COSMETIC PRODUCT SAFETY ASSESSMENT

HEMERA NAIL POLISH

Customer Reference:

Part B: Cosmetic Product Safety Assessment

CONFIDENTIAL

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Cosmetic Product Safety Assessment

Hemera Nail Polish

Customer Reference:

Product Information

A product to be used by adults intended to be applied on nail plates (client information). Predominant exposure would be to the nails and cuticle. Exposure to the skin, although not intended –may sometimes be inevitable in normal and reasonably foreseeable conditions of use. Due to nature of the product, exposure to the eyes, inhalation and ingestion is unlikely.

Formulation

See Appendix One for product formulation data

Assessment Conclusion

This cosmetic product is considered as safe under normal and reasonable foreseeable conditions of use. The ingredients are legally permitted as per Cosmetic Regulation (EC) No 1223/2009 and its amendments and the safety assessment has been carried out in accordance to Article 3 of this regulation. They must comply with the relevant purity standards for cosmetic ingredients. It is assumed that these ingredients do not contain any undisclosed impurities/contaminants that would affect the conclusions reached. The product must be manufactured in accordance with EU Guidance on Good Manufacturing Practice.

Under normal or reasonably foreseeable conditions of use, a product made to this formulation is unlikely to produce an abnormally high number of adverse reactions. The product will give users the level of safety they can reasonably expect when used as directed.

The toxicological data available on the individual substances and the end product, including all chemical and/or biological interactions and human exposure via intended and likely routes have been taken into account in this assessment. Whenever a NO(A)EL value is available for a specific substance, its Margin of Safety (MoS) has been calculated and taken into account. Where applicable, relevant systemic and local toxicity end points of the chemicals ingredients in this formulation have been considered as part of this risk assessment.

Labelling Warnings and instructions for use

Warnings

Use in a well-ventilated area; Do not inhale directly.
Avoid contact with eyes; Rinse eyes immediately if product comes into contact with them.
Keep away from heat or flame.
Keep out of reach of children.

Instructions of Use

As per manufacturer's instructions.

Fragrance Allergen Labelling

THERE ARE NO ALLERGENS WHICH ARE REQUIRED TO BE DECLARED ON THE PRODUCT LABEL AS PER ANNEX III TO COSMETIC REGULATION (EC) NO 1223/2009.

Reasoning

Product Toxicity Review

If used as directed, use of this product formulation should be uneventful in the majority of the general population.

Effects of the product as provided on the skin

The formulation as supplied may cause slight skin irritation especially if exposure is prolonged and/or repeated. However, under normal conditions of use, the likelihood of causing skin irritancy will be very low.

Repeated exposure to the formulation as supplied is unlikely to produce allergy by skin contact.

Exposure to this product is unlikely to result in phototoxic effects.

Unlikely to cause damage to internal organs following the skin contact.

Effects of the product as provided on the eye

Eye contact is unlikely to occur during normal use.

Accidental exposure of the eye to the formulation as supplied may result in eye irritation.

Effects following ingestion of the product as provided

Ingestion is an unlikely route of exposure.

The formulation as supplied if swallowed is likely to cause irritation to the mouth and upper digestive tract.

Effects following inhaling of the product as provided

Prolonged inhalation of high concentrations may induce drowsiness, headache, loss of coordination and narcosis. In severe over exposure this may lead to coma and death. Also inhalation may cause irritation of the nose and upper respiratory tract.

Ingredient Toxicity Review

Most of the ingredients are widely used and have history of safe use in humans. Butyl Acetate is non-mutagenic, mild irritant to eyes, mild skin irritant but not sensitizer to humans. It has been reviewed by CIR expert panel and considered safe for use in cosmetics at the level used in this nail care product. Similarly, Ethyl acetate is the ester of ethyl alcohol and acetic acid. It has been approved by US FDA as Generally recognised as safe (GRAS), a color additive exempt from certification, secondary direct food additive and indirect food additive. It is relatively nontoxic when administered through various routes of administration. It can cause eye irritation, has low potential for skin irritation and is a non skin sensitiser. It has been reviewed by CIR expert panel and considered safe for use in cosmetics at the level used in this nail care product. Both butyl acetate and ethyl acetate may induce drowsiness or dizziness if exposed to significant amounts. Due to this inherent risk, it is recommended that the product should be used in well ventilated areas. Therefore, following labelling is recommended: *Use in a well-ventilated area; Do not inhale directly.* Also since these two ingredients are highly flammable substances following labelling is also recommended: *Keep away from heat or flame.*

Nitrocellulose is a cellulose derivative. It has been approved by US FDA as indirect food additive. It is not acutely toxic by oral administration. It is not a skin and eye irritant, a sensitizer, mutagen, carcinogen or reproductive/developmental toxicant. It has also been evaluated by CIR expert panel and concluded to be safe at the level used in this formulation. Isopropyl Alcohol is widely used in cosmetics. It is not skin irritant or skin sensitizer. It may cause serious eye irritation. Therefore, following warning is recommended: *Avoid contact with eyes; Rinse eyes immediately if product comes into contact with them*. CNS depression and behavioural effects have been documented in humans for isopropyl alcohol at relatively high concentrations unlikely to result from cosmetic product exposure. It has been reviewed by CIR expert panel and considered safe for use in cosmetics at the level used in this formulation.

As a leave-on product, repeated and long-term exposure is expected albeit limited systemic exposure is anticipated. Due to nature and/or the expected exposure levels of the ingredients, the formulation is expected to be of low systemic toxicity. Therefore, significant systemic toxicity is not expected in the short, medium or long term with repeated exposure to the product under normal and reasonably foreseeable use. Where adequate data is available, a Margin of Safety (MoS) has been calculated to be > 100, thus supporting the safety of the ingredient as formulated in this product.

Overall, taking into account the intended application, frequency of exposure and, the toxicological profiles of the individual ingredients as well as the supplier ensuring that the ingredients are of high purity, the product is not expected to cause damage to human health in the short, medium or long term under normal and reasonably foreseeable conditions. Although it cannot be totally discounted that a few susceptible individuals may experience allergic or other idiosyncratic reaction with the product particularly if already sensitised to one of the ingredients.

Margin of Safety Review

Where a NOAEL is available for a chemical ingredient that is considered as a toxicological concern, the Margin of Safety (MoS) has been calculated as greater than 100 taking into consideration any known data on dermal absorption and bioavailability. It is generally accepted that the MoS should be a least 100 to declare a substance safe for use in a finished product and the safety of this formulation is further supported by this uncertainty factor.

See Appendix One for a toxicological review of the formulation ingredients

Exposure Scenario

Product Class: Nail and cuticle products	**IFRA Category:** Category 8
Product Subclasses: Nail varnish and remover products, Nail varnish / Nail make-up,	**Product Group:** NAIL VARNISH
Product Group: Cosmetic	**Part of body exposed to undiluted**: Apply on nails
Product Name: Hemera Nail Polish	
Targeted Population: Adult	
Amount per application (g): 0.3	**Number of applications per day**: 2-3 times per week
Physical Form: Liquid	**Total Amount applied per day (g)**: 0.05
Skin Surface Area of Application (cm²): 4	**Amount per Unit Area of Skin per day (mg/cm²/day)**: 12.5
	Estimated Daily Exposure (mg/kg/day): 0.833
Exposure Time Neat: 3360 min, 156 x / year	**Retention Factor**: 1
Exposure Time Dilute: Not Applicable	
Exposure Time Solvent Inhalation: Inhalation - 5mins. Inhalation rate: 23.1 litres/min	**Exposure Time Aerosol Inhalation**: Not Applicable

Fragrance Composition

This formulation does not contain a synthetic fragrance and therefore a fragrance safety evaluation as per IFRA code of practice is not applicable to this product.

Microbiological Quality

Microbiological specifications:

To comply with the EN ISO 17516:2014 standard for Cosmetics — Microbiology — Microbiological limits, the following maximum limits apply:

Category 2: Other cosmetic products.
Total Aerobic Mesophilic Microorganisms (Bacteria plus yeast and mould): ≤ 1000 cfu/g or 1000 cfu/ml of the product. Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Candida albicans must not be detectable in 1 g or 1 ml of the cosmetic product.

The microbiological specifications for the product have been supplied and based upon the conclusions therein, meet the minimum industry requirements specified in European Standard EN ISO 17516:2014 Cosmetics – Microbiology – Microbiological limits for cosmetic products.

Ref.: MICROBIOLOGY QUALITY ANALYSIS TEST REPORT, Hemera Nail Polish, Date: 25 February 2019,
Microbial Limits Test Report, Hemera Nail Polish, Date: 19-Feb-19

Preservative challenge test:

The efficacy of the preservation of a cosmetic product has to be assessed experimentally in order to ensure microbial stability and preservation during storage and use.

The preservative efficacy test results for this product have been supplied and based upon the conclusions made therein appear to meet the industry standard requirements specified in ISO 11930:2012 (E), Cosmetics — Microbiology — Evaluation of the antimicrobial protection of a cosmetic product.

Ref.:TEST REPORT Preservative Efficacy (Challenge) Test –ISO 11930:2012, Hemera Nail Polish, Date: 02/04/2019
PRESERVATIVE EFFICACY (CHALLENGE) TEST REPORT ISO 11930:2012, Hemera Nail Polish, Date: 10 April 2019

Property	Method	Specification
Aerobic Mesophilic Bacteria		<10 CFU/g
Yeast and Mold		<10 CFU/g
Pseudomonas aeruginosa, Candida albicans, Escherichia coli, Staphylococcus aureus,		Absent

Product Stability

The physical stability of the finished product should be established, ensuring that no changes in its physical state

occur during transport, storage or handling of the product. To make sure that no stability problems are induced by the type of container and packaging used, physical stability tests should be carried out with inert containers and those intended to be used on the market.

It is assumed that the responsible person has selected all pertinent criteria required to evaluate the stability of this cosmetic product during reasonable foreseeable conditions of storage.

The stability report has been provided by the supplier and based upon the conclusions made therein, this cosmetic product appears to be stable under reasonably foreseeable storage conditions.

Ref.: Cosmetic Stability Report, Hemera Gel Lacquer, Date: 04/06/2019,
TEST REPORT – Period After Opening PAO ISO 11930 Test at end of Shelf Life, Hemera Nail Polish, Date: 04/06/2019,
Stability Test Report, Hemera Nail Polish, Date: 06/06/2019

Packaging Material Information

It is assumed that the responsible person has identified the most applicable testing required to determine the packaging stability and its interaction with the cosmetic product contained within it. Taking into consideration the information supplied to the assessor, there appears to be no immediate health concern due to the grade and characteristics of packaging materials in direct contact with the final product.

Impurities/Traces/Prohibited Substances

Where the specification is provided it is noted that this product does not contain any impurities at levels likely to cause harm to the user. The purity specification of the raw material ingredients have been reviewed where they have been provided by the supplier at the time of assessment. It is found that the raw materials do not contain any prohibited ingredients listed in Annex II to Regulation (EC) No 1223/2009 at concentration likely to cause harm to the user when used as directed under normal and reasonably foreseeable conditions of use.

As per the test conducted for impurities present in the product, benzene, toluene, methanol, formaldehyde and phthalates were not detected.

Ref.: Test Report No: SHCPCH170402074E, Date: Jan. 08 2019

Presence of Nanomaterials

In accordance to Cosmetic Regulation (EC) No 1223/2009, a nanomaterial is an insoluble or biopersistant and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm.

The supplier has confirmed that this cosmetic product does not contain any nanomaterials that are known to them with the meaning of the definition as stated in Cosmetic Regulation (EC) No 1223/2009.

Serious/Undesirable effects

The following data of the serious undesirable effects and/or undesirable effects have been supplied at the time of assessment and these are detailed below.

The manufacturer has clarified that this product has been introduced into the market recently. Therefore, there is no known undesirable effect and/or serious undesirable effect data.

Ref.: Clarification statement, Date: 21 March 2019.

Specific Use Considerations

N/A

Assessor's Credentials and Approval of Part B

This product was evaluated by N. KACHHELA who is qualified by education, training and experience to evaluate the safety of cosmetic product formulations.

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N. KACHHELA,M.S. Pharm (Pharmacology & Toxicology)
Intertek Health, Environmental & Regulatory Services (HERS)

Date: August 16, 2019

This product was reviewed by D. SANCHEZ CARVAJAL who is qualified by education, training and experience to evaluate the safety of cosmetic product formulations.

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D. SANCHEZ CARVAJAL, BSc (Veterinary), MSc (Toxicology)
Intertek Health, Environmental & Regulatory Services (HERS)

Date: August 16, 2019

Appendix One: Product Formulation Data and Toxicological Review of Ingredients

Formulation

The chemical names shown below refer to the raw materials used to formulate this product. The identity of the raw materials may be based on alternative nomenclature such as IUPAC name, Chemical name, INCI name or generic trade name. Furthermore, there may be instances where several CAS number exist for the same chemical ingredient. Where this has occurred, the most appropriate substitute will have been used where one has not been provided.

INCI Name	% Concentration	% Active	Activity in Product	CAS No	Chemical Name
BUTYL ACETATE	50	100	50	123-86-4	N-BUTYL ACETATE
ETHYL ACETATE	25	100	25	141-78-6	ETHYL ACETATE
NITROCELLULOSE	15	100	15	9004-70-0	NITROCELLULOSE, 1,4-DI(PHENYL)-1,2,4-TRIAZOL-4-IUM-3-YL]-PHENYLAZANIDE
ISOPROPYL ALCOHOL	10	100	10	67-63-0	ISOPROPYL ALCOHOL, METHYLETHANOL

Toxicological Review of Ingredients

Chemical Name: N-Butyl acetate			
Function: Butyl Acetate isused as solvents innail polish, nail polish removers, basecoats, and other manicuringpreparations (CIR Compendium 2012).			
Regulatory Status (Toxicological Risk Assessment Report):			
Exposure	**NOAEL**	**Safety Factors**	**MoS**
DERMAL	259 mg/kg	0	MoS For Adult: 621.6

Summary Data:

Cosmetic Functions : Masking / Solvent for nail care preparations, nail varnishes and removers. A strong smelling solvent with distinct narcotic properties. Primary routes of exposure to n-Butyl Acetate are by inhalation, ingestion, through skin and eye contact. The intensity of its odour will help minimise exposure to the vapour. Prolonged or repeated contact with the skin may cause degreasing leading to dermatitis in sensitive individuals. Chronic exposure to vapours (that is, repeated or prolonged) may cause conjunctivitis with a concentration of 200 - 400 ppm causing eye irritation and injury that have persisted for several days (MSDS information, March 2008). Ethyl and Butyl Acetate were relatively nontoxic when administered orally, dermally or by inhalation to rabbits, rats, mice and guinea pigs. Moderate to severe irritant in unrinsed rabbit eyes and a mild irritant in rinsed rabbit eyes at 25%. Butyl Acetate was not a sensitizer in either mice or guinea pigs but was a mild skin irritants but not sensitizers to humans. Nonmutagenic when tested by the Ames procedure, did not induce mitotic aneuploidy in yeast and chromosomal aberrations in Chinese hamster fibroblasts. Butyl Acetate was not teratogenic when inhaled. (CIR Compendium 2009).
Repeated exposure of rats for 90-days at dose concentrations of 0, 750, 1500 and 3000 ppm, no adverse effects were observed at dose concentration up to 750 ppm. NOAEC is determined as 750 ppm (REACH Dossier, 2013).

Chemical Name: Ethyl Acetate			
Function:ETHYL ACETATE is used us perfuming, solvent in cosmetic products (Coslng, 2013)			
Regulatory Status (Toxicological Risk Assessment Report):			
Exposure	**NOAEL**	**Safety Factors**	**MoS**
ORAL	900 mg/kg bw/day	Not reported	MoS For Adult: 4320

Summary Data:

Cosmetic Functions: Perfuming / Solvent. A strongly smelling solvent which will defat the skin which as supplied is classified as highly flammable (R11) according to the EU Directive 67/548/EEC. Prolonged and/or excessive exposure to the vapour may cause drowsiness and narcosis. The ester of ethyl alcohol and acetic acid. A liquid material used in fragrances and flavour mixtures, FEMA number 2414 and CoE number 191. Ethyl acetate is approved for use as synthetic flavoring substances and adjuvants as direct food additive (CFR 21, 182.60). The permissible dietary exposure for ethyl acetate is 117 mg/day taking 2000 ppm as NOEL from 13-week inhalation exposure study. Recommended use is at up to 10% in the fragrance concentrate and at up to 1400 ppm in the flavour. At a low concentration in a cosmetic product, it is not expected to produce adverse health effects. The oral LD50 of rat and rabbit were 5600 and 4940 mg/kg bw/d respectively. The LC50 of rat exposed for 6 hours and mouse exposed for 2 hours is 58 and 44 mg/L respectively. The dermal LD50 of rabbit is >1800 mg/kg bw. The subcutaneous LD50 in guinea pigs is 3000mg/kg

bw. Ethyl acetate is irritant to mucous membrance. At high concentrations, it may be a CNS depressant. Pulmonary edema, seizures, hepatic damage, decreased cardiac contractility were observed in animals exposed with ethyl acetate. Ames, micronucleus and chromosomal aberrations in Chinese hamster ovary cells showed negative results. Although few chromosomal aberration studies at 9 mg/mL and sister chromatid exchange assay in CHO cells at 4.02 mg/mL showed positive results, ethyl acetate is concluded to be non genotoxic. Repeated inhalation toxicity study in rats for 90-days at dose concentrations of 0.002, 0.01 and 0.043 mg/L showed reduced body weight, decreased cholinesterase activity, pathologic changes in liver, cerebral cortex, thyroid and adrenal glands at mid and high doses. The NOAEL was determined to be 0.002 mg/L. Repeated oral 90-day study through gavage at a dose concentrations of 30, 900 and 3600 mg/kg bw/day showed decreased body weight, food consumption and organ weights at high dose. The oral NOAEL was determined to be 900 mg/kg bw.

The ingredient is not acutely toxic via oral, dermal and inhalation, a skin irritatant, an eye irritatant, a skin sensitizer, mutagenicity/genotoxicity carcinogenic, a reproductive toxicant. Low bioaccumulative potential.No data about the phototoxic. Based on this information and other scientific literature on this ingredient, safety concerns are not expected with this ingredient for use in cosmetics when formulated to be non-irritating.

Chemical Name: Nitrocellulose, 1,4-di(phenyl)-1,2,4-triazol-4-ium-3-yl]-phenylazanide

Function: Widely used in nail polish. Functions in cosmetics as a dispersing agent – non-surfactant and as a film former. Used in the manufacture of paper and paperboard products used in food packaging, centrifuge tubes, membranes used in protein blotting, coating slides for embedding media, a binder in printing inks and wood coatings. Used in propellants, smokeless powder, rocket fuel, ball powder, mortar increment and some explosives (These uses are likely related to polymers with a higher degree of nitration than those used in cosmetics) (CIR, 2013).

Regulatory Status (Toxicological Risk Assessment Report):

Exposure	NOAEL	Safety Factors	MoS
ORAL	4500 mg/kg bw/day	not reported	MoS For Adult: 36000

Summary Data:

Cosmetic Functions : Film Forming / Suspending Agent-Nonsurfactant. Nitrocellulose is also described as Cellulose, nitrate or known as (CosIng, April 2013). Nitrocellulose a highly flammable compound is formed by reacting nitric acid with cellulose itself has low toxicity and is not a skin and eye irritant, a sensitizer, mutagen, carcinogen or reproductive/developmental toxicant. It has many industrial uses due to its properties as a film forming of nitrocellulose lacquers, photography film and cosmetics. Once applied it produces a shiny, tough, nontoxic, non irritating and non allergenic film that adheres well to the nail plate. The film is also oxygen permeable, allowing gas exchange between the atmosphere and the nail plate which ensures healthy nail growth. In a match controlled study and in a retrospective cohort study of 2490 male workers from a plastic factory suggest a possible association between rectal cancer and celluose nitrate production (Cavender FL, 1983. J Occup. Med. 25 (3): 219-30); Marsh GM, 1983. J Occup. Med. 25 (3): 219-30 (1983). Nitrocellulose has been described as a potential but very rare contact allergen in nail varnishes; in one report there was 1 in 13,126 patients tested for contact sensitivity to Nitrocellulose (Castelain, M et al. 1997. Contact Dermatitis, 26, 266). Other few cases of its sensitising effects have been reported also but to other types of cosmetics namely, lip and sunscreen products (QUARTIER, S et al, 2006; Swinnen, I et al. 2012. Allergic contact dermatitis to copolymers in cosmetics – case report and review of the literature. Contact Dermatitis 2006: 55: 257–267; Swinnen, I et al. 2012. Allergic contact dermatitis caused by C30-38 Olefin/Isopropyl Maleate/MA copolymer in cosmetics. Contact Dermatitis, 2012:67, 306-320).

The ingredient is not acutely toxic by oral administration. It is not a skin and eye irritant, a sensitizer, mutagen, carcinogen or reproductive/developmental toxicant. A NOAEL of 4500 mg/kg bw/day based on a 2 year repeated-dose study in mice is selected for MoS calculation. The dose was administered as 3% nitrocellulose in the dietary feed (CIR, 2013). It is not bioaccumulative. No information for phototoxicity was available. Based on this information and other scientific literature on this ingredient, safety concerns are not expected with this ingredient for use in cosmetics.

Chemical Name: Isopropyl Alcohol, Methylethanol

Function: Antifoaming agents; fragrance ingredients; solvents; viscosity decreasing (CIR, 2012)

Regulatory Status (Toxicological Risk Assessment Report):

Exposure	NOAEL	Safety Factors	MoS
ORAL	400 mg/kg bw/day	Not reported	MoS For Adult: 4800

Summary Data:

Cosmetic Functions : Antifoaming / Perfuming / Solvent / Viscosity Controlling / Viscosity Decreasing-Agent. Isopropanol is a commonly used industrial solvent and also, as a disinfectant (OECD SIDS). The mammalian/human toxicological properties of isopropanol have been well characterized in multiple animal species and humans for a variety of exposure routes, exposure durations and toxicity endpoints. Isopropanol is considered to be more toxic to the central nervous system than ethanol, with similar effects. Both ingestion and inhalation at high concentrations can result in the rapid onset of CNS depression with subsequent coma and death. In metabolism studies with rats and mice, up to 92% of the administered dose (via i.v. or inhalation) of isopropanol was exhaled as acetone, CO2 and the unmetabolized alcohol (Slauter et al., 1994). Approximately 3-8% of the administered dose was excreted in urine as isopropanol, acetone, and a metabolite tentatively identified as isopropyl glucuronic acid. Isopropanol is readily absorbed from the GI tract and persists in the circulation longer than ethanol. Alcohol dehydrogenase oxidises most isopropanol to acetone. Acetone may be further metabolized to acetate, formate, and finally CO2. Acute toxicity: Low acute toxicity (OECD SIDS). The oral LD50 ranged from 4710 - 5840 mg/kg (rat, rabbit, mouse, dog) and the dermal LD50 > 12870 mg/kg. The acute inhalation LC50 ranged from 53 mg/L (2 hr, mouse) to 72.6 mg/L (4 hr, rat). Prolonged inhalation exposure may produce central nervous system depression and narcosis. Irritation: Isopropanol was non-irritating to skin when applied to rabbit but moderately irritating to eyes on conjunctival instillation (maximum Draize score 37/110) (references as cited in OECD SIDS). Sensitisation: Non-sensitising in guinea pig maximization test (Buehler's method) (reference as cited in OECD SIDS). Non-sensitizing according to a human volunteer dermal sensitization study using for 80.74% isopropyl alcohol in a spray concentrate and 2.85% isopropyl alcohol in a hair dye formulation human exposure study (CIR, 2012). An 80.74% spray concentrate did not demonstrate any potential for dermal sensitization in 9 human subjects (CIR, 2012). A 2.85% hair dye base formulation of isopropyl alcohol and 1.95% isopropyl acetate caused no dermal sensitization upon exposure to 109 human test subjects in a human RIPT study (CIR, 2012). Mutagenicity/Genotoxicity: Non mutagenic or genotoxic. Isopropanol was negative with or without metabolic activation in mammalian cell gene mutation (HGPRT, sister chromatid exchange, chromosome aberration) assays and in bacterial reverse mutation test in vitro. Similarly, no evidence of genotoxicity or clastogenicity was observed in vivo in mouse micronucleus test. Repeat dose toxicity: The repeated exposure to isopropanol has been evaluated in rats and mice by the inhalation and oral routes. The only adverse effects-in addition to clinical signs identified from these studies were to the kidney. Inhalation exposure of rats and mouse to 0, 100, 500, 1500 or 5000 ppm for 6h/day, 5 days/week for 13 weeks resulted in no mortalities. Narcotic effects were observed during exposures to 1500 and 5000 ppm, decrease in body weights and increased incidence of hyaline droplets in the kidney (male rats only) was also observed at 5000 ppm. The NO(A)EL was 1500 ppm. In another study, no significant differences were seen between rats exposed to 400 ppm and the control. Marked local irritation was observed at 1000 ppm and above including changes in haematology and serum chemistry parameters. Neurobehavioural evaluation including functional observatory battery (FOB), motor activity and neuropathology showed no changes in FOB but there was increased motor activity noted at 5000 ppm. However, no treatment-related lesion in the nervous system was reported. Isopropanol was administered in the drinking water to rats for 27 weeks at equivalent doses of 600 or 2300

mg/kg bw/d (males) and 1000 or 3900 mg/kg bw/d (females); respectively. No gross or microscopic changes were noted; there was effect on the body weight at the highest dose. When administered at concentrations of 1%, 2%, 3% and 5%, respectively; in the drinking water of rats for up to 12 weeks, isopropanol caused dose-dependent increase in organ weights (liver, kidney, adrenal glands)and hyaline casts and droplets in the kidney. The NOEL was determined to be 1% (ca. 870 mg/kg bw/d). Carcinogenicity potential of isopropanol was examined in a dermal application study in mouse; no increase incidence of skin tumours was reported when applied 3 times/week for 52 weeks. Also, in lifetime inhalation study in rats exposed to 0, 500, 2500 or 5000 ppm 6 days /week for 24 months and mice treated for 18 months, no tumorigenic activity was detected. Consistent with the subchronic studies results, exacerbation of chronic renal disease was noted in animals at 2500 together with urine chemistry changes indicative of kidney damage. Narcosis and hypoactivity was at 5000 ppm and in some at 2500 ppm during exposure. The NOEL was identified to be 500 ppm. Isopropanol was non-reprotoxic in 1- and 2-generation studies when administered to rats orally (by gavage and in drinking water). The developmental toxicity of isopropanol has been characterized in rat and rabbit developmental toxicity studies and in a rat developmental neurotoxicity study. The rats were dosed by oral gavage at 400, 800 or 1200 mg/kg from gestational days 6 through 15. The rabbits were dosed by oral gavage at 120, 240 or 480 mg/kg from gestational days 6 through 18. These studies indicate that isopropanol is not a selective developmental hazard. Isopropanol produced developmental toxicity in rats, but not in rabbits. In the rat, the developmental toxicity occurred only at maternally toxic doses and consisted of decreased fetal body weights, but no teratogenicity. These data suggest the developmental NOAEL is 400 mg/kg/day for rats and 480 mg/kg/day for rabbits. The lowest reported NOAEL of 400 mg/kg bw/d in the developmental study in rat is considered the most conservative for use in the calculation of the safety margin. Photo-induced toxicity: No data available showing phototoxicity including photo-allergenicity with isopropanol. Human data: A subacute study of daily oral intake of isopropanol (2.6 or 6.4 mg/kg body weight) by groups of 8 men for 6 weeks had no effect on blood cells, serum or urine and produced no subjective symptoms. There have been a number of cases of poisoning reported due to the intentional ingestion of isopropanol, particularly among alcoholics or suicide victims. These ingestions typically result in a comatose condition. Pulmonary difficulty, nausea, vomiting, and headache accompanied by various degrees of central nervous system depression are typical. In the absence of shock, recovery usually occurred. Human volunteers reported that exposure to 400 ppm isopropanol vapors for 3 to 5 minutes caused mild irritation of the eyes, nose and throat. Although isopropanol produced little irritation when tested on the skin of human volunteers, there have been reports of isolated cases of dermal irritation and/or sensitization. The use of isopropanol as a sponge treatment for the control of fever has resulted in cases of intoxication, probably the result of both dermal absorption and inhalation (OECD SIDS). In addition, prolonged, repeated exposure may cause skin defatting Dermal / percutaneous absorption: Isopropanol (IPA), as a 70% aqueous solution, was applied under occluded conditions to the shaved backs of rats, 84-86% of the dose was recovered at the application sites. Dermal absorption rates was calculated by two independent methods; the values obtained were 0.78 mg/cm2/h and 0.85 mg/cm2/hr for males and 0.77 mg/cm2/hr and 0.78 mg/cm2/hr for females, respectively (Boatman et al., 1998). The calculated permeability coefficient was 1.35 to 1.50 cm-3/hr which according to the author demonstrates that in rats, isopropanol is rapidly absorbed dermally when applied under occlusive conditions. Ten healthy adult volunteers applied a commercially available isopropanol-containing hand rub to their hands every 10 min over a 4 h period. Blood isopropanol levels were measured at the beginning and end of the study. At the end of the study, measurable blood levels (range 0.5-1.8 mg/l) were recorded in nine subjects indicating that isopropanol could be absorbed through intact skin in humans (Turner et al; 2004). The absorption of isopropanol was measured in the blood of twelve volunteers (six male and six female) following repeated application of two hand rubs containing different concentrations of ethanol (45% and 70% w/w, respectively). The total amount of absorbed isopropanol was measured as 309.5 mg; therefore, based on the amount applied, the proportion absorbed was calculated to be 1.1, and 0.7%; respectively. In a further study, during 10 surgical hand disinfections, volunteers were exposed for a contact time of 30 min within a period of 80 min to a total of 200 ml of hand rub, corresponding to 71g and 109.2g isopropanol, respectively. Total amount absorbed was reported to be 598.6 mg and 471.6 mg which based on the applied dose is equivalent to 0.8% and 0.4% absorption, respectively. These data suggest that the absorption of isopropanol applied on the skin is really low and below 1%. Margin of Safety: NOAEL: 400 mg/kg bw/d; Dermal Absorption (Dap) = 1% References OECD/SIDS Initial Assessment Profile, 2-Propanol (CAS No. 67-63-0). Accessed on 24/06/2013 at: http://www.chem.unep.ch/irptc/sids/OECDSIDS/67630.pdf Slauter R, Coleman D, Gaudette N, McKee R, Masten L, Gardiner T, Strother D, Tyler R, and Jeffcoat A. 1994. Disposition and pharmacokinetics of isopropanol in F-344 rats and B6C3F1 mice. Fundam. Appl. Toxicol. 23:407-420. Kramer Axel: Absorption of alcohol hand disinfectants; propan-2-ol after excessive hygienic and surgical hand disinfection (alcohol based rub). Accessed on 24/06/2013 at: http://webbertraining.com/files/library/docs/88.pdf Boatman RJ, Perry LG, Fiorica LA, English JC, Kapp RW Jr, Bevan C, Tyler TR, Banton MI, Wright GA (1998) Dermal absorption and pharmacokinetics of isopropanol in the male and female F-344 rat. Drug Metab Disp 26: 197-202. Accessed on 24/06/2013 at: http://dmd.aspetjournals.org/content/26/3/197.full.pdf Turner P, Saeed B

and Kelsey MC; 2004: Dermal absorption of isopropyl alcohol from a commercial hand rub: implications for its use in hand decontamination. Journal of Hosp. Infection, Vol. 56(4):287-290

Overall Conclusion:

The ingredient is not acutely toxic by oral or dermal administration or inhalation. It is not a skin irritant or sensitizer. It causes severe eye irritation and has low bioaccumulation potential. It is not mutagenic, a developmental toxicant and it is not classifiable as to its carcinogenicity. No data was available for phototoxicity. Central nervous system depression and behavioural effects have been noted at extremely high concentrations. Based on this information and other scientific literature on this ingredient, safety concerns are not expected with this ingredient for use in cosmetics when formulated to be non-irritating and at concentrations where the central nervous system depression and behavioural effects are no longer a concern.

Margin of Safety Calculation

INCI Name	Conc. (% w/w)	SED mg/kg	NOAEL/NOEL mg/kg bw/day	MoS
BUTYL ACETATE	50	0.41700000	259	621.6
ETHYL ACETATE	25	0.20800000	900	4320
NITROCELLULOSE	15	0.12500000	4500	36000
ISOPROPYL ALCOHOL	10	0.08300000	400	4800

Note: In the absence of NO(A)EL data, the Margin of Safety (MoS) has not been calculated.
Unless otherwise determined and in the absence of literature or other experimental data, a Dermal Absorption (DAp) of 100% is taken as the worst case scenario.
NO(A)EL: No Observed Adverse Effect Level; MoS: Margin of Safety; SED Systemic Exposure Dosage
Calculation of Margin of Safety: MoS = NO(A)EL / SED

References for skin surface area, exposures, body weight and application quantities are derived from EU guidance and literature sources.
These are held on file at intertek.

The following conditions apply to this assessment:
1. This product was not evaluated for heavy metal or lead content by the undersigned.
2. This product was not assessed for compliance with regulations, other than as described above, by the undersigned.
3. This product has not been evaluated for potential physical injury such as choking hazard, aspiration risk, or mechanical irritation by the undersigned.
4. It was assumed that all ingredients in the product were disclosed and are accurate as listed in the report table, subject to valid request.
5. Based upon the information supplied, unless otherwise stated in this report and subject to a valid request, being made, it was assumed that neither this product, nor the ingredients used in the product, contained any impurities/contaminants that would cause toxicity in a consumer.
6. This evaluation is relevant solely to the conditions described herein. Any substitution of ingredients, increase in concentrations of use, or change of use pattern will necessitate a new evaluation.
"Valid request" refers to request from supplier of formulation to Intertek.
7. Toxicological profiles are stored within an in-house database at Intertek.

For European Legislation only: This formulation will be assessed by Intertek in accordance with PART B , Annex I to Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (Official Journal L 342, 22 December 2009, pp. 59–209). The safety assessment is based upon the chemical specification and toxicological profile of the ingredients as supplied at the time of assessment and an assessment of the final cosmetic product. The supplier to this safety assessment is advised to ask for a new safety evaluation if any change in formulation occurs, change in raw materials used, abnormally high number of adverse events are recorded, changes in recommended uses or other circumstances that may affect the safety of this product.

END OF REPORT

This report is made solely on the basis of your instructions and/or information and materials supplied by you. It is not intended to be a recommendation for any particular course of action. Intertek does not accept a duty of care or any other responsibility to any person other than the Client in respect of this report and only accepts liability to the Client insofar as is expressly contained in the terms and conditions governing Intertek's provision of services to you. Intertek makes no warranties or representations either express or implied with respect to this report save as provided for in those terms and conditions. We have aimed to conduct the Review on a diligent and careful basis and we do not accept any liability to you for any loss arising out of or in connection with this report, in contract, tort, by statute or otherwise, except in the event of our gross negligence or wilful misconduct.