Journal of Cleaner Production 19 (2011) 429–437

Contents lists available at ScienceDirect

Journal of Cleaner Production

journal homepage: www.elsevier.com/locate/jclepro

Applying the precautionary principle to consumer household cleaning product development

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ARTICLE INFO

Article history:
Received 25 January 2010
Received in revised form
8 July 2010
Accepted 8 July 2010
Available online 16 July 2010

Keywords:
Product development
Toxic chemicals
Household cleaning
Precautionary principle
Disinfectant

ABSTRACT

Hazardous chemicals are pervasive in household disinfectant products. Many ingredients have established associations with acute and chronic human health conditions as well as with environmental damage. Although these associations are suggested but not proven, they are of great concern. This article describes the application of the precautionary principle to the selection of an anti-microbial active ingredient for a botanical disinfectant when significant uncertainty exists around the hazard and risk of traditional disinfectant active ingredients. We show that application of the precautionary principle does not stifle innovation and facilitates a responsible approach to product development.

1. Introduction

Protecting the environment and human health through responsible consumerism has emerged as an important shift in buyer behavior (Thogersen, 2006). As a result, both consumer demand for and availability of green household cleaners have significantly increased. Although many factors influenced this change, the direct relationships demonstrated between conventional cleaning product ingredients and negative environmental and human health effects such as eutrophication (Conley et al., 2009), air pollution (Nazaroff and Weschler, 2004; Destaillats et al., 2006; Kwon et al., 2008), and endocrine disruption (Diamanti-Kandarakis et al., 2009; Rudel et al., 2003) have had a significant impact on the consumer view of household product safety. In addition to the negative relationships that have been established, there are also ingredients that are suspected of having unintended negative consequences but for which direct relationships to health and the environment have not been demonstrated (Ahn et al., 2008).

This level of uncertainty introduces a formidable challenge for product development scientists who aim to formulate products with superior human health and environmental safety profiles. Due to the complexity of biological systems, establishing causal relationships between an ingredient and an ecological or physiological effect requires such rigorous inquiry that by the time a cause–effect relationship is established and accepted, myriad exposures have occurred which could have been prevented. Managing scientific uncertainty in ingredient safety assessments requires a well-designed system of evaluation and ranking to categorize the severity of potential hazards that ingredients and formulated products pose to consumers and to the environment. The most widely used principle to guide such characterization in the face of scientific uncertainty is the Precautionary Principle (PP) which can be summarized as follows: “when an activity raises the threat of harm to human health and the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically”(Raffersperger and Tickner, 1996). By taking preventive action in the face of uncertainty and developing alternatives, the PP prevents additional exposures and can protect human health and the environment despite the absence of conclusive evidence of a negative effect.

One of the major points of opposition to the use of the PP, particularly in product development, is that its application stifles innovation by requiring proof of safety prior to introducing a new technology (Kriebel et al., 2001). In the case of pharmaceutical development, the benefit of innovation can often outweigh the risk or hazard associated with uncertain effects. For example, innovation in treatment for terminal illnesses such as stage IV cancers or HIV/AIDS can result in saving or significantly extending a patient’s life, therefore, the benefit of remission or cure outweighs the risk of

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doi:10.1016/j.jclepro.2010.07.008

unknown adverse effects. Conversely, from the perspective of a green household cleaning formulation the risk of harming human health and/or the environment far outweighs the benefit of providing consumers with the latest innovation in household cleaning. In addition, launching a product that is later found to be wholly or in part unsafe for health or the environment contradicts the central tenant of green chemistry, which is to provide safer alternatives. This does not suggest that innovation is not the goal of green product developers; however, safety as defined by the developer supersedes innovation as a priority. For this reason, the early green product lines followed a "less bad" philosophy in order to provide alternatives to existing products on the market. Due to the increase in demand for sustainable, safe products the market has changed and product developers have more raw material options thereby evolving green product development from the pursuit of "less bad" to the pursuit of true innovation.

Despite the introduction of green offerings in almost every household cleaner category, disinfectants and sanitizers have had no significant green alternatives introduced to date. As these products are required to be registered with the US Environmental Protection Agency, are classified as pesticides, and have highly regulated claims it may be a function of the inability to communicate human health or environmental safety claims that has prevented the greening of the category. Notwithstanding the constraints imparted by the regulations, green consumers are faced with a situation in which they must use a conventional anti-microbial pesticide if they desire to kill microorganisms in their homes. Considering the green consumer's awareness around chemical exposure they are faced with a disinfection dilemma: protecting their family from germs or protecting their family from potentially harmful chemical exposures. As such, developing a hard surface disinfectant formulated with safer active and inert ingredients would not only present a significant innovation in the green and disinfectant spaces, but would also provide a solution to this consumer dilemma.

In January 2010 this concept became a reality with the introduction of an EPA registered disinfectant that kills germs botanically. This article describes the application of the PP to anti-microbial ingredient selection for and development of this natural hard surface disinfectant, and describes how its application in consumer product development can act to foster innovation and produce viable alternatives to potentially hazardous chemistries.

2. Determining uncertainty: anti-microbial active ingredients

Of the registered disinfectants available in the consumer market, the most common active ingredients are quaternary ammonium compounds and sodium hypochlorite. Another ingredient, Triclosan, is used more predominately in anti-microbial hand washes but is also utilized in several registered surface disinfectants. A review of the scientific literature reveals evidence which suggests relationships between these conventional disinfectant active ingredients and serious human health and environmental issues such as asthma and respiratory sensitization (Bernstein et al., 1994; Burge and Richardson, 1994; Leroyer et al., 1998; Nickmilder et al., 2007; Nielsen et al., 2007; Preller et al., 1996; Purohit et al., 2000; Shakeri et al., 2008; Zock et al., 2001; Medina-Ramon et al., 2005), air pollution (Kwon et al., 2008; Odabasi, 2008; Fiss et al., 2007), bioaccumulation and reproductive toxicity in wildlife (Fair et al., 2009; Fry, 2005), and bacterial resistance (Levy, 2001; Gaze et al., 2005; Russell et al., 1998; Sundheim et al., 1998; Aiello and Larson, 2003). However, causal relationships have not been definitively established. As such, in considering active ingredients for a natural surface disinfectant with a superior human health and environmental safety profile evaluating the uncertain effects of these ingredients is necessary.

2.1. Triclosan

Used as an anti-microbial since the 1960s, triclosan (TCS) is a broad spectrum anti-microbial commonly found in anti-bacterial products spanning personal and household care. TCS prevents fatty acid synthesis in the cell membrane by inhibiting the activity of the NADH-dependent enoyl-acyl carrier protein reductase (FabI enzyme), or its homolog, the *InhA* gene (McMurry et al., 1998, 1999; Heath and Rock, 2000; Slyden et al., 2000; Parikh et al., 2000; Chauncheun et al., 2001; Heath et al., 1998; Hoang and Schwezer, 1999; Heath et al., 2000). This mechanism of action is similar to some antibiotics and research suggests that TCS may confer cross-resistance to antibiotics (Aiello and Larson, 2003; McMurry et al., 1988). However, the true potential for TCS containing household products to cause cross-resistance to antibiotics is unknown.

TCS has been linked to hormone disruption in animals, specifically fish, frogs, and rats (Ciniglia et al., 2005; Ishibashi et al., 2004; Matsumura et al., 2005; Zorrilla et al., 2009; Foran et al., 2000; Veldhoen et al., 2006). More recently, studies suggest that TCS may have the potential to disrupt the endocrine system in humans which is of significant concern as the chemical is essentially ubiquitous and has been measured in breast milk at levels of 2000 μg/kg lipid and 3790 μg/L in human urine (Ahn et al., 2008; Allmyra et al., 2006; Calafat et al., 2008; Gee et al., 2008; Chen et al., 2007; Adolfsson-Erici et al., 2002). However, a cause–effect relationship between TCS and endocrine disruption has not been definitively proven in humans or in wildlife. Therefore, the risk of endocrine disruption resulting from human or animal exposure to TCS containing cleaning products is unknown.

Due to its structural similarity to toxic and environmentally persistent compounds such as dioxins, the secondary reactions and environmental fate of TCS have been of special interest. For example, one study showed that TCS in formulation has the ability to react with chlorine in tap water to produce 2,4-dichlorophenol, 2,4,6-trichlorophenol, and chloroform although the risk introduced by these exposures was not determined (Fiss et al., 2007). In other studies, the photodegredation of TCS also resulted in the formation of 2,4-dichlorophenol as well as other toxic compounds such as, 2,8 dichlorodibenzodioxin, and dichlorohydroxydiphenyl (Latch et al., 2003; Sanchez-Prado et al., 2006). As several reports show that TCS is commonly found in sources that are directly exposed to sunlight, such as surface water and streams, it can be suggested the presence of TCS increases the risk of exposure to its toxic degradation products (Hua et al., 2005; Kolpin et al., 2002). In addition to streams and surface water, there have been reports that TCS present in wastewater is difficult to remove, remains after sewage treatment, and also remains in sludge and biosolids (Chu and Metcalfe, 2007; Heidler and Halden, 2007). However, the presence of TCS degradation products in the environment has not been connected to the presence of TCS in the environment; therefore, it is uncertain what proportion of the environmental load is the result of degradation of TCS versus other sources. In addition, no relationships have been established regarding the presence of TCS in wastewater, sludge, and biosolids to specific human health or environmental issues.

2.2. Quaternary ammonium compounds

Among the most common biocides found in household disinfectants are quaternary ammonium compounds (QACs). While the mechanism of action can differ according to structure and, specifically, chain length, QACs typically kill bacteria by inserting

themselves into the microorganism's lipid bilayer thereby causing a membrane disruption that results in the leakage of intracellular constituents (Ioannou et al., 2007). The antibiotic resistance potential of QACs has been well characterized and several resistance genes have been identified (Chapman, 2003). The QAC resistance genes are found on mobile genetic elements that can spread through horizontal genetic transfer, but serial transfer has also been reported. Despite the well characterized resistance genes, the presence and expression of such genes do not necessarily confer resistance to antibiotics and disinfectants and, as such, QAC disinfectants continue to be a commonly used anti-microbial technology and have not been identified as a major risk for causing resistance (McCay et al., 2010).

The most significant area of debate related to QACs is the suggested potential for exposure to result in respiratory sensitization and asthma. Several studies have demonstrated the relationship between prolonged exposure to QACs and occupational asthma or respiratory sensitization (Bernstein et al., 1994; Burge and Richardson, 1994; Preller et al., 1996; Purohit et al., 2000; Rosenman et al., 2003; Zock et al., 2007). However, despite the significant evidence in professional settings, the risk of developing asthma or respiratory sensitization from using disinfectants with QAC active ingredients has not been described in a household setting. Overall, no definitive link between QAC exposure and respiratory effects has been established in professional or domestic settings. However, the strong correlation between exposure, illness and the biochemical evidence that QACs are immune adjuvants suggests that certain health effects such as the dramatic increases in pediatric asthma and dermatitis may be related to QAC exposure (Militello et al., 2006; Akinbami and Schoendorf, 2002).

Reproductive and developmental issues related to QAC exposure have also been reported (Maher, 2008). In one report, a murine colony experienced significant developmental and reproductive effects after transferring research institutions. Upon careful examination of all variables, the investigator determined that the change to a QAC disinfectant to clean housing for the colony was the source of the breeding problem. After transitioning back to a non-QAC disinfectant the breeding issues within the colony resolved (Maher, 2008). While these results have not been reproduced in humans and QACs have not been specifically identified as human reproductive or developmental toxicants, there are several epidemiological studies that show significant associations between occupation as a cleaning person/biocide exposure and increased odds of birth defects including cleft palate and neural tube defects such as spina bifida (Blatter et al., 1996; Brender et al., 2002; Lorente et al., 2000). Similar relationships were found by the National Birth Defects Prevention Study which associated the largest number of birth defects with occupation as a cleaning person where central nervous system defects were the most prevalent abnormalities (Herdt-Losavio et al., 2010). However, while these higher rates of birth defects may be related to QAC exposure, additional research is required to determine causation.

Skin irritation and sensitization are other areas of concern related to QACs and health (Basketter et al., 2004; Schallreuter et al., 1986). While it is widely agreed that QACs can be irritating, like other irritants, QACs may be formulated in a way that mitigates irritation which can be confirmed by clinical studies. The potential for skin sensitization after repeated exposure is more widely debated and the data are inconsistent. Unlike irritants, skin sensitization cannot be mitigated through formulation as this is the result of an immune response (Schallreuter et al., 1986; Larsen et al., 2004). However, because the data are inconclusive QACs have not been classified as dermal sensitizers.

The data available for characterizing the environmental persistence of anti-microbial QACs are inconsistent. Several studies report successful biodegradation of anti-microbial QACs in activated sludge and other environments by *Pseudomonas*, *Aeromonas*, and *Serratia* species (Patrauchan and Oriel, 2003; Sautter et al., 1984; van Ginkel et al., 1992). Conversely, anti-microbial QACs are commonly detected in treated wastewater and sewage sludge with the highest concentrations being reported in sediment near sites of wastewater discharge (Ferrer and Furlong, 2002; Ford et al., 2002; Garca et al., 2001; Li and Brownawell, 2009; Shibukawa et al., 1999). Due to their positive charge, it is not surprising that QACs readily adsorb to the negatively charged surfaces of sludge, soil and sediment, although their ability to biodegrade in these environments is not certain. As a result, the environmental persistence of QACs has not been determined.

2.3. Sodium hypochlorite

Often referred to as household bleach, sodium hypochlorite (SH) is a widely used anti-microbial ingredient in both consumer and industrial cleaning products. The broad spectrum activity of SH is a result of its ability to denature and aggregate essential proteins in microorganisms which effectively destroys them (Winter et al., 2008). Due to this physical mechanism of action SH has not been linked to anti-microbial resistance.

From an environmental perspective, the most significant concern related to SH is its secondary reactions which create halogenated volatile organic compounds (VOX) (Nazaroff and Weschler, 2004; Kwon et al., 2008; Odabasi, 2008). Emissions of VOX present human health risks, including cancer, and VOX react with other pollutants in the atmosphere to destroy stratospheric ozone (Morello-Frosch et al., 2000; Kerr and Stocker, 1986; Woodruff et al., 2000). The ability of the secondary reactions of SH to create VOX is well documented and studies evaluating SH-containing household cleaners, dishwashing detergents, and laundry additives have reported secondary reaction products including chloroform and carbon tetrachloride (Odabasi, 2008; Olson and Corsi, 2004; Shepherd et al., 1996). In addition to being VOX which contribute to indoor and outdoor air pollution, both of the aforementioned chemicals are probable human carcinogens. However, the contribution of halogenated VOCs produced by SH-containing household products to human and environmental effects has not been fully characterized.

In addition, several studies have evaluated the effects of SH exposure in an occupational setting. Researchers in Europe determined through a series of studies that occupational exposure to SH can result in serious respiratory effects. The first study conducted by the group showed that domestic cleaning women experience a significantly higher risk of asthma and chronic bronchitis than women not working as cleaning personnel (Medina-Ramon et al., 2003). Two subsequent studies with the same population were conducted to identify the specific occupational exposures that resulted in the increase of respiratory problems (Medina-Ramon et al., 2005, 2006). In the first study, frequent use of bleach was independently associated with respiratory symptoms, and most significantly asthma. Exposure to chlorine gas at levels up to 0.7 ppm was recorded during normal use of diluted and undiluted SH by cleaners. In the follow-up study, exposure to SH was shown to aggravate pre-existing obstructive lung disease where those with a history of the disease experienced worsening of respiratory symptoms on days worked as a domestic cleaner and days where more time was spent cleaning. Mean levels of airborne chlorine measured during cleaning with diluted and undiluted SH ranged from 0.4 to 1.3 ppm. In addition to the suggested relationship between adverse respiratory effects and SH use, the concentration of chlorine gas measured during cleaning activity in these studies is especially concerning as the severe inhalation toxicity of chlorine

gas has been described in detail including reports of several fatalities (Agabiti et al., 2001; Bonetto et al., 2006; Parimon et al., 2004). The National Institute for Occupational Safety and Health (NIOSH) has established recommended permissible occupational exposure limits of chlorine gas at 0.5 ppm per day with higher levels requiring personal protective equipment. Based on the established exposure limits of NIOSH it could be suggested that the level of chlorine gas that SH using domestic cleaning personnel are exposed to on a daily basis may increase their risk of respiratory effects secondary to chlorine gas inhalation, although this has not been proven definitively. Inhalation toxicity related to the use of SH has also been reported in avian populations (Wilson et al., 2001). In one case, a psittacine avian colony enclosure was cleaned with a 5% solution of sodium hypochlorite and resulted in a mortality rate of 20% and a respiratory related morbidity rate of 49% of flock members (Wilson et al., 2001). Pathological examinations revealed tracheal and pulmonary lesions similar to those observed in mammalian skin after direct contact with bleach. However, despite the available data, a causal relationship between chronic SH use and long term respiratory sequale has not been established.

In aquatic organisms, the majority of the toxicology work regarding exposure to SH and chlorinated compounds is based on effects of pulp mill effluent on wild aquatic populations. The most commonly described effects are reproductive including decreases in sex steroid hormone levels, gonad size, and fecundity, alterations in secondary sex characteristics, and delayed sexual maturity, all of which significantly decreased when pulp bleaching processes transitioned to elemental chlorine free and total chlorine free processing methods (Hewitt et al., 2008; Valenti et al., 2006). Similar reproductive effects have been described in avian populations, although a definitive relationship between SH exposure and reproductive effects has not been proven in aquatic or terrestrial wildlife (Fry, 2005; Khan et al., 2008).

3. Limitations of risk based analyses

As evidenced, there is a significant body of evidence showing adverse human health and environmental effects related to conventional anti-microbial active ingredients. However, because the true nature of the exposure–effect relationships is unknown, risk assessment is not sufficient to accurately assess the safety of these ingredients. The inability to conduct risk-based assessments is due to a combination of factors including the absence of reliable models or methods to measure an effect, and that many of the effects are chronic and therefore difficult to measure in the absence of extensive longitudinal data.

In order to determine if an anti-microbial active ingredient is appropriate to use, some assessment of safety or hazard must be conducted. When risk cannot be adequately addressed there is no basis for action unless the precautionary principle is applied to assess hazard. As such, in the case of anti-microbial active ingredients, application of the precautionary principle allows for an adequate assessment of ingredient hazard to determine if a safer alternative should be sought out.

4. Categorizing and evaluating uncertainty

Clearly, there are many areas of uncertainty related to common anti-microbial active ingredients. In order to evaluate the level of uncertainty that exists, it is useful to explicitly state what undesirable attributes of a chemical are certain and uncertain based on categories of importance to the reviewer. Table 1 demonstrates the categories used in this evaluation: acute effects, chronic effects, air quality, water quality, wildlife effects, environmental persistence, animal derivative, anti-microbial resistance, and natural resource use. After a thorough literature review, negative attributes are listed and the category in which they fall is marked with either a check mark (representing certainty) or a question mark (representing uncertainty). Using the completed table, the human health and environmental effects of the ingredients are evaluated according to certainty or uncertainty following the process depicted in Fig. 1. Using the precautionary principle, negative attributes of the anti-microbial active that are uncertain result in the exclusion of that ingredient from the formulation development palate. For negative attributes that are well established, through a research and mitigation strategy the ability to remove the negative impacts of an ingredient can be evaluated. For example, if an ingredient has the potential to irritate the skin, prototypes can be developed and tested for *in-vitro* and clinical irritation in formulation. If the negative impact, in this case skin irritation, is removed via the mitigation strategy the ingredient can be used.

Using QACs as an example, in Table 1 there are several attributes that present a potential public health or environmental hazard including the use of natural resources to create the ingredient and the potential to irritate the skin. As previously reviewed in this paper, there is scientific uncertainty around the acute effects, chronic effects, microbial resistance, and environmental persistence of QACs. Although causation has not been established for any of these attributes, because their actual effects are uncertain

Table 1
Negative Attributes of QACs, Sodium Hypochlorite, and Triclosan.

Negative attributes	AE	CE	AQ	WQ	WE	EP	AI	MR	NR
QACs									
Respiratory sensitization & asthma	?	?							
Dermal sensitization	?	?							
Reproductive & developmental effects		?			?				
Microbial resistance								?	
Persists in the environment						?			
Synthetic									✓
Dermal irritation	✓								
Sodium Hypochlorite									
Effects of secondary reactions on health	?	?			?				
Chronic respiratory effects		?							
Reproductive effects in wildlife					?				
Reacts with ozone to produce halogenated VOCs			✓						
Acute respiratory irritant	✓				✓				
Corrosive	✓				✓				
Triclosan									
Effects of degradation products on human health and the environment	?	?	?	?	?				
Endocrine disruption		?			?				
Microbial resistance								?	
Synthetic									✓
Forms dioxin-like compounds when exposed to sunlight	✓	✓		✓	✓				
Persists in the environment						✓			

AE = Acute Effects, CE = Chronic Effects, AQ = Air Quality, WQ = Water Quality, WE = Wildlife Effects, EP = Environmental Persistence, AI = Animal Derived Ingredients, MR = Microbial Resistance, NR = Natural Resource Use.
✓ = certainty of negative effect,? = uncertainty of negative effect.

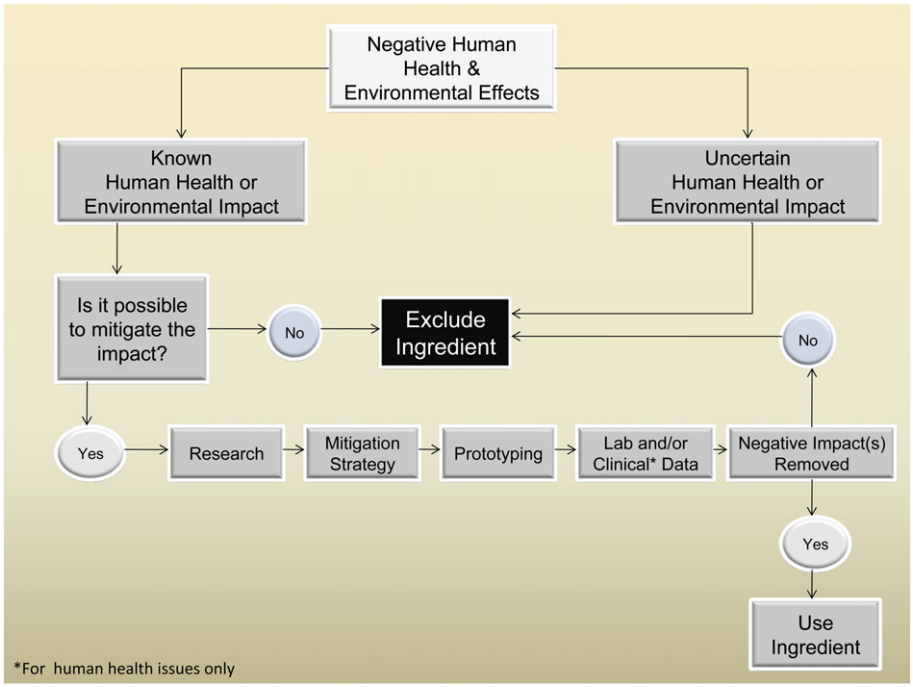

Fig. 1. Process for evaluating ingredients and formulations under the precautionary principle.

a mitigation strategy cannot be developed and validated as parameters for safety have not been established. According to the PP, the inclusion of QACs in a disinfectant formulation raises the threat of human harm and, as such, this ingredient should be avoided and substituted with an alternative active ingredient. A similar assessment can be applied to TCS and SH.

However, this precautionary approach effectively eliminates all conventional anti-microbial active ingredients, which introduces a significant challenge for developing an anti-microbial surface disinfectant. A survey of active ingredients approved for use in EPA-registered products revealed several options for organic acid actives and botanical actives based on essential plant oils. The broad spectrum anti-microbial activity of naturally derived citric and lactic acid is well known and these active ingredients are widely used in both consumer and commercial household and personal care products (Hellstrom et al., 2006; Lopes, 1998; Turner et al., 2004). However, the efficacy of these organic acids is optimal under acidic conditions which can result in products that are irritating to eyes and skin (Berner et al., 1988; Swanson et al., 1995; Mangia et al., 1996). Therefore, despite their minimal environmental and human health impacts, their potential for eye and skin irritation typically precludes them from being utilized as active ingredients in registered disinfectants classified as EPA toxicity category IV; EPA's lowest toxicity category. Due to this limitation, organic acids did not move on to prototyping and botanical active ingredients were evaluated in more detail. Of the essential oils registered as pesticides, thyme oil differentiated itself by virtue of its anti-microbial efficacy and safety profile and was chosen for a more detailed review of authenticity.

4.1. Thymol

Thymol, or 5-methyl-2-isopropyl-1-phenol, is a monoterpene derived from the essential oil of the *Thymus vulgaris* (thyme) plant. The thyme plant is generally recognized as a safe natural seasoning (21 CFR 182.10) and essential oil (21 CFR 182.20) by the US Food and Drug Administration (FDA) and thus is a common food additive. Historically, thyme has been used for medicinal purposes in many cultures spanning topical to oral routes and is still recommended by Germany's Commission E for treatment of respiratory ailments such as bronchitis and whooping cough. As humans and other living organisms have been exposed to thymol via physical contact and diet on a regular basis for literally thousands of years thymol is known to be well tolerated and its safety profile has been well characterized.

The anti-microbial and pharmaceutical properties of thymol have also been thoroughly described (McOmie et al., 1949; Juven et al., 1994; Mahmoud, 1994; Shapiro and Guggenheim, 1995; Edris, 2007; Xu et al., 2008). The broad spectrum anti-microbial efficacy of thymol results from its ability to disrupt the cytoplasmic membrane of microbes by increasing its permeability and depolarizing its potential resulting in rapid efflux of cellular constituents (Xu et al., 2008). Thymol is recognized by the EPA as a registered pesticide and by the FDA as an allowable active ingredient in several Over the Counter Drug monographs making thymol a common chemical found in US households (Table 2).

Several studies have been conducted to evaluate the potential for thymol to cause antibiotic resistance (Walsh et al., 2003; Shapira and Mimran, 2007; Palaniappan and Holley, 2010; El-Shouny and

Table 2
FDA OTC Monographs listing thymol as an allowable active ingredient.

OTC Monograph	Sub-Category
Acne	N/A
Antifungal	N/A
Cough cold	Nasal decongestant
Dandruff/Suborrheic Dermatitis/Psoriasis	N/A
External analgesic	Anesthetic
	Fever Blister, Cold sore
	Poison Ivy/Oak/Sumac
Oral health care	Anesthetic/Analgesic
Relief of oral discomfort	N/A
Skin protectant	Astringent

Magaam, 2009). In one study, clinical and environmental isolates of *Pseudomonas aeruginosa* were found to be resistant to six common antibiotics, however, when these same isolates were exposed to botanical antimicrobials, including thymol, they were completely inactivated (El-Shouny and Magaam, 2009). Another study evaluated the effect of botanical antimicrobials against a selection of antibiotic resistant bacterial strains (Palaniappan and Holley, 2010). Results showed that not only were the resistant strains susceptible to inhibition by thymol, but a combination of thymol and the antibiotic the strain previously showed resistance to resulted in efficacy against the strain. The minimum inhibitory concentrations (MIC) of resistant and non-resistant *Escherichia coli* strains to thymol have also been determined. While the MICs for were heightened for the resistant mutants, resistant mutants were completely inactivated when exposed to higher concentrations of thymol (Walsh et al., 2003). This study also showed that under laboratory conditions bacterial exposure to thymol can lead to reduced susceptibility to chloramphenicol, although this was not deemed to be clinically relevant. Overall, thymol has not been shown to cause antibiotic resistance and has been shown to be effective against a variety of multi-antibiotic resistant strains of bacteria.

Because thymol is delivered as a component of the essential oil of the *T. vulgaris* plant, the safety profile reflects the skin irritation potential common to essential oils. Clinical dermatology studies of thymol show that the ingredient can be irritating and that the irritation is dose dependent. For example, pure thymol (100%) is extremely irritating to the skin (McOmie et al., 1949). However, in studies of lower concentrations, such as a 1% thymol solution, irritation is not seen (Nethercott et al., 1989; Fisher, 1989). The dose dependent nature of thymol's irritation potential suggests that proper formulation could mitigate irritation.

While thymol does not have components that are known or suspected sensitizers, there have been reports of weak sensitization under occlusive conditions at concentrations of 1–5% (Fisher, 1989; Djerassi and Berowa, 1966; Dohn, 1980; Itoh et al., 1988). It has also been reported that thymol can react with formaldehyde and ethanolamine to cause compound allergy (Smeenk et al., 1987). However, the majority of literature reports cases where, under the same conditions, thymol exposure does not result in any sensitization reaction which is consistent with the results of animal toxicology studies (Nethercott et al., 1989; Meneghini et al., 1971; Nishimura et al., 1984; Klecak et al., 1977). In addition, the historical use of thymol in personal care and herbal preparations has established the ingredient's safety for topical applications. As well as this established history of safety, the intensive toxicology reviews undertaken as part of monograph development and pesticide registration by FDA and EPA, respectively, have resulted in thymol being approved for use in eight over the counter drug monographs and as an active ingredient for registered pesticides, including minimum risk pesticides (Table 2). As a result, the evidence supports that thymol is not a sensitizer, although due to the presence of case reports in the literature clinical evaluations of sensitization must be completed for formulations using thymol as part of the standard product safety qualification procedure.

The evaluation of the negative attributes associated with thymol is summarized in Table 3 and identifies acute effects as an area of certainty which requires the research and execution of a mitigation strategy for a formulation using this ingredient. Specifically, skin irritation requires further investigation and mitigation. No areas of uncertainty regarding potentially negative attributes were identified for thymol. Following the process described in Fig. 1, hard surface disinfectant prototypes were developed using a thymol concentration of 0.05%. The inert ingredients included in the prototype formulation were selected based on the Precautionary Principle and are listed in Table 4. The mitigation strategy developed for thymol consisted of three phases: toxicity assessments, performance testing, and skin safety testing.

Table 3
Negative attributes of thymol.

Negative Attributes	AE	CE	AQ	WQ	WE	EP	AI	MR	NR
Thymol									
Dermal irritation	✓								

AE = Acute Effects, CE = Chronic Effects, AQ = Air Quality, WQ = Water Quality, WE = Wildlife Effects, EP = Environmental Persistence, AI = Animal Derived Ingredients, MR = Microbial Resistance, NR = Natural Resource Use.
✓ = certainty of negative effect.

In the first phase, the acute toxicity of the prototype was calculated using a weighted average of the ingredient toxicities as specified by the UNECE Globally Harmonized System (GHS) Additivity Formula and revealed that the prototype is non-toxic with an LD50 of >431,910 mg/kg (oral, rat). The aquatic toxicity was calculated using the UNECE GHS method and the LC50 for the prototype was calculated as >125 mg/L which shows that the prototype is non-toxic to aquatic life. In phase two, the prototype was tested for anti-microbial efficacy and cleaning performance and met the microbiological requirements for an EPA registered disinfectant and desired cleaning performance standards (data not shown). Having passed the basic safety requirements of the preliminary qualification, to complete the third and final phase of qualification the potential negative effect of thymol was addressed through pre-clinical *in-vitro* and clinical skin irritation and sensitization studies to confirm formula safety and address the area of concern captured in Table 3.

4.2. *In-vitro irritection®* assay for dermal irritancy

To determine the acute dermal irritation of the disinfectant prototype with a 0.05% thymol active concentration, the *in-vitro* Dermal Irritection® Assay was conducted by a third-party laboratory (*In-Vitro* International, Irvine, California). This assay is a standardized, quantitative acute dermal irritation test that has been described in detail (Mast and Rachui, 1997). In short, test materials are applied to a synthetic biobarrier where conformational changes in macromolecular complexes are used to determine dermal irritation. Dermal irritancy potential is expressed as a Human Irritancy Equivalent (HIE) score, where the classification for a dermal non-irritant is an HIE score of 0.00–0.90, 0.90–1.20 for borderline non-irritant/irritant, and >1.20 for irritant classification. Results show that in a volume-dependent dose-response study HIE values were 0.40, 0.46, 0.72, 0.86 and 1.02 for volumes of 25 μL, 50 μL, 75 μL, 100 μL, and 125 μL respectively. Although one dose's HIE score was in the lower limit of the borderline non-irritant/irritant category (HIE = 1.02 for 125 μL dose) this material was classified as a dermal non-irritant. As such, the next step in the eradication strategy,

Table 4
Ingredient list for 0.05% thymol disinfectant.

Ingredients
Thymol as a component of Thyme Oil (0.05% anti-microbial active)
Sodium Lauryl Sulfate
Copper Sulfate Pentahydrate
Citric acid
Essential oils and Botanical extracts for fragrance including: Oregano oil, lemongrass oil, blue atlas cedar bark oil, lemon peel oil, lemon fruit extract, orange bergamot mint leaf extract.

clinical dermatology testing, was conducted to establish a clinical correlation.

4.3. Human repeat insult patch test for dermal irritation and skin sensitization

The Human Repeat Insult Patch Test (HRIPT) was conducted under Good Clinical Practice according to standardized methods at a third-party laboratory to evaluate if repeated dermal contact could induce primary or cumulative irritation and/or allergic contact sensitization (Consumer Product Testing Company, Fairfield, New Jersey)(McNamee et al., 2008). Briefly, subjects were semi-occlusively patched on the upper back between the scapulae with 0.2 mL of the 0.05% thymol disinfectant prototype after the volitization period. The induction phase consisted of patch application and clinical grading three times per week for three weeks followed by a rest period. At the conclusion of the two week rest period the challenge phase began where a patch was applied to a virgin test site adjacent to the original induction patch site. The patch was removed and clinically graded at twenty-four and 72 h post-application. Fifty-four subjects completed the study. Results showed only one reaction during the course of the study where prior to application eight of induction one subject experienced level one erythema and slight edema at the test site which completely resolved by application nine. No other visible skin reactions occurred. These results did not indicate potential for dermal irritation or contact sensitization for the disinfectant prototype with an active concentration of 0.05% thymol.

The three phase mitigation strategy demonstrated that the disinfectant prototype containing 0.05% thymol did not exhibit the negative human health effect of concern (irritation) and that thymol was appropriate for inclusion in this disinfectant formula. The microbiological, cleaning performance, ocular irritation (data not shown), and skin safety data lead to the selection of this 0.05% thymol prototype as the final formula, which was fully qualified and launched in January 2010 as the first botanical disinfectant available from Seventh Generation.

5. Conclusions

Toxics reduction efforts such as the Massachusetts Toxics Use Reduction Act (TURA) in conjunction with increasing awareness about the impact of consumer products on human health and the environment have driven the greening of the cleaning products industry. Consumer concerns about these risks are now driving change in the marketplace at the same time that innovative regulatory strategies such as the Massachusetts TURA are evolving to develop safer and more sustainable products. It is these trends which support the use of a PP based model to account for the potential for harm from chemicals that may achieve widespread use. By factoring these uncertainties into the product development equation from the outset, the PP presents a more complete set of design parameters. Rather than stifle innovation, the example of thyme oil based disinfectants illustrates that the PP can actually drive innovation and result in safe and sustainable products and solutions.

Acknowledgements

The author would like to thank Katie Lang and Tim Fowler of Seventh Generation and Dr. Larry Weiss of CleanWell Company for their thorough review of and thoughtful comments on this manuscript.

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