I am Betty Bridges of the Fragranced Products Information Network (www.fpinva.org), a grassroots effort to increase awareness and educate on the impact of fragrance on health. I have been compiling, reviewing, and disseminating information on fragrance for over a decade. I receive 2-3 e-mails each week from people with asthma, migraines, and other health problems struggling to work and function in scent laden workplaces. They are protected from second hand smoke, but there is no such protection from second hand fragrance.

Bridges B.
Fragrances and health.
Environ Health Perspect. 1999 Jul;107(7):A340.

Bridges B.
Fragrances and allergic reactions.
J Am Board Fam Pract. 2001 Sep-Oct;14(5):400-1.

Bridges B.
Fragrance: emerging health and environmental concerns
Flavours and Fragrance. 2002 Sept-Oct; 17 (5) 361-371

Scented Products: An overlooked source of indoor air pollution
Presented at the EPA/Air & Waste Management Conference
Indoor Air Quality Problems and Engineering Solutions
July 22, 2003 **(Provided as an attachment)**

SCENTED PRODUCTS: Health concerns at home and at work
Poster presentation at the NIOSH Symposium
Steps to a Healthier US Workforce
October 2004

Scented Products as Sources of VOCs: Implications for Susceptible Populations
Abstract accepted for presentation at the
AWMA Annual Conference & Exhibition 2005

No evaluation of indoor air quality and its impact on health can be complete without considering the effects of the widespread of fragrance in multiple products used on a daily basis in homes, workspaces, and other public places. The ubiquitous exposure to poorly studied fragrance chemicals has resulted in escalating voluntary and involuntary exposures to unknown substances which contrary to public assumption, have not been evaluated by regulatory agencies for safety to the general public, children, the elderly, and other sensitive populations.

Exposure starts before birth from fragrance chemicals in mothers' bodies (1) and continues with ingestion of mother's milk. (2) Products for infants and children are scented often with materials known to cause allergies (3) and persist in body tissues. Children and infants are also exposed to every scented product used in the household. An infant held close is breathing in fragrance from clothes washed in highly scented detergents and laundry products, perfumes and colognes, shampoo, and other scented products used by the caregiver transferring to the child's skin, hair, and clothes. Exposure continues throughout life.

Users of scented products are often not aware of the continued presence of the products they use and are rarely aware of the intensity of the scents. By design, the olfactory system detects changes in chemicals in the environment and cannot detect the same odor for long periods of time. The background of fragrance materials that are ubiquitous in indoor environments leads to increased usage of scented products by consumers to keep the same level of awareness of

fragrance and to companies formulating products with even more enduring and intense fragrance.

Fragrance can be defined as materials added to impart an odor to a product or mask the odor of other ingredients in the product. **Fragrance materials may be natural, synthetic, or combinations. Scented products are those that contain fragrance.**

Annual Sales of Common Scented Products

Type of scented product	**Annual Sales**
Cosmetics & toiletries	$29.8 billion
Perfumes, colognes, & similar products	>$ 6.65 billion
Laundry detergents & fabric softeners	$ 6 billion
Environmental Fragrance (Fragrance emitting devices, scented candles, incense, oils, plug-ins, etc.)	> $ 3 billion
Household cleaners	$ 1.7 billion

The use and exposure to fragrance has increased phenomenally. With synthesis of fragrance chemicals supplies of raw materials became reliable and economical. Some 80-90% of fragrance materials are now synthesized. (4) Use of fragrance has increased ten-fold since the 1950s and the industry doubled in size during the 1980s. (5) Literally millions of pounds of fragrance chemicals are used annually to scent products most do not have even basic toxicity data available. Of 54 fragrance materials that are used at 1 million pounds or more annually only 2 have a full set of basic toxicity data. (6) This basic toxicity data does not include assessment for effects via inhalation.

Composition, use, and characteristics of fragrance have changed in the past 25 years. Fragrance has gone from subtle, special occasion use to potent, immediately powerful and long-lasting formulations not only in perfumes, but also in toiletries, cleaners, detergents, fabric softeners, and other products. Traditionally the scent of a good perfume lasted 6-8 hours. Now the scent from laundry products lasts for weeks, if not months. Three to five synthetics which are immediately powerful, quickly diffuse into the air, and have odors which may last for weeks may make up to 80% of the formulation. (7)

Widespread usage and exposure has lead to health concerns. There are growing numbers of people that experience significant negative heath effects from fragrance including those with migraines, allergies, sinusitis, rhinitis, asthma and other pulmonary diseases. Collectively this represents large numbers of people that are especially sensitive to indoor air pollutants.

Health conditions that may be negatively impacted by indoor pollutants including fragrances

Disease or Condition	Estimates of Those Affected
Allergies & Related Conditions	40 - 50 million
Skin allergies to fragrance	1.7 - 4.1%
Rhinitis	40 million
Chronic Sinus Infections	35 million
Asthma	Over 20.3 million
Chemical Sensitivities	6 - 16%
Chronic Obstructive Lung Disease	15 million
Migraines	28 million

In spite of the ubiquitous exposure, there is little regulation or monitoring of the use of fragrance or the materials that are in them. Fragrance formulas are considered trade secrets and do not have to be revealed to the public or regulatory agencies. Regulation is fragmented, there are few laws in place, and these are rarely enforced. By all accounts the fragrance industry is primarily self-regulated with little oversight.

As early as 1977, the fragrance industry was aware inhalation was a potential route of exposure. A doctoral dissertation by William Troy, now one of the lead scientists in the fragrance industry described inhalation studies on 14 common fragrance materials. Mice were exposed to these materials for one minute and were observed for changes in breathing patterns which indicate irritancy to the airways and lungs. Ten of the 14 materials were moderately to severely irritating to the upper airways and 1 material caused pulmonary irritation. Troy concluded this was an effective means of evaluating fragrance chemicals for sensory and pulmonary irritation, structure played a role in irritancy, and further efforts should be made to evaluate fragrance materials for respiratory effects. (8)

In spite of this recommendation, the industry has only recently put a program to evaluate inhalation effects. (9) This program is extremely limited and involves representative product types and formulas. While the average fragrance formulation contains 100 chemicals, these representative formulas only contain 9 of the approximate 3000 fragrance chemicals in use. While the industry insists scented products are safe, the truth is much is not known about the safety of fragrance materials. As research becomes available, it supports concerns.

A recent study suggests that even short term exposures to common synthetic musk compounds affected the ability of aquatic wildlife to protect itself from environmental toxins. (10) There has been a growing focus on synthetic musk compounds which are used in all types of scented products. While levels of synthetic musks in any one product are generally low, the widespread use and lipholic nature has resulted in presence in breast milk in general populations and bioaccumulation in human tissue and in the environment.(11) Available data indicates acute toxicity of these materials are low, (12, 13) but concerns have been raised regarding persistency and long term effects. Some of these materials and their breakdown products have estrogenic activity. (14, 15) Musk xylene has a particular affinity for adult female tissue and crosses the

placental barrier in animals. (16) Others have carcinogenic activity in animal studies. (17) While synthetic musks are not considered high volume chemicals, they are ubiquitous in indoor environments. (18)

While the research is limited, the available data supports concerns and need for further research. Some key findings.

- In order to be detected by the olfactory system, materials must be volatile and of low molecular weight, by design fragrance chemicals are volatile organic compounds (19)
- Fragrance chemicals react with ozone to form small particles and toxic substances (20)
- Burning scented candles can add small particles, toxic substances, and soot to indoor air (21, 22)
- Around 70% of fragrance chemicals are sensory irritants to some degree (23)
- In a survey of the general population, 15% found fragrance to be a lower airway irritant (24)
- Fragrance is one of the most frequently cited chemicals triggers for asthma (second only to tobacco smoke) (25)
- The Institute of Medicine found similar levels of evidence for tobacco smoke (in adults and school age children), fragrance, and formaldehyde as chemical triggers for asthma Executive Summary: Clearing the Air: Asthma and Indoor Air Exposures (2000) Institute of Medicine, http://books.nap.edu/books/0309064961/html/9.html#pagetop
- Even low-level exposures such as those in scent strips in magazines can trigger asthma attacks with moderate and severe asthmatics the most susceptible. (26)
- In a large study of migraine patients, almost 50% were triggered by perfume (27)

The fragrance issue is complex and there is limited awareness in the general population or the medical and scientific communities. There are increasing patient and clinical accounts of exposure to fragrance triggering and exacerbating a number of health conditions. Thus far, industry has not adequately addressed concerns regarding the impact of multiple sources of fragrance on indoor air quality and health.

There is an immediate need for regulatory agencies to educate on the impact of scented consumer products on sensitive populations. Research is needed to determine mechanisms by which fragrance negatively impacts respiratory health. There is a need for a cooperative process with industry to determine problematic materials and find suitable substitutes.

Thank you for your consideration of these comments,

Betty Bridges, RN
Fragranced Products Information Network
http://www.fpinva.org

References:

1. Adibi JJ, P.F., Jedrychowski W, Camann DE, Barr D, Jacek R, Whyatt RM. 2003. Prenatal exposures to phthalates among women in New York City and Krakow Poland. *Environ Health Perspect* 111:1719-1722.
2. Rimkus, G.G., and Wolf, M. 1996. Polycyclic musk fragrances in human adipose tissue and human milk. *Chemosphere* 33:2033-2043.
3. Rastogi, S.C., Johansen, J.D., Menne, T., Frosch, P., Bruze, M., Andersen, K.E., Lepoittevin, J.P., Wakelin, S., and White, I.R. 1999. Contents of fragrance allergens in children's cosmetics and cosmetic-toys. *Contact Dermatitis* 41:84-88.
4. Laszlo P. Somogyi, B.R., Yasuhiko Sakuma , and x. 2001. Aroma Chemicals and the Flavor & Fragrance Industry. Chemical Economics Report. p. 503.5000 A.
5. Somogyi, L., Kishi, A. 2001. Special Chemicals Update Program: Flavors and Fragrances. SRI Consulting.
6. Bridges, B. 2003. Scented Products: An overlooked source of indoor air pollution. In AWMA conference *Indoor Air Quality Problems and Engineering Solutions*.
7. Calkin, R.R., and Jellinek, S.J. 1994. Perfumery: Practice and Principles. John Wiley & Sons, Inc. 152-153.
8. Troy, W.F. 1977. The comparative respiratory irritation potential of fourteen fragrance raw materials.: St. John's University.
9. RIFM. 2004. RIFM Respiratory Safety Program: Indoor Air Quality.
10. Luckenbach, T., Corsi, I., and Epel, D. 2004. Fatal attraction: synthetic musk fragrances compromise multixenobiotic defense systems in mussels. *Mar Environ Res* 58:215-219.
11. Muller, S., Schmid, P., and Schlatter, C. 1996. Occurrence of nitro and non-nitro benzenoid musk compounds in human adipose tissue. *Chemosphere* 33:17-28.
12. Ford, R.A., Api, A.M., and Newberne, P.M. 1990. 90-day dermal toxicity study and neurotoxicity evaluation of nitromusks in the albino rat. *Food Chem Toxicol* 28:55-61.
13. Christian, M.S., Parker, R.M., Hoberman, A.M., Diener, R.M., and Api, A.M. 1999. Developmental toxicity studies of four fragrances in rats. *Toxicol Lett* 111:169-174.
14. Bitsch, N., Dudas, C., Korner, W., Failing, K., Biselli, S., Rimkus, G., and Brunn, H. 2002. Estrogenic activity of musk fragrances detected by the E-screen assay using human mcf-7 cells. *Arch Environ Contam Toxicol* 43:257-264.
15. Seinen, W., Lemmen, J.G., Pieters, R.H., Verbruggen, E.M., and van der Burg, B. 1999. AHTN and HHCB show weak estrogenic--but no uterotrophic activity. *Toxicol Lett* 111:161-168.
16. Suter-Eichenbeger, R., Altorfer, H., Lichtensteiger, W., and Schlumpf, M. 1998. Bioaccumulation of musk xylene (MX) in developing and adult rats of both sexes. *Chemosphere* 36:2747-2762.
17. Apostolidis, S., Chandra, T., Demirhan, I., Cinatl, J., Doerr, H.W., and Chandra, A. 2002. Evaluation of carcinogenic potential of two nitro-musk derivatives, musk xylene and musk tibetene in a host-mediated in vivo/in vitro assay system. *Anticancer Res* 22:2657-2662.

18. Fromme, H., Lahrz, T., Piloty, M., Gebhart, H., Oddoy, A., and Ruden, H. 2004. Occurrence of phthalates and musk fragrances in indoor air and dust from apartments and kindergartens in Berlin (Germany). *Indoor Air* 14:188-195.
19. Leffingwell, J.C. 2002. Olfaction.
20. Sarwar, G., Olson, D.A., Corsi, R.L., and Weschler, C.J. 2004. Indoor fine particles: the role of terpene emissions from consumer products. *J Air Waste Manag Assoc* 54:367-377.
21. de Kok TM, H.J., Kleinjans JC, Briede JJ. 2004. Radicals in the church. *Eur Respir J* 24:1069–1070.
22. Knight, L., A. Levin, Mendenhall, C. 2001. Candles and incense as potential sources of indoor air pollution: market analysis
and literature review. U.S. Environmental Protection Agency, National Risk Management Research Laboratory Research Triangle Park.
23. Ohloff, G. 1994. *Scent and fragrances.* New York:: Springer-Verlag.
24. Larsson, M.L., Frisk, M., Hallstrom, J., Kiviloog, J., and Lundback, B. 2001. Environmental tobacco smoke exposure during childhood is associated with increased prevalence of asthma in adults. *Chest* 120:711-717.
25. Eriksson, N.E., Lowhagen, O., Nilsson, J.E., Norrlind, K., and Wihl, J.A. 1987. Flowers and other trigger factors in asthma and rhinitis--an inquiry study. *Allergy* 42:374-381.
26. Kumar, P., Caradonna-Graham, V.M., Gupta, S., Cai, X., Rao, P.N., and Thompson, J. 1995. Inhalation challenge effects of perfume scent strips in patients with asthma. *Ann Allergy Asthma Immunol* 75:429-433.
27. Kelman, L. 2004. Osmophobia and taste abnormality in migraineurs: a tertiary care study. *Headache* 44:1019-1023.

Scented Products:
An overlooked source of indoor air pollution

Betty Bridges

Fragranced Products Information Network

Presented at the EPA/Air & Waste Management Conference

Indoor Air Quality Problems and Engineering Solutions

July 22, 2003

ABSTRACT

Though fragrance is generally considered pleasant, the numbers of complaints related adverse effects of fragrance have increased. Fragrance is frequently cited as triggering and exacerbating health conditions such as asthma, allergies, and migraine headaches. Chemicals used in fragrance are volatile compounds that can irritate the respiratory system.

The fragrance and flavors industry has increased more than tenfold since the early 1950s. The industry experienced its fastest growth and doubled in size form 1980 to1989. This growth has resulted in exposure to virtually every segment of the population, both through use and second-hand exposures. In spite of widespread exposure, there has been little focus on the impact of scented products on indoor air quality and health.

Information was gathered by looking at both types and specific chemicals used in fragrance, assessing available use data, and reviewing scientific, medical, industry, and regulatory literature. There is high potential for exposure to several hundred chemicals used in fragrance due to their high volume use and/or high use in consumer products. These materials are volatile organic compounds and can contribute to indoor air pollution. Presence of synthetic musk compounds in blood, adipose tissue, and human breast milk indicates significant exposure to these materials. Studies suggest that synthetic musk compounds cross the placental barrier. Concerns have been raised over potential impact on reproductive health, the developing fetus, and nursing infants.

One of the major areas of concern is impact on respiratory health. Fragrance is one of the most frequently cited triggers for asthma. An EPA-sponsored literature review by the Institute of Medicine identified fragrance, along with environmental tobacco smoke and formaldehyde as chemical triggers for asthma. The increase in use of fragrance has paralleled the increase in asthma rates. Hispanics and African-Americans are more heavily impacted by asthma. These same population groups are also more likely to use fragrance. These and other factors support further investigations into the impact of fragrance on indoor air quality and on health.

INTRODUCTION

Indoor air quality has both immediate and long-term impact on health. Acute effects of poor air quality include headaches, irritation of eyes, nose, and throat, fatigue, as well as exacerbation of conditions such as asthma, allergies, and other respiratory related disorders. Long-term exposure to indoor air pollutants is thought to contribute to the development of asthma, cancer, and other chronic disease.

There has been considerable focus on indoor air pollutants such as second hand smoke, while other common indoor air pollutants have received scant attention. Consumer products which are generally used indoors represent significant exposures to indoor air pollutants. A large

percentage of these products are scented. Fragrance is a common indoor air pollutant present in most environments, yet has received little scrutiny of its effects on health.

Products such as perfumes and colognes are obviously scented products and represent a significant exposure to fragrance. However, products such as scented toiletries, cleaners, laundry products, environmental fragrance and other such items represent even greater sources of exposure. Pesticides and tobacco products are often overlooked as scented products.

Even foods are a source or exposure to these materials. Many of the same materials used to scent products are used as flavors in foods. Slightly less than half of the aroma chemicals and other materials used by the fragrance and flavors industry are used as flavors. Slightly more than half are used as fragrance. Around 25% of raw fragrance materials produced is used to scent cosmetics and toiletries which include perfumes and colognes, 34% are used to scent cleaners, and 41% are used in other applications.[i] The primary focus of this review is fragrance use.

For the purpose of this review the following definition of fragrance will be used.

> **Materials added to give a product a scent or mask the odor of other substances in a product. Materials used may be synthetic, natural, or both. A scented product is one which contains fragrance.**

Traditionally perfumes have been reserved for special occasion use. Functional products such as soaps and detergents often contained scent at low levels to mask unpleasant odors of other ingredients in the product. These masking fragrances usually had a generic scent with all brands smelling pretty much the same. This has changed.

Now each product is uniquely scented and the fragrance is formulated to last for days, if not weeks. Whole advertising campaigns focus on the scent of the product rather than its performance. Fragrance is added to every conceivable household and personal care item. Environmental fragrance in the form of scented candles, scented oils, and air fresheners are found in many homes.

The use and exposure to scented products have skyrocketed over the past three decades. The use of fragrance has increased 10 fold since the 1950s. The industry doubled its size in the 1980s.[ii] This growth is reflected in sales of materials used to scent products. In 2000 the estimated world wide sales of fragrance/flavors materials were $14 billion, with the United States as the largest consumer of these materials.[iii]

This phenomenal growth translates into widespread exposure to scented products in the indoor environment. In order for a scent to be detected, materials must be airborne. By design fragrance quickly gets into the air, diffuse, and lingers.[iv] Some of each scented product used by each person ends up in the air. Add sources of environmental fragrance such as air fresheners and materials used to clean and maintain, and there are ever changing complex mixtures of volatile compounds which add significantly to indoor air pollution.

Scented Products: An Overlooked Source of Indoor Pollution

There are established and emerging health and environmental concerns related to fragrance. In general there is a large void in available data. What is available is widely scattered and rarely viewed as a whole. The industry is secretive with little regulatory oversight. Complex social and economic factors further complicate the issues. A through evaluation of the impact of fragrance on indoor air quality, health, and the environment is long overdue.

METHODS

Multiple sources must be used to provide an overview of the issues. Even then, much of the data available is general rather than specific as the research in many areas simply has not been done or has not been published. Searches must be intuitive with one source leading to another.

The Internet proved to be a most valuable resource. There is a growing availability of information from regulatory agencies, universities, research institutes, industry, and other sources available online. Even libraries are now accessible online so that catalogs, databases, and other resources can be assessed. Many full text articles from databases can be obtained as well.

Search terms used included but were not limited to:

- perfume OR fragrance OR perfumes OR fragrances OR scented OR scents
- Original Search Phrase AND asthma
- Original Search Phrase AND respiratory
- Original Search Phrase AND lungs
- Original Search Phrase AND inhalation
- Original Search Phrase AND airway
- Original Search Phrase AND sinusitis
- Original Search Phrase AND rhinitis
- Terms that relate to synthetic musks
- Essential oils
- Names of individual fragrance chemicals

Resources searched included, but were not limited to the following:

- Medline
- Toxnet
- Other governmental databases
- Environmental Protection Agency web pages
- Food and Drug Administration web pages
- Center for Disease Control web pages
- American Lung Association web pages
- Virginia Commonwealth University Libraries (both online and physical locations)

- Google Internet Search Engine and the resulting links
- Chemweb web pages (includes a number of searchable databases related to business and chemistry)
- Chemfinder web pages (indexes sites on chemicals that are available online)
- International Fragrance Association web pages
- Allured Online Flavors and Fragrance Materials Database
- European Union web pages
- Leffingwell & Associates web pages (an extensive site with numerous resources and links on the fragrance and flavors industry)
- Fragrance and flavors companies' web pages
- Aldrich Chemical Company web pages (a large number of MSDS on fragrance chemicals are available)
- US Patent Office web pages

RESULTS & DISCUSSION

Fragrance Materials & Assessment of Available Data

Historically, materials used in fragrance were obtained from plant or animal sources. Today, materials from animal sources are rarely used in perfumes or scented products which are mass marketed. Oils from plants are still used, but have been largely replaced with synthetics for which the supply is more stable and more economically feasible to use. Around 80-90% of the materials used are synthesized.[v]

The nine major starting materials for synthesis of fragrance chemicals are:

- Turpentine oil
- C2-C5 petrochemicals
- Benzene
- Phenol
- Toluene
- Xylenes
- Cresols
- Naphthalene
- Cyclopentene

While there is considerable health and safety data on the starting materials, the available data on most fragrance chemicals is scant. In order to assess available information on materials used in fragrance, the identity of these materials must be established. There are over 3000 materials in common use by the fragrance industry. The European Union has a listing of around 2700 materials used in fragrance.[vi] Allured Publishing has an online database for fee that lists over 4000 materials used in flavors and fragrance.[vii] There is considerable overlap between the lists. A master list of around 5000 substances was compiled from these sources. Materials such as aspartame that are not used as fragrance ingredients were omitted.

Scented Products: An Overlooked Source of Indoor Pollution

The EPA, while not regulating fragrance per se, has interests in fragrance as an environmental pollutant. Further the EPA is involved in regulatory activities regarding chemicals, including those used in fragrance. One of those activities is collecting use data on chemicals. Under the Toxic Substance Control Act, companies are required to report every four years volumes of use on specific chemicals when they are manufactured or imported into the US at volumes of 10,000 or more annually.

Chemicals that are manufactured or imported into the US at levels of 1 million pounds or more annually are known as High Production Volume (HPV) chemicals. There were around 3000 substances that met the criteria for HPV chemicals in 1990. These were assessed for toxicity data in six basic areas. Of these materials 43% have no basic toxicity data available. Only 7% have a full set of basic data. [viii]

The 1990, 1994, and 1998 HPV lists were cross-referenced with the master list of fragrance chemicals. Using the EPA's Master Summary for the Chemical Hazard Data Availability, the availability of basic toxicity data in six basic toxicity areas chemicals was assessed. Four hundred seven chemicals were found.

Areas of Assessment of Chemical Hazard Data

- Acute toxicity - immediate toxic effects
- Chronic toxicity - long term toxic effects
- Teratogenicity or developmental and reproductive toxicity - impact on reproduction and/or developing fetus
- Mutagenicity - does it cause direct damage to DNA in cells
- Ecotoxicity - is it toxic to the environment
- Environmental fate - is it broken down or does it accumulate in the environment

Data was only available for the 351 chemicals that are on the 1990 HPV list. Of these 351 chemicals, 63 are a part of an effort the EPA is involved in to develop basic toxicity data on materials that are internationally HPV.

Less than 18% of the materials have all the sets of basic toxicity data and more than 10% have none. Over 45% are missing three or more sets of data. Less than 23% have been assessed for chronic toxicity and reproductive data is missing on over half of the materials. About 50% of these materials have potential for high exposure in consumer products.

Tables 1 and 2 summarize the findings.

Table 1: Summary of available data for HPV flavor/fragrance materials

Total number of areas data are available		
6 of six	62	17.6%
5 of six	70	19.9%
4 of six	59	16.8%

Scented Products: An Overlooked Source of Indoor Pollution

3 of six	49	13.9%
2 of six	48	13.6%
1 of six	27	7.7%
0 of six	36	10.2%

Table 2: Specific areas data are available for HPV flavor/fragrance chemicals

Acute	300	85.4%
Chronic	79	22.5%
Reproductive	166	47.2%
Mutagen	222	63.2%
Eco	221	62.9%
Fate	230	65.5%

The EPA has asked industry to provide toxicity data in the six basic areas. The fragrance industry has volunteered to provide toxicity data on 66 materials. This indicates either primary usage or high volume usage in fragrance or flavors. Fifty-four of these materials are on the 1990 HPV list and have been assessed for available data. The available data on HPV flavors/fragrance materials which has been sponsored is summarized in the tables below.

Clearly there is less data publicly available on materials that are primarily used by the fragrance and flavors industries. Only 2 have available data in all six areas and a third has no data available. Over 72% are missing three or more sets of data. Only two materials have chronic toxicity data and over 70% are missing reproductive data. Tables 3 and 4 summarize the findings.

Table 3: Summary of available data for industry sponsored HPV flavor/fragrance materials

6 of six	2	3.7%
5 of six	3	5.5%
4 of six	10	18.5%
3 of six	8	14.8%
2 of six	10	18.5%
1 of six	3	5.5%
0 of six	18	33.3%

Table 4: Specific areas data are available for industry sponsored HPV flavor/fragrance chemicals

Acute	36	68.5%
Chronic	2	3.7%
Reproductive	16	29.6%
Mutagen	23	42.6%

Scented Products: An Overlooked Source of Indoor Pollution

Eco	21	38.9%
Fate	20	37%

Exposures

The vast majority of people in this country use scented products of one type or another. Most use or are exposed to numerous sources of fragrance on a continual basis. Products such as shampoos, soaps, lotions, hair sprays, makeup, and other cosmetics and toiletries usually have fragrance added either to impart a scent to product or to mask the odor of other ingredients. Perfumes and colognes are products marketed for their scent. Worldwide sales in the personal care industry are around $122 billion annually.[ix] US sales are around $29 billion annually.[x] Sales of perfumes and colognes alone were over $5 billion in the US. [xi] Per capita spending in the US on perfumes and colognes is around $21 per year.[xii] Household cleaning products had sales of $2.4 billion in 2001.[xiii] Sales of laundry products topped $8 billion.[xiv] Sales of home fragrances are over $2 billion annually with sales of candles making up over $900 million of the total.[xv]

In addition to personal care, household cleaning, and maintenance items, there is considerable use of fragrance in other consumer products. Trash bags now come in scented versions. Products to clean and maintain appearance on automobiles are also scented. A scented car wash is now an option in many self-service car washes. Scent is added to plastic flower pots. Paints and pesticides often contain fragrance to mask odors of other ingredients in the products. Tobacco products such as cigarettes contain flavors/fragrance chemicals to enhance the flavor, especially lower tar and nicotine brands.[xvi] Fragrance is used in pesticides to cover the odor and make the products more acceptable to consumers. Just about anything imagined may contain fragrance.

There is also use of fragrance in industrial and commercial products. Most disinfectants and cleaners contain fragrance. Even materials such as metal cutting fluids may contain fragrance. Fragrance may also be added as an odorant to products that are toxic and have low odor in order to give an olfactory warning of exposure.

The National Human Activity Pattern Survey (NHAPS) collected data on human exposures to common pollutants. According to the NHAPS Reports 63% of the 4723 participants used air fresheners in their homes, 47% used perfumes, colognes, aftershave, or other type of fragrance, and 43.7% used toilet bowl deodorizers. Use of scented products varied among ethnic groups. Black and Hispanics were more likely to use scented products, while those of Asian decent were less likely to use such products. This supports industry demographics of ethnic use of fragrance.[xvii]

Studies suggest there is exposure even before birth. Synthetic musk compounds cross the placental barrier in animal studies.[xviii] These materials bioaccumulate in human tissue and are found in breast milk.[xix] The long term implications are not known.

Impact on Air Quality

Scented Products: An Overlooked Source of Indoor Pollution

Materials used in fragrance are volatile organic compounds (VOCs) and contribute to air pollution. There are literally millions of pounds of fragrance chemicals used in the US each year. Much of these chemicals end up in the air. VOCs are also a concern as they play a role in formation of smog. A Norwegian study found measurable levels of synthetic musk compounds in outdoor air, even in remote areas.[xx] Most scented products are used inside and the impact on outdoor air is usually via dryer vents and exchange of inside air to the outside.

Though there is some impact on outdoor air, there is a larger impact on indoor air. Many of the materials in fragrance are air, heat, and light sensitive. Once in the air they may break down. At times the breakdown products are more harmful than the parent compound.[xxi] Further as materials mix in the air, new compounds may be formed. Fragrance contributes to the every changing mixture of VOCs in indoor air.

Terpenes are common materials used in scented products. Oxidation of common terpenes forms strong respiratory irritants.[xxii] It has been shown that in the presence of ozone at levels present in indoor air, common terpenes such as limonene react with ozone to form small particles.[xxiii] In addition, many fragrance chemicals are trigeminal or sensory irritants. Around 70% of fragrance chemicals are trigeminal irritants to one degree or another.[xxiv] This accounts for reports of areas of eye, nose, and throat irritation from fragrance chemicals.

Candles, incense, scented oils, fragrance emitting devices, and other products designed to scent the air are very popular. These products are a source of indoor air pollution. Any candle or incense will emit products of combustion as it is burned. The less cleanly it burns, the more soot and other small particles are produced. Candles that are heavily scented tend to burn less clean and produce more pollutants. Emissions from candles and incense include acrolein, formaldehyde, acetaldehyde, benzene and particulate matter.[xxv]

Health Concerns

There is little general awareness even within the health care community as to the concerns related to fragrance except for effects on the skin. This lack of awareness is in part a reflection of the lack of information available in medical literature. The impact of fragrance on health is an emerging health topic. As with all emerging concerns, research lags far behind clinical and patient accounts.

Skin

The skin was long thought to be the primary route of exposure to scented products. Most of the focus of safety assessment has related to skin exposures and absorption. The vast majority of medical literature on fragrance relates to skin effects. Only what pertains to exposures via air will be addressed in this review. Materials used in fragrance are known to absorb through the skin

and act as sensitizers and irritants. Those severely allergic to fragrance may develop symptoms from fragrance in the air without having to come in direct contact. Airborne contact dermatitis is well documented in medical literature.[xxvi] Further inhalation of fragrance chemicals can alter the immune response of the skin. Contact with the skin does not have the same effects.[xxvii]

It is now known skin is not the only route of exposure. Materials used in scented products may also enter and/or impact the body through respiratory pathways, olfactory and intranasal pathways, trigeminal nerves and via ingestion. No matter the route of exposure, once in the body, materials can potentially impact any body tissue, organ, or system.

Respiratory

Air passing through the airways and into the lungs exposes this pathway to whatever materials are in the air. Further the lungs provide a very efficient transport of materials from the air into the blood stream. There has been relatively little examination of the respiratory route as an exposure to fragrance materials. As early as the 1977 it was recognized by the fragrance industry that the respiratory system was a potential route of exposure to fragrance chemicals.[xxviii]

A 1977 study, conducted as partial fulfillment of earning a doctorate degree evaluated 14 common fragrance materials for their potential to cause sensory and pulmonary irritation.[xxix] Decreased respiratory rate was the criteria for sensory irritation and increased respiratory rate was the criteria for pulmonary irritation. Materials that cause both sensory and pulmonary were considered respiratory irritants.

Mice inhaled the materials at three different levels to determine sensory irritation. Exposures were for one minute at each level. One material was found to produce no sensory irritation, 3 caused only slight effects, 6 caused mild to moderate effects, and 4 caused marked effects.

The eight materials causing mild to marked effects were further evaluated to determine pulmonary irritancy. Pairs of mice were exposed to the materials, one via nasal inhalation and one via a tracheal cannula. One material isojasmone caused both a decrease in respiratory rate via nasal inhalation and an increase in respiratory rate via tracheal cannula indicating it is a pulmonary irritant. This material is irritating to both the upper and lower airways.

Subchronic aerosol studies were done in the late 1970s and the early 1980s on fragrance formulations.[xxx] A composite of these studies was published in 1999 and concluded these studies supported the conclusions that fragrance mixtures would not pose a hazard based on repeated and exaggerated exposures to animals. The formulations tested are no longer in use, though materials used still are in use.

A review of the literature on 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone commonly known as Iso E Super stated exposure to the general population is via inhalation, the skin from use, and ingestion from contamination of water or food.[xxxi]

There are no published industry studies that examine the impact on human airways and respiratory system from inhalation of scented products. There is no commercial testing available to determine if fragrance chemicals are respiratory allergens. The industry acknowledges scented products can act as irritants triggering and exacerbating asthma and allergies.[xxxii] The industry recommends courtesy in cases where asthma is triggered by scented products. In addition industry recommendations state, "We recommend a personal "scent circle" guide: no one should be aware of your fragrance unless he or she steps inside your circle - approximately an arms length from your body."

Unfortunately it is impossible to keep airborne substances within a "scent circle". Further many raw fragrance materials are developed to rapidly disperse in the air and linger. High impact scented products have been the trend since the mid-1980s.[xxxiii]

Perfumes and scented products are frequently cited as triggers for asthma by patients. The Institute of Medicine reviewed the literature on the impact of indoor air pollutants on asthma. Fragrance was placed in the same category as tobacco smoke and formaldehyde in triggering asthma in adults and school age children.[xxxiv] Virtually all organizations and agencies that deal with respiratory health list perfumes, fragrance, or strongly scented products as triggers for asthma[xxxv, xxxvi] In spite of frequent clinical and patient accounts of fragrance impacting respiratory health, there has been relatively little focus on how or why fragrance is problematic.

In a Swedish study, 16% of the general population reported perfume to be a lower airway irritant[xxxvii] and forty percent of asthmatics reported strong odors which included perfumes as triggers for asthma.[xxxviii] MSDS information often class materials used in fragrance as respiratory irritants.[xxxix]

Hairspray was found to be a trigger for asthma and thought to be due to the perfume.[xl]
In a survey of asthmatics, 72% cited perfumes and colognes as a trigger.[xli] A review of clinical forms of allergy to fragrance included asthma.[xlii] Tobacco smoke and perfumes are among the most common triggers for asthma.[xliii] A Tulane study of patients that cited fragrance as a trigger for their asthma found that popular perfumes were triggers for asthma.[xliv]

While perfumes are well recognized as triggers for asthma, there is much less information available regarding its potential to cause asthma. Environmental factors associated with development of asthma in children include living near a perfume factor[xlv] and use of perfume in the home.[xlvi] A woman who demonstrated perfumes in her job developed occupational asthma due to perfumes.[xlvii] Those working in the perfume industry have a higher incidence of asthma.[xlviii] A health care worker sprayed in the face with perfume experienced an anaphylactic reaction and developed respiratory sensitivity to perfumes.[xlix]

Odor is a complicating factor in evaluating responses to fragrance. It is often difficult to evaluate what role odor may have in triggering respiratory responses. Nose clips were used to block olfactory pathways and participants were exposed to perfume. Even when odor was not a factor, perfumes still triggered respiratory responses[l, li] Involvement of sensory pathways could not be ruled out.

Scented Products: An Overlooked Source of Indoor Pollution

While fragrance materials are recognized as respiratory irritants, there have been no published studies conducted to determine if specific fragrance materials may be respiratory sensitizers. Generally fragrances do not contain proteins that would cause classic allergic reactions. However, they do contain low molecular weight materials that may bind with body proteins. In skin allergies, these materials are thought to act as a hapten binding with body proteins to form allergens.[lii] Once sensitized to a particular substance, even very low exposures may trigger symptoms. Continued exposure can cause sensitivity to lower and lower levels.

There are no commercially available tests to determine if fragrance materials may cause respiratory sensitization in a similar manner as skin allergies. Other low molecular weight substances such as isocyanates can cause both skin and respiratory sensitization.[liii, liv] There is suggestive evidence that skin exposures can play a role in respiratory sensitization and respiratory exposures may play a role in skin sensitization.

Common fragrance materials such as terpenes have been found to disrupt the normal protective mechanisms of skin tissue and allow penetration of substance that would not normally enter the body through the skin.[lv] No studies have been done to determine if these materials may impact the respiratory system in a similar manner.

Specific studies are not available on why scented products may cause, trigger, or exacerbate respiratory conditions. Evidence suggests several mechanisms may be involved and fragrance materials may act as:

- Respiratory irritants
- Sensory irritants
- Allergens or sensitizers
- Disruptors of tissues' normal protective mechanisms

Neurological

Olfactory pathways have a direct connection to the brain. Odors are known to have both psychological and physical effects via the nervous system. It is also know that toxic materials can reach the nervous system through olfactory pathways. However, this route of exposure is generally thought to be slow. Research indicates there are other pathways from the nasal cavity to the brain.

> **"The olfactory neural pathways provide both intraneuronal and extraneuronal pathways to the brain. The intraneuronal pathway involves axonal transport and requires hours to days for drugs to reach different brain areas. The extraneuronal pathway probably relies on bulk flow transport through perineural channels which deliver drug directly to the brain parenchymal tissue, to the cerebrospinal fluid (CFS), or to both. This extraneuronal pathway allows therapeutic agents to reach the CNS within minutes."** ***(Frey, W, Intranasal Delivery: Bypassing the Blood-Brain Barrier to Deliver Therapeutic Agents to the Brain and Spinal Cord. Drug Delivery Technology. 2002 Jul/Aug. 2 (5) 46-49)***

Materials that are of small molecular weight and high fat solubility are more easily transported via these pathways. These same properties are necessary for olfaction. Fragrance chemicals are of low molecular weight and have high fat solubility.

Materials used in scented products can impact the nervous system. Solvents and other materials used have known neurological effects. (AETT) was a raw fragrance material put into use in the 1950s. It was found to have serious neurological effects. It caused skin and organs to turn a bluish color and especially targeted the nervous system. It was found to readily absorb through the skin.[lvi] The material caused permanent nerve damage. It was voluntarily withdrawn from use in 1978. Musk ambrette was put into use in the 1920s. It was found to be phototoxic, an allergen, cause atrophy of testicles in lab animals, and have neurotoxic effects. It was voluntarily withdrawn from use in direct skin contact products in 1985. It was still found in products in testing by the FDA in 1991.[lvii]

Other than studies specifically on AETT, there is only one other published industry study assessing the neurotoxic potential of fragrance chemicals.[lviii] The industry does not routinely scrutinize fragrance materials for neurological effects. Scented products are routinely marketed with claims of relaxation or altering mood. Though the effects are said to be psychological[lix], research indicates it is likely these materials have pharmaceutical effects.

Hyperactivity in mice was induced by administering caffeine. Inhaling lavender oil decreased motility to near normal levels.[lx] In other experiments, linalool and linalyl acetate were administered to mice via inhalation. Motility was decreased by 30-40%.[lxi] Other research suggests that fragrance chemicals may act on the same receptors in the brain as alcohol and tobacco.[lxii]

Inhalation of fragrance chemicals affected autonomic nervous system parameters such as blood pressure and pulse as well as mood.[lxiii] Different enanitiomers or structural orientations of the same chemicals impacted the pharmacological and psychological effects. Inhalation of (+) limonene led to increases systolic blood pressure and subjective increased alertness and restlessness. Inhalation of (-) limonene led to increased systolic blood pressure but had no effects subjective assessment of mood. Inhalation of (-) carvone caused increases in diastolic blood pressure, pulse, and subjective restlessness. Inhalation of (+) carvone caused increases in both systolic and diastolic blood pressure. This work suggests there both pharmacological and psychological effects of fragrance chemicals.

Other inhalation studies support physiological effects of fragrance as well. Blood flow to the brain was increased when 1-8 cineole was inhaled.[lxiv] Linalool was reported to have anticonvulsive effects.[lxv] Inhalation of essential oils modulates sympathetic activity causing changes in plasma levels of adrenalin.[lxvi]

Neurological effects of scented products are not necessarily undesirable. There has been a long history of using essential oils and other fragrant materials for medicinal purposes. Materials such as lavender have been used for relaxing effects. Use of essential oils is a part of alternative

medicine modalities such as massage. However, as with any other treatment method, it should be specific to the individual and what is helpful to one, may be harmful to another. Dosing everyone, especially without their knowledge or permission is unacceptable.

The majority of fragrance chemicals are sensory irritants which can cause burning of the eyes, nose, and throat. There is increasing evidence that there is a neurological component to asthma which can be triggered by sensory irritants. Scented products can clearly impact the nervous system. To what extent fragrance chemicals may be neurotoxins is really not known as there is not routine assessment of neurological effects.

Reproductive

Nitromusks have been in use since the early 1900s. They are found in blood, fat tissue, and breast milk of the general population[lxvii] and in the environment.[lxviii] In Europe they are being phased out because of health and environmental concerns. Nitromusks are still widely used in the US.

In animal studies of musk xylene there was significant transplacental passage and exposure via mother's milk. Levels in adult females were 3.5 - 6.8% higher than that in males. This difference was unrelated to fat and was not present in offspring.[13] In a study of women with gynecological problems there was an association between levels of nitromusks and clinical parameters.[lxix]

Polycyclic musks were developed in the 1950s. Because of concerns related to nitromusks, they have often been used as replacements. With usage, it has been found that polycyclic musks also bioaccumulate in human tissue and the environment. There are health concerns related to these compounds as well.

Macrocyclic musks may be either synthetic or natural. Natural musks are rarely used because of expense and animal cruelty concerns. Synthetic macrocyclic musks are more biodegradeable than other synthetic musks, but are also more expensive than nitromusks and polycyclic musks. Muscone, a natural musk, was found to be weakly estrogenic.[73]

In general, the toxicology of synthetic musk compounds has not been fully explored, especially in relationship to reproductive effects. It has been known since the early 1980s these materials are present in the environment.[lxx] The presence of these substances was discovered in breast milk in the early 1990s.[lxxi]

Citral, a material that is common in both flavors and fragrance has been found in animal studies to cause enlargement of the prostate gland,[lxxii] neural changes in pelvic area of older male animals, [lxxiii] and to have estrogenic effects.[lxxiv] Musk ambrette, a material voluntarily withdrawn from use by the industry, caused atrophy of the testicles in male lab animals.[lxxv] In a recent study there was an association between diethyl phthalate, which is a common solvent in scented products, and sperm damage in human males.[lxxvi]

Carcinogenic aspects

Scented Products: An Overlooked Source of Indoor Pollution

Screening for carcinogenic activity is not a routine part of safety assessment of raw fragrance materials. A few materials have been assessed for carcinogenic activity.

Musk xylene and musk tibetene were found to have carcinogenic activity in animal studies, more than likely by a non-genotoxic mechanism.[lxxvii] Musk ketone is thought to increase the carcinogenic activity of other materials.[lxxviii] When human breast cancer cells were exposed to synthetic musk compounds, there was an increased growth rate from exposures to musk ketone, musk xylene, metabolites of musk xylene, and the polycyclic musk known as AHTN.[lxxix]

In National Toxicology Program studies, coumarin was found to increase the incidence of tumors of the lungs and kidneys. It is not known whether the mechanisms involved are specific to the species of animals tested (rodents) or if the findings are applicable to humans. Coumarin was also found to negatively impact the kidneys, the liver, and the stomach.[lxxx] Methyleugenol was found to increase the incidence of tumors in the liver, stomach, mammary glands, and other sites.[lxxxi] Safrole is classed as a NTP anticipated human carcinogen.[lxxxii]

Most fragrance materials have not been assessed for carcinogenic activity. The lack of available data is a concern as there is widespread exposure from scented products to every segment of the population. The information that is available is troubling. The presence of synthetic musk compounds in adipose tissue and breast milk indicates it is present in breast tissue. There is evidence that synthetic musk compounds may increase carcinogenic effects of other materials, are suspected carcinogens, and have estrogenic activity. Traditionally women have been heavier users of scented products from perfumes to toiletries, to household cleaners and laundry products. That these products contain chemicals that have estrogenic effects and carcinogenic activity should raise concerns related to reproductive issues and breast cancer. Additional research is needed.

Social Considerations

The social issues regarding fragrance are complex. Scented products are usually considered pleasant. People generally feel they have a right to use what ever products they like on their person. Certainly scented products are not seen as harmful.

In addition the physiology of the sense of smell complicates matter. There is adaptation to odors. When exposed to the same odor for a relatively short period of time, the ability to smell that odor decreases. This means that those that are around or use scented products are often not aware of their presence.

This has several implications. Manufactures tend to use more intense and long lasting scent so their products will stand out from the background of fragrance that is always in the air. Those that use scented products often use more or reapply frequently and are completely oblivious their fragrance is intrusive. When there are complaints related to use of scented products, the response

is often one of surprise and resentment. There is often a conflict between those that feel they have a right to wear and use scented products and those that have adverse effects from them.

A parallel is often drawn between second hand smoke and second hand fragrance. In the case of cigarettes, the personal right to smoke is forfeited due to the rights of others not to be exposed to materials that may be harmful to their health. Logically, a case can be made for the fragrance issue as well. However, there are some important differences. A smoker can refrain from smoking in public spaces, scented products continue to volatilize long after they are applied. There is considerably more data and awareness regarding the dangers of second hand smoke. Because of this laws and policies are now in place regarding smoking.

Due to the difficulty in avoiding scented products, those that have adverse effects from exposures to scented products often find it difficult to function in the workplace and in social environments. Even grocery shopping and seeking medical care becomes complicated. Very often it is a case of choosing between working and health.

There are many complex issues regarding fragrance. These issues need to be assessed and reasonable solutions worked out. Research is needed to provide data so policies can be based on sound science. Education is needed to increase awareness of concerns.

CONCLUSION

The materials used to scent products are volatile organic compounds. Some of each scented product used by each person ends up in the air. Additional sources are cleaners, products designed to scent the air such as candles and scented oils, and laundry products. Collective these products significantly impact indoor air quality. The materials used in fragrance have both known and unknown health concerns. Fragrance formulas are complex and the components may be broken down by air, heat, and light. By design, they diffuse into the air and linger for long periods of time.

Though there has been little research on the impact of airborne fragrance chemicals on health, the lungs provide an efficient means of entry of materials into the body. Once a material enters the body, there is potential for impact on any tissue, organ, or body system. Systemic effects need to be considered. Other than acute dermal and oral toxicity, testing for systemic effects is not generally a part of the routine assessment for safety of fragrance chemicals. There is limited data available regarding systemic effects.

Some substances that enter the body are broken down and eliminated from the body fairly rapidly. Other materials may be eliminated much slower and even accumulate in body tissues. Materials that are soluble in fat are more likely to accumulate in fatty tissue of the body. Chemicals used in fragrance are generally fat soluble. Synthetic musk compounds pose concerns related to bioaccumulation in the body and the potential for carcinogenic activity and as a hormone disruptor needs to be evaluated.

The materials in fragrance are respiratory and sensory irritants. Those with asthma, allergies, and other upper and lower respiratory problems are especially susceptible to the effects. More research is needed to pinpoint problematic materials and determine how scented products trigger and exacerbated asthma and other disorders.

Exposure to the chemicals that are used in fragrance is ubiquitous. Virtually every segment of the population has a lifetime of exposure starting before birth. A through assessment of the impact of scented products on health is needed. As with other indoor air pollutant, it is prudent to decrease exposures.

REFERENCES

---

[i] Leffingwell. 1999 - 2002 Flavor & Fragrance Industry Leaders. June 30, 2003. Available at: http://www.leffingwell.com/top_10.htm. Accessed July 13, 2003

[ii] Lazzlo Somogyi, Akihiro Kishi. Flavors and Fragrances: Specialty Chemicals Update Program Dec 2001. Available at: http://scup.sric.sri.com/Public/Reports/FLAVO000/Abstract.html Accessed July 13, 2003

[iii] Lazzlo Somogyi, Akihiro Kishi. Aroma Chemicals and the Flavor and Fragrance Industry. Chemical Economics Handbook. Aug 2001. 503.5000

[iv] Robert R. Calkin, J. Stephen Jellinek; Perfumery: Practice and Principles: pg 152-153; John Wiley & Sons, Inc 1994

[v] Laszlo P. Somogyi, Birgitta Rhomberg, Yasuhiko Sakuma AROMA CHEMICALS AND THE FLAVOR AND FRAGRANCE INDUSTRY., Chemical Economics Handbook.) p. 503.5000 A. 1992

[vi] The Scientific Committee on Cosmetic Products and Non-food Products Intended for Consumers. The 1st Update of the Inventory of Ingredients Employed in Cosmetic Products: Section II : Perfume and Aromatic Raw Materials. October 24, 2000. Available at: http://europa.eu.int/comm/food/fs/sc/sccp/out131_en.pdf Accessed July 13, 2003

[vii] Flavor and Fragrance Materials Online: Allured Publishing 2003. Available at: http://www.devoapps.com/ffm/

[viii] Chemical Hazard Data Availability Study: High Production Volume (HPV) Chemicals and SIDS Testing: US Environmental Protection Agency. 2002 URL: http://www.epa.gov/chemrtk/hazchem.htm Accessed July 13, 2003

[ix] Glenn Koser. State of the Industry 2001: Part 1Global Cosmetic Industry, VOL:168, ISS:6, PG:20+, June 2001.

[x] Bill Morrison, Scott Schmitt. Cosmeceuticals Drive Healthy Growth Rates. (Personal Care) Chemical Week, VOL:163, ISS:44, PG:46(2), December 05, 2001.

[xi] Lorri Grube. Uncommon Scents. Global Cosmetic Industry, VOL:168, ISS:4, PG:36+, April 2001.

[xii] His and hers triumphs over theirs. Market Europe, VOL:11, ISS:4, PG:5, April 2000.

[xiii] Branna, Tom. Plenty of opportunities in household cleaning: new cleaning ideas hold promise. happi-Household & Personal Products Industry, VOL:38, ISS:12, PG:53(8), December 2001.

[xiv] Jewett ,Barbara. New was the buzz word in the laundry sector in 2000. Soap & Cosmetics, VOL:77, ISS:1, PG:19+, January 2001.

[xv] MacDonald, Veronica. Environmental Fragrance Market. happi-Household & Personal Products Industry, VOL:38, ISS:9, PG:51, September 2001.

[xvi] Stanfill, SB and Ashley DL. Quantitation of Flavor-Related Alkenylbenzenes in Tobacco Smoke Particulate by Selected Ion Monitoring Gas Chromatography-Mass Spectrometry. Agric. Food Chem., 48 (4), 1298 -1306, 2000.

[xvii] Ethnic Fragrance Market. Chemical Marketing Reporter, VOL:251, ISS:22, PG:25, June 02, 1997.

[xviii] Suter-Eichenbeger R, Altorfer H, Lichtensteiger W, Schlumpf M. Bioaccumulation of musk xylene (MX) in developing and adult rats of both sexes. Chemosphere. 1998 Jun;36(13):2747-62.

[xix] Liebl B, Mayer R, Ommer S, Sonnichsen C, Koletzko B.
Transition of nitro musks and polycyclic musks into human milk.Adv Exp Med Biol. 2000;478:289-305.

[xx] Kallenborn R, Gatermann R, Rimkus GG. Synthetic musks in environmental samples: indicator compounds with relevant properties for environmental monitoring.J Environ Monit. 1999 Aug;1(4):70N-74N.
[xxi] Li TH, Turpin BJ, Shields HC, Weschler CJ. Indoor hydrogen peroxide derived from ozone/d-limonene reactions. Environ Sci Technol. 2002 Aug 1;36(15):3295-302.
[xxii] .Indoor Air 2000 Jun;10(2):82-91 Formation of strong airway irritants in terpene/ozone mixtures. Wolkoff P, Clausen PA, Wilkins CK, Nielsen GD
[xxiii] Wainman T, Zhang J, Weschler CJ, Lioy PJ. Ozone and limonene in indoor air: a source of submicron particle exposure.Environ Health Perspect. 2000 Dec;108(12):1139-45.
[xxiv] John C. Leffingwell PD. Olfaction. February 2002. Available at: http://www.leffingwell.com/olfaction.htm. Accessed July 13, 2003.
[xxv] Candles and Incense as Potential Cources of Indoor Air Pollution: Market Analysis and Literature Review. US Environmental Protection Agency: Research and Development. January 2001 http://www.epa.gov/ordntrnt/ORD/NRMRL/Publications/329600R01001.htm
[xxvi] Huygens S, Goossens A. An update on airborne contact dermatitis.Contact Dermatitis. 2001 Jan;44(1):1-6.
[xxvii] Hosoi J, Tsuchiya T. Regulation of cutaneous allergic reaction by odorant inhalation.J Invest Dermatol. 2000 Mar;114(3):541-4.
[xxviii] Opdyke DL. Safety testing of fragrances: problems and implications. Clin Toxicol. 1977;10(1):61-77.
[xxix] Troy, W.R.. The comparative respiratory irritation potential of fourteen fragrance raw materials. Doctoral dissertation 1977
[xxx] Fukayama MY, Easterday OD, Serafino PA, Renskers KJ, North-Root H, Schrankel KR. Subchronic inhalation studies of complex fragrance mixtures in rats and hamsters. Toxicol Lett. 1999 Dec 20;111(1-2):175-87.
[xxxi] 1-(1,2,3,4,5,6,7,8-Octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)ethanone: Review of Toxicological Literature. National Toxicology Program. July 2001
http://ntp-server.niehs.nih.gov/htdocs/Chem_Background/ExSumpdf/IsoESuper.pdf Accessed July 14, 2003
[xxxii] SPEIAC Position on Asthma and Allergies. Scented Products Education and Information Association of Canada. http://www.scentedproducts.ca/asthmapositioncanada.htm Accessed July 14, 2003
[xxxiii] Robert R. Calkin, J. Stephen Jellinek; Perfumery: Practice andPrinciples: pg 85-86; John Wiley & Sons, Inc 1994
[xxxiv] Institute of Medicine: Clearing the Air: Asthma and Indoor Air Exposures (2000) Executive Summary; pg 9 http://books.nap.edu/books/0309064961/html/9.html Accessed July 14, 2003
[xxxv] American Lung Association Offers Indoor Air Tips for People with Asthma and Allergis. American Lung Association. September 1997. http://www.lungusa.org/press/envir/asnairt.html
[xxxvi] Asthma and Indoor Environments - Asthma Facts. US Environmental Protection Agency. Last updated on Tuesday, June 17th, 2003 http://www.epa.gov/iaq/asthma/introduction.html Accessed July 14, 2003
[xxxvii] Larsson ML, Frisk M, Hallstrom J, Kiviloog J, Lundback B. Environmental tobacco smoke exposure during childhood is associated with increased prevalence of asthma in adults. Chest. 2001 Sep;120(3):711-7.
[xxxviii] Private communication with M. Larsson, lead author of above article
[xxxix] MSDS sheet for Methyl dihydrojasmonate. Aldrich Chemical Company. 2001
[xl] Schlueter DP, Soto RJ, Baretta ED, Herrmann AA, Ostrander LE, Stewart RD.
Airway response to hair spray in normal subjects and subjects with
hyperreactive airways. Chest. 1979 May;75(5):544-8.
[xli] Shim C, Williams MH Jr. Effect of odors in asthma. Am J Med. 1986 Jan;80(1):18-22.
[xlii] Meynadier JM, Meynadier J, Peyron JL, Peyron L. [Clinical forms of skin manifestations in allergy to perfume] Ann Dermatol Venereol. 1986;113(1):31-41.
[xliii] Eriksson NE, Lowhagen O, Nilsson JE, Norrlind K, Wihl JA.
Flowers and other trigger factors in asthma and rhinitis--an inquiry study. Allergy. 1987 Jul;42(5):374-81.
[xliv] Asthmatics' reactions to common perfumes.Today's findings from the AAAAI Annual Meeting unveil new research on allergic triggers and cutting-edge asthma treatments. American Academy of Allergy, Asthma and Immunology Press Release. March 4, 2000 http://www.aaaai.org/media/news_releases/2000/03/000304.html
[xlv] Revich BA. [Air pollution and the prevalence of bronchial asthma among the pediatric
population of Moscow] Med Tr Prom Ekol. 1995;(5):15-9.

[xlvi] Bener A, Abdulrazzaq YM, Al-Mutawwa J, Debuse P. Genetic and environmental factors associated with asthma.
Hum Biol. 1996 Jun;68(3):405-14.
[xlvii] Baur, X., Schneider, E.M., Wieners, D. & Czuppon, A.B. Occupational asthma to perfume. Allergy 54 (12), 1334-1335
[xlviii] Ross DJ, Keynes HL, McDonald JC.SWORD '97: surveillance of work-related and occupational respiratory disease in the UK. Occup Med (Lond). 1998 Nov;48(8):481-5.
[xlix] Lessenger JE. Occupational acute anaphylactic reaction to assault by perfume spray in the face. J Am Board Fam Pract. 2001 Mar-Apr;14(2):137-40.
[l] Millqvist E, Lowhagen O. Placebo-controlled challenges with perfume in patients with asthma-like symptoms.Allergy. 1996 Jun;51(6):434-9.
[li] Millqvist E, Bengtsson U, Lowhagen O. Provocations with perfume in the eyes induce airway symptoms in patients with sensory hyperreactivity. Allergy. 1999 May;54(5):495-9.
[lii] Smith CK, Moore CA, Elahi EN, Smart AT, Hotchkiss SA. Human skin absorption and metabolism of the contact allergens, cinnamic aldehyde, and cinnamic alcohol.Toxicol Appl Pharmacol. 2000 Nov 1;168(3):189-99.
[liii] Rattray NJ, Botham PA, Hext PM, Woodcock DR, Fielding I, Dearman RJ, Kimber. Induction of respiratory hypersensitivity to diphenylmethane-4,4'-diisocyanate (MDI) in guinea pigs. Influence of route of exposure. Toxicology. 1994 Mar 11;88(1-3):15-30
[liv] Ebino K, Ueda H, Kawakatsu H, Shutoh Y, Kosaka T, Nagayoshi E, Lemus R,
Karol MH. Isolated airway exposure to toluene diisocyanate results in skin sensitization.
Toxicol Lett. 2001 Apr 8;121(1):79-85.
[lv] Vaddi HK, Ho PC, Chan YW, Chan SY.Oxide terpenes as human skin penetration enhancers of haloperidol from ethanol and propylene glycol and their modes of action on stratum corneum. Biol Pharm Bull. 2003 Feb;26(2):220-8.
[lvi] Spencer PS, Sterman AB, Horoupian DS, Foulds MM. Neurotoxic fragrance produces ceroid and myelin disease. Science. 1979 May 11;204(4393):633-5.
[lvii] Wisneski HS, Havery DC. Nitro musks in fragrance products: an update of FDA findings. Cosmetics and Toiletries June 1996 v111 n6 p73(4)
[lviii] Gressel Y, Troy WR, Foster GV. Safety evaluation of four bicyclic musk fragrance-chemicals relative to the neurotoxin, acetyl ethyl tetramethyl tetralin (AETT). Dev Toxicol Environ Sci. 1980;8:53-8.
[lix] Aroma-Chology Defined. Sense of Smell Institute. 2002
http://www.senseofsmell.org/resources/aromachology.asp
[lx] Buchbauer G, Jirovetz L, Jager W, Dietrich H, Plank C.
Aromatherapy: evidence for sedative effects of the essential oil of lavender after inhalation.
Z Naturforsch [C]. 1991 Nov-Dec;46(11-12):1067-72.
[lxi] Jirovetz L, Jager W, Buchbauer G, Nikiforov A, Raverdino V. Investigations of animal blood samples after fragrance drug inhalation by gas chromatography/mass spectrometry with chemical ionization and selected ion monitoring. Biol Mass Spectrom. 1991 Dec;20(12):801-3.
[lxii] Aoshima H, Hamamoto K. Potentiation of GABAA receptors expressed in Xenopus oocytes by perfume andphytoncid. Biosci Biotechnol Biochem. 1999 Apr;63(4):743-8.
[lxiii] Heuberger E, Hongratanaworakit T, Bohm C, Weber R, Buchbauer G. Effects of chiral fragrances on human autonomic nervous system parameters and self-evaluation. Chern Senses. 2001 Apr;26(3):281 -92.
[lxiv] Nasel C, Nasel B, Samec P, Schindler E, Buchbauer G. Functional imaging of effects of fragrances on the human brain after prolonged inhalation. Chem Senses. 1994 Aug;19(4):359-64.
[lxv] Elisabetsky E, Brum LF, Souza DO. Anticonvulsant properties of linalool in glutamate-related seizure models. Phytomedicine. 1999 May;6(2):107-13.
[lxvi] Haze S, Sakai K, Gozu Y. Effects of fragrance inhalation on sympathetic activity in normal adults.
Jpn J Pharmacol. 2002 Nov;90(3):247-53.
[lxvii] Ott M, Failing K, Lang U, Schubring C, Gent HJ, Georgii S, Brunn H. Contamination of human milk in Middle Hesse, Germany--a cross-sectional study on the changing levels of chlorinated pesticides, PCB congeners and recent levels of nitro musks.Chemosphere. 1999 Jan;38(1):13-32.

[lxviii] Gatermann R, Biselli S, Huhnerfuss H, Rimkus GG, Hecker M, Karbe L. Synthetic musks in the environment. Part 1: Species-dependent bioaccumulation of polycyclic and nitro musk fragrances in freshwater fish and mussels. Arch Environ Contam Toxicol. 2002 May;42(4):437-46.
[lxix] Eisenhardt S, Runnebaum B, Bauer K, Gerhard I. Nitromusk compounds in women with gynecological and endocrine dysfunction.Environ Res. 2001 Dec;87(3):123-30.
[lxx] Yamagishi T, Miyazaki T, Horii S, Kaneko S. Identification of musk xylene and musk ketone in freshwater fish collected from the Tama River, Tokyo. Bull Environ Contam Toxicol. 1981 May;26(5):656-62.
[lxxi] Liebl B, Ehrenstorfer S. [Nitro-musk compounds in breast milk]Gesundheitswesen. 1993 Oct;55(10):527-32.
[lxxii] Engelstein D, Shmueli J, Bruhis S, Servadio C, Abramovici A. Citral and testosterone interactions in inducing benign and atypical prostatic hyperplasia in rats. Comp Biochem Physiol C Pharmacol Toxicol Endocrinol. 1996 Oct;115(2):169-77.
[lxxiii] Golomb E, Scolnik M, Koren R, Servadio C, Sandbank U, Abramovici A. Effects of senescence and citral on neuronal vacuolar degeneration in ratpelvic ganglia. Neurotoxicology. 2001 Feb;22(1):73-7.
[lxxiv] Geldof AA, Engel C, Rao BR. Estrogenic action of commonly used fragrant agent citral induces prostatic hyperplasia. Urol Res. 1992;20(2):139-44.
[lxxv] Spencer PS, Bischoff-Fenton MC, Moreno OM, Opdyke DL, Ford RA. Neurotoxic properties of musk ambrette. Toxicol Appl Pharmacol. 1984 Sep 30;75(3):571-5.
[lxxvi] Duty SM, Singh NP, Silva MJ, Barr DB, Brock JW, Ryan L, Herrick RF, Christiani DC, Hauser R. The Relationship between Environmental Exposures to Phthalates and DNA Damage in Human Sperm Using the Neutral Comet Assay. Environ Health Perspect. 2003 Jul;111(9):1164-9.
[lxxvii] Apostolidis S, Chandra T, Demirhan I, Cinatl J, Doerr HW, Chandra A.
Evaluation of carcinogenic potential of two nitro-musk derivatives, musk xylene and musk tibetene in a host-mediated in vivo/in vitro assay system.Anticancer Res. 2002 Sep-Oct;22(5):2657-62.
[lxxviii] Mersch-Sundermann V, Schneider H, Freywald C, Jenter C, Parzefall W, Knasmuller S. Musk ketone enhances benzo(a)pyrene induced mutagenicity in human derived Hep G2 cells. Mutat Res. 2001;495(1-2):89-96.
[lxxix] Bitsch N, Dudas C, Korner W, Failing K, Biselli S, Rimkus G, Brunn H. Estrogenic activity of musk fragrances detected by the E-screen assay using human mcf-7 cells.Arch Environ Contam Toxicol. 2002 Oct;43(3):257-64.
[lxxx] National Toxicology Program Studies. Coumarin: http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr422.html Accessed July 14, 2003
[lxxxi] National Toxicology Program Studies Methyleugenol: http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr491.html Accessed July 14, 2003
[lxxxii] National Toxicology Program Studies Safrole: http://ntpserver.niehs.nih.gov/htdocs/CHEM_H&S/NTP_Chem9/Radian94-59-7.html Accessed July 14, 2003