Perfumed substances: beyond beautiful

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Perfumed substances: beyond beautiful

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ABSTRACT

Fragrance refers to any natural or synthetically ingredient intended to produce a particular scent. Perfumed components are used in a large variety of consumer products from perfumes to skin products such as creams, lotions, detergents, and various other personal and household products.

Considering the diversity of chemical products and the specific ways each individual reacts, widely symptoms can be expected from exposure to scented products. Synthetic scents chemicals can interfere with normal healthy process because some ingredients from perfumed products can be absorbed through the skin and reach the systemic circulation.

Symptoms triggered by exposure to fragrances can encompass contact dermatitis, pigmented contact reactions, skin irritations, hormonal disturbance being the core cause of some disorders like gynecomastia, cancers, etc.

Keywords: fragrances, safety, health

INTRODUCTION

The story of perfume has begun in antiquity, when the Egyptians used incense in religious rituals due to its special smell and purifying properties [23]. Each odorant compound has a unique pattern of neural signals because it stimulates only a specific population of olfactory sensory neurons and each cell/neuron responds uniquely to different odors [2]. In recent decades, synthetic fragrance compounds have become basic components of daily care products: sun protection creams, shampoos, body lotions, products for the scalp, hair, lip balm, and also household cleaning products (detergents, room sprays, scented candles, scented products for cleaning furniture, dishes, etc.). Basically, the huge trends of consumerism have led to the excessive use of these synthetic substances [12].

About 2600 different structures belonging to different chemical classes have been identified in perfume industry: aliphatic, aromatic aldehydes, Schiff bases, saturated and unsaturated alcohols, polyols and their esters, cyclic terpenes, aliphatic and aromatic amines, amides, oximes, carboxylic acids (saturated, unsaturated, cyclic and aromatic), esters (acetates, phthalates, salicylates, butyrates, isobutyrates, valerates, isovalerates), coumarins, dioxanes, epoxides, lactones, halogenated derivatives, nitriles, phenols, quinolines, sulfur compounds [3].

The fragrance industry is extremely complex, but it must be taken into account the continuous interaction with such perfumed products, some of their components can be absorbed through the skin and reach the systemic circulation. A complex absorption process has been observed in the case of alkylated derivatives of nitrobenzene for which absorption is favored by the reservoir capacity of the skin from where the substance diffuses over time, but the degree of absorption is still small compared to other derivatives such as coumarins and phenyl-ethyl alcohols [3].

There are two main ways for fragrance molecules to enter in the body: through the skin or the respiratory system. Knowing the complexity of the chemical constituents in perfumed products and the fact that some organisms are more vulnerable during the exposure due to pathological diseases, it is important to know the potential adverse reactions arising to the exposure to these products, with a negative impact on human health.

Potential health risks associated with the exposure to natural volatile oils and their constituents

The use of essential oils is increasing due to the high demand for natural ingredients. Most fragrances are haptens, after their binding to proteins, they become allergens and are able to induce an immune reaction. Some fragrances need to be activated before they can bind to proteins. This process can take place by autoxidation or photoactivation; if this activation occurs outside the body, the substance is a prehapten. On the other hand, prohaptens, are converted to immunogenic haptens within the skin, usually by enzymatic catalysis. It is not always clear whether a substance is a prehapten, a prohapten, or both, since both activation pathways can lead to the same products, such as geraniol (geranial, epoxy-geraniol, and epoxy-geranial) [19,22].

Lavender volatile oil contains terpenes, linalool, linalyl acetate and caryophyllene along with over 450 substances. The chemicals considered to be the most allergenic are linalool and linalyl acetate, linalool being used in allergy patch tests to confirm the allergenic potential of lavender oil [7,16]. Nineteen cases of photosensitivity and contact dermatitis have been reported in the literature due to the skin use of products with lavender oil. Linalool and linalyl acetate are photosensitive compounds, the oxidation products contributing to increased skin sensitization and irritation [16].

Peppermint volatile oil (containing menthol, menthone, 1,8-cineole, methyl acetate, limonene, α-pinene, β-pinene, etc.) can cause allergic contact cheilitis when it is used on the lips [16].

Limonene is a compound found not only in the peppermint volatile oil but also in many other perfumed products intended for a large consumption as a mixture of two enantiomers (R and S-limonene). This is important because limonene and other components can react with ozone in the house air, obtaining formaldehyde as well as ultrafine particles. By using unscented products in the home cleaning process, the level of odorous pollutants can be reduced by up to about 99% within 4 weeks [20].

In addition, ozonolysis of limonene leads to oxidation products such as 4-acetyl-1-methylcyclohexene, 4-oxopentanal and 3-isopropenyl-6-oxoheptanal, which can cause cytotoxic effects on bronchial and alveolar epithelial cells as well as the release of inflammatory cytokines. 3-Isopropenyl-6-oxoheptanal stimulates the release of IL-6, IL-8 and TNF-α from bronchial and alveolar cell lines. These effects can lead to a hyperreactivity of the bronchial mucosa with important consequences in the development of bronchial asthma as well as other allergic or non-allergic diseases of the respiratory tract [9,11].

Rosemary volatile oil is often found in care products such as bath salts, bath oil, body gels, soaps. The main constituents of rosemary volatile oil are α-pinene, β-pinene eucalyptol, camphor, limonene, bornyl acetate, camphene, β-myrcene. Rosemary volatile oil can cause allergic contact dermatitis associated with chronic, occupational exposure [16].

Cases of allergic contact dermatitis have been reported for the volatile oil obtained from rose flowers for subjects occupationally exposed (aromatherapists and chemists). Rose essential oil contains β-ionones, compounds that are responsible for the fruity smell of rose essential oil [16,18]. According to some experimental studies on prostate adenocarcinoma cell lines, it was shown that α and β-ionone promote tumor invasion and malignant cells multiplication even after a short-term exposure to these compounds. α-Ionone is an agonist of PSGR (prostate-specific G-protein coupled receptor), considered a tumor marker for prostate cancer, the intensity of the agonistic activity being inversely proportional to the concentration of α-ionone [14,15].

Geraniol and citronellol are considered to be the most allergenic components of rose essential oil.

Lime volatile oil contains high concentrations of coumarins and furocoumarins such as dimethoxycoumarin, psoralen, 5-methoxy-psoralen, 8-methoxy-psoralen, 5,8-dimethoxypsoralen but also monoterpenes like d-limonene and citral. The main adverse reactions produced by coumarins and furocoumarins are photodermatitis and phototoxic adverse reactions uncorelated to the body's immune response. Inflammatory skin reactions that occur as a result of the interaction of UVA rays with these compounds applied to the skin can range from pigmentation, blisters to burns [1,19].

Potential health risks associated with exposure to synthetic fragrance products

At the end of the 19th century the use of synthetic fragrances represented the beginning of a new stage in perfumery [24].

The musk aroma consists of alkylated derivatives of nitrobenzene (4-tert-butyl-2,6-dimethyl-3,5-dinitroacetophenone, 2,6-dinitro-3-methoxy-4-tert-butyl-toluene, 1,1,3,3,5-pentamethyl-4,6-dinitro-2H-indene, 1-tert-butyl-3,4,5-trimethyl-2,6-dinitrobenzene, 1-tert-butyl-5-dimethyl-2,4,6-trinitrobenzene). The main sources of exposure to synthetic musk are scented personal care or household products. The results of a study that assessed the health impact associated with exposure to nitro-musk highlighted that it could be disruptive to the hypothalamic-ovarian hormone pathway [21].

Since nitro-musk derivatives are lipophilic substances, they can be distributed in adipose tissue and can be excreted in breast milk; placental diffusion of galaxolide, a polycyclic musk, can expose the fetus to possible teratogenic phenomena [12,21].

Experimental studies have also shown that nitro-musk derivatives are enzyme inhibitors of CYP1A and CYP3A. The estrogenic effects of musk derivatives lead to some diseases: gynecomastia, hormone-dependent ovarian and breast cancer, polycystic ovary syndrome [10,12,17].

Javanol and polysanthol, synthetic compounds widely used in the perfume industry, give the specific smell of sandalwood. They influence both cell surface G protein-coupled olfactory receptors and the human nuclear estrogen receptor (α-ER). In experimental studies, javanol and polysanthol behaved as specific ER agonists, the estrogenic activity of the odorant molecules being confirmed by measuring their proliferative effect on the division of human breast cancer cells [11,13].

Thus, ingredients with potential hormonal activities in perfumed products lead to hormonal disorders mediated by estrogenic imbalances, carcinogenic effects, reproductive diseases, possible teratogenic consequences on the fetus, etc.

Lilial is a synthetic lily-flavored compound, the D enantiomer being the one that strongly imprints the floral scent. In 2022, the EU banned the use of lilial in cosmetic products as a result of its inclusion by the European Chemicals Agency in the list of substances that raise serious concerns regarding its toxicological profile like allergenic capacity, the damage to the reproductive system and the capacity to induce topical sensitization.

In experimental studies, lilial demonstrated estrogenic activity on hormone-dependent breast cancer cells, activity correlated with cancer cells proliferation. Even if the estrogenic activity is not comparable to that of nitro-musk derivatives for which there are a lot of data, its inclusion in the list of endocrine disruptors is important [5,8].

The electronic cigarette is an emerging phenomenon that is becoming increasingly popular with smokers worldwide, the use of the volatile constituents for their manufacture are odor carriers. Penetration route of vapors from electronic cigarettes is pulmonary and lung damage induced by the gaseous mixture is due to incompletely elucidated mechanisms. The inhaled chemicals can have a direct cytotoxic action on various lung cells, which can lead to inflammation and cell necrosis; additionally, the inhalation of the basic ingredients of electronic cigarettes (propylene glycol and glycerin) can lead to changes in the homeostatic state of lung immune cells, which causes an imbalance and triggers massive inflammation [6].

Flavoring additives are an important component of tobacco products which can directly influence the product preference and a mean to attract younger consumers. Aerosols from e-cigarettes have smell and taste. There are a few studies which evaluated the toxicity of specific flavors from cigarettes. Specifically, exposure to cinnamaldehyde, 2-methoxycinnamaldehyde, and diacetyl has been shown to cause cytotoxicity at concentrations commonly found in e-cigarette liquids. More recently, it has been demonstrated that benzene is formed as a result of the thermal decomposition of benzaldehyde, a compound responsible for the sweet, almond-like odor [4].

Some derivatives: δ-tetradecalactone, linalool, D-limonene, piperonal, neral and geranial could generate free radicals, suggesting that these flavoring additions can increase the oxidative process with repercussions on health [4].

CONCLUSION

The spectrum of reactions frequently identified following exposure to natural volatile oils components of care products includes contact dermatitis, pigmented contact reactions, skin irritations, especially in conditions of increased humidity, auto-oxidation.

There is a direct exposure of the ingredients from the fragrance products to the skin, nose, eyes, mouth and respiratory system, which can cause dermatological, immunological, respiratory problems. Perfumed ingredients from cosmetic products are regulated to the same safety requirements as other cosmetic components (emulsifiers, dyes, bleaches, solvents, surfactants, antifoams, etc.); the safety for consumers is very important, but the complexity of the odorous chemical compounds in these products cannot guarantee the absence of possible side reactions on human health.

As a result, an additional research is required to identify the potential fragrance compounds incriminated in the appearance of different adverse reactions and the cellular process triggered by them in experimental studies, along with a preventive attitude towards excessive use by reducing daily exposure.

References

1. Alessandrello C, Gammeri L, Sanfilippo S, Cordiano R, Brunetto S, Casciaro M, et al. A spotlight on lime: a review about adverse reactions and clinical manifestations due to *Citrus aurantiifolia*. Clin Mol Allergy. 2021;24;19(1):12.
2. Anju S, Kumar R, Aier I, Semwal R, Tyagi P, Varadwaj P. Sense of smell: structural, functional, mechanistic advancements and challanges in human olfactory research. Curr Neuropharmacol. 2019;17(9):892.
3. Bickers DR, Calow P, Greim HA, Hanifin JM, Rogers AE, Saurat JH, et al. The safety assessment of fragrance materials. Regul Toxicol Pharmacol. 2003;37(2):218-73.
4. Bitzer ZT, Goel R, Reilly SM, Elias RJ, Silakov A, Foulds J, et al. Effect of flavoring chemicals on free radical formation in electronic cigarette aerosols. Free Radic Biol Med. 2018;20(120):72-79.
5. Charles AK, Darbre PD. Oestrogenic activity of benzyl salicylate, benzyl benzoate, bezyl butylphenylmethylpropionate (Lilial) in MCF7 human breast cancer cells *in vitro.* J Appl Toxicol. 2009;422-424.
6. Crotty Alexander LE, Bellinghausen AL, Eakin MN. What are the mechanisms underlying vaping induced injury? J Clin Invest. 2020;130(6):2754-2756.
7. De Groot A, Schmidt E. Essential oils, Part V: Peppermint oil, Lavander oil and Lemongrass oil. Dermatitits. 2016;27(6):235-237.
8. Jablonská E, Míchal Z, Křížkovská B, et al. Toxicological investigation of lilial. Sci Rep. 2023;13:18536.
9. Lipsa D, Barrero-Moreno J, Coelham M. Exposure to selected limonene oxidation products: 4-OPA, IPOH,4-AMCH induces oxidative stress and inflamation in human lung epithelial cell lines. Chemosphere. 2018;19:937-945.
10. Luckenbach T, Epel D. Nitromusk and Polycyclic Compounds as Long-Term Inhibitors of Cellular Xenobiotuc Defense Systems Mediated by Multidrug Transporters. Environ Health Perspect. 2005;113(1):17-24.
11. Pastor-Nieto MA, Gatica-Ortega ME. Ubiquity, Hazardous Effects and Risks Assesment of Fragrances in Consumer Products. Curr Treat Options Allergy. 2021;8(1):24-41.
12. Patel S. Fragrance compunds: The wolves in sheep's clothing. Med Hypotheses. 2017;102:107-111.
13. Pick H, Etter S, Baud O, Schmauder R, Bordoli L, Schwede T, et al. Dual activities of odorants on olfactory and nuclear hormone receptors. J Biol Chem. 2009;284(44):30547-55.
14. Radis- Baptisa J. Do synthetic fragrances in personal care and household products impact indoor air quality and pose health risks? J Xenobiotics. 2003;13:123-124.

15. Sanz G, Leray I, Grebert S, Antoine S, Acquistapace A, et al. Structurally related odorant ligands of the olfactory receptor OR51E2 differentialy promote metastasisemergence and tumor growth. Oncotarget. 2017;8(31):4330-4341.
16. Sarkic A, Stappen I. Essential oils and their single compounds in cosmetics-A critical review. Cosmetics. 2008;5(1):5-9.
17. Schnell S, Martin-Skilton R, Fernandes D, Porte C. The interference of nitro- and polycyclic musks with endogenous and xenobiotic metabolizing enzymes in carp: an in vitro study. Environ Sci Technol. 2009;43(24):9458-64.
18. Schulz H. Fragrance and Pigments. Odoriferous Sustances and Pigments. Ecyclopedia of Rose Science 2003;231-240.
19. Sharmeen JB, Mahomoodally FM, Zengin G, Maggi F. Essential oils as natural sources of fragance compounds and cosmetics and cosmeceuticals. Molecules. 2021;26(3):1-4.
20. Steinneman A. The fragranced products phenomenon: air quality and health, science and policy. Air Qual Atmos Hlth. 2021;14:235-241.
21. Taylor KM, Weisskopf M. Shine J. Human exposure to nitro musks and the evaluation of their potential toxicity: an overview. Environ Health. 2014;13:1-6.
22. Uter W. Contact allergy to fragrances: current clinical and regulatory trends. Allergol Select. 2017;1(2):190-199.
23. https://www.mcgill.ca/oss/article/history/story-perfume
24. https://reportagens.bondalti.com/en/article/perfumes-the-fragrances-of-chemistry/