Safety Assessment of *Zanthoxylum piperitum*-derived Ingredients as Used in Cosmetics

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All interested persons are provided 60 days from the above release date (October 2,2022) to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available for review by any interested party, and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

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ABBREVIATIONS

AICIS	Australian Industrial Chemicals Introduction Scheme
CFR	Code of Federal Regulations
CIR	Cosmetic Ingredient Review
CPSC	Consumer Product Safety Commission
Council	Personal Care Products Council
Da	Daltons
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
DMSO	dimethyl sulfoxide
FDA	Food and Drug Administration
FEMA	Flavor and Extract Manufacturers Association
GRAS	generally recognized as safe
HRIPT	human repeated insult patch test
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide
MW	molecular weight
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
OECD	Organization for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
RIFM	Research Institute for Fragrance Materials
TG	test guideline
US	United States
VCRP	Voluntary Cosmetic Registration Program

INTRODUCTION

The safety of the following 4 *Zanthoxylum piperitum*-derived ingredients as used in cosmetics is reviewed in this safety assessment.

Zanthoxylum Piperitum Fruit Extract
Zanthoxylum Piperitum Oil
Zanthoxylum Piperitum Peel Extract
Zanthoxylum Piperitum Peel Water

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), collectively, the *Zanthoxylum piperitum*-derived ingredients are reported to function as skin conditioning agents, skin protectants, cosmetic biocides, cosmetic astringents, and fragrance ingredients in cosmetic products (See Table 1).[1] The Expert Panel for Cosmetic Ingredient Safety (Panel) routinely does not review ingredients that function only as fragrance ingredients, because, as fragrances, the evaluation of the safety of these ingredients is the purview of the Research Institute for Fragrance Materials (RIFM). Although Zanthoxylum Piperitum Oil is only reported to function as a fragrance ingredient in cosmetics, according to the *Dictionary*, the safety of this ingredient was neither previously nor currently the subject of review by RIFM; thus, it is included in this review.

These *Zanthoxylum piperitum*-derived ingredients may contain hundreds of constituents, some of which may have the potential to cause toxic effects. In this assessment, the Panel will review the potential toxicity of each of the *Zanthoxylum piperitum*-derived ingredients as a whole, complex mixture; toxicity from single components may not predict the potential toxicity of botanical ingredients.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. The published data in this document were identified by conducting an exhaustive search of the world's literature. A list of the search engines and websites that are used, and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is available on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data may be provided by the cosmetics industry, as well as by other interested parties and is included and summarized, where appropriate.

An assessment report on *Zanthoxylum piperitum* extract has been published by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS; now known as the Australian Industrial Chemicals Introduction Scheme (AICIS)).[2] Because the ingredient in that assessment is identified as *Zanthoxylum piperitum* extract, it is possible that the data could pertain to either Zanthoxylum Piperitum Fruit Extract or Zanthoxylum Piperitum Peel Extract; although, it is not clear which ingredient is being reviewed specifically, these data are included and may inform safety in this review. Please note that this source provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when this source is cited.

The names of the ingredients in this report are written in accordance with the INCI naming conventions, i.e., capitalized without italics or abbreviations. When referring to the genus and species from which the ingredients are derived, the standard taxonomic practice of using italics is followed (e.g., *Zanthoxylum piperitum*). It is often not known how the substance being tested in a study compares to the cosmetic ingredient. In the report text, if it is known that the material being tested is a cosmetic ingredient, the INCI naming convention will be used (e.g., Zanthoxylum Piperitum Fruit Extract). However, if it is not known that the test substance is the same as the cosmetic ingredient, the taxonomic naming conventions (e.g., a *Zanthoxylum piperitum* extract) will be used.

CHEMISTRY

Definition and Plant Identification

All of the *Zanthoxylum piperitum*-derived ingredients named in this assessment have the generic CAS No. 97404-53-0.[1] The definitions for the *Zanthoxylum piperitum*-derived ingredients are presented in Table 1.

Zanthoxylum piperitum (common names, Japanese pepper and Sichuan pepper)[1] is native to East Asia and prevalent in Japan.[3] It bears a tiny red fruit between August and September. The fruit includes the pericarp, which is a portion of the fruit that surrounds the seeds.

Chemical Properties

According to a submission to NICNAS, a *Zanthoxylum piperitum* extract has an average molecular weight (MW) of constituents equivalent to < 500 Daltons (Da) and a water solubility value of 5.69 mg/l - 1.56 g/l.[2] These and other properties are presented in Table 2.

Method of Manufacture

Method of manufacture data on the *Zanthoxylum piperitum*-derived cosmetic ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted. However, in the Composition and.

Impurities section that follows, some methods of manufacture are presented; how closely these methods are to cosmetic ingredient manufacture is unclear.

Composition/Impurities

The main pungent components of *Zanthoxylum piperitum* fruit are shanshool and shamshoolamide.[4] Not much is known about the constituents of Zanthoxylum seed.

Zanthoxylum piperitum extract

According to NICNAS, the degree of purity of a *Zanthoxylum piperitum* extract (supercritical carbon dioxide extract) is 100%, and it does not contain any additives/adjuvants.[2] The three constituents present at the highest concentrations in the *Zanthoxylum piperitum* extract tested are: linalyl acetate at 30-50% %, linalool at 10-20% and limonene at 5-10% , accounting for 56.13% (ranging from 45 - 80%) of the composition of the *Zanthoxylum piperitum* extract. Composition data on *Zanthoxylum piperitum* extract from the NICNAS report is included in Table 3.[2]

Zanthoxylum piperitum pericarp was also utilized to create an extract.[5] In this method, 420 g of pericarp was obtained, homogenized in methanol, and the 4.2 g of extract was obtained. The fractions that contained amides were further purified, which resulted in the amides that are shown in Table 4.

Zanthoxylum Piperitum Oil

Composition data on *Zanthoxylum piperitum* fruit oil are found in Table 5.[6] Data on the major components of *Zanthoxylum piperitum* oil (from whole plant) are found in Table 6.[7] Volatile components of *Zanthoxylum piperitum* oil include hydrocarbons and alcohols, primarily D-limonene (37.9%), sabinene (13.3%), and β-myrcene (7.17%).[7]

Zanthoxylum Piperitum Peel

In one experiment, analysis of volatile compounds from the skin of the mature fruit were ground with a mortar and pestle in liquid nitrogen, then extracted with 6ml methyl t-butyl ether (MTBE) at room temperature. After centrifugation, the extract was transferred into a new vial, and 200µg of methyl decanoate was added as an internal standard. The extract was then analyzed with GC-MS. The percent composition can be found in Table 7. [3]

The composition of a methanolic extract of *Zanthoxylum piperitum* peel was determined.[8] In this method, 440 g of the fruit peel was utilized to extract 50 g of methanol extract, which was subjected to column chromatography to get fractions 1 through 8. These fractions were then further purified by column chromatography to give the compounds shown in Table 7.

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics, and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

According to 2022 VCRP data, Zanthoxylum Piperitum Fruit Extract is reported to be used in 180 cosmetic products (Table 8).[9] Although this ingredient has the highest reported frequency of use for the ingredients in this group, and it is used in numerous product categories, the results of a concentration of use survey provided by the Council in 2021 only report concentration of use data for Zanthoxylum Piperitum Fruit Extract in one product category; according to the survey, it is used at a maximum use concentrations up to 0.01% in spray body and hand spray products.[10] Zanthoxylum Piperitum Peel Extract is the only other ingredient in this report that is reported to be in use; it is reported to be used in 12 formulations at maximum use concentrations up to 0.0022%. According to VCRP and Council survey data, 2 of the 4 ingredients, i.e., Zanthoxylum Piperitum Oil and Zanthoxylum Piperitum Peel Water, are not currently in use in cosmetic products (Table 9).

Cosmetic products containing *Zanthoxylum piperitum*-derived ingredients may incidentally come in contact with the eyes or mucous membranes (concentration data for these formulation-types not provided). It should be noted that Zanthoxylum Piperitum Fruit Extract is reported to be used in 1 baby product (use concentration not provided). Additionally, some of the ingredients are used in cosmetic sprays and powders, and could possibly be inhaled; for example, Zanthoxylum Piperitum Fruit Extract and Zanthoxylum Piperitum Peel Extract are reported to be used in products that are known to be sprayed (up to 0.01% in body and hand products and up to 0.0000018% in night products, respectively), and Zanthoxylum

Piperitum Peel Extract is reported to be used in face powders at a maximum use concentration of 0.0000022%. In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[11-13]

Although products containing some of these ingredients may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients (and without consumer habits and practices data or particle size data related to this use technology), the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

The *Zanthoxylum piperitum*-derived ingredients are not restricted from use in any way under the rules governing cosmetic products in the European Union.[14]

Non-Cosmetic

Zanthoxylum piperitum extract appears on the Flavor and Extract Manufacturers Association's (FEMA) list of flavoring ingredients that are classified as generally recognized as safe (GRAS), under the 1958 food additives amendment to the US Federal Food, Drug, and Cosmetics Act.[15]

As a result of its lemon-like aroma and pungent taste, Japanese pepper (Rutaceae, *Zanthoxylum piperitum*) is commonly used in Japanese dishes as a spice and for seasoning to mask unpleasant odors that arises from fish and meat ingredients.[3] Specifically, the fresh young leaves of the plant, as well as the fruit pericarp, are used as spices in Japanese cuisine.[4] According to another source, fruit peels and leaves of *Zanthoxylum piperitum* (Rutaceae) have been used in Japan for centuries as spices to preserve foods.[8]

Zanthoxylum piperitum is among the Korean medicinal plants (Korean salad plants), so named due to their content of purported bioactive compounds, mainly antioxidant phenolics.[16]

TOXICOKINETIC STUDIES

Dermal Penetration

Zanthoxylum piperitum extract

NICNAS noted that given the low molecular weight of the components of *Zanthoxylum piperitum* extract (supercritical carbon dioxide extract, < 500 Da), its water solubility (5.69 mg/l – 1.56 g/l), and a log P_{ow} of 2.9 – 4.4, there is potential for *Zanthoxylum piperitum* extract t(Da)o cross biological membranes.[2]

Absorption, Distribution, Metabolism, and Excretion

Zanthoxylum Piperitum Fruit Extract

The pharmacokinetics of a mixture containing *Zanthoxylum piperitum* fruit was studied using 16 subjects (fasted).[17] The mixture had the following composition: *Zanthoxylum piperitum* fruit, ginger, ginseng, and maltose. A randomized, open-label, three-arm, three-period protocol was used. The mixture was administered orally to each subject in doses of 2.5, 5, and 10 g. Blood samples were collected just before and at the following intervals after administration: 0.25, 0.5, 1, 2, 3, 4, 8, 12, 24, and 48 h. Plasma fractions were stored prior to analysis by high performance liquid chromatography. Of the 6 compounds measured, hydroxy-α-sanshool, a constituent of *Zanthoxylum piperitum* fruit, had the highest plasma concentration. The plasma concentration of hydroxy-α-sanshool reached the maximum concentration within 30 min after administration. Its median half-life was 1.6 to 1.7 h, indicating rapid absorption and elimination. The maximum concentration of hydroxy-α-sanshool in the plasma was 0.76 to 2.66 μM.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Data on the acute toxicity of *Zanthoxylum piperitum*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

Short-Term, Subchronic, and Chronic Toxicity Studies

Data on the short-term, subchronic, and chronic toxicity of *Zanthoxylum piperitum*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Data on the developmental and reproductive toxicity of *Zanthoxylum piperitum*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

GENOTOXICITY STUDIES

The genotoxicity studies summarized below are presented in Table 10.

In the Ames test (Organisation for Economic Co-operation and Development test guideline (OECD TG) 471), a *Zanthoxylum piperitum* extract (carbon dioxide, extract, in acetone) was evaluated using the following bacterial strains: *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100, and *Escherichia coli* strain WP2uvrA.[2] At concentrations up to 5000 µg/plate (with and without metabolic activation), results were negative. The genotoxicity of a *Zanthoxylum piperitum* extract (supercritical carbon dioxide extract, in dimethyl sulfoxide (DMSO)) in human lymphocytes was evaluated in the mammalian cell micronucleus test (OECD TG 487). The test concentrations were up to 640 µg/ml (without metabolic activation) and up to 320 µg/ml (with metabolic activation). Results indicated that the test substance was neither clastogenic nor aneugenic in the presence or absence of metabolic activation.

CARCINOGENICITY STUDIES

Data on the carcinogenicity of *Zanthoxylum piperitum*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

OTHER RELEVANT STUDIES

Cytotoxicity

Zanthoxylum piperitum extract

It is claimed that *Zanthoxylum piperitum* extract displays anti-cancer activity by inducing apoptosis in human cell lines. This activity was studied on human cancer cell lines (Calu-6 for human pulmonary carcinoma and SMU-601 for human gastric carcinoma) was measured using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay.[16] Serial dilutions of *Zanthoxylum piperitum* extract (dried methanol extract) were prepared by dissolving the extract in DMSO, followed by dilution with medium to yield the following final concentrations: 25, 50, 100, 200, 400, and 800 µg/ml. Optical density was recorded using a micro plate reader at 540 nm. Distilled water served as the positive control, and DMSO served as the solvent control. Controls and samples were assayed in duplicate for each concentration and replicated three times for each cell line. Cytotoxicity was obtained by comparing absorbance between the samples and the control. The values obtained were then used to calculate the concentration of *Zanthoxylum piperitum* extract required to cause a 50% reduction (IC_{50}, in µg/ml) in growth (cell number) for each cell line. In the Calu-6 cell line, the IC_{50} value for *Zanthoxylum piperitum* extract was 470.4 ± 13.1 µg/ml. In the SMU-601 cell line, the IC_{50} value for *Zanthoxylum piperitum* extract was 349.0 ± 9.1 µg/ml. Additionally, a dose-dependent inhibition of cell proliferation was observed in this study.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Sensitization

Human

Zanthoxylum piperitum extract

The skin sensitization potential of 2% *Zanthoxylum piperitum* extract (super critical carbon dioxide extract) in ethanol: diethyl phthalate (1:3 w/w) was evaluated in a human repeated insult patch test (HRIPT) involving 110 subjects.[2] Two different samples of the test substance were tested on each subject. During induction, the test substance (on a 3.62 cm^2 occlusive patch) was applied to the same location on the back of each subject 3 times per week for a total of 9 applications. Test sites were examined for dermal irritation at each visit prior to re-application of the test substance. Approximately 10 to 21 d after the final visit of the induction phase, the challenge phase was initiated. The test substance was applied for ~ 24 h to a new site on the back. Test sites were examined for signs of dermal irritation or sensitization. The test substance did not elicit skin irritation or sensitization during the challenge phase and was classified as a non-sensitizer.

OCULAR IRRITATION STUDIES

Data on the ocular irritation potential of the *Zanthoxylum piperitum*-derived ingredients reviewed in this safety assessment were neither found in the published literature, nor were these data submitted.

SUMMARY

The safety of the following 4 *Zanthoxylum piperitum*-derived ingredients as used in cosmetics is reviewed in this safety assessment: Zanthoxylum Piperitum Fruit Extract, Zanthoxylum Piperitum Oil, Zanthoxylum Piperitum Peel Extract, and

Zanthoxylum Piperitum Peel Water. According to the *Dictionary*, collectively, the *Zanthoxylum piperitum*-derived ingredients are reported to function as skin conditioning agents, skin protectants, cosmetic biocides, cosmetic astringents, and fragrance ingredients in cosmetic products.

Zanthoxylum piperitum (i.e., Japanese pepper; Rutaceae) is native to East Asia and prevalent in Japan. It bears a tiny red fruit between August and September. The available composition data indicate that *Zanthoxylum piperitum*-derived ingredients consist of numerous volatile aromatic and aliphatic hydrocarbons.

According to 2022 VCRP data, Zanthoxylum Piperitum Fruit Extract is reported to be used in 180 cosmetic products. The results of a concentration of use survey provided by the Council in 2021 only reported maximum use concentration data for Zanthoxylum Piperitum Fruit Extract in one product category (i.e., at up to 0.01% in body and hand spray products). Zanthoxylum Piperitum Peel Extract is the only other ingredient in this report for which use concentration data are being reported; this ingredient is being used at maximum use concentrations of up to 0.0022%.

Zanthoxylum piperitum extract appears on the FEMA list of flavoring ingredients that are classified as GRAS, under the 1958 food additives amendment to the US Federal Food, Drug, and Cosmetics Act.

NICNAS noted that given the low molecular weight of the components of *Zanthoxylum piperitum* extract (supercritical carbon dioxide extract, < 500 Da), its water solubility (5.69 mg/l - 1.56 g/l), and a log P_{ow} of 2.9 - 4.4, there is potential for *Zanthoxylum piperitum* extract to cross biological membranes.

The pharmacokinetics of a mixture containing *Zanthoxylum piperitum* fruit was studied using 16 subjects (fasted). The mixture was administered orally to each subject in doses up to 10 g. Hydroxy-α-sanshool, a constituent of *Zanthoxylum piperitum* fruit, had the highest plasma concentration (maximum concentration range: 0.76 to 2.66 μM). Its median half-life was 1.6 to 1.7 h, indicating rapid absorption and elimination.

A *Zanthoxylum piperitum* extract (supercritical carbon dioxide extract, in acetone) was not mutagenic in an Ames test when tested at concentrations of up to 5000 μg/plate, with or without metabolic activation. Results were also negative in an in vitro micronucleus test, whereby human lymphocytes were incubated with *Zanthoxylum piperitum* extract (supercritical carbon dioxide extract, in DMSO) at concentrations up to 640 μg/ml (without metabolic activation) and up to 320 μg/ml (with metabolic activation). Neither a statistically nor biologically significant increase in the number of micronucleated cells was observed, and the test substance was neither clastogenic nor aneugenic to human lymphocytes.

Apoptosis of *Zanthoxylum piperitum* extract in human cancer cell lines (Calu-6 for human pulmonary carcinoma and SMU-601 for human gastric carcinoma) was measured using the MTT assay to evaluate anti-cancer activity potential. The following concentrations (in DMSO) were tested: 25, 50, 100, 200, 400, and 800 μg/ml. In the Calu-6 cell line, the IC_{50} value for *Zanthoxylum piperitum* extract was 470.4 ± 13.1 μg/ml. In the SMU-601 cell line, the IC_{50} value for *Zanthoxylum piperitum extract* was 349.0 ± 9.1 μg/ml. Additionally, a dose-dependent inhibition of cell proliferation was observed.

The skin sensitization potential of 2% *Zanthoxylum piperitum* extract (supercritical carbon dioxide extract) in ethanol: diethyl phthalate (1:3 w/w) was evaluated in an HRIPT involving 110 subjects. During induction, the test substance (on a 3.62 cm^2 occlusive patch) was applied repeatedly to the back. At challenge, the test substance was applied for ~ 24 h to a new site on the back. The test substance induced neither skin irritation nor sensitization.

DATA SOUGHT

The CIR is seeking, at a minimum, the following information on all *Zanthoxylum piperitum*-derived ingredients as used in cosmetics:

- method of manufacture data
- composition and impurities data
- irritation and sensitization data, at maximum concentrations of use
- clarification as to the ingredient evaluated in the NICNAS assessment

TABLES

Table 1. Definitions and reported functions of the ingredients in this safety assessment.[1]

Ingredient/CAS No.	Definition & Structures	Function(s)
Zanthoxylum Piperitum Fruit Extract 97404-53-0 (generic)	Zanthoxylum Piperitum Fruit Extract is the extract of the fruit of *Zanthoxylum piperitum.*	Skin-Conditioning Agents - Miscellaneous
Zanthoxylum Piperitum Oil 97404-53-0 (generic)	Zanthoxylum Piperitum Oil is the oil obtained from the fruit and fruit pericarp of *Zanthoxylum piperitum*.	Fragrance Ingredients
Zanthoxylum Piperitum Peel Extract 97404-53-0 (generic)	Zanthoxylum Piperitum Peel Extract is the extract of the peels of *Zanthoxylum piperitum*.	Cosmetic Biocides
Zanthoxylum Piperitum Peel Water 97404-53-0 (generic)	Zanthoxylum Piperitum Peel Water is the aqueous solution of the steam distillate obtained from the peel of *Zanthoxylum piperitum*.	Cosmetic Astringents; Fragrance Ingredients; Skin Protectants; Skin-Conditioning Agents - Miscellaneous

Table 2. Chemical properties of a *Zanthoxylum piperitum* extract[2]

Property	Value
Physical Form (@ 20ºC and 101.3 kPa)	liquid
Molecular weight (Da; average of constituents)	< 500
Density (g/ml)	0.8984 – 0.9284
Water solubility (g/l) (estimated)	0.00569 – 1.56
Partition coefficient (log P_{ow}) (estimated)	2.9 – 3.9 (aliphatic terpene constituents); 4.2 - 4.4 (aliphatic cyclic constituents)
Vapor pressure (kPa, @ 24 °C)	0.0249
Melting point (°C)	< -20 – 156 (based on primary constituents)
Boiling point (°C)	176 – 421 (based on primary constituents)
Flash point (ºC, @ 101.3 kPa	39

Table 3. Composition data on a *Zanthoxylum piperitum* extract[2]

***Zanthoxylum piperitum* extract (supercritical carbon dioxide extract)**	
Constituents	***Percent composition***
linalyl acetate	30 - 50
linalool	10 - 20
limonene	5 - 10
3-cyclohexene-1-methanol, α, α,4-trimethyl-, 1-acetate	1 - 5
bicyclo [3.1.0] hexan-2-ol, 2-methyl-5-(1- methylethyl)-, 2-acetate; bicyclo [3.1.0]hexan-2-ol, 2-methyl-5-(1- methylethyl)-, 2- acetate, (1*R*,2*S*,5*S*)- *rel*-	5 - 15
2,6,8,10-dodecatetraenamide, *N*-(2-hydroxy-2- methyl propyl)-, (2*E*,6*E*,8*E*,10*E*)-	1 - 10

Table 4. Composition data on *Zanthoxylum piperitum* fruit pericarp[5]

***Zanthoxylum piperitum* fruit (fruit pericarp ethyl acetate extract)**		
Constituents	**Quantity (mg)**	**% composition***
(6RS) -(2E,7E,9E)-6-hydroxy-*N*-(2-hydroxy-2-methylpropyl)-11-oxo-2,7,9-dodecatrienamide	5.4	0.13%
(11RS)- (2E,7E,9E)-11-hydroxy-*N*-(2-hydroxy-2-methyl-propyl)-6-oxo-2,7,9-dodecatrienamide	4.8	0.11%
(10RS,11SR)-dihydroxy-*N*-(2-hydroxy-2-methylpropyl)-2,6,8-dodecatrienamide	10.1	0.24%
(10RS,11RS) -(2E,6Z,8E)- dihydroxy-*N*-(2-hydroxy-2-methylpropyl)-2,6,8-dodecatrienamide	4	0.10%
(6RS,11SR)-6,11-dihydroxy-*N*-(2-hydroxy-2-methylpropyl)-2,7,9-dodecatrienamide)	17.2	0.41%
(6RS,11RS) -(2E,7E,9E)-6,11-dihydroxy-*N*-(2-hydroxy-2-methylpropyl)-2,7,9-dodecatrienamide)	9.5	0.23%

* percent composition calculated from 4.2 grams of extract

Table 5. Composition data on a *Zanthoxylum piperitum* fruit oil[6]

	Ripe Fruit	**Dried Pericarp**
Constituents	**Relative Content***	**Relative Content***
Hydrocarbons		
aromadendrene	0.01	-
2-carene	0.01	trace
β-caryophyllene	0.23	0.08
α-copaene	-	trace
β-cubebene	0.02	0.01

Table 5. Composition data on a *Zanthoxylum piperitum* fruit oil[6]

	Ripe Fruit	Dried Pericarp
Constituents	**Relative Content***	**Relative Content***
p-cymene	trace	trace
decane	0.01	trace
β-elemene	0.02	0.01
p-ethyltoluene	0.01	trace
(*E, E*)-α-farnesene	-	0.03
germacrene D	0.23	0.12
α-humulene	0.06	0.01
isomer of farnesene	-	0.01
D-limonene	6.04	5.55
(E)-β-ocimene	0.01	0.01
p-mentha-1,4,8-triene	0.02	0.01
4-methyldecane	-	-
myrcene	0.92	0.83
(Z)-β-ocimene	0.02	trace
(*E*)-β-ocimene	0.01	0.01
β-phellandrene	3.64	3.35
α-pinene	0.02	0.01
β-pinene	0.01	0.01
sabinene	0.03	0.03
α-selinene	0.02	-
β-selinene	0.01	-
α-terpinene	trace	trace
γ-terpinene	-	trace
terpinolene	-	trace
toluene	0.01	-
undecane	0.08	0.01
Alcohols		
8-acetoxylinalool	0.06	0.06
benzyl alcohol	-	trace
bisabolol	0.10	0.12
δ-cadinol	trace	0.11
(*E*)-carveol	0.01	0.01
(*Z*)-carveol	0.01	0.01
citronellol	0.28	0.05
3,7-dimethyl-1,5-octadiene-3,7-diol	0.01	0.01
elemol	0.11	0.03
endo-1-bourbonanol	0.05	0.03
β-eudesmol	0.02	0.01
geraniol	5.81	1.67
(Z)-3-hexenol	-	trace
1-hydroxylinallol	0.06	0.06
isopulegol	0.05	0.05
ledol	0.01	trace
linalool	0.44	0.15
p-mentha-(E)-2,8(9)-dienol	-	0.01
4-(1-methylethyl) benzenemethanol	0.04	0.01
1-methyl-4-(1-methylethyl) 2-cyclohexen-1-ol	0.12	0.05
2-methylpropanol	-	trace
myrtenol	0.02	0.01
piperitol	0.04	0.01
1,2-propanediol	-	0.34
spathulenol	0.03	0.01
terpinen-4-ol	0.03	0.01
1-terpineol	0.06	0.03
α-terpineol	0.01	0.05
δ-terpineol	0.03	0.01
Aldehydes		
citronellal	8.55	1.36
4-ethylbenzaldehyde	-	-
geranial	1.79	0.06
(*E,E*)-2,4-hexadienal	0.01	trace
neral	0.31	0.04
Esters		
cinnamyl acetate	0.02	0.01
citronellyl acetate	0.11	0.07
ethyl hexanoate	0.01	-
geranyl acetate	21.10	3.33
geranyl butyrate	0.03	0.02
isobutyl hexanoate	0.09	0.02

Table 5. Composition data on a *Zanthoxylum piperitum* fruit oil[6]

	Ripe Fruit	Dried Pericarp
Constituents	**Relative Content***	**Relative Content***
linalyl acetate	0.33	0.33
methyl benzoate	0.01	-
methyl cinnamate	0.56	0.16
methyl hexanoate	0.01	-
neryl acetate	0.02	-
α-terpinenyl acetate	0.12	0.12
Ketones		
cryptone		0.06
1-(3,4-dimethylphenyl) ethanone	0.03	Trace
isomer of ethylacetophenone	0.03	0.01
piperitone	0.31	0.08
valeranone	0.04	0.03
Acids		
acetic acid	0.02	Trace
heptanoic acid	0.01	0.01
hexanoic acid		0.02
3-hexenoic acid	0.04	0.01
octanoic acid	0.01	0.01
Others		
caryophyllene oxide	0.02	0.01
1,8-cineole	0.15	-
2,5-dihydro-3-methyl furan	0.02	Trace

* = Relative content; average values are calculated by comparing the peak area of each compound with that of the internal standard, which is assigned the numerical value of 1, *n* = 3
- Quantity unlisted

Table 6. Composition data on a *Zanthoxylum piperitum* whole plant oil[7]

Constituents	***Percent composition***
citronellal	7.1
citronellyl acetate	-
cryptone	8.5
cuminal	6.2
geranyl acetate	15.3
limonene	18.0
linalool	-
β-myrcene	-
phellandral	5.2
β-phellandrene	-

Table 7. Composition data on *Zanthoxylum piperitum* peel extract [3,8]

***Zanthoxylum piperitum* fruit peel extract (methyl *t*-butyl ether extract) [3]**	
Constituents	**Percent composition**
β-caryophyllene	1.1%
citronellal	1.9%
D-limonene	44.3%
β-phellandrene	24.8%
volatile terpenes	0.012 (fresh weight)
***Zanthoxylum piperitum* fruit peel extract (methanol extract) [8]**	
Constituents	**Quantity (mg)**
3-*O*-caffeoylquinic acid	24.6
4-*O*-caffeoylquinic acid	8.3
(+)-catechin	10.1
(-)-epicatechin	27.8
procyanidin B1	14.2
procyanidin B2	24.7
procyanidin B4	17.6
hyperin	27.2
quercitrin	3.7
proanthocyanidin	2.10

Table 8. Frequency (2022) and maximum concentrations of use (2021) according to duration and exposure[9,10]

	Zanthoxylum Piperitum Fruit Extract		Zanthoxylum Piperitum Peel Extract	
	# of Uses	**Max. Conc. of Use (%)**	**# of Uses**	**Max. Conc. of Use (%)**
Totals*	**180**	**0.01**	**12**	**0.0000018-0.0022**
Duration of Use				
Leave-On	*157*	*0.01*	*6*	*0.0000018-0.0022*
Rinse off	*23*	*NR*	*6*	*0.0022*
Diluted for (bath) Use	*NR*	*NR*	*NR*	*NR*
Exposure Type				
Eye Area	4	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation - Sprays	77[a];58[b]	0.01	3 [a]	0.0000018
Incidental Inhalation - Powders	58[b]	NR	NR	0.0000022; 0.0022[c]
Dermal Contact	172	0.01	9	0.0000018-0.0022
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	6	NR	3	NR
Hair-Coloring	NR	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	5	NR	1	NR
Baby Products	1	NR	NR	NR

* Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a]It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays
[b]Not specified that these products are sprays or powders, but it is possible the use can be as a spray or powder, therefore the information is captured in both categories
[c]It is possible that these products may be powders, but it is not specified whether the reported uses are powders

Table 9. *Zanthoxylum piperitum*-derived ingredients with no reported uses[9,10]

Zanthoxylum Piperitum Oil
Zanthoxylum Piperitum Peel Water

Table 10. Genotoxicity studies[2]

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results
IN VITRO					
Zanthoxylum piperitum extract (carbon dioxide extract)	0, 1.5, 5, 15, 50, 150, 500, 1500 and 5000 µg/plate	acetone	*S. typhimurium* strains TA1535, TA1537, TA98, and TA100, and *E. coli* strain WP2uvrA (tests 1 and 2). *S. typhimurium* strains TA100 and TA1537 (test 3)	Doses with and without metabolic activation (tests 1 and 2). Doses without metabolic activation (test 3). Positive controls with metabolic activation: 2-aminoanthracene and benzo[a]pyrene. Positive controls without metabolic activation: 9-aminoacridine and 4-nitroquinoline-1-oxide	No biologically relevant increases in frequency of revertant colonies for any bacterial strain, either with or without metabolic activation. Two instances of slight increase in revertants (in different tests). These findings not dose-related and were not considered biologically relevant because they were within the range of historical negative controls. Test substance classified as non-genotoxic
Zanthoxylum piperitum extract (carbon dioxide extract)	Concentrations up to 260 µg/ml and up to 640 µg/ml (without metabolic activation). Concentrations up to 320 µg/ml (with metabolic activation)	DMSO	Human lymphocytes	Mammalian cell micronucleus test (OECD TG 487).	Inhibition of the cytokinesis block proliferation index at all test conditions. No statistically- or biologically significant increase in number of micronucleated cells with or without metabolic activation. Negative and positive controls performed as expected. Test substance not clastogenic or aneugenic to human lymphocytes

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