

The Sweet Smell of Poison: Notably Deleterious Effects of Fragrances on Health and the Environment



By: Elizabeth A. Vail

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Introduction

The purpose of this paper is to explain and discuss in detail the harmful effects of ingredients commonly found in fragrances and scented personal care products, the health and environmental ramifications of repeated exposure to such products, and possible regulatory solutions for reducing exposure and mitigating effects to health and the environment.

Fragrances and fragranced personal care products present an emerging health and environmental issue because they are xenobiotics (chemical compounds such as a drug, pesticide, or carcinogen that is foreign to a living organism) containing volatile organic compounds that can trigger anaphylactic reactions, cause biological, metabolic, and immunological responses, and accumulate in the body and environment over time. According to the Committee on Science and Technology, U.S. House of Representatives (USHR), chemicals used in fragrances are synthetic compounds capable of causing cancer, birth defects, central nervous system disorders, and allergic reactions (USHR, 1986). Currently, there are over 5000 chemicals, such as benzaldehyde, di(2-ethylhexyl) phthalate, xylene, and toluene, used in fragrance and personal care products, but only about 1500 have been tested for safety (FDA, 1999).

Albert Baur unintentionally created the first synthetic nitrogenous musk in 1888 while attempting to create a more effective form of TNT. Once he attributed the odor of his concoction to the symmetry of nitrite groups, the vanilla and violet scents soon followed. Later in 1931, polycyclic synthetic fragrances were inadvertently created when the DuPont Company's Wallace Carothers led the team of Julian Hill and Edgar Spanagel to conduct cyclic polymerization experiments in hopes of creating synthetic, less-expensive replacements for rubber and silk. During their experiments, they noted that some of the polycyclic compounds produced an aroma that emulated the musk fragrance. DuPont sold this discovery to a perfume manufacturer under the trade name "Astrotone" (Hermes, 1996).

Although chronic and autoimmune diseases such as asthma were rare in 1900, they have now grown to epidemic proportions (Doyle, 2000). According to the World Health Organization, more than 300 million people are affected by asthma worldwide and it killed 255,000 people in 2005. Its prevalence tends to be highest in Western countries; conversely, it is virtually absent in parts of rural Africa (Doyle, 2000). Since 1980, asthma mortality rates increased more than 50% among all American genders, age groups, and ethnic groups, while the mortality rate for children under 19 years old increased nearly 80% (NCHS, 2001).

This paper will present information that correlates the pandemic of chronic diseases, such as asthma, with the prevalence of commonly found toxins in fragrances and personal care products.

Phthalates

Phthalates are widely used in industry as plasticizers, solvents, denaturing agents, solubilizers, fixatives, and coatings of enteric medications, and are found in items such as lubricants, PVC, medical tubing, jelly rubber, perfumes, cosmetics, deodorants, and personal care products (Pereira *et al.*, 2007). The Research Institute for Fragrance Materials reported an annual use of approximately 4000 tonnes of diethylphthalate (DEP) in preparation of fragrance mixtures alone (Api, 2001). Between 2003-2004, Greenpeace commissioned a quantitative analysis of 36

randomly selected perfumes. Of all the samples, 34 tested positive for DEP with levels as high as 22,299 mg/kg, or 2.2% by weight (Calvin Klein's Eternity for Women). Due to the variety of commercial and manufacturing uses, human exposure is high and metabolites of DEP and diethylhexylphthalate (DEPH) have been detected in urine samples of a high percentage of individuals screened for phthalate exposure (Hokanson *et al.*, 2006).

Concern for phthalate exposure has risen since it is transmitted via placental transfer and breast milk, and studies have positively correlated exposure to the occurrence of birth and reproductive health defects, particularly among males, hepatic tissue damage, and its cumulative multi-generational effects (Pereira *et al.*, 2007).

Concern for male reproductive health and its potential link to endocrine disrupting chemicals has arisen since sperm counts, altered sex ratios, increased incidence of hypospadias (a birth defect of the urethra that involves an abnormally placed urinary opening), cryptorchidism (absence of one or both testes from the scrotum), and the doubling of testicular cancer over the past 40 years have risen dramatically (Wilson *et al.*, 2004). Phthalate esters, such as DEP and DEPH, have been shown to induce malformations in male rats when administered to the doe during in utero sexual differentiation.

Two separate in vivo studies were conducted in which 10 timed-pregnant rats were dosed with 750 mg of DEPH daily on days 14-18 of gestation. On the 18th gestational day, the does were anesthetized and the fetuses were removed, their RNA was prepared, and the fetal testes were examined. PCR amplification was used to isolate insulin-like hormone 3 (Insl3), one of the three male hormones required for normal sexual differentiation and is uniquely responsible for the development of gubernacular cords (structures that lower testes to the scrotal position) (Wilson *et al.*, 2004).

The results indicated that the phthalate ester DEPH reduced the prevalence of Insl3 by approximately 80% in males compared to the control litters. This was expressed by either elongated, filamentous, or absent gubernacular cords of the male DEPH exposed rat testes. In addition, the male DEPH exposed rat fetuses also produced less testosterone, which was associated with abnormal fetal Leydig cell hyperplasia (Wilson *et al.*, 2004).

In effect, the phthalate esters demasculinized the male rat offspring by causing a delay in the fetal Leydig cells which resulted in hyperplasia (proliferation of the cells rather than differentiation), cryptorchidism, and lower levels of testosterone and Insl3 (Wilson *et al.*, 2004).

A second study noted that DEPH acted as an androgen antagonist, an initiator of liver and testicular cancer in rats, and interfered with tamoxifen-induced apoptosis in human breast cancer cells due to its estrogenicity (as an estrogen agonist) (Hokanson *et al.*, 2006). The endocrine disrupting activities of phthalates

“altered endocrine-regulated physiological activities by binding with steroid hormone receptors or interacted within the cellular environment to up- or down-regulate expressions of endocrine receptors or the hydrocarbon receptors, a group of nuclear receptors regulating expression of cytochrome P450-associated enzymes that metabolize hydrocarbon chemicals (Hokanson *et al.*, 2006).”

It was further stated that

“chemically initiated changes in gene expression may lead to changes in protein synthesis, resulting in altered metabolism of endobiotics or xenobiotics, altered function of endocrine-regulated physiological systems, developmental changes, decreased immune surveillance-associated protection against transformed cells, and/or decreased normal immune system response to infectious agents...Exposure of phthalates to pregnant animals caused morphological changes in the embryo that resulted in teratogenic effects which occurred even when in utero concentrations were lower than environmental levels...DEPH significantly altered gene expression in the MCF-7 cells, an estrogen-dependent human cell line used in this study. A total of 805 genes out of the 2400 genes [about 33.5%] spotted on the NEN2400 chip were either up-regulated by a factor of two, or down-regulated by at least 50%. Two of the genes are essential for fetal brain/central nervous system development (Hokanson *et al.*, 2006).”

Fetal brain and central nervous system impairment manifests itself as lissencephaly and faciogenital syndrome with variable symptoms such as altered anal-to-genital distance, attention deficit hyperactive disorder (ADHD), sperm acrosomal defects, and cognitive impairment (Hokanson *et al.*, 2006).

A third study was conducted to assess the hepatic toxicity of DEP and determine the effects of exposure over 3 generations. The parental generation was dosed at 2.85 mg/kg body weight (100 g)/day, the F1 generation at 1.425 mg/kg body weight (100 g)/day, and the F2 at 0.57 mg/kg body weight (100 g)/day. Although normal breeding was observed, there was reduction in litter number in the F1 generation for the DEP treated rats. Additionally the liver-to-body weight ratio increased significantly in the F1 and F2 generations of the DEP treated rats, and was much more prominent in the F2 generation of DEP treated rats (Pereira *et al.*, 2007).

Substances produced by the liver, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and serum and liver triglycerides all showed a significant increase in the F1 and F2 generations compared to the control and parental generations. The F2 generation of DEP-exposed rats had the highest levels of those substances. Conversely, the levels of cholesterol, glutathione (GSH), and glutathione reductase (GR) were significantly decreased as compared to the controls and parental generation. The F2 generation of DEP-exposed rats had the lowest levels of these substances (Pereira *et al.*, 2007). Liver histology showed severe fatty degeneration in the hepatocytes, vacuolations, and granular deposits of the hepatocytes in the centrilobular and periportal area in the DEP treated rats (Pereira *et al.*, 2007), which substantiated such changes.

It is evident from this study that DEP exposure over three generations leads to an increasingly toxic effect in the F1 and F2 generations, even when the dose is attenuated between the parental, F1 and F2 generations respectively. Increased hepatic secretions, such as ALT and AST, indicated significant hepatocyte damage in the F2 generation, which led to leakage of those enzymes from the tissues, as was evident from the liver histology (Pereira *et al.*, 2007).

Cholesterol, which acts as a precursor to various hormones of the endocrine system, was decreased. Several phthalate monoesters are known to activate peroxisome proliferator-activated receptor alpha (PPAR- α), which contains enzymes for respiration and for cholesterol and lipid metabolism, and PPAR- γ , which regulates fatty acid storage and glucose metabolism. Lower concentrations of phthalate is required for activation of PPAR- α (Hurst and Waxman,

2003). PPAR- α directly regulates the expression of genes involved in gluconeogenesis. Since fatty acids are ligands for PPAR- α , phthalate-induced activation of PPAR- α would explain the simultaneous effect of peroxisome proliferation, reduced levels of cholesterol, and hepatic gluconeogenesis expressed as elevated triglyceride levels, while causing a decrease in β -oxidation, the process by which fatty acids in the form of Acyl-CoA molecules are broken down in mitochondria and in peroxisomes to generate Acetyl-CoA (Pereira *et al.*, 2007). Since PPAR- α is necessary for lipid metabolism, prolonged chronic exposure to DEP over three generations resulted in significant increase in serum triglyceride levels (Pereira *et al.*, 2007).

The enhanced toxicity levels found in the F2 generation of DEP-treated rats corresponded to the significantly reduced levels of GSH and GR. GSH acts as an antioxidant in reduction processes, while GR causes the conversion of glutathione disulphide, the precursor of GSH, to GSH. Depletion of GSH and GR due to DEP exposure was the main cause of enhanced toxicity in the F2 generation (Pereira *et al.*, 2007).

This study provided evidence that continuous exposure to DEP over multiple generations leads to significant and increasingly detrimental effects for each subsequent generation. DEP exposure is high due to transplacental transfer, transfer through mother's milk, exposure through diet, and manufactured products. Although the dose was attenuated for each subsequent generation in this study, the level of exposure to humans in the natural environment appears to be increasing. It is the most susceptible pollutant for human exposure at both the infant and adult stages of life (Pereira *et al.*, 2007). Such continued exposure could have deleterious impacts on the health of the individuals exposed and their offspring. Further, it seems reasonable to suspect the role of phthalates in the occurrence of chronic diseases such as diabetes, obesity, and Alzheimer's.

Acute Toxicity of Fragrance Products

The nervous system has the tremendous capacity and responsibility of regulating biological functions so we may see, smell, taste, have balance, move limbs, and respond to stimuli normally. Some chemicals contained in fragrances and personal care products interfere with the normal performance of the nervous system. Repeated insults to the nervous system are cumulative and cause irreparable damage to the airway and cause devastating neurological disorders that impair the quality of life (USHR, 1985).

Fragrances can affect health by causing a wide array of anaphylactic symptoms such as difficulty breathing, difficulty concentrating, chest pain, coughing, headache, blurred vision, nausea, and hives. Since the effect of such exposure is cumulative, exposure could lead to multiple chemical sensitivities, airway wall remodeling, and neurotoxicity.

Chronic airway inflammation can lead to airway wall remodeling and permanent structural changes in the airway. Asthma attacks are marked by bronchial hyper-responsiveness, restricted airflow, and the prevalence of mucus in the lungs and airways. This occurs when the over-sensitized immune system sends leukocytes such as mast cells, eosinophils, and neutrophils to the lungs to defend the host from a pathogen. The leukocytes release histamine, heparin, superoxides, proteases, elastases, and other substances that attract additional leukocytes to defend the host (Tirouvanziam *et al.*, 2006). This leads to epithelial cell edema, muscle constriction, vascular leakage, and mucus hypersecretion in the airway. In chronic and permanent airway remodeling, epithelial cells lose their cilia and often slough off, leaving nerves

exposed. Mucus gland hyperplasia, smooth muscle hypertrophy, vascular proliferation, and loss of elastic fibers are characteristic of this condition (Ruiz Schütz *et al.*, 2009). Airway wall remodeling can occur due to inflammation even in mild cases of asthma.

Since the body makes use of oxidation reactions to elicit an immune response reaction, it uses reduction to halt the reaction. Glutathione, supplied by the liver, is the body's most abundant antioxidant and halts the oxidation reactions. If liver damage exists, possibly due to phthalate exposure, and cannot supply enough Glutathione, the body's ability to mitigate the inflammatory response will be greatly compromised, the white blood cells will continue to oxidize proteins, cells die and release toxins such as proteases and elastases into the airway, and mucus builds up. The immune response, in the form of inflammation initiated to help the host, ultimately damages delicate tissue and can lead to permanent scarring (Tirouvanziam *et al.*, 2006).

A study was conducted over a 3-year period on 186 groups of mice to examine the neurotoxic effects of fragrances. Mice were chosen because they are a readily available mammalian species, an extensive quantitative correlation exists between the effects of irritant chemicals on mice and on humans, and mice are less sensitive than most humans to irritant airborne chemicals, so there was little risk of a false positive result (Anderson and Anderson, 1998).

Four commercially available samples of cologne were purchased locally and one additional fragrance was imported from France. Dosing ranged from 0.05 - 3.0 g of fragrance product and the number of experiments ranged from 8 – 80. Neurotoxicity, in the form of respiratory pattern changes, and changes to posture, tilt, tone, tremor, gait, and responsiveness was evaluated.

It was observed that many exposures produced up to a 25% decrease in respiratory frequency for 3 consecutive minutes. Each of the fragrance products produced "some respiratory changes, which were characteristic of sensory irritation [perception of irritancy], and four of the fragrance products produced pattern changes characteristic of pulmonary irritation (Anderson and Anderson, 1998)." More severe behavioral abnormalities after the mice were exposed to fragrance products also occurred. Abnormal behavior included changes to posture (abnormal hunching of the back), gait (dragging it's abdomen or placing feet improperly), muscle tone, tremors, abnormal repetitive movements (for example: lip smacking, eye, ear, or tail twitching, rapid circling around the cage oblivious to obstructions), and an increase to responsiveness to stimuli. Some mice developed facial edema, piloerection (goosebumps), localized cyanosis, severe lacrimation, exophthalmus (increase in the volume of the tissue behind the eyes), severe vocalization, paralysis of 1 or 2 limbs, and overall, 5 mice died (Anderson and Anderson, 1998).

This experiment indicated evidence that some fragrance products produce toxic effects in at least one mammalian species. Humans exposed to these products may experience similar asthma-like symptoms and neurotoxic effects such as dizziness, ataxia, increased aggression, etc.

According to Dr. Peter Spencer, director of the Institute of Neurotoxicology, "synthetic chemicals were generally regarded as safe as artificial flavoring additives and widely employed as synthetic musks in soaps, creams, perfumes, after-shave lotions, and detergents... In 1955, Musk Tetralin was introduced into fragrance preparations without testing for chronic toxicity and, in 1977, voluntarily withdrawn by the fragrance industry after repeated exposure to the unbroken skin of rats had demonstrated degeneration of the brain neurons and structural changes in spinal cord and nerves

supplying limbs. An unusual sign was increased irritability... The second neurotoxic fragrance compound. Musk Ambrette, was introduced in the 1920s, used in quantities exceeding 100,000 lb/yr for over 50 years, and has yet to be removed from the marketplace. Hundreds of other compounds used in fragrance formulations remain to be tested for chronic neurobehavioral toxicity (USHR, 1985).”

Further, Dr. Leonard Goodstein, Executive Officer of the American Psychological Association stated,

“The Environmental Protection Agency estimates there may be as many as 50,000 chemicals in everyday use, and approximately 1,000 new chemicals are introduced each year... Exposed individuals can become confused and disoriented and lose their ability to remember, to comprehend the world around them, or the rationally calculate the likely consequences of their behavior. Normal social and emotional reactions can be lost, and afflicted individuals may become excessively timid and afraid of leaving the house, or touchy and overly aggressive, or they may take on the irrational behaviors and mental states or severe psychosis... Very serious consequences of neurotoxicity can be seen in children if their mothers were exposed during the pregnancy, even though the mother may have exhibited few if any symptoms of toxicity. The child is not protected against toxic chemicals in the womb, and the developing nervous system appears to be more vulnerable to the neurotoxicity than in the adult... Although some neurotoxic effects may become less apparent as the child matures into adulthood, they can reappear as a premature loss of mental ability in the aged (USHR, 1985).”

Neurotoxicity is preventable and is one of the earliest warning signs of chemical toxicity. Some neurotoxins have been found to cause damage to the myelin sheath that surrounds the nerve fibers of the central and peripheral nervous system and can irreversibly diminish or destroy motor ability and organ function (USHR, 1985). Chronic toxicity may have an early symptom-free phase, but can lead to permanent disorders such as asthma, cancer, and autoimmune disease (Agmon-Levin and Shoenfeld, 2009) which may develop after years of repeated exposure and have been related to the same chemicals that cause neurotoxicity (USHR, 1985). Chemical testing and early detection of neurotoxicity may help prevent the pandemic of such diseases.

Phototoxicity of Personal Care Products

Personal care products, such as lotions, facial creams, and lipsticks are commonly and voluntarily used to fragrance, hydrate, and protect the skin from burning when exposed to solar radiation. Lotions are commonly encouraged as a skin protectant due to fluctuations and the depletion of the ozone layer and the influx of more intense UV radiation. Unfortunately, several constituents of these products have been identified as substances that have hazardous, synergistic interactions with skin biomolecules when exposed to UV radiation (Hans *et al.*, 2008). Photochemical reactions occur which change the O₂ molecule found within cellular systems to a reactive oxygen species such as O₂⁻, OH⁻, H₂O₂ which oxidizes the molecules within the cell causing hemolysis or mutation (Hans *et al.*, 2008).

A study was performed using ten different lipsticks and eight facial creams bought at a local store. The samples were dissolved in double-distilled, deionized water or ethyl alcohol, studied *in vitro* with human red blood cells collected from HIV negative volunteers, and exposed to natural sunlight.

The results revealed that all the facial creams and three lipsticks were either alkaline or acidic. Since these products varied from the natural pH of the skin, they were found to be able to affect ionic transport, membrane permeability, and membrane ionic selectivity. Some lotion ingredients, such as alpha-mono-stearoyl-isoglycerol, are known to facilitate absorption into the skin (Suzuki *et al.*, 2002), while chemical reduction due to solar decomposition also increases permeability and absorption. These personal care products were “tested for their phototoxic potential and have shown significant absorption in the UV range of sunlight (Hans *et al.*, 2008).”

These products have also been shown to be photomutagenic, affecting large sections of the chromosome in murine lymphoma cells. In human trials, the photosensitized chemicals were able to interact with skin biomolecules, including erythrocytes. A strong positive correlation was found to exist between lipid peroxidation and photohemolysis for both facial creams and lipsticks.

Contrary to the desired effect these personal care products were promoted to produce, the “repeated use of the photosensitive cosmetic products should be avoided as their phototoxicity may lead to skin aging including other anomalies like erythema, edema, and photomutation (Ruegger *et al.*, 2002).” Further, the presence of these persistent pollutants in an environment exposed to increased levels of UV radiation due to ozone depletion may have detrimental consequences to the natural biota and ecology of any region where these substances exist (Verma *et al.*, 2008).

Effects of Fragrances on the Environment

Synthetic fragrances found in perfumes, lotions, and personal care products (e.g. soap, shampoo, laundry detergents, air fresheners, etc.) are persistent environmental pollutants, are produced in quantities that rival agrochemicals, resist intensive biodegradation (Smital *et al.*, 2004), and can accumulate over time. They enter the environment through wastewater effluent from sewage systems and from run-off from landfill residues. Although these substances are present in the concentration range of 10^{-9} – 10^{-12} M, they are significant because of their toxicity and tendency to accumulate in aquatic environments, such as aquatic sediments (Lahr *et al.*, 2003), and subsequently, aquatic organisms (Luckenbach, Corsi, and Epel, 2004).

A fluoroscopy study was conducted using Rhodamine B (RB) to determine if synthetic musk was able to affect the multixenobiotic (MXR) defenses -- ATP dependent pumps that remove toxins from a cell (Kartner, Riordan, and Ling, 1983) -- of the marine mussel, *Mytilus californianus* (Conrad, 1837).

Gill tissue, collected via biopsy punch, was obtained from the mussels and was exposed to several test compounds that included the nitrogenous musk ketone (MK), musk xylene (MX), the polycyclic musk Galaxolide (GAL), the known xenobiotics Verapamil hydrochloride (VER) and Quinidine (QUI), and several other compounds. The tissues were incubated and rocked gently in fresh seawater and varying concentrations of the test compounds, and were then washed in fresh seawater. The test was repeated three times and the results were standardized using the control samples (Luckenbach, Corsi, and Epel, 2004).

It was determined that there was dose-dependent accumulation of the xenobiotic compounds in each of the samples, and inhibitory effects were higher in nitrogenous musks than polycyclic musks. This illustrates that synthetic musks are effective xenobiotic inhibitors of MXR

transporters in marine mussels (Luckenbach, Corsi, and Epel, 2004). To paraphrase, these compounds inhibited the first line of defense within the cell so that it no longer expelled toxins (which was evident due to the presence of RB). This is significant because not only did the tissue absorb the toxic substrate, with the xenobiotic defense inhibited, the cell also absorbed additional toxins.

A second study examined the result of MXR inhibition on the embryonic development of the marine worm, *Urechis caupo*. Exposure to MXR inhibitors caused a “350-fold decrease in the cell division rate” and “increased the frequency and severity of embryonic deformities (Smital *et al.*, 2004).”

The presence of MXR inhibitors in already polluted waters could increase the mutagenic risk of organisms in the aquatic environment. The type of MXR inhibitor present in aquatic environments is virtually irrelevant; however, the consequence of the chemicals’ presence is an increase in intracellular accumulation of other xenobiotics (Smital *et al.*, 2004). MXR inhibitors act as a synergist for the effect of toxins, even when those toxins are at the defined “low-dose” or “non-toxic” levels. Unexpected and unknown toxic effects caused by the accumulation of xenobiotics other than the known pollutant are significant, because [or especially when] the level of the known xenobiotic may remain under the defined toxic threshold (Smital *et al.*, 2004).

Regulations

Fragrances and fragranced personal care products may smell pleasant, but they contain volatile organic compounds, increase dermal and inhalation exposure to hazardous compounds, and trigger acute allergic and asthmatic reactions. Synthetic fragrances and personal care products containing synthetic fragrances are an environmental and public health hazard.

Approximately 20 million Americans have asthma, which accounts for approximately 24.5 million missed work days for adults, and approximately 5,000 deaths from asthma annually (ALA, 2005). The prevalence of asthma increased 73.9% from 1980-1996 (CDC, 2002), mostly among women and children, and asthma rates in children under the age of five increased more than 160% from 1980-1994 (CDC, 1998).

According to a United States Environmental Protection Agency (USEPA) study (Cooper *et al.*, 1992), the twenty most common chemicals found in thirty-one commercial fragrance products include, but are not limited to the following compounds:

Acetone	Limonene	b-Citronellol
Benzaldehyde	Linalool	b-Myrcene
Benzyl acetate	Methylene chloride	Nerol
Benzyl alcohol	a-Pinene	Ocimene
Camphor	g-Terpinene	b-Phenethyl alcohol
Ethanol	a-Terpineol	a-Terpinolene
Ethyl acetate	1,8-Cineole	

Many of these substances are benzene derivatives, aldehydes and many other known toxins and sensitizers that are capable of causing allergic reactions, central nervous system disorders, birth defects, and cancer.

According to a study conducted by the National Academy of Sciences (NAS) in which seven categories (such as cosmetics, food additives, and pharmaceuticals) were examined, chemicals in commerce that are manufactured in large volumes are not tested for neurotoxicity at all, nor were ninety percent of chemicals manufactured in small volumes. Further, the USEPA's Office of Toxic Substances adopted the NAS recommendations for neurotoxicity testing, but seldom requires testing of new and existing chemicals (USHR, 1986).

Section 5 of the Toxic Substances Control Act (TSCA) defines new chemicals as any chemical substance not on the TSCA Chemical Substances Inventory (published in 1979); however, regulatory requirements as defined under TSCA apply only to general consumer and industrial chemicals. They do not apply to pesticides, drugs, food additives, cosmetics, or tobacco products. TSCA continues to state that "many new chemicals cannot support [the] cost of testing before production begins. TSCA requires that we do not unduly impede innovation. Many chemicals could support the cost of testing after they have been in production for some time." TSCA § 4(f) provides that if a chemical substance or mixture presents a significant risk of serious or widespread harm to human beings from cancer, gene mutations, or birth defects, the administrator shall, within a 180 day period after receiving such information, initiate "approval action" to prevent or reduce the extent of the risk. Unfortunately, if TSCA is not permitted to require toxicity testing, data cannot be submitted to the TSCA administrator (USHR, 1986).

The federal General Accounting Office conducted an independent study and questioned the USEPA's position on TSCA § 4(f), and found that the USEPA designated only two chemicals for priority review. The USEPA argued that substantial amounts of data are necessary before a chemical may be designated for TSCA § 4(f) review. They do not regulate many chemicals due to the 180-day limit because the time parameter does not allow the USEPA to collect enough data to determine risk. The USEPA's self-imposed restrictive interpretation of TSCA § 4(f) has prevented the expedited regulation of chemicals suspected of causing mutagenesis, birth defects, and cancer (USHR, 1986).

The USEPA determined that cosmetics are regulated by the Food and Drug Administration (FDA) under the Food, Drug, & Cosmetic Act. However, the FDA Cosmetic Labeling Manual, codified in the Code of Federal Regulations, 740.10, § 21 states "Although the FD&C Act does not require that cosmetic manufacturers or marketers test their products for safety, the FDA strongly urges cosmetic manufacturers to voluntarily conduct whatever toxicological or other tests are appropriate to substantiate the safety of their cosmetics. If the safety of a cosmetic is not adequately substantiated, the product may be considered misbranded and may be subject to regulatory action unless the label bears the following statement: Warning--The safety of this product has not been determined."

Gas Chromatography studies were performed on *Eternity* by the Research Institute for Fragrance Materials laboratories on two different samples that were sent in original packaging to the laboratories. Summary of discrepancy results stated that the materials in *Eternity* were not adequately tested for safety and there were legitimate concerns over the safety of the product. The product did not carry the required warning label as required by the FDA; however, the FDA does not have the authority to recall hazardous products.

California Regulations

The California Safe Cosmetics Act of 2005 (SB 484 which commenced January 1, 2007) requires the manufacturer of any cosmetic product subject to regulation by the FDA that is sold in the state to provide the Department of Health Services with a list of its cosmetic products that are sold in the state and contain ANY ingredient that is a chemical identified as causing cancer or reproductive toxicity. The California Sherman Food, Drug, and Cosmetic Law prohibits a person from manufacturing or selling any cosmetic that is misbranded. A violation of this provision is a crime.

The cosmetic industry is one of many subject to the Proposition 65 (Prop 65) warning requirements. If any of the Prop 65-listed chemicals constitute an ingredient, then the product is subject to a Prop 65 warning. Due to the trade secret status of fragrances, the cosmetic industry is historically not required to divulge fragrance ingredients. If the ingredients are not listed, then enforcement for the correct Prop 65 labeling could not occur.

California Health and Safety Code, § 41700 and Sacramento Air Quality Management District Rule 402 state, "Except as otherwise provided in Section 41705, no person shall discharge from any source whatsoever such quantities of air contaminants or other material which cause injury, detriment, nuisance, or annoyance to any considerable number of persons or to the public, or which endanger the comfort, repose, health, or safety of any such persons or the public, or which cause, or have a natural tendency to cause, injury or damage to business or property."

With such laws in place, one could easily develop a false sense of security. Unfortunately, and perhaps due to budgetary constraints, toxicity testing and enforcement of the aforementioned regulations, at least at the state level, is "not a priority," so enforcement has fallen by the wayside.

Recycling Fragrances

The fragrance industry is a multi-billion dollar industry, so the number of products sold is substantial. According to the North American Industry Classification System (NAICS) 2002 Economic Census (NAICS code 446120), \$6.3 billion was spent in cosmetic, beauty supply, and perfume specialty stores alone. This volume of products sold does not include department store, grocery market, bulk retail stores, or products imported from outside the country or purchased from the global internet marketplace.

When fragrance bottles are disposed of, they contain fragrance residues. These residues are classified as Resource Conservation Recovery Act (RCRA) hazardous wastes, so when people dispose of their fragrances or fragrance containers, the volume of RCRA hazardous waste entering landfills increases. An increase to the volume of RCRA hazardous waste entering landfills has the potential to impact human health and the environment.

To mitigate RCRA hazardous wastes entering landfills, companies such as Parallel Products (<http://www.parallelproducts.com>) recycle waste perfume at their National Recovery Center in Kentucky and convert the waste perfume to ethanol. Oil and gas companies purchase the recycled ethanol and add it to automobile gasoline to help meet cleaner air standards.

Conclusion

Population trends such as increases in diseases such as asthma, diabetes, and cancer are due only in part to genetic predisposition. Studies have shown that environmental stressors such as xenobiotics, neurotoxins, DEP, and DEPH present in fragrances, personal care products, and manufactured products can overwhelm and interfere with the body's normal immunological responses and may even trigger cascading sequences that cause mutation to the genome and initiate these conditions.

It makes one suspect that it is more economically advantageous for regulators to take the "do nothing" approach to protecting the public health and environment from these toxins compared to actively regulating them and the seemingly overwhelming volume of products imported and exported that contain them.

Asthma accounts for one-quarter of all emergency room visits in the United States, with 2 million emergency room visits each year (NCHS, 2001). Direct health care costs for asthma in the United States total more than \$11.5 billion annually with indirect costs (lost productivity) adding another \$4.6 billion for a total of \$16.1 billion. Reduced productivity due to death represented the largest single indirect cost related to asthma, approaching \$1.7 billion annually (ALA, 2005). These costs are associated with asthma alone, and do not include economic costs associated with special needs individuals, diabetes, or cancer, nor do they account for the impact these conditions have on quality of life.

Consumers should be informed of chemical exposure on product labels and educated on the problems that exposure can lead to. Once an individual notices symptoms, he/she has been overexposed and is at risk of developing neurotoxic disorders, asthma, and cancer (USHR, 1986). Further, mental health and primary care physicians should be trained to recognize and treat toxicological exposures and symptoms (USHR, 1985). The best medicinal practice would be to prevent the onset of disease by educating patients rather than just treating symptoms or referring patients to specialists.

Perhaps it is economically advantageous for people to be ill rather than ban such products from the marketplace. Economic gains from purchases made through the sale of products containing these toxins are far greater than losses incurred through health care and decreased productivity. The cost to individuals for health care is actually a financial gain for the medical industry, especially when phthalates are found in medical tubing, enteric coatings on pharmaceuticals, etc. However, this would be appalling and morally inexcusable.

The European Cosmetics Association, and European Economic Community have exemplified efforts taken to help protect their populations and have banned 1,371 chemicals and regulates 188 additional chemicals used in personal care products (EEC, 2008). The United States FDA has banned 8 chemicals and restricts 3 (CFR, 2008).

Arguments against exposure to chemicals found in synthetic fragrance and fragranced personal care products parallels similar arguments against exposure to second-hand smoke. Given the extent of information that is currently available, federal and state regulators must not hesitate, but take a more proactive stance to protect public health and the environment.

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Literature Cited

(* denotes primary literature sources)

*Agmon-Levin, N., Shoenfeld, Y. (2009). Prediction and prevention of autoimmune skin disorders. *Arch Dermatol Res.* 301, 57-64.

American Lung Association (ALA), Epidemiology & Statistics Unit, Research and Program Services. (May 2005). *Trends in Asthma Morbidity and Mortality*

*Anderson, R., Anderson, J. (1998). Acute toxic effects of fragrance products. *Archives of Environmental Health.* 53 (No. 2), 138-146.

*Api, A.M. (2001). Toxicological profile of diethyl phthalate: a vehicle for fragrance and cosmetic ingredients. *Food and Chemical Toxicology.* 39: 97-108.

Centers for Disease Control (CDC). (1998). *Surveillance for Asthma: United States, 1960-1995*, MMWR: 47(SS-1).

Centers for Disease Control (CDC). (2002). *Surveillance for Asthma: United States, 1980-1999*, MMWR: 51(SS01), 1-13.

Code of Federal Regulations (CFR). (2008). Title 21. §§ 250.250 and 700.11 - 700.35.

Cooper, S., Raymer, J., Pellizzari, E., Thomas, K., Castillo, N., Maewall, S. (1992). Polar organic compounds in fragrances of consumer products. United States Environmental Protection Agency (USEPA). Report RTI/4948-31A-01FR.

Doyle, Rodger (June, 2000). By the Numbers: Asthma Worldwide. *Scientific American*, 282, 30.

European Parliament and the Council of the European Union (EEC). (2008). Directive 76/768/EEC.

Food and Drug Administration (FDA). (April 28, 1999). Commissioner's Video Teleconference.

*Hans, R., Agrawal, N., Verma, K., Misra, R., Ray, R., Farooq, M. (2008). Assessment of the phototoxic potential of cosmetic products. *Food and Chemical Toxicology.* 46, 1653-1658.

Hermes, Matthew (1996). *Enough for One Lifetime: Wallace Carothers, Inventor of Nylon*. Washington D.C.: American Chemical Society; Philadelphia: Chemical Heritage Foundation, 163-164.

*Hokanson, R., Hanneman, W., Hennessey, M., Donnelly, K.C., McDonald, T., Chowdhary, R., Busbee, D.L. (2006).DEPH, bis(2)-ethylhexyl phthalate, alters gene expression in human cells: possible correlation with initiation of fetal development abnormalities. *Human & Experimental Toxicology*. 25: 687-695.

*Hurst, C., Waxman, D. (2003).Activation of PPARAlpha and PPARgamma by environmental phthalate monoesters. *Toxicological Sciences*. 74, 297-308.

Kartner, N., Riordan, J. R., & Ling, V. (1983). *Science*, 221, 1285-1288.

*Lahr, J., Maas-Diepeveen, J., Stuijzand, S., Leonards, P., Drüke, J., Lückner, S., Espeldoorn, A., Kerkum, L., van Stee, L., Hendricks, A. (2003).Responses in sediment bioassays used in the Netherlands: can observed toxicity be explained by routinely monitored priority pollutants?. *Water Research*. 37, 1691-1710.

*Luckenbach, T., Corsi, I., Epel, D. (2004).Fatal attraction: Synthetic musk fragrances compromise multixenobiotic defense systems in mussels. *Marine Environmental Research*. 58, 215-219.

National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC). (2001).New Asthma Estimates: Tracking Prevalence, Health Care and Mortality.

*Patsouris, D., Mandard, S., Voshol, P., Escher, P., Tan N.S., Havekes, L., Koenig, W., März, W., Tafuri, S., Wahli, W., Müller, M., Kersten, S. (2004).PPAR- α governs glycerol metabolism. *The Journal of Clinical Investigation*. 114: 94-103.

*Pereira, C., Mapuskar, K., Rao, C. (2007).Chronic Toxicity of diethyl phthalate-A three generation lactational and gestational exposure study on male Wistar rats. *Environmental Toxicology and Pharmacology*. 23, 319-327.

Perivier, H. (2005).An investigation of chemicals in 36 eaux de toilette and eaux parfum. Greenpeace Toxic Campaign. Greenpeace International. 1-16.

*Schell, L., Gallo, M., Ravenscroft, J., DeCaprio, A. (2009).Persistent organic pollutants and anti-thyroid peroxidase levels in Akwesasne Mohawk young adults. *Environmental Research*. 109, 86-92.

*Ruegger, J., Schuetz, B., Hermann, K., Hein, R., Ring, J., Abeck, D. (2002).UV-induced skin changes due to regular use of commercial sunbeds. *Photodermatology Photoimmunology Photomedicine*. 18, 223-227.

* Ruiz Schütz, V., Drewiacki, T., Nakashima, A., Arantes-Costa, F., Prado, C., Kasahara, D., Leick-Maldonado, E., Martins, M., Tibério, I. (2009). Oral tolerance attenuates airway inflammation and remodeling in a model of chronic pulmonary allergic inflammation. *Respiratory Physiology & Neurobiology*. 165, 13-21.

*Smital, T., Luckenbach, T., Sauerborn, R., Hamdoun, A., Vega, R. Epel, D. (2004).Emerging contaminants-pesticides, PPCPs, microbial degradation products and natural substances as inhibitors of multixenobiotic defense in aquatic organisms. *Mutation Research*. 552, 101-117.

*Suzuki, A., Yamaguchi, T., Kawasaki, K., Hase, T., Tokimitsu, I. (2002). Alpha monoisostearyl glyceryle ether enhances percutaneous penetration of indometac in vivo. *J. Pharm. Pharmacol.* 54, 1601-1607.

*Teasdale, T., Owen, D. (2005). A long-term rise and recent decline in intelligence test performance: The Flynn Effect in reverse. *Personality and Individual Differences.* 39: 837-843.

*Tirouvanziam, R., Conrad, C., Bottiglieri, T., Herzenberg, Leonore., Moss, R., Herzenberg, Leonard. (2006). High-dose oral N-acetylcysteine, a glutathione prodrug, modulates inflammation in cystic fibrosis. *PNAS.* 103-12, 4328-4633.

*Verma, K., Agrawal, N., Misra, R., Farooq, M., Hans, R. (2008). Phototoxicity assessment of drugs and cosmetic products using *E. coli*. *Toxicology in Vitro.* 22, 249-253.

*Wilson, V., Lambright, C., Furr, J., Ostby, J., Wood, C., Held, G., Gray, E. (2004). Phthalate ester-induced gubernacular lesions are associated with induced *Ins13* gene expression in the fetal rat testis. *Toxicology Letters.* 146: 207-215.

U.S. House of Representatives (USHR), Committee on Science & Technology. (October 8, 1985). *Neurotoxins: At Home and the Workplace.* Report 99-68.

U.S. House of Representatives (USHR), Committee on Science & Technology. (September 16, 1986). *Neurotoxins: At Home and the Workplace.* Report 99-827.