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Original and faked perfumes: a 90-day repeated-dose dermal toxicity study in Wistar rats

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ABSTRACT

The fragrance industry frequently establishes self-imposed restrictions on certain ingredients to ensure consumer safety of their products. However, locally produced counterfeits remain unregulated and may impose serious adverse health effects. This study was conducted to evaluate possible local and systemic toxic effects associated with repeated daily exposure to 3 different original and 3 fake perfumes using Wistar rats as a model. A total of 84 adult Wistar rats were randomly allocated into 7 different groups. At the end of the experiment, all animals were weighed, sacrificed humanely and blood samples were collected for hematology and serum biochemistry analyses. A thorough necropsy was carried out and major organs were dissected and weighed, and different tissues samples were collected and examined histologically. All animals survived the entire experiment without showing any abnormal behavior, local or systemic clinical signs. There were no significant changes between different groups and control group in all parameters examined. Although in this study no harmful effects were detected in rats after repeated exposure to either original or fake perfumes, regulatory guidelines that protect consumers and mandate perfume makers to declare a list of components on their products must be established.

KEYWORDS: *Fragrance; perfumes; environmental exposure; local and systemic allergies; toxic substances*.

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1. INTRODUCTION

Perfume, a word derived from the Latin word “per fumum” which means “through smoke” is known for more than 4000 years (Herz, 2011). Humans have used perfumes in a fragrance and or in personal health care products (Park and Hong, 2024, Carvalho et al. 2016). Originally, perfumes were made from natural aromatic plants, however, as industrial ages came about, many rather synthetic perfumes become more popular and affordable for many people to use (McMullen and Dell’Acqua, 2023, Gupta et al. 2015). Therefore, perfumes today represent a large industry with significant economic value on a global level. Synthetic perfumes are customized by a combination of several different substances into a special formula to produce the final perfume product (Roberts and Schum 2003).

Original perfumes are expensive and not available for a large population of people. The increased demand for cheaper and affordable perfumes has encouraged the development and growth of a parallel fake perfume industry. Fake perfumes

depend mostly on low-quality raw materials or substandard concentrations to produce synthetic materials with close similarity to the natural ones, or to compose new compounds, which are close to the well-known brands (Roberts and Schum 2003, Chisvert and Salvador 2007). Not only this fake perfume industry has a negative economic impact on genuine perfumes, but also contain toxic solvents, banned fragrance ingredients, and dangerous levels of ingredients that are restricted in genuine one, and represents a substantial risk to human and public health (Marques et al. 2006, Chisvert and Salvador 2007, Aghoutane et al. 2023).

Analytical studies have revealed that most synthetic perfumes contain several toxic chemicals such as linalool (LIL), limonene (LIM), α-pinene (APN) and eugenol (EUG) (Yazar et al. 2011, Bartsch et al. 2016). Most of these compounds are known to cause severe adverse health effects through skin contact such as allergic dermatitis and inhalation such as respiratory irritation and potentially asthma (Li et al., 2024). Furthermore, advanced analytical methods have exposed banned compounds present in the finished product of perfumes such as musk, phthalates and parabens (Thyssen et al. 2009). These materials also have been cited to cause serious health effects in many studies including mucosal irritation, asthma, headache, nausea and skin allergies (Mukherjee Das et al., 2022, Akunna et al. 2011, Chisvert et al. 2013, Siti Zulaikha et al. 2015).

While most previously conducted studies concerning perfume safety have focused on respiratory reactions to repeated exposure to perfumes (Wolkoff and Nielsen 2017), limited research have been conducted to evaluate perfume effects on other body organs. Therefore, this study was designed to evaluate possible health effects of original and fake perfumes on the skin and other body organs.

2. MATERIALS AND METHODS

Test materials
Three different kinds of original perfumes labeled as O1, O2 and O3 and 3 fake perfumes labeled as F1, F2 and F3 were used in the study. Original perfumes were selected randomly and purchased from local retailers after the product certificate of origin and authenticity was ascertained. Locally produced fake perfumes were purchased from local shops that compile and mix their own products using different ingredients.

Animals and ethical approvals
The study protocol was reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of Jordan University of Science and Technology (JUST).

Male and female, adult Albino Wistar rats were obtained from the animal house of JUST. The rats were kept in clear-sided cages in groups of 3 to 5 rats per cage and environmentally controlled animal house (12/12-hour light cycles, ambient temperature of 22-24 ^{o}C and 55-65 relative humidity). The rats were fed locally produced rat's feed and offered freshwater *ad libitum*. The rats were left to acclimatize to the working environment for one week before starting the experiment.

Study design
Seven different groups (12 rats each; 6 males and 6 females) were used in the experiment. Animals were randomly assigned into one of the following groups: negative control, O1, O2 and O3 for the original perfumes and F1, F2 and F3 for the fake perfumes. A 2cm x 2cm square area of skin located on the dorsal inter-scapular region of each rat was shaved and disinfected. Different treatments were sprayed topically at the shaved areas once per day for 90 convective days. Shaving and disinfection of the test area were repeated at weekly basis. In the control group, rats were not treated with any product. The animals were initially weighed just before the start of the topical application. During the whole experiment, the rats were monitored twice daily for any clinical abnormalities, feed and water intake. At the end of the experiment, the final weight of all rats was obtained again and recorded. At the day of necropsy, all animals were sacrificed using pentobarbital overdose and blood was collected immediately by cardiac puncture and placed in plain and EDTA-containing blood tubes.

Hematological and biochemical parameters
Hematological parameters including red blood cells count (RBC), white blood cell count (WBC), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and platelet count were determined immediately using an automated hematology analyzer (ABC vet hematology analyzer, France).

For serum biochemistry, serum was obtained by centrifugation of plain blood tubes at 5000 g for 10 minutes. Serum was collected and stored at -20 ^{o}C until used in the analysis. Clinical chemistry parameters including alkaline phosphatase (ALP), alanine aminotransferase (ALT), total protein, albumin, urea, creatinine and glucose were measured using commercially available kits and reagents according to manufacturer's instructions.

Gross examination
All rats were subjected to a thorough necropsy examination to detect any gross lesions involving any of the internal organs. The livers, kidneys, adrenal glands and testicles were carefully dissected and all adventitial adipose tissues were removed before the organs were weighed. Tissue samples from various organs including livers, lungs and hearts were obtained fixed in 10% formalin solution for routine histopathology examination.

Histopathology examination
Formalin-fixed tissues were cut and processed routinely in an automatic processor for histopathological examination. The prepared glass slides were stained by Hematoxylin and Eosin stain [H&E] and examined blindly by a certified veterinary pathologist.

Statistical analysis
Differences between groups in values of hematology, serum biochemistry body weights, and organ weights were statistically evaluated using independent t-test. Statistical analysis was performed using IBM SPSS Software program (version 23). All recorded data were expressed as mean ± SD.

3. RESULTS

All animals survived the entire experiment. Animals appeared to tolerate the topical application of all perfumes [original and fake] without showing any local or systemic signs of irritation or discomfort. There were no abnormal clinical signs such as skin hyperemia, skin rashes, coughing, sneezing, nasal and/or eye discharge in any of the rats during the entire period if the experiment. There were also no abnormal behavioral changes observed such as irritation, agitation, hiding, scratching, appetite loss or reduced water intake in any of the rats.

The mean body weights and selected organ weights of male and female rats in different groups are illustrated in Figure 1. No significant differences were detected in the mean values of the body weight or organ weights between the control and treated rats Table 1 Table 2, respectively.

Table 1. Mean±SD of body weight (g) and various organ weights (g) of male Wistar rats after repeated exposure to 3 different original and 3 different fake perfumes for 90 consecutive days.

Parameters	Groups (n=6)						
	Control	Original perfumes			Fake perfumes		
		O1	O2	O3	F1	F2	F3
Initial body weight	138±18	145±20	168±20	153±17	123±8	166±10	149±17
Final body weight	333±56	356±42	372±30	363±38	356±34	354±18	353±30
Liver weight	11±2	12±1	12±1.5	13±1.7	11±1	12±1	12±1
Liver weight/final body weight	0.03	0.03	0.03	0.04	0.03	0.03	0.03
Right kidney weight	1±0.02	1.2±0.1	1.2±0.1	1.3±0.2	1.3±0.2	1.2±0.1	1.3±0.1
Left kidney weight	1±0.02	1.2±0.1	1.1±0.16	1.3±0.1	1.2±0.1	1.2±0.1	1.2±0.1
Right adrenal gland weight	0.05±0.01	0.06±0.01	0.03±0.01	0.08±0.03	0.04±0.01	0.06±0.02	0.05±0.03
Left adrenal gland weight	0.06±0.01	0.05±0.02	0.04±0.01	0.08±0.02	0.04±0.02	0.06±0.01	0.07±0.01
Right testicle weight	2.4±0.4	2.7±0.17	2.3±0.75	2.6±0.2	2.5±0.14	2.7±0.4	2.5±0.1
Left testicle weight	2.3±0.3	2.4±0.17	2.3±0.8	2.6±0.4	2.2±0.3	2.9±0.4	2.5±0.1

Table 2. Mean±SD of body weight (g) and various organ weights (g) of female rats after repeated exposure to 3 different original and 3 different fake perfumes for 90 consecutive days.

Parameters	Groups (n=6)						
	Control	Original perfumes			Fake perfumes		
		O1	O2	O3	F1	F2	F3
Initial body weight	125 ± 16	127 ± 10	145 ± 17	133 ± 17	123 ± 5	132 ± 28	121 ± 14
Final body weight	242 ± 19	238 ± 14	247 ± 30	249 ± 23	231 ± 25	2415 ± 16	228 ± 23
Liver weight	7.0 ± 0.6	9 ± 0.7	9 ± 0.5	9 ± 0.6	9 ± 1	9 ± 0.7	9 ± 0.9
Liver weight/final body weight	0.03	0.04	0.04	0.04	0.04	0.04	0.04

Right kidney weight	0.8 ± 0.2	0.7 ± 0.3	0.9 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
Left kidney weight	0.7 ± 0.1	0.8 ±0.1	0.9 ± 0.1	0.9 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1
Right adrenal gland weight	0.6 ± 0.01	0.05 ± 0.01	0.04 ± 0.01	0.06 ± 0.02	0.04 ± 0.01	0.06 ± 0.01	0.06 ± 0.01
Left adrenal gland weight	0.06 ± 0.01	0.06 ± 0.02	0.06 ± 0.01	0.06 ± 0.03	0.04± 0.01	0.06 ± 0.01	0.06 ± 0.01

The mean values of various hematological parameters in male and female rats in different groups are illustrated in Table 3. No significant differences in the mean value of WBC, RBC, platelet count, PCV, MCV and MCH were detected between the groups. Furthermore, differential WBC count failed to express any significant differences between the groups.

Table 3. Mean±SD of hematology parameters in male and female Wistar rats after repeated exposure to 3 different original and 3 different fake perfumes for 90 consecutive days.

Sex	**Parameters**	**Groups (n=6)**						
		Control	Original perfumes			Fake perfumes		
			O1	O2	O3	F1	F2	F3
Males	WBC $\times 10^3/\mu l$	9 ± 1.4	8 ± 1	10 ± 3	9 ± 2	10 ± 2	9 ± 1	10 ± 0.5
	RBC $\times 10^6/\mu l$	10 ± 0.4	9 ± 0.3	9 ± 0.1	10 ± 0.7	9 ± 0.2	9 ± 0.4	10 ± 0.6
	Hemoglobin g/dl	16 ± 0.5	16 ± 0.6	16 ± 0.7	16 ± 0.9	16 ± 0.3	15 ± 0.7	15 ± 0.5
	Hematocrit %	49 ± 1.3	47 ± 1	46 ± 0.9	50 ± 3	45 ± 0.8	46 ± 2.4	44 ± 2
	MCV fl	51 ± 1.6	52 ± 0.8	53 ± 3	52 ± 2	52 ± 1.2	53 ± 1.7	51 ± 1.4
	MCH pg	17 ± 0.8	18 ± 0.5	18 ± 1	17 ± 0.6	17 ± 4	17 ± 18	16 ± 0.5
	Platelets $\times 10^3/\mu l$	663 ± 47	608 ± 49	726 ± 62	483 ± 75	857 ± 43	700 ± 133	583 ± 43
	Lymphocytes %	77 ± 3	78 ± 4	76 ± 4	75 ± 5.4	68 ± 3.5	70 ± 5.6	78 ± 5
	Neutrophils %	17 ± 3	16 ± 5	16 ± 4	18 ± 5.3	22 ± 5	20 ± 4	14 ± 5
	Eosinophils %	3 ± 1	2 ± 1.4	2 ± 2	3 ± 1.6	5.3 ± 2.5	2.7 ± 1.4	2 ± 1
	Basophils %	0.2 ± 0.4	0.0	0.0	0.0	0.0	0.0	0.0
	Monocytes %	3 ± 2	3 ± 1	6 ± 2	3 ± 3	4 ± 3	8 ± 3	5 ± 3
Females	WBC $\times 10^3/\mu l$	6.5 ± 1	6.3 ± 1	7 ± 1	7 ± 0.5	6 ± 1	9 ± 1	6 ± 2
	RBC $\times 10^6/\mu l$	8 ± 0.5	8 ± 1	8 ± 0.3	8 ± 0.3	8 ± 0.3	9 ± 0.5	8 ± 0.4
	Hemoglobin g/dl	16 ± 1	16± 1	15 ± 1	15 ± 0.4	15 ± 1	16 ± 0.1	16 ± 0.5
	Hematocrit %	45 ± 2	43 ± 4	44 ± 2	44 ± 1	42 ± 2	48 ± 3	44 ± 2
	MCV fl	56 ± 2	57 ± 2	55 ± 1	55 ± 2	56 ± 1	53 ± 1	54 ± 2
	MCH pg	20 ± 1	21 ± 3	19 ± 0.4	18 ± 3	20 ± 1	18 ± 1	19 ± 1
	Platelets $\times 10^3/\mu l$	715 ± 98	690 ± 166	670 ± 137	700 ± 57	781 ± 85	537 ± 141	684 ± 51
	Lymphocytes %	75 ± 4	75 ± 8	79 ± 4	74 ± 10	77 ± 7	71 ± 7	82 ± 3
	Neutrophils %	21 ± 5	21 ± 9	13 ± 3	18 ± 7	18 ± 6	23 ± 8	14 ± 2
	Eosinophils %	3 ± 2	2 ± 2	4 ± 2	3 ± 1	3 ± 2	1 ± 1	2 ± 2
	Basophils %	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Monocytes %	2 ± 1	3 ± 1	4 ± 1	6 ± 4	3 ± 1	5 ± 2	3 ± 2

The mean values of selected serum biochemical parameters in male and female rats are illustrated in Table 4 and Figure 1. No significant differences were detected between any of the examined parameters between different groups.

Table 4. Mean±SD of serum biochemistry parameters in male and female Wistar rats after repeated exposure to 3 different original and 3 different fake perfumes for 90 consecutive days.

Sex	Parameters	Groups (n=6)						
		Control	Original perfumes			Fake perfumes		
			O1	O2	O3	F1	F2	F3
Males	ALT IU/L	45 ± 13	41 ± 10	43 ± 8	63 ± 11	38 ± 8	66 ± 18	44 ± 12
	AST IU/L	124 ± 57	167 ± 81	163 ± 71	160 ± 41	142 ± 76	242 ± 82	129 ± 34
	Total protein g/dL	6.9 ± 0.5	6.8 ± 0.5	7 ± 0.8	6.5 ± 0.4	6.3 ± 0.5	6.3 ± 0.4	6.6 ± 0.9
	Albumin g/L	43 ± 7	42 ± 4	40 ± 7	43 ± 2.5	45 ± 7	40 ± 3	45 ± 5
	Creatinine mg/dL	0.6 ± 0.3	0.5 ± 0.2	0.4 ± 0.1	0.4 ± 0.1	0.5 ± 0.2	0.4 ± 0.1	0.5 ± 0.1
	Urea mg/dL	42 ± 8	46 ± 6	49 ± 7	53 ± 8	50 ± 9	46 ± 12	53 ± 9
	Glucose mg/dL	70 ± 17	79 ± 30	80 ± 13	73 ± 13	74 ± 27	96 ± 24	98 ± 34
Females	ALT IU/L	47 ± 8	34 ± 9	40 ± 11	61 ± 13	49 ± 17	58 ± 19	56 ± 14
	AST IU/L	156 ± 12	157 ± 56	141 ± 47	173 ± 48	207 ± 86	169 ± 88	208 ± 89
	Total protein g/dL	6 ± 1	7 ± 0.6	7 ± 0.7	7 ± 0.8	7 ± 0.9	7 ± 0.7	7 ± 0.5
	Albumin g/L	48 ± 4	43 ± 4	46 ± 7	41 ± 4	48 ± 6	41 ± 8	43 ± 3
	Creatinine mg/dL	0.4 ± 0.1	0.6 ± 0.2	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.5 ± 0.1	0.4 ± 0.1
	Urea mg/dL	44 ± 3	56 ± 9	50 ± 11	53 ± 5	51 ± 11	53 ± 4	53 ± 9
	Glucose mg/dL	96 ± 9	67 ± 8	75 ± 11	76 ± 17	96 ± 27	94 ± 22	69 ± 9

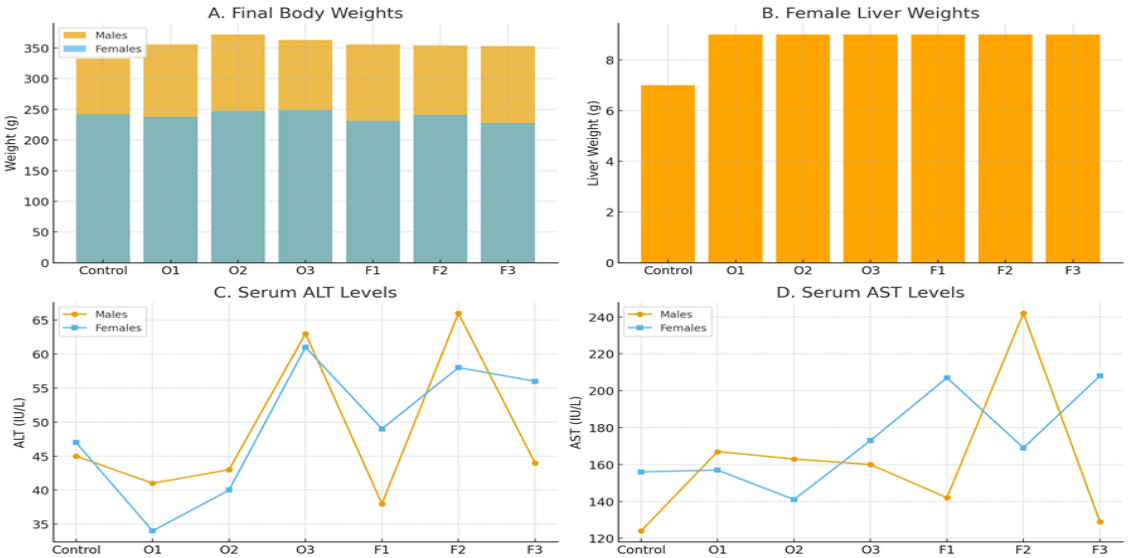

Figure 1. Effects of repeated exposure to perfumes on body weight and serum biochemistry in Wistar rats. (A) Final body weights of male and female rats after 90 days of exposure to original (O1–O3) and counterfeit (F1–F3) perfumes compared with controls. (B) Absolute liver weights in female rats. (C) Alanine aminotransferase (ALT) activity in male and female rats. (D) Aspartate aminotransferase (AST) activity in male and female rats. Values are means ± SD. No statistically significant differences were observed. Histologically, all examined tissues were within normal limits. No significant gross or histopathological alterations were found between different animal groups.

4. DISCUSSION

Most of the current knowledge regarding fragrance toxic effects has been compiled about inhalational exposure in an indoor setting. The potential harmful effects of inhaled fragrances on airway and cardiovascular health have been reported (Pistollato et al., 2021, Brunn et al. 2004, Chisvert et al. 2013). Yet, important concerns over potential toxic effects of perfumes especially fake ones after topical application on the skin are still exist today. Therefore, this study is the first to investigate potential systemic effects of perfumes after repeated exposure to the skin for an extended period of time.

Counterfeit perfume industry is growing worldwide on a fast pace due to huge increase in demands. Locally produced counterfeit perfumes are very common and affordable to most people. These perfumes are oil-based and mimic genuine perfumes in color, and smell. The chemical composition of these perfumes usually is not declared on the bottle. Therefore, exposure to unknown and may be harmful chemicals in counterfeit perfumes presents a serious risk public health. Despite its vast distribution, there are no regulatory guidelines that govern the quality and ensure safety of perfumes in Jordan. In addition, there are no studies that could be cited in recent literature that evaluated the safety and health risks associated with the repeated use of such perfumes in this region of the world. Therefore, this is the first study that was conducted to comprehensively investigate possible clinical and behavioral alterations associated with daily exposure to original and fake perfumes in a rat model.

Although in this study, the chemical components of the tested perfumes were not determined, most perfumes are known to contain several toxic substances (Brunn et al. 2004, Chisvert et al. 2013). Parabens which are widely used preservatives in many products such as cosmetics, shampoos, shaving gels and perfumes have received increasing concerns due to their adverse effects on human fertility and breast cancer development (Koch et al. 2003, Perez-Fernandez et al. 2013). Phthalates are a group of chemicals that are used in many products including perfumes. Phthalates are classified as endocrine disrupters and have been also shown to cause spermatogenic injury in young male rats, and were associated with insulin resistance in adults (Wang and Qian 2021). Linalool, oak moss absolutes, coumarin and furanocoumarin are considered important constituents of most perfumes are known to cause oxidative cell damage, hormonal imbalances, allergies, and carcinogenesis (Burr 2008, Saalu et al. 2009, Polańska et al. 2010, Akunna et al. 2011).

Unlike the results presented in this study, one study in Wistar rats has reported significant weight loss, and a significant decrease in liver weight, liver volume, and liver weight/body weight ratio after repeated exposure by inhalation to 2 different Nigerian made perfumes for 77 to 154 days (Akunna et al. 2011). Liver enzyme activities were also elevated in this Nigerian study, indicating substantial liver damage (Akunna et al. 2011).

In line with the current results, David et al. (2019) concluded that chemicals in perfumes are unlikely to cause adverse effects such as headaches or asthma attacks. The results obtained from other published questionnaire studies may be due to methodological weakness (David et al., 2019). Hananeh et al. (2021) reported that daily exposure to both original and fake perfumes in rats significantly increased mast cell counts in the liver and lungs, even in the absence of obvious pathological lesions. Their histopathological analysis, using specialized stains, revealed subtle tissue-level changes that provided valuable mechanistic insight (Hananenh et al., 2021). By comparison, studies that omit histopathological evaluation may present incomplete findings, as they risk missing such early or subclinical biological responses.

Differences in the results obtained in our study and those reported previously by others could be explained by differences in perfume components and their concentrations, variations in experimental, and laboratory procedures (Ashcroft et al. 2024).

Even though the current study showed that there are no adverse effects on the use of locally prepared counterfeit perfumes, it’s crucial to apply restricted monitoring procedures and apply analysis of counterfeit perfumes at the market to determine the presence and levels of hazardous compounds.

5. CONCLUSIONS

Although in this study, no harmful effects were detected in rats after repeated exposure to either original or fake perfumes, regulatory guidelines that protect consumers and mandate perfume makers to declare a list of components on their products must be established.

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Declaration of interest statement
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability
The data that support the findings of this study are available from the corresponding author upon request.

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