrah et al. 2004) led to the investigation of their causality in breast cancer incidence. Findings suggest that increasing personal care product use, particularly in the underarm area, may be linked to increasing breast cancer rates in humans (Harvey and Darbre 2004). However, the causal or mechanistic pathway for such interaction has yet to be clarified (Darbre 2006).

5. Regulatory Status

a. US Environmental Protection Agency and Food and Drug Administration

Butylparaben is regulated by the US Environmental Protection Agency (US EPA) under the Toxic Substances Control Act (TSCA). Other paraben classes are not currently defined under regulatory language, and butylparaben was removed as a permissible pesticide from the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) as of 1998. The use of butylparaben is allowed as a preservative and is permitted for use in the minimal amount needed to induce the intended effect (Masten 2005). Parabens are also permitted by the Food and Drug Administration (FDA) as a food additive at levels of 0.1% (Soni, Carabin et al. 2005).

b. European Union/EFSA

The chemical class of parabens is permitted in food and cosmetics up to 0.8% for combinations of parabens or up to 0.4% for any one ester by the European Union Directive No 95/2/EC. Additionally, the European Food Safety Authority (EFSA) has established a group Acceptable Daily Intake (ADI) for methyl- and ethylparaben of 0-10 mg/kg based on reduced sperm production in rats exposed orally to these compounds. They were unable to establish an ADI for propyl- or butylparaben (Soni, Carabin et al. 2005). It was noted by the Joint Expert Committee on Food Additives (JECFA) by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO) that propylparaben should be excluded from the group ADI due to its adverse effects in experimental settings (Darbre and Harvey 2008).

c. Japan

The use of parabens in food products in Japan is also permitted and is currently unregulated by the Japanese government (Soni, Carabin et al. 2005).

6. Alternatives

Personal care products containing water or certain living material need more aggressive preservatives to prevent microbial growth. In these instances, one alternative to parabens may be found in a synthetic formulation known as Phenoxyethanol, inspired by a naturally occurring anit-bacterial in the sage plant (Nakanishi, Wilson et al. 1969; Rastogi 2000). Additionally, for oil-based or powder-form personal care products, a less active ingredient may be used for preservation. In these cases, the anti-oxidant properties found in substances like grapefruit seed extract, grape seed extract or tocopherol (vitamin E) may be sufficient to preserve the product from microbial development (Aburjai and Natsheh 2003).

7. Conclusion

The widespread use of esters of p-hydroxybenzoic acid, or parabens, warrants consideration of their toxic effect within wildlife and humans, notwithstanding current evidence of their potentially negative impact to human and animal health. Based on a variety of findings in such

diverse study designs as orally dosed rats, subcutaneously injected mice and cohort studies on human breast tissue, estrogenic and genotoxic effects from parabens are likely occurring. Given the unnecessary nature of paraben use in personal care products and the potential for more naturally occurring alternatives to be used, informed individuals can make the choice to avoid these products. As the market shifts and companies realize a demand for more organic or natural products, so will their production practices.

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F. OXYBENZONE

1. Overview

Benzophenone-3 (BP-3), also known as **oxybenzone**, belongs to a group of organic chemicals used to protect skin from ultraviolet solar radiation (UV) exposure. BP-3 is added to sunscreens as a UV filter, up to a maximum FDA approved concentration of 6%. BP-3 is one of the most common UV filters, used in approximately 60% of sunscreen products in 2003, despite having the highest reported incidence of photodermatitis, as compared to other marketed UV filters. The FDA and other foreign government consumer protection organizations have deemed BP-3 to be a safe and effective UV filter. However, due to its chemical and physical properties, BP-3 is capable of bioaccumulation in humans as well as wildlife, and studies have detected BP-3 in fish and aquatic environments. BP-3 may enter the human body via skin absorption, and biomonitoring studies have demonstrated that BP-3 is present in the urine of a substantial portion of the U.S. population. A serious concern that continues to be addressed regarding BP-3 arises from studies that have demonstrated BP-3 to possess estrogenic activity and therefore capable of endocrine disruption. Scientists have even advised that BP-3 be used only as a last line of sun exposure defense, especially in children, in the event that no other alternative UV filters exists. In addition to endocrine disruption, several scientists theorize that BP-3-containing sunscreens may themselves actually increase the risk of skin cancer. Fortunately, there are alternative UV filters that may be utilized for sun protection. TiO2 and ZnO are inorganic UV filters that are generally considered to be safe due to their inorganic properties. The public must be made aware of the potential harmful effects of BP-3 until further testing can validate its complete safety.

2. Introduction

a. Relevance

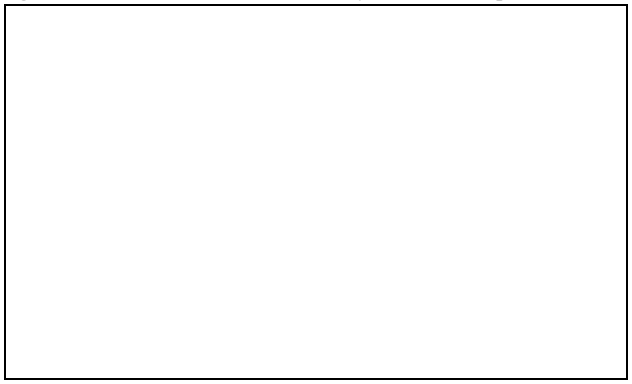
Benzophenone-3 (BP-3, a colorless crystalline solid in physical form (Nash), also known as **oxybenzone**, 2-hydroxy-4-methoxybenzophenone, Eusolex 4360, or Escalol 567. BP-3 belongs to a group of organic chemicals used to protect skin from ultraviolet solar radiation (UV) exposure. BP-3, added to sunscreens as a UV filter up to a maximum FDA approved concentration of 6% (Hexsel et al.), absorbs both UVA (320-400 nm) and UVB (280-320 nm) radiation, and thus provides broad-spectrum UV protection (Sambandan and Ratner). According to Nash, BP-3 is one of the most common UV filters, and was used in approximately 60% of sunscreen products in 2003, despite it having the highest reported incidence of photodermatitis, as compared to other marketed UV filters (Fisher; Nash; Knobler et al.; DeLeo, Suarez and Maso; Szczurko et al.; Schauder and Ippen; Janjua et al.; Hayden, Roberts and Benson; Okereke, Abdel-Rhaman and Friedman; R. Jiang et al.). While sunscreen products were originally developed to protect against sunburn, other dangers of UV radiation exposure have since been identified. Initially, sunscreens were designed to protect only against UVB exposure, by increasing the sun protection factor (SPF), through use of such active ingredients as para-aminobenzoic acid (PABA), a known effective UVB filter (Sambandan and Ratner). UVB radiation damage induces erythema and causes DNA damage through pyrimidine dimer formation (Moyal; Matsunaga, Hieda and Nikaido; Lautenschlager, Wulf and Pittelkow). Recent research and the 2007 FDA sunscreen labeling proposal, however, have placed a significantly heavier emphasis on UVA protection, as approximately 95% of the total UV radiation to reach the earth's surface is UVA, with the remaining 5% consisting of UVB (Y. Jiang et al.). UVA damage is associated with photoaging and tanning (Moyal; Matsunaga, Hieda and Nikaido;

Lautenschlager, Wulf and Pittelkow) and is capable of eliciting indirect DNA damage through the formation of reactive oxygen species (ROS) (Dahle and Kvam; Marrot and Meunier). High UVA exposure has also been associated with immunosuppression that likely may play an indirect role in photocarcinogenesis and development of melanoma (Madan et al.; van Kranen et al.; Lavker et al.; Stoebner et al.). Interestingly, BP-3 may actually also photogenerate (by reacting with UV light) highly destructive ROS in the skin (Hanson, Gratton and Bardeen; Serpone et al.) that are capable of causing oxidative DNA damage, an established mechanism of carcinogenesis (Cooke et al.). Therefore, some scientists even theorize that instead of protecting skin from UV radiation, BP-3-containing sunscreens may themselves increase risk for melanoma (Garland, Garland and Gorham "Could Sunscreens Increase Melanoma Risk?; Farmer and Naylor; Garland, Garland and Gorham "Re: Effect of Sunscreens on Uv Radiation-Induced Enhancement of Melanoma Growth in Mice"). In addition, studies reviewed here have also shown BP-3 to be an active endocrine disrupting chemical, capable of mimicking estrogen in the body, leading to possible developmental abnormalities.

b. Physical data

BP-3 (CAS No. 131-57-7), chemical formula $C_{13}H_{10}O$, molecular weight 182.22 g/mol, is a photostable and lipophillic compound. BP-3 is an aryl-ketone, with a geranium or rose-like odor, occurring naturally in some flowering plants (Crinnion). It is soluble in various organic solvents, such as alcohol, but insoluble in water. BP-3 is not compatible with reducing or oxidizing agents, and decomposition of BP-3 produces carbon monoxide and carbon dioxide fumes (USDHHS "National Toxicology Program: Ntp Technical Report on the Toxicology Andccarcinogenesis Studies of Benzophenone (Cas No. 119-61-9) in F344/N Rats and B6c3f1 Mice (Feed Studies)").

Figure 1 – General structure of an oxybenzone compound.



c. Uses

BP-3 belongs to the benzophenone family, consisting of 12 derivatives that have been utilized in many commercial products in addition to sunscreens, including beauty creams, skin lotions, lipsticks, bubble baths, shampoos, hair dyes, and hair sprays, in order to increase product durability and stability (Schlumpf, Cotton et al.). Benzophenones have also been used in the manufacturing of pharmaceuticals, including hypnotics and antihistamines, agricultural chemicals, insecticides (Hayashi et al.), and as an additive in adhesive formulations, coatings, and plastic (USDHHS "National Toxicology Program: Ntp Technical Report on the Toxicology Andccarcinogenesis Studies of Benzophenone (Cas No. 119-61-9) in F344/N Rats and B6c3f1 Mice (Feed Studies)").

3. Environment and Exposure

a. Environmental/ecological fate

Due to their photostability and high lipophillicity (Poiger et al.), UV filters, including BP-3, are able to bioaccumulate in both wildlife and humans (Vela-Soria et al.). Residues of BP-3 and other UV filters have been detected in fish and aquatic environments (Balmer et al.; Buser et al.;

Nagtegaal et al.). UV filters are released from wastewater treatment plants (WWTPs), and thus can be found in surface waters (Balmer et al.). In addition to release from WWTPs, swimming has also been shown to release UV filters into aquatic environments (Balmer et al.). Buser et al. found that UV filter levels (lipid-based tissue concentrations) in fish from lakes with WWTP UV filter inputs had considerably lower UV filter levels than fish from rivers with WWTP UV filter inputs, providing evidence for increased bioavailability and bioaccumulation for UV filters in rivers (Buser et al.).

Balmer et al. (2005) investigated for the occurrence of BP-3 in water and fish from Swiss lakes and rivers, and in both untreated wastewater (WWTP influent) and treated wastewater (WWTP effluent). Lakes were selected to cover recreational/swimming activities and inputs for WWTPs. Analysis was conducted using gas chromatography/mass spectrometry (GC/MS). Results indicated that BP-3 was present in untreated wastewater, and that seasonal variation existed, in which higher loads were found during the warmer season than during the colder season. BP-3 was found at considerably lower levels in treated wastewater, indicating substantial treatment occurred in the plants, according to the authors. Samples taken from water and fish from various Swiss lakes contained low but detectable levels of BP-3, suggesting potential for bioaccumulation and bioconcentration. Nagtegaal et al. (1997) conducted similar experiments in 1991 and 1993, evaluating German lakes for the presence of BP-3. Their study findings also demonstrated that BP-3 was widespread in fish and water, but that levels found in the water samples were mostly below detection limits. The authors concluded that fish might be used as a biomonitor for lipophillic compounds, such as BP-3, contaminating surface waters.

Because BP-3 has a high octanol:water partition coefficient and is not water soluble, BP-3 will partition in sediment and soil, and the adsorption of BP-3 to soil is proportional to the amount of organic content in the soil (USDHHS "National Toxicology Program: Ntp Technical Report on the Toxicology Andccarcinogenesis Studies of Benzophenone (Cas No. 119-61-9) in F344/N Rats and B6c3f1 Mice (Feed Studies)").

b. Wildlife effects

A 2006 study by Kunz et al. investigated estrogenic activity of UV filters, including BP-3 and BP-2, both in vitro and in vivo. In vitro activity was measured utilizing recombinant yeast cells that express rainbow trout estrogen receptors. A very strong transactivation of estrogen receptors on the yeast cells was found for BP-1, only 87 times less than potent than the response for estrogen itself on rainbow trout estrogen receptor alpha, while BP-3 showed a submaximal response. In vivo estrogenic activity, via vitellogenin induction, was measured in fathead minnows following a 14-day UV filter exposure. No in vivo estrogenic activity was seen for BP-3, but vitellogenin induction was observed for BP-1 and BP-2 at very high concentrations.

4. <u>Human Health and Exposure</u>

a. Health effects

UV filters have been reported to enter the human body via skin absorption, through use of cosmetics or personal care products, such as sunscreens (Felix, Hall and Brodbelt; Hayden, Roberts and Benson; R. Jiang et al.; Hagedorn-Leweke and Lippold), or indirectly, spreading through the biosphere and into the food chain (Kupper et al.; Schlumpf, Durrer et al.; Cuderman and Heath; Balmer et al.; Schmid et al.; Nakata et al.). BP-3 and its metabolite, 2,4-dihydroxybenzophenone, have been detected in human urine four hours after dermal application of sunscreen products containing BP-3 (Hayden, Roberts and Benson; Felix, Hall and Brodbelt).

In a Swiss university hospital monitoring study conducted by Schlumpf et al., 85.2% of breast milk samples were detected to contain UV filters (Schlumpf, Kypke et al.), suggesting bioaccumulation (Hany and Nagel) and human exposure during early child development (Schlumpf, Durrer et al.). Kadry et al. also found BP-3 to be readily absorbed from the gastrointestinal tract (Kadry et al.). Some toxic effects have been identified, including hepatotoxicity and photodermatitis, but benzophenones overall, are reported to be generally safe for topical application in humans (Vela-Soria et al.). However, there is now mounting evidence that BP-3 and other benzophenone family member compounds are capable of interfering with the endocrine system (Vela-Soria et al.). BP-3 is the first member of the benzophenone family to be classified as an "endocrine active chemical" (EAC), as it has stimulated proliferation of MCF-7 cells, a breast cancer cell line, in vitro (Schlumpf, Cotton et al.). Additionally, in rats and piglets, BP-3 undergoes biotransformation to form BP-1 and BP-8 (Kasichayanula et al.; Jeon et al.; Okereke, Abdel-Rhaman and Friedman; Nakagawa and Suzuki), and evidence suggests that BP-1 may actually possess stronger estrogenic activity than BP-3 (Suzuki et al.; Takatori et al.; Kawamura et al.; Morohoshi et al.). BP-3 (Schlumpf, Schmid et al.; Ma et al.) and BP-1 (Heneweer et al.) also have been shown to possess antiandrogenic activity in vitro, and a BP-3 and BP-1 additive estrogenic effect on pS2-gene transcription in MCF-7 cells has also been reported (Heneweer et al.).

A highly cited study evaluating six UV screens and estrogenicity by Schlumpf et al. (2001) remains the most important study to date, regarding an association between BP-3 and endocrine disruption. In vitro studies conducted by Schlumpf et al. reported that the maximum activity of BP-3 actually reached the level of full agonist E2 in the MCF-7 cell proliferation assay, and the cell proliferation increased in a dose-dependent manner for five of the six tested UV filters. Another in vitro assay, evaluating secretion of pS2 protein, an estrogen regulated protein, into the cell culture medium, showed that BP-3 significantly increased pS2 secretion. In contrast to the in vitro assay results, BP-3 only showed weak estrogenic activity in vivo, and in vivo estrogenic activity was only observed in three of the six compounds. In vivo testing, done via a rat uterotrophic assay, measured uterine weight increases following four-day oral administration in powdered feed. Schlumpf et al. pointed out that another recent study (25 from Schlumpf 2001) reported BP-3 to be inactive in the uterotrophic assay, and Schlumpf et al. also mentioned that the BP-3 dose level utilized was ineffective for their in vivo study. The study authors concluded that a precise quantitative comparison between in vitro and in vivo results was not possible, but because of the differences found between the two test types, additional in vivo testing of the UV screens is definitely supported due to the in vitro estrogenic activity findings. Schlumpf et al. write, based on their observations, "that there is a need to reconsider the potential benefits of extensive UV screen use both from a medical and an ecologic perspective."

A 2003 study by Ma et al. investigated in vitro antiandrogenic effects of BP-3 on the human breast cell carcinoma cell line MDA-kb2, which expresses functional androgen receptors (AR). Study results showed significant androgen antagonism by BP-3 in vitro, at concentration levels below the point of cytotoxicity, providing further evidence for BP-3 and endocrine disruption. Suzuki et al. (2004) also evaluated the estrogenic and antiandrogenic effects of 17 benzephenone derivatives with hormone-responsive reporter assays on MCF-7, described earlier and NIH3T3, a rat fibroblast cell line. Their results showed that BP-3 has no antiandrogenic activity and weak estrogenic activity in vitro. In vivo testing, conducted via an uterotrophic assay, for estrogenic activity on ovariectomized rats, could not confirm the observed weak in vitro estrogenic activity

result for BP-3. Unlike the in vivo results of Suzuki et al., Schlumpf et al. (2001) did find weak in vivo estrogenic activity in their study utilizing ovariectomized rats. Incidentally, in this study BP-2 appears to be one the benzophenone derivatives with the highest estrogenic and antiandrogenic activity in vitro. BP-2 was not tested for in vivo estrogenic activity. As mentioned earlier, BP-3 is metabolized to BP-1 and BP-8, and in this study, BP-1 demonstrated moderate estrogenic activity and weak antiandrogenic activity in vitro, with significant estrogenic activity in vivo at the highest concentration. BP-8 only demonstrated a very weak antiandrogenic effect in vitro. The authors concluded that although some benzophenone derivatives elicit estrogenic activity in vitro, overall, benzophenones pose a fairly low endocrine disrupting risk to humans.

Schlect et al. (2004) looked at gene expression of the estrogen receptors (ER), alpha and beta, the estrogen-related receptor 1 (ERR1), and the aryl hydrocarbon receptor (AhR) in rats following a five-day treatment of BP-2, BP-3, or estradiol (E2) in the pituitary, uterus, and thyroid of ovariectomized rats. ERα, ERβ, and ERR1 are all transcription factors that mediate estrogenic responses, while AhR mediates toxic and estrogenic responses of many common pollutants and contaminants. Study findings from this multi-organic risk assessment showed that BP-2 and BP-3 both affected gene expression for the four receptors, with BP-2 demonstrating similar effects to that of E2 in the three organs tested. As observed in the Suzuki et al. (2004) study, BP-3 did not seem to elicit an estrogen-like effect, while BP-2 clearly displayed estrogenic activity. A "classical marker" for estrogenic potency is measurement of uterine weight increases, and in their study, Schlect et al. observed that BP-2, like E2, displayed a significant uterine weight gain following five day treatment. The BP-3 uterotrophic effect observed by Schlumpf et al. (2001), utilized higher concentrations of BP-3 for their testing, as noted by Schlect et al. Although BP-3 did not display endocrine activity on "classical estrogenic markers" as BP-2 did, the authors concluded that BP-3 does have some kind of regulatory effect on receptor expression, and that this effect may still be harmful.

Schreurs et al. (2002) investigated BP-3 and other UV filters for in vitro and in vivo estrogenicity, and found BP-3 to be the strongest activator of transcriptional activity for human estrogen receptors in the human embryonal kidney 293 cells reporter gene in vitro assay. BP-3 also was assessed for in vivo estrogenic activity in a transgenic zebrafish assay, however none of the UV filters, including BP-3, displayed any estrogenic activity.

Several other studies evaluated and found that BP-2 elicited strong estrogenic effects. Seidlova-Wuttke and Wuttke (2004) found that BP-2 displayed pure estrogenic effects in the vagina, uterus, and bone of ovariectomized rats, thus mimicking E2. Schmutzler et al. (2007) saw that BP-2 interfered with thyroid hormone homeostasis in rats, by inactivating thyroid peroxidase (TPO), an enzyme responsible thyroid hormone biosynthesis (1 and 2 from schmutzler 2007). In a 2004 study, Jarry et al. reported a multiple-organic endocrine disrupting activity following a five-day treatment of ovariectomized rats with BP-2. By measuring gene expression of marker genes in the uterus, liver, vagina, and pituitary, the authors demonstrated that BP-2 was capable of E2-agonist activity in a dose-dependent manner.

b. Biomonitoring Studies

A 1997 study by Hayden et al. exposed nine human volunteers for 12 hours to BP-3-containing sunscreens (via generous but realistic forearms application) in order to assess if BP-3 is absorbed

into systemic circulation. The authors estimated that a significant amount of BP-3 penetrated the dermal barrier (between 1 and 2% of the total applied amount) over a 10-hour period, and that a considerable amount of BP-3 (either unchanged BP-3 or its' metabolites) was then excreted in urine (48 hours after application). The authors also state that their findings were consistent with both in-vitro and animal research studies. At the time of this study, it was generally assumed that very little of a topically applied product actually made it into systemic circulation. Hayden et al. suggest that sunscreens not be the only method used for sun protection and that if no alternative protection is available, BP-3-containing sunscreens should not be applied to large surface areas of skin for extended periods of time. Particular attention should be made for children, according to the authors, as children have under-developed processes of elimination as well as larger surface area per body weight as compared to adults, in regards to systemic availability of topically applied products.

In 2004, Janjua et al. also reported finding BP-3 in the urine (and plasma) of 32 Danish volunteers who underwent daily whole-body topical application of BP-3-containing sunscreen for one week. This study reaffirmed that BP-3 is capable of being systemically absorbed following skin penetration and subsequent bodily removal of any remaining BP-3 by urinary excretion. Although Janjua et al. did not estimate the amount of BP-3 absorbed, they suspect a systemic uptake of milligrams per application. The sunscreen application density for the Janjua et al. study was 2 mg/cm^2 (containing 6% BP-3), while the application density was approximately six times higher (12.4mg/cm^2) for the Hayden et al. study (containing 10% BP-3). The authors also evaluated the effects that BP-3 had on the hypothalamic-pituitary axis following whole-body topical application of BP-3-containing sunscreen, and found no significant effects on reproductive hormone levels. As with 1997 Hayden et al. study, Janujua et al. cautioned to the possible dangers of sunscreen use in children, as young children have less developed drug elimination systems that could lead to higher uptake and bioaccumulation of UV filters, such as BP-3.

A 1990 study by Bronaugh et al. evaluated the percutaneous absorption of BP-3 in monkeys. The authors administered BP-3, with an acetone vehicle, and assessed absorption (% applied dose) on unoccluded skin (a 1cm^2 abdominal area) via urinary excretion 24 hours after application. BP-3 application density was 4 μg/cm^2, and the authors found that 44% of the applied dose was absorbed through the monkey skin. Bronaugh et al. also examined BP-3 volatility via evaporation on a Teflon disc, and reported a 57% loss after 3 hours and 99% lost after 24 hours (Bronaugh et al.).

As part of the 2003-04 National Health Examination Survey (biomonitoring study) evaluating chemical exposure in a representative sample of the U.S general population, Calafet et al. (2008) detected BP-3 in 96.8% of urine samples taken from survey volunteers aged six and older. The authors concluded that BP-3 was prevalent in the general U.S. population in 2003-04, and since BP-3 is still used in sunscreens and other cosmetics, it is likely still prevalent in the general U.S. population.

c. Toxicology Studies

BP-3 was nominated for experimental animal toxicity testing by the National Institute for Environmental Health Sciences based on its potential for consumer and occupational exposure. The National Toxicology Program (NTP) conducted the testing, and results were released for

chronic toxicity (14-week feed studies) and long-term toxicity (2-year feed studies) in 2000 and 2006, respectively.

Results of the 14-week studies indicate that the liver is the primary target of BP-3 toxicity in both rats and mice, while the kidney was identified as a target organ in rats only. There was some evidence of hematopoietic system toxicity in rats. Rats, overall, appeared to be more sensitive to BP-3, and the NTP concluded that BP-3 was slightly toxic. No developmental toxicity was observed and no data were available for reproductive toxicity in the literature at the release of the 14-week study results in 2000. In regards to genetic toxicity testing, the standard Ames test showed BP-3 to be non-mutagenic, as did the mouse lymphoma cell mutagenicity test (USDHHS "National Toxicology Program: Ntp Technical Report on the Toxicity Studies of Benzophenone (Cas No. 119-61-9) Administered in Feed to F344/N Rats and B6c3f1 Mice").

Conclusions from the 2006 NTP 2-year toxicity and carcinogenicity studies were that BP-3 caused kidney cancer in male rats, liver tumors in male mice, and histiocytic sarcomas in female mice. Some associations were also seen with BP-3 leukemia in male and female rats and liver tumors in female mice. Male and female mice saw increased rates of metaplasia of the epithelium in the nose and hyperplasia of the spleen (USDHHS "National Toxicology Program: Ntp Technical Report on the Toxicology Andccarcinogenesis Studies of Benzophenone (Cas No. 119-61-9) in F344/N Rats and B6c3f1 Mice (Feed Studies)").

In 2009, The European Food and Safety Authority (EFSA) conducted toxicological evaluation of BP-3, due to its use in food packaging and potential for migration into food if no functional barrier exist (EFSA). BP-3 is used as an initiator in printing inks cured by UV radiation in food packaging. The EFSA Scientific Panel on food contact materials, enzymes, flavourings, and processing aids (CEF) evaluated the risk of BP-3 in breakfast cereals. Rat studies identified the liver and kidney as the primary target organs for BP-3 toxicity. Negative *in vivo* and *in vitro* studies allowed the Panel to conclude that BP-3 has no genotoxic potential. The Panel also concluded that short-term consumption to BP-3 in cereal, at current levels, does not pose a threat to human health.

5. Regulatory Status

a. FDA

In the United States, the FDA regulates sunscreens as over-the-counter drugs, thus recognizing these products as safe and effective for photoprotection (Kullavanijaya and Lim; Food and Drug Administration). BP-3, along with 15 other sunscreen drugs, also known an UV filters or sunscreen actives, were approved for use in the latest version of the FDA Sunscreen Monograph Final Rule, issued in 1999 (Hexsel et al.). Recently (as of December 2009), the FDA also approved a new active sunscreen ingredient, Ecamsule, bringing the total to 17, for FDA-approved active sunscreen ingredients (Sambandan and Ratner). The maximum FDA-approved concentration for BP-3 in sunscreens is 6%. According to a 2008 EPA sunscreen report, BP-3 provides considerable UVA and extensive UVB protection (USEPA). The FDA classifies all 17 sunscreen drugs as either organic or inorganic filters. In the United States, BP-3 is known by its US Adopted Name (USAN), oxybenzone, as well as by one of its more than 20 trade names, while many other countries use the International Nomenclature Cosmetic Ingredient nomenclature, benzophenone-3.

b. Other countries

Like the United States, Canada (Health Canada) and Australia (Therapeutic Goods Administration) both regulate sunscreens as over-the-counter drugs, while the European Union, South America, South Africa, and Japan regulate sunscreens as cosmetics. According to Sambandan and Ratner, classification of sunscreens as over-the-counter drugs rather than cosmetic products requires a more stringent approval process. Canada allows a maximum BP-3 concentration of 6% (HC), while the TGA in Australia allows BP-3 in concentrations up to 10% (TGA). The Scientific Committee on Consumer Products of the European Commission allows cosmetic sunscreen products in Europe to have a maximum concentration of 6% and 0.5% in other types of cosmetic products (SCCP).

6. Alternatives

Two inorganic (previously known as physical) UV filters, titanium dioxide (TiO_2) and zinc oxide (ZnO), are photostable, broad-spectrum sunscreen drugs capable of protection via reflecting, scattering, or absorbing UV, visible, and infrared radiation (Hexsel et al.). Generally, ZnO offers stronger UVA protection and TiO_2 offers better UVB protection (Sambandan and Ratner). The method of protection and the amount of sunscreen needed for application is dependent on particle size. Until recently, inorganic UV filters were not as popular for aesthetic reasons, as a thick coating was necessary to achieve the proper level of UV protection. Recent technological advances, however, have developed microfine or nanoparticles (20-100nm) of TiO2 and ZnO, that are transparent on the skin and thus cosmetically more acceptable (Sambandan and Ratner). Due to their inert properties, TiO_2 and ZnO are generally considered safe alternatives to organic UV filters, such as BP-3. However, concern over nanoparticles' ability to penetrate the skin and achieve systemic exposure has led to re-evaluation of their toxicity (Nash). Overall, studies evaluating dermal penetration of metal oxides have shown these compounds to remain on the top layer of skin and not penetrate through the skin (Nash). Studies evaluating other toxicological properties of inorganic UV filters are ongoing.

7. Conclusion

The FDA and other foreign government consumer protection organizations have deemed BP-3 to be a safe and effective UV filter. BP-3 is one of the most common UV filters, used in approximately 60% of all sunscreen products, despite having a high incidence of photodermatitis. Due to its chemical and physical properties, BP-3 is capable of bioaccumulation in humans as well as wildlife, and studies have detected BP-3 in fish and aquatic environments, including the influent and effluent of WWTPs. Additionally, BP-3 can enter the human body via skin absorption, and biomonitoring studies have demonstrated that BP-3 is present in the urine of a substantial portion of the U.S. population. A serious concern that continues to be addressed regarding BP-3 arises from studies that have demonstrated BP-3 to possess estrogenic activity and therefore capable of endocrine disruption. Arguments have been made that the concentrations of BP-3 utilized in experimental animal studies are much higher than those typically found in sunscreens and other personal care products, but in the 1990s, environmental health scientists proposed the "low-dose hypothesis, which claims that high-dose toxicity testing does not adequately measure the effects that environmental chemicals, particularly endocrine disruptors, can elicit at low doses. Some study authors have even advised that BP-3 only be used as a last line of defense, in the event that no other alternative UV filters exist, particularly for children, who possess under-developed elimination systems. Concern has even been raised that use of BP-3-containing sunscreens may actually increase the risk for

melanoma through photogeneration of harmful ROS in the skin. Fortunately, there are alternative UV filters that may be utilized for sun protection. TiO_2 and ZnO are inorganic UV filters that are generally considered to be safe due to their inorganic properties. The public must be made aware of the potential harmful effects of BP-3 until further testing, including dose-response studies, can validate its complete safety.

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G. TRICLOSAN

1. Overview

Triclosan (2,4,4' –trichloro-2'-hydroxydiphenyl ether) is polychloro phenoxy phenol that is currently used as an antibacterial or antifungal additive in household products such as hand soaps, toothpastes, and cosmetics, and in commercial products like pesticides and also as a material preservative (1). Broad-spectrum antimicrobial agents like triclosan are used to inhibit the growth of or kill bacteria, fungi, and some viruses. It can be found in concentrations of 0.1 – 1.0% in consumer applications and up to 10% in commercial applications (1). The use of triclosan has become increasingly wide spread due to recent outbreaks of bacterial infections like Methicillin-Resistant Staphylococus aureus (MRSA). Despite its widespread use, the human health and environmental effects of triclosan are muddled in controversy and review. As of 2008 the Environmental Protection Agency's (EPA) human health risk assessment of the compound is under review, while recent scientific literature has focused on triclosan's emerging and harmful presence in aquatic environments and presence in the human body. Consumer products are the primary source of human exposure with ingestion, absorption, and inhalation all being routes of entering the body, while aquatic concentrations of triclosan are attributed to wastewater entering streams and rivers through untreated runoff and inefficient wastewater treatments facilities. Concentrations of triclosan in the human body and water supply are of increasing concern because of their potentially negative effects on endocrinology, reproductive and developmental toxicity, antibacterial resistance, and potential for carcinogenic activity. Though scientific inquiry into triclosan's effect on human health and the environment is ongoing, government protection agencies continue to evaluate the scientific data to shape their policy on the use and regulation of the compound. Raised awareness of triclosan is necessary to mitigate the risk in these possible areas of concern. The most direct and effective methods are to simply wash hands according to Centers for Disease Control (CDC) procedure and to not purchase items with triclosan as an additive. Alcohol or peroxide based soaps in combination with CDC guidelines will effectively remove bacteria from skin surfaces and is one easy way to reduce CEC exposure and use. Triclosan-free consumer products are readily available and have been proven by multiple public health studies to be as effective as soaps containing the antimicrobial.

2. Introduction

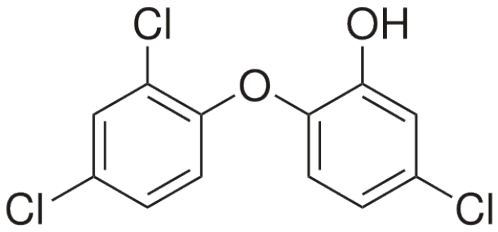
a. Relevance

Despite the existence of numerous published studies concluding that triclosan provides no added benefit to soaps, the use of triclosan-containing products persists (2). As a broad-spectrum antimicrobial agent, triclosan inhibits the growth or kills bacteria and funghi. Triclosan's molecular function in antimicrobials is as an inhibitor of lipid biosynthesis; specifically it inhibits the enzyme enoly-acyl carrier protein reductase (ENR) (3). Triclosan was originally introduced in the early 1970's by the healthcare industry but has since spread rapidly into many household products (1). A 2000 study found that 75% of liquid soaps, 30% of bar soaps, and 25% of toothpastes contained an antimicrobial agent; triclosan being the most prevalent (4). The prevalence of triclosan in consumer products is of growing concern with regards to both human and environmental health. It has long been thought that since humans do not have the ENR enzyme, triclosan would not pose a threat to us, but recent studies have shown possible links between the bioaccumulation of triclosan in the human body and negative health effects such as antibiotic resistance, endocrine disruption, chronic health effects, and a link to dioxin levels (5).

In addition to human health risks, triclosan also poses risks to aquatic environments and organisms. The compound enters these ecosystems easily because many water treatment plants fail to remove the compound from waste water and agricultural and industrial runoff enter streams directly without being treated (6). As a result, one study found triclosan to be one of the most frequently detected contaminants in water supplies, and it occurred at the highest concentrations (6). Once in these ecosystems, triclosan has the ability to bioaccumulate in fish and plant species, with the highest risk pertaining to first step producers like algae and the development of some fish species (7). Bioaccumulation is the ability for a chemical to accumulate and remain stable in an organism. Triclosan's lipophilic nature allows it to bioaccumulate in the tissues of organisms until it reaches levels that can be harmful to the organism.

b. Physical Data

Triclosan (2,4,4' –trichloro-2'-hydroxydiphenyl ether) is a polychloro phenoxy phenol. It is a chlorinated aromatic compound with functional groups representative of both phenols and ethers (1).



The molecular formula for triclosan is $C_{12}H_7C_{13}O_2$. Triclosan is most commonly found in the form of a white powder and is only slightly soluble in water. It is however soluble in ethanol, methanol, and ether (5).

c. Uses

Triclosan is primarily used as a broad-spectrum antimicrobial agent applied as an additive in many household products such as soaps, toothpastes, cosmetics, and cleaners. Its primary function in these products is to prevent the growth and reproduction of bacteria and funguses (1). It is also used as an additive in plastic products to prevent degradation from microbes (1). Triclosan is also used commercially as a pesticide and material preservative (1).

3. <u>Environment and Exposure</u>

a. Environmental/Ecological Fate

In recent years, triclosan has been found throughout the environment, in surface water, soil, and in human and fish tissues. A 2002 U.S. Geological Survey study found that out of 95 contaminants in U.S. streams, triclosan was one of the most frequently detected, and appeared in the some of the highest concentrations (8). Triclosan's presence in the environment can be attributed to two major sources: household disposal of triclosan-containing products down drains, and storm and urban water runoff. 95% of triclosan's uses are in household products such as antibacterial soaps and cleaners and when used in this capacity, triclosan is disposed of

down household drains (9). When used in domestic settings the wastewater is treated before being released into surface waters, but removal efficiency for triclosan varies widely across states and countries from 'complete removal' to below 10% removal (10). The discrepancies in reporting are largely due to treatment plant capabilities and environmental conditions for biological degradation. A Swiss study showed 95% removal when plants used mechanical clarification, nitrification, flocculation, and filtration (11), while a British study found rates less than 58% for treatment plants with shorter retention times and the use of trickling filters (10). It is biological degradation though, that is identified across studies to be the main removal mechanism of triclosan in treatment plants; up to 79% as reported in one study (11). When triclosan is used in urban and agricultural settings as an additive in outdoor cleaners or pesticides, the runoff is untreated, and flows directly into streams, rivers, and lakes. In a 2000 U.S. Geological Survey study focused on observing this type of contamination, it found that 57% of streams and lakes where agricultural and urban runoff were present contained concentrations of triclosan (6).

b. Wildlife Effects

As a result of treatment plant inefficiencies and untreated urban and agricultural runoff, triclosan is present in aquatic environments and aquatic organisms. While the current understanding of triclosan's effect on aquatic wildlife is limited, there is evidence to suggest that triclosan presents a toxic risk to aquatic environments and organisms. It has been found to bioaccumulate in fish at concentrations thousands of times higher than that of the water in which they live. Concentration factors in fish have been found in the range 3,700 to 8,400 times higher than in the water column (12). Methyl triclosan, a transformation of triclosan that is stable in the environment, poses an increased risk to bioaccumulation in aquatic organisms. Once methylated, the lipophilicity of triclosan increases and the likelihood of photodegradation decreases, both of which contribute to bioaccumulation (5). Triclosan enters the fish's body through the filtration in of contaminated water their gills and from aquatic food sources that have already absorbed the compound. A Japanese study of triclosan observed toxic effects of the compound as an endocrine disruptor and on early development of Medeka fish (13). Further research has shown that the presence of triclosan in the water column affects the structure and function of algal colonies. These studies have focused on algae within areas of wastewater effluent, and have observed decreases in the health and population of algal communities (7). As first step producers the effects on algal colonies reverberate through the aquatic ecosystem and ultimately disrupt the cycle of the ecosystem.

4. Human Health Effects and Exposure

Multiple studies have found bioaccumulation of triclosan in humans and examined the possible human health implications associated with its presence. A 2000 study by Swedish scientists found concentrations in three out of five breast milk samples tested (14). Furthermore, a 2003-2004 National Health Examination Study found triclosan in 75% of urine samples tested in the study (15). Triclosan enters the human body via ingestion (water and fish), absorption (use of triclosan-containing hand soaps), and also inhalation (use of triclosan-containing paints and cleaners). The presence of triclosan in humans is well documented, but there are conflicting reports on the adverse health effects its presence can cause. To date, research has focused on triclosan's effect on antibiotic resistance, toxicity, chronic health effects,and link to dioxins.

a. Antibiotic Resistance

The development of bacterial resistance to antibiotics is of international concern for scientists as widespread over/misuse of antibacterial products continues. The emergence of contagious infections like Methicillin-resistant Staphylococcus aureus (MRSA) has lead to increased use and demand of antibacterial agents like antibacterial triclosan. Triclosan presents a concern in terms of antibiotic resistance because of its mode of action. It targets bacteria in the same way many antibiotics do; by targeting specific enzymes within the bacteria (15). The concern is that bacteria will develop resistance to the mode of action employed by both triclosan and other antibiotics, rendering both ineffective. It is important to acknowledge that, while triclosan has been associated with antibiotic susceptibility, there is a relative lack of scientific research that provides a direct link between triclosan and antibiotic resistance. One ten-year study found no link between triclosan use and antibiotic resistance of MRSA and *P. aeruginosa* (16). In another study from 2001, scientists found that mutated strains of bacteria resistant to triclosan also showed resistance to antibiotics used in the treatment of tuberculosis (17). Though these findings appear contradictory, scientists can all agree that the development of antibiotic resistance is a process that occurs in a 'step-wise fashion' and the threat of resistance development will grow with increased use of antibacterial products like triclosan (5). The common recommendation by active scientists in the field is to eliminate the unnecessary applications of antibacterial agents like triclosan in order to preserve the effectiveness of the compound in its more important uses.

b. Toxicity to Humans

It is widely reported and accepted that triclosan, in 'classic toxicological' terms, is non-toxic to humans. However, there is evidence of contact dermatitis, or skin irritation, as a result of exposure to triclosan (18). Furthermore, there is also a link between triclosan use and photoallergic contact dermatitis (PACD), which happens when parts of the skin that are exposed to triclosan are also exposed to the sun (18).

c. Chronic Health Effects

Growing concern surrounding triclosan's effect on the human thyroid led to a study in 1983 regarding the interaction between triclosan and thyroid metabolism. The study was conducted on mice and concluded that triclosan had a hypothermic effect on the body, which lowered body temperature, and had a "non-specific depressant effect on the body's central nervous system" (19). The study hypothesized that triclosan blocks the metabolism of the thyroid because it mimics the chemical structure of the thyroid hormone (19). Another general health concern arose over triclosan's role in producing cholorform. Chloroform, a byproduct of triclosan and chlorine-treated water, is a known carcinogen and its relationship to triclosan was the subject of several conflicting studies in 2007. One reported chloroform increases as high as 40% while another reported no increase in cholorform production over a range of exposure durations (20, 21).

d. Dioxin Link

Dioxins are families of compounds that can be highly carcinogenic. Of the 210 known dioxins, 17 are considered to be of public health concern (22). The combination of triclosan and chlorinated water under UV radiation has been shown to produce dioxins, something some scientists feared happening in river water (22). Despite the possible concerns of dioxin formation, a 2005 study concluded that dioxins formed from triclosan are of no public health

concern because of the "low concentrations of reactive oxygen species in natural waters and the low efficiency of the direct photolysis" necessary to form dioxin groups (23).

5. Regulatory Status

a. U.S. Environmental Protection Agency

There are currently twenty antimicrobial registrations for triclosan that are monitored by the EPA (1). They are registered under the Federal Insecticide, Fungicide, and Rodentcide Act (FIFRA) of 1972. The EPA regulates triclosan's use in agricultural and industrial settings where it is used in pesticides and as a material preservative. The EPA completed triclosan's Registration Eligibility Decision (RED) for pesticides and preservatives uses in 2008 (1). As part of this decision, the EPA conducted a human health risk assessment for the compound that included an evaluation of occupational and residential exposures and consideration of scientific research on triclosan's effect on endocrinology, developmental and reproductive toxicity, chronic toxicity, and carcinogenicity (1). The result of the EPA's study was that triclosan's use in agricultural and industrial products met the 'statutory safety standard' defined in FIFRA (1). The original RED decision made by the EPA in 2008 incorporated National Health and Nutrition Examination Survey (NHANES) data from 2003-2004. Since that RED decision in 2008, the NHANES has released results from a 2005-2006 study. In light of the findings of this more recent study, the EPA has announced that it will revisit its RED decision on triclosan and announce its decision regarding triclosan's future RED in 2013 (1).

b. Food and Drug Administration

The Food and Drug Administration (FDA) regulates triclosan's use in over the counter products such as cosmetics, hand soaps, and toothpastes. The FDA oversees the use of triclosan in these products under the Federal Food, Drug, and Cosmetic Act (FFDCA) of 1938. The FDA currently has no restrictions on the use of triclosan in consumer products and states that 'triclosan is not currently known to be hazardous to humans' (2). In addition to this finding, the agency also found that soaps containing triclosan do not perform better than soaps without the ingredient (2). Despite their stance on triclosan usage, the FDA acknowledges that the ongoing scientific research studying the compound's effects on human health merits further review, a review they are currently collaborating with the EPA to complete (2). Until a regulatory and scientific review of triclosan occurs, the FDA 'doesn't have sufficient safety evidence to recommend changing consumer use of products' containing triclosan (2).

c. European Union and Canada

European dissatisfaction with triclosan use began as early as 2000 when the Danish National Board of Health urged consumers against the routine use of antimicrobial agents like triclosan for fear of causing environmental contamination (24). That same year scientists in Finland warned consumers of the possible link between antimicrobial agents and antibiotic resistance (25). In response to growing fears and scientific evidence, the European Union (EU) in 2010 announced a ban on triclosan's use in plastics that came in contact with food products (26). The ban on triclosan is currently in litigation in the EU General Court under an appeal from Microban International (26). In Canada, triclosan was recently assessed for health and environmental concerns under their Chemicals Management Plan. The review was completed by members of the Ministry of Health and Ministry of Environment, and concluded that while levels of triclosan in consumer products do not pose a direct threat to human health, when these products get washed down the drain, the resulting contamination is harmful to aquatic environments (27). In

response to this study Canadian officials announced they would begin consultations with industry leaders on reductions in triclosan use for 2012 (27).

6. Alternatives

When used in medical settings for people with weakened immune systems or as a sanitation tool, there are no readily available alternatives to triclosan. In these cases the compound provides an important healthcare benefit. There are however a few simple alternatives to using triclosan-containing household products. First, it is important to acknowledge the multiple organizations that have found no added benefit to products containing triclosan compared to those that do not contain the compound. Among these institutions include the FDA and Mayo Clinic (2). Regarding the use of triclosan-containing hand soaps, the Center for Disease Control and Prevention (CDC) recommends 'vigorous hand washing in warm water for at least ten seconds' to effectively remove germs from skin surfaces (28). Additionally, the CDC recommends the use of alcohol or peroxide based soaps for extra assurance (28). Regarding other triclosan-containing household products, consumers should be aware of the many triclosan-free products available in stores. These include triclosan-free cutting boards, toothpastes, and cosmetics.

7. Conclusion

Triclosan is one of the most commonly used antimicrobial agents in the world. Due to overuse, inefficient wastewater treatment, and untreated agricultural and urban runoff, triclosan has become one of the most present contaminants in water across the world, and as a result has bioaccumulated in humans and aquatic organisms. The first conclusion to be made from this investigation is that the research on triclosan and its environmental and human health effects is young and limited. This must be considered in any evaluation of triclosan, recommendation of its use, or potentially negative effects. Second, is that triclosan is emerging as one of the most commonly found contaminants in aquatic environments and human bodies. The final conclusion is that triclosan does pose a threat to environmental and human health, but the extent and scope of this threat is yet to be found. Considering these threats and the relative ineffectiveness of triclosan in household products, consumers can avoid exposure to triclosan and further pollution of water by purchasing triclosan-free products and adopting behaviors that reduce their use of the compound.

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II. GLOSSARY

Acceptable Daily Intake – Commonly referred to as ADI, acceptable daily intake refers to the amount of a substance (food additive, veterinary drug residue, or pesticide) that can be ingested daily over a lifetime without substantial risk.
Aerobic/Anaerobic processes - Aerobic process describes a process that can only occur in environmental conditions in which oxygen is present, such as atmospheric conditions or highly-oxygenated surface waters. Anaerobic describes a process under conditions with little available oxygen, such as sediment layers, where natural degradation may be extremely difficult.
Alkyl group – An alkyl group is a functional group or side-chain that, like an alkane, consists solely of single-bonded carbon and hydrogen atoms.
Ames test - A bioassay that uses a set of histiodine auxotrophic metants of Salmonella typhimurium for detecting mutagenic and carcinogenic compounds.
Amphoteric - A molecule or ion that can react as an acid as well as a base.
Antiandrogen - Antiandrogens are a class of chemical that block androgen receptors, decreasing the production of male hormones, in turn affecting the regulation of masculine secondary sex characteristics.
Antibacterial - A characteristic of a compound capable of killing or slowing the growth of bacteria.
Antimicrobial – A characteristic of a compound capable of killing or slowing the growth of microbes, a group of microorganisms including bacteria, fungi, and protozoans.
Antioxidant - A molecule capable of inhibiting the oxidation (loss of electrons) of another.
Autoimmunity - The failure of an immune system to recognize natural components of its surrounding organism, allowing for an immune response against its own cells and tissues.
Bioaccumulation - A measure of the persistence of a chemical. Highly persistent chemicals will tend to stay stored in biological systems, and can accumulate over time either in an organism or in the environment.
Bioconcentration - A process leading to a higher concentration of a substance in an organism than in environmental media to which it is exposed.
Biomonitoring – A population-based (segmented by age, race, ethnicity, or sex) assessment of human exposure to environmental chemicals. Samples analyzed for environmental chemicals and their metabolites include blood, urine, and breast milk.
Biotransformation - The series of chemical reactions that occur in a compound, especially a drug, as a result of enzymatic or metabolic activities by a living organism.
Carcinogen - Any substance, radionuclide, or radiation that is an agent directly involved in causing cancer.
Chemical Abstracts Services Number – commonly referred to CAS number in literature, this is a number assigned to a specific chemical compound by the American Chemical Society.
Comet assay – Also known as Single Cell Gel Electrophoresis assay, this is a technique for the detection of DNA damage at the level of the individual eukaryotic cell.
Cytotoxicity - Pertaining to an agent, such as a drug or virus, that exerts a toxic effect on cells.
Degradation - Conversion of an organic compound to one containing a smaller number of carbon atoms, or the process of breaking down a chemical. This occurs in many ways, such as via biodegradation and photochemical degradation.
Dermal absorption - Absorption, or uptake, of a substance through the skin.

Detergent - A synthetic cleansing agent resembling soap in the ability to emulsify oil and hold dirt, and containing surfactants which do not precipitate in hard water; may also contain protease enzymes and whitening agents.
Dose-Response Relationship - A relationship that describes the changing effect of varying levels of exposure/dosage to a chemical over time.
Endocrine disruptor - Any chemical with the ability to cause adverse structural or functional changes to the endocrine system, which can result in harm to human or animal reproduction and development. For parabens too.
Environmental fate - The environmental fate of a particular chemical is where, ultimately, the chemical can be found and detected (or what happens to it after it is released into the environment). For example, the environmental fate of a harmless chemical may be complete degradation in waste water treatment, while more persistent chemicals may end up stored in sediment layers or organisms. Environmental fate is a factor of what environmental medium the chemical is in (air, water, or soil), how easily it can be transported through that media, and the rate of degradation.
Erythema - Localized redness of skin in areas of variable size.
Estrogenic - A chemical that acts in a similar manner to estrogen (the primary female sex hormone) within an organism. Estrogen is found within all vertebrates and even some insects, making estrogenic foreign contaminants extremely dangerous.
GC/MS - Gas chromatography/Mass Spectroscopy, a method of separating and identifying different substances within a test sample.
Genotoxicity - Pertaining to an agent that induces toxic, lethal, or heritable effects to nuclear and extranuclear genetic material in cells.
Hematopoietic system - The macrophage system, including all phagocytotic cells such as histiocytes, macrophages, reticular cells, monocytes, and microglia, except the granular white blood cells. Also known as the reticuloendothelial system.
Hepatotoxicity - Pertaining to an agent capable of damaging the liver.
Hydrolysis - a chemical reaction during which molecules of water are split into hydrogen cations) and hydroxide in the process of a chemical mechanism, typically catalyzed by an acid or base.
Hydrophilic - Having an affinity for, attracting, adsorbing, or absorbing water. 'Hydrophobic' describes the opposite, and is also often interchanged with 'lipophilic', which describes a molecule's affinity for lipids (which resemble a non-aqueous environment).
Hyperplasia - Increase in cell number causing an increase in the size of a tissue or organ.
Immunologic – Relating to the structure or function of the immune system.
In vitro - Refers to studies or tests performed on components of an organism that have been isolated from their standard biological context.
In vivo – Refers to studies or tests performed on living organisms in their normal and intact state.
Intravenous – Within or administered into a vein.
Lipophillicity - Refers to the ability of a chemical compound to dissolve in fats, oils, lipids, and non-polar solvents. It is conceptually similar to hydrophobicity.
Mechanism – In the biological sciences, a mechanism refers to the chemical procedure by which a reaction takes place.
Melanoma - A benign or malignant tumor composed of melanocytes.

Metabolite - A product of intermediary metabolism, or the chemical product of a metabolic degradation process, or biodegradation. For example, nonylphenol is a product of the degradation of nonylphenol ethoxylate in wastewater treatment processes.
Metaplasia - Transformation of one form of tissue to another.
Morphological – Relating to the structure or form of an organism without regard to function.
Mutagenicity - Pertaining to an agent that raises the frequency of mutation above the spontaneous or background rate.
Nanoparticles - A particle sized between 1 and 100 nanometers in diameter. Also known as 'ultrafine' particles.
NHANES – the National Health and Nutrition Examination Survey is conducted by the United States Centers for Disease Control and Prevention, and is a program of studies designed to assess the health and nutritional status of adults and children in the United States.
Octanol:Water Partition Coefficient - the ratio of concentrations of a compound in the two phases of a mixture of two immiscible solvents at equilibrium (here, octanol and water). The partition coefficient can be used to measure how hydrophilic or -phobic a substance is. In medical practice, partition coefficients are useful for example in estimating distribution of drugs within the body. Hydrophobic drugs with high partition coefficients are preferentially distributed to hydrophobic compartments such as lipid bilayers of cells while hydrophilic drugs (low partition coefficients) preferentially are found in hydrophilic compartments such as blood serum.
Ovariectomy - The excision of an ovary.
Parabens - a group of chemical compounds commonly used in the commercial manufacturing industry as preservatives in products such as food, drugs and cosmetics; esters of p-hydroxybenzoic acid, and come in multiple forms including methylparaben, propylparaben and butylparaben.
Percutaneous absorption - The process of absorption through the skin from topical application.
pH – A measure of the acidity or basicity of a solution, using a scale from 1 to 14. Low pH values (below 7) represent acidic conditions, while high pH values (above 7) represent basic conditions. Neutral water has a pH of 7.
Photoaging - Damage that is done to the skin from prolonged exposure, over a person's lifetime, to UV radiation.
Photocarcinogenesis - Sum of a complex of simultaneous and sequential biochemical events that ultimately lead to the occurrence of skin cancer.
Photodermatitis - Reaction of the skin caused or elicited by exposure to sunlight; may be phototoxic or photoallergic, and can also result from topical application, ingestion, inhalation, or injection of mediating phototoxic or photoallergic material.
Photogenerate - Generated by exposure to sunlight.
Photoprotection - The use of a physical (hat) or chemical (PABA) barrier to reduce UV light exposure.
Photostability - The incorporation of stabilizers in polymers, such as ultraviolet absorbers, to prevent photodegradation.
P-Hydroxybenzoic acid – A chemical compound vital to the formation of parabens.
Preservative – in the chemical processing and commercial production industries, the term preservative typically refers to a substance with the ability to prevent microbiological growth
Reactive oxygen species - Extremely reactive (due to an unpaired electron) molecules and ions of oxygen (superoxide, hydrogen peroxide, and hydroxyl radical) that may be toxic to cells; causing damage to such cellular macromolecules as DNA, lipids, and protein. ROS contribute to cancer, heart disease, and cerebrovascular disease.

Solubility – The ability or tendency for a substance to be dissolved into water or water-like substances such as blood or urine.
Spermatogenesis - The meiotic replication of male primary germ cells.
Surfactant - A type of chemical used to reduce the surface tension of a liquid, effectively increasing the ability of that solution to mix with particles that would otherwise be highly resistant.
Transactivation - Increased rate of gene expression directed by either viral or cellular proteins. These regulatory factors (diffusible gene products) act in trans -- that is, act on homologous or heterologous molecules of DNA.
Transcription - The process by which ribonucleic acid (RNA) is made from deoxyribonucleic acid (DNA).
Transgenic (zebrafish) assay - A transgenic assay is a method of measuring the effects of a substance on a living organism by using genetic material from an organism that has been transplanted into another so that the host acquires the genetic traits of the transferred genes in its chromosomal composition.
Unoccluded - Not obstructed.
Uterotrophic assay - An assay that measures an estrogenic chemical's effect on the uterus; typically evaluated by uterine weight changes due to imbibition (absorption) of water and subsequent cell growth.
Vitellogenin induction (assay) - An assay used to measure vitellogenin, a yolk protein precursor, production in fish following exposure to endocrine disrupting compounds.
Volatility - The tendency of a substance to vaporize.
Wastewater Treatment - The removal of contaminants from wastewater (both runoff and domestic) and household sewage by physical, chemical, and biological processes.

III. ACRONYMS and UNITS

A. Acronyms

ADI – Acceptable Daily Intake
AE - Alcohol Ethoxylate
AhR - Aryl Hydrocarbon Receptor
AP - Alkylphenol
APE - Alkylphenol Ethoxylate
BP - Benzophenone (12 derivatives)
CAS Number – Chemical Abstracts Service Number
CDC – Centers for Disease Control and Prevention
CEF - Food contact materials, enzymes, flavorings and processing aids
DNA – Deoxyribonucleic acid
E2 - Estradiol
EAC - Endocrine Active Chemical
EDC - Endocrine Disrupting Compound
EFSA - European Food and Safety Authority
EFSA – European Food Safety Authority
EPA (US EPA) – the United States Environmental Protection Agency
ER - Estrogen Receptors
EU – European Union
FAO – Food and Agriculture Organization

FDA (US FDA) – the United States Food and Drug administration
FIFRA – Federal Insecticide, Fungicide and Rodenticide Act
GC/MS - Gas Chromatography/Mass Spectrometry
HC - Health Canada
JECFA – Joint Expert Committee on Food Additives
LOAEL - Lowest Observed Adverse Effect Levels
NHANES – National Health and Nutrition Examination Study
NOAEL - No Observed Adverse Effect Levels
NP(E) - Nonylphenol (Ethoxylate)
NTP - National Toxicology Program
OP(E) - Octylphenol (Ethoxylate)
PABA - Para-Aminobenzoic Acid
ROS - Reactive Oxygen Species
SCCP - Scientific Committee on Consumer Products of the European Commission
SPF - Sun Protection Factor
TGA - Therapeutic Goods Administration, Australia
TiO_2 - Titanium Dioxide
TSCA – Toxic Substance Control Act
USAN - US Adopted Name
WHO – World Health Organization
WWTPs - Wastewater Treatment Plants
ZnO - Zinc Oxide

B. Units

µg/L – microgram per liter; 10^{-6} grams per liter

IV. Resources

EPA, EWG, etc.

V. Regulations

DRAFT – April 13, 2012
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