Safety Assessment of Hexamethylene Diisocyanate (HDI) Polymers as Used in Cosmetics

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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of 19 hexamethylene diisocyanate (HDI) polymers as used in cosmetics. The functions of HDI polymers include anticaking agents, viscosity increasing agent – aqueous, and film formers. These ingredients are copolymers, the monomers of which include HDI or other diisocyanates. The HDI monomer can cause occupational asthma and other ailments. The Panel determined that there would be no significant residual isocyanate monomers in these ingredients. The Panel concluded that 17 of these ingredients are safe in cosmetics in the present practices of use and concentration and the available data are insufficient to make a determination that 2 of these ingredients, Bis-Hydroxyethyl Acrylate Poly(1,4-Butanediol)-9/TMHDI Copolymer and 1,4-Butanediol/Succinic Acid/Adipic Acid/HDI Copolymer, are safe.

INTRODUCTION

This is a review of the available scientific literature and unpublished data relevant to assessing the safety of 19 hexamethylene diisocyanate (HDI; also known as 1,6-diisocyanatohexane) polymers, listed below, as used in cosmetics. These ingredients are copolymers, the monomers of which partially consist of HDI, or other diisocyanates. According to the *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*), the reported functions of HDI polymers include viscosity increasing agents – aqueous, anticaking agents, and film formers (Table 1).[1]

- HDI/Trimethylol Hexyllactone Crosspolymer
- Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer
- Bis-Hydroxyethyl Acrylate Poly(1,4-Butanediol)-9/TMHDI Copolymer
- Bis-Isostearyl 1,4-Butanediol/HDI/Hydrogenated Dimer Dilinoleyl Alcohol Copolymer
- Bis-Lauryl Cocaminopropylamine/HDI/PEG-100 Copolymer
- Bis-Methoxy PEG-10 Dimethyl MEA/HDI/Bis-PEG-10 Dimethicone Copolymer
- 1,4-Butanediol/Succinic Acid/Adipic Acid/HDI Copolymer
- Cholesterol/HDI/Pullulan Copolymer
- Decyl HDI/PEG-180 Crosspolymer
- Diethylene Glycol/DMAP Acrylamide/ PEG-180/HDI Copolymer
- HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer
- HDI/PEI-45/SMDI Crosspolymer
- HDI/PPG/Polycaprolactone Crosspolymer
- Methoxy PEG-17/Methoxy PEG-11/HDI Crosspolymer
- Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer
- PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether
- PPG-26/HDI Copolymer
- Steareth-100/PEG-136/HDI Copolymer
- Stearyl HDI/PEG-50 Copolymer

The CIR Panel has reviewed several of the constituents of these ingredients (Table 2).[2-12] Polyethylene glycols (PEGs), PEG-10 Dimethicone, Adipic Acid, Succinic Acid, Cholesterol, Pullulan, Glycerin, and Stearyl Alcohol were determined to be safe as used. Methoxy PEG-10, Decyltetradeceth-20, Steareth-100, and PPG-26 were determined to be safe when formulated to be non-irritating. Polyacrylamides are safe as used; the acrylamide monomer is limited to 5 ppm in formulation.[13]

The ingredients in this report are copolymers, each of which is synthesized, in part, from the monomer HDI or other diisocyanate analogs. These ingredients are grouped together because their copolymers are generated from these in-common diisocyanate monomers. Exposure to diisocyanates, such as HDI, in the work place is one of the leading causes of occupational asthma.[14] Airway irritation and asthma-like symptoms, hypersensitivity pneumonitis, rhinitis, and accelerated lung deterioration have also been associated with exposure to diisocyanates. Diisocyanates can also cause irritant and allergic contact dermatitis, as well as skin and conjunctival irritation. Diisocyanates may act to generate haptens by reacting with and covalently bonding to endogenous proteins to induce an immune response. Hapten formation is believed to be a mechanism for recognition of an allergen by the immune system and subsequent development of allergic responses. The ingredients in this report are not diisocyanates, but are end products of a polymerization process that includes HDI, or an analog, as one of the starting materials (monomers). Accordingly, quantification of any residual diisocyanate in the final cosmetic ingredient may be paramount to determining safety.

CHEMISTRY

Definition and Structure

The definitions and approximate structures of the HDI polymers in this safety assessment are provided in Table 1. These structures are best representations based on the definitions provided in the *Dictionary*.[1]

This group is composed of copolymers, the monomers of which include some analog of HDI (Figure 1).

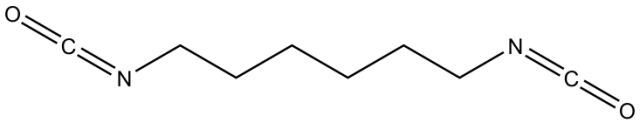


Figure 1. Hexamethylene Diisocyanate.

The other 3 diisocyanate monomers herein are analogs of HDI, namely trimethylhexanediisocyanate (TMHDI), saturated methylene diphenyldiisocyanate (SMDI), and the HDI isocyanaurate trimer (Figure 2).

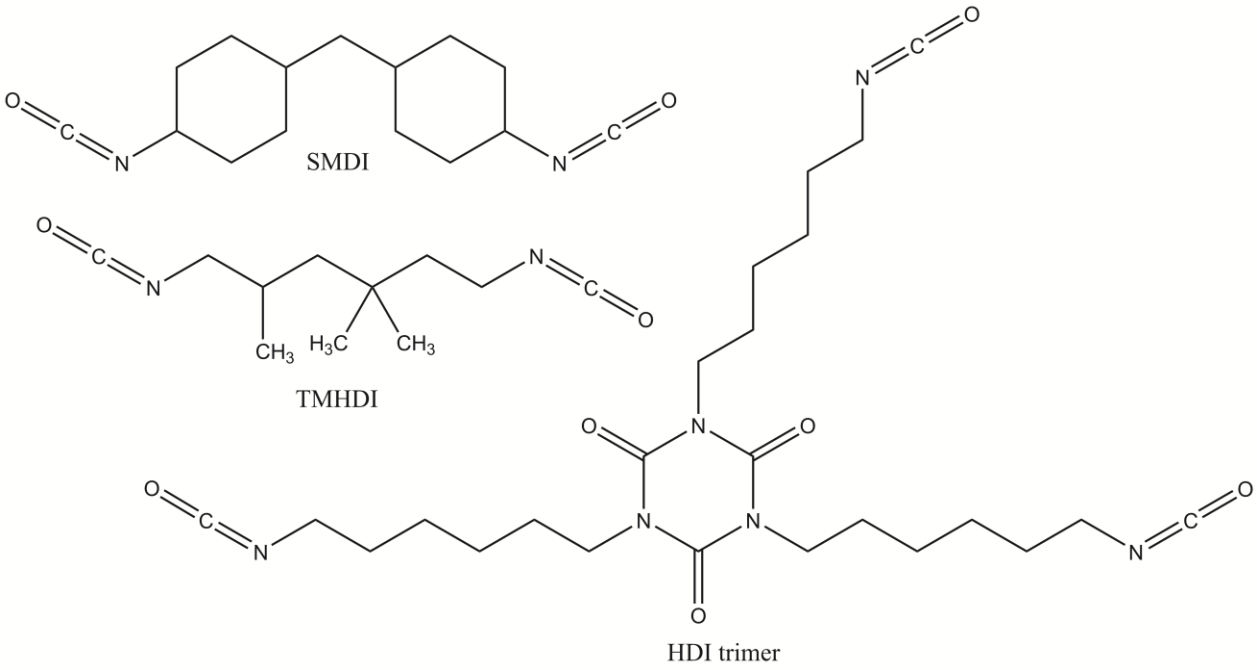


Figure 2. HDI analogs.

These polymers are produced by reactions of HDI with alkoxy-group-containing monomers, such as alcohols and polyethers, which also may be used as end-capping units (Figure 3).

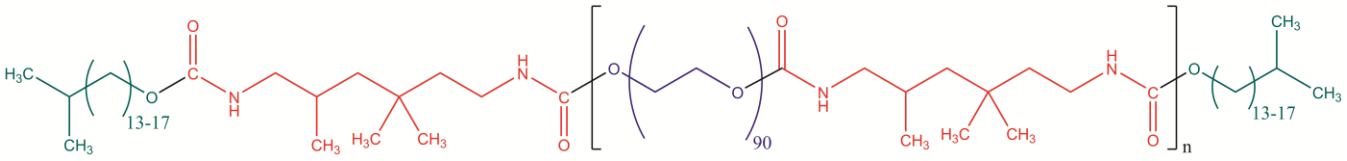


Figure 3. **Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer** (one possible representative structure).

Some of these polymers are linear, but when tri-functional monomers (e.g., glycerin) are used as reactants, branched or cross-linked structures are probable. The degree of polymerization of these ingredients can be controlled to obtain a product having a desired functionality, such as rheology modifier. Accordingly, the molecular weights and molecular volumes of these ingredients could vary widely, unless otherwise noted in use specifications. These polymers, by virtue of their monomers, contain both hydrophilic and hydrophobic groups. The ratio of hydrophilic and hydrophobic groups may vary within one ingredient name. In the absence of ingredient-explicit specifications, estimating some of the chemical and physical properties of these ingredients is challenging. These ingredients can potentially range from liquid to solid, soluble to insoluble, or non-penetrating to penetrating into the skin. However, aside from the potential presence of a diisocyanate or end-capping agent residue, these ingredients are likely to be similar to polyurethane-type polymers.

Physical and Chemical Properties

The physical and chemical properties of each of these ingredients could vary widely depending on method of manufacture and the resulting structure and molecular weight distribution. Available reported physical and chemical properties are presented in Table 3.

A supplier reported that HDI/Trimethylol Hexyllactone Crosspolymer was available in two grades for use in cosmetics (Table 4).[15-17] The particle size distribution for grade 1 was reported to be: 100% <100 µm, 33.8% <10 µm, 5.5% <1 µm. The particle size distribution for grade 2 was reported to be: 100% <100 µm, 87.5% <10 µm, 7.1% <1 µm. Analysis of HDI/Trimethylol Hexyllactone Crosspolymer from a second supplier showed that the overall distribution was: 100% <100 µm, 15.15% ≤10.42 µm, and 0% <1 µm. Another source reported that the average particle size to be 12-18 µm.[18] A fourth source reported that the average particle size range of HDI/PPG/Polycaprolactone Crosspolymer was 12-19 µm.[19]

The mean molecular weight of Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer is >7000 Da; 1.5% of this ingredient was reported to be <1000 Da and 1.2% was <500 Da.[20] It was reported that the molecular weight of Bis-Methoxy PEG-10 Dimethyl MEA/HDI/Bis-PEG-10 Dimethicone Copolymer is >1000 Da.[21] In an analysis of Bis-Lauryl Cocaminopropylamine/HDI/PEG-100 Copolymer, HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer, and Steareth-100/PEG-136/HDI Copolymer, no compounds <1000 Da were detected.[22-25] The molecular weight of HDI/PPG/Polycaprolactone Crosspolymer was reported to be >10,000 Da.[26] The molecular weights of three batches of PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether were reported to range from approximately 4000-75,000 Da.[27]

Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer is reported to be fully crosslinked, and its molecular weight is reported to be infinite.[28] This polymer contains a 0.9% soluble fraction (in tetrahydrofuran) with a molecular weight >1000 Da.

HDI/C12-14 Alkyl Tartrate Hydrogenated Dilinoleyl Alcohol Copolymer, as supplied, is reported to be stable for 16 weeks at temperatures from 5-50˚C.[25]

Method of Manufacture

HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer is reported to be manufactured by the condensation of an isocyanate component (HDI) and molecules containing hydroxyl groups, specifically esters of tartaric acids and alkylic diol (di-C12-14 alkyl tartrate/hydrogenated dilinoleyl alcohol).[23] Polymerization is terminated by the addition of ethyl alcohol (i.e., ethyl alcohol end caps the polymer).

HDI/Trimethylol Hexyllactone Crosspolymer is reported to be manufactured by mixing an isocyanate prepolymer (HDI/trimethylolpropane/ε-caprolactone) and a solvent for aqueous suspension polymerization at 30-100˚C for 1-6 h.[18] The resulting polymer is washed with water. The product is dried at 95˚C, followed by classification, sterilization, and packaging. Alkylation and end-capping agents are not used in this process.

HDI/PPG/Polycaprolactone Crosspolymer is reported to be manufactured by the same process as the HDI/Trimethylol Hexyllactone Crosspolymer, with the addition of propylene oxide/D-glucitol in the mix for the aqueous polymerization.[19]

Steareth-100/PEG-136/HDI Copolymer and Bis-Lauryl Cocaminopropylamine/HDI/PEG-100 Copolymer are manufactured by placing pre-dried polyethylene glycol and diisocyanate together with a catalyst.[29] The reaction is allowed to proceed to completion to consume the free diisocyanate. A high boiling aliphatic alcohol or surfactant molecule is used to consume the unreacted isocyanate groups at the ends of the polymer chains and thereby act as an end-capping agent.

Impurities

HDI

The residual amount of HDI in HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer raw material was reported to be <0.5 ppm (Table 5).[23] The residual diisocyanate was reported to be below the limit of detection (0.017%) for Bis-Lauryl Cocaminopropylamine/HDI/PEG-100 Copolymer and Steareth-100/PEG-136/HDI Copolymer; there was no free HDI detected for either of these ingredients at temperatures up to 150˚C.[30] Residual HDI was <100 ppm in HDI/Trimethylol Hexyllactone Crosspolymer and HDI/PPG/Polycaprolactone Crosspolymer.[18,19] No residual HDI was detected (detection limit <20 ppm) in an analysis of 3 batches of PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether.[27]

In an analysis of a skin care cream and a makeup cream that contained HDI/Trimethylol Hexyllactone Copolymer (preformulated with silica; 5% as a plastic powder), and HDI/PPG/Polycaprolactone Crosspolymer (preformulated with silica; 2.4% as a plastic powder), the amount of HDI monomer was below the limits of detection (0.4 ppm) in both of these products.[31]

Other Impurities

Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer and Bis-Lauryl Cocaminopropylamine/HDI/PEG-100 Copolymer were reported to contain <1 ppm mercury, <3 ppm arsenic, and <10 ppm lead.[32]

In an analysis of HDI/PPG/Polycaprolactone Crosspolymer, ε-caprolactone was present at 240 ppm and D-glucitol at 0.07 ppm, but there was no trimethylolpropane detected (detection limit <2 ppm) or propylene oxide (detection limit <1 ppm).[19]

In an analysis of 3 batches of HDI/Trimethylol Hexyllactone Crosspolymer, it was reported that the levels of ε-caprolactone ranged from 66 to 73 ppm and trimethylolpropane from 4 to 12 ppm.[18]

According to a product safety sheet, Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer is not expected to contain antimony, arsenic, bismuth, cadmium, chromium, copper, iron, lead, mercury, manganese, nickel, palladium, platinum, or tin; extraction experiments detected no organic materials into water.[33] Zinc may be present as a technical impurity at <25 ppm. Dibutyl phosphate may be present at a maximum concentration of approximately 100 ppm. Zinc 2-ethylhexanoate may be present at a maximum concentration of approximately 80 ppm. At the end of the drying process, it is expected that there will be approximately 1% residual water and no volatile organic materials will persist. Butylhydroxytoluene (BHT) may be present as a technical impurity at <20 ppm. The extractable oligomer (< approximately 1000 Da) of this crosspolymer was present at a concentration of <1%.

In an analysis of 3 batches of PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether, ethylene oxide (detection limit <1 ppm) and dioxane (detection limit <10 ppm) were not detected.[27] Formaldehyde was detected at 1 or 2 ppm in these samples.

USE

Cosmetic

The safety of the cosmetic ingredients included in this safety assessment is evaluated based on the data the Panel receives from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected cosmetic use of ingredients. The FDA collects data from manufacturers on the use of individual ingredients in cosmetics by cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). Those received from the cosmetic industry are submitted in response to a survey conducted by the Personal Care Products Council (Council) of the maximum reported use concentrations by category.

According to 2016 VCRP data, HDI/Trimethylol Hexyllactone Crosspolymer has the greatest number of reported uses (385 formulations), which includes 378 leave-on products and 7 rinse-off products (Table 6).[34] Fifty-three of these formulations are powders, 11 are lipsticks, and 360 result in dermal contact. The other ingredients that had reported uses were used in 24 or fewer cosmetic formulations.

According to the 2015 Council survey, the highest maximum concentration of use of the ingredients in this safety assessment was reported to be 31% for HDI/Trimethylol Hexyllactone Crosspolymer in foundations, a leave-on product.[35,36]

Table 7 lists the HDI polymers with no reported uses.

Concentration of use data were received for Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer, but uses were not reported in the VCRP, therefore, it should be presumed that there is at least 1 use for the reported concentration. This is also true for Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer and HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer.

HDI/Trimethylol Hexyllactone Crosspolymer, HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer, and Methoxy PEG-17/Methoxy PEG-11/HDI Crosspolymer were reported to be used in formulations that come in contact with mucus membranes (highest concentration reported to be 15.1% HDI/Trimethylol Hexyllactone Crosspolymer in lipsticks). HDI/Trimethylol Hexyllactone Crosspolymer, HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer, and Methoxy PEG-17/Methoxy PEG-11/HDI Crosspolymer were reported to be used in formulations that could be incidentally ingested (highest concentration reported to be 15.1% HDI/Trimethylol Hexyllactone Crosspolymer in lipsticks). HDI/Trimethylol Hexyllactone Crosspolymer, Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer, HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer, HDI/PPG/Polycaprolactone Crosspolymer, and PEG-240/HDI Copolymer Bis-Decyletradeceth-20 Ether were reported to be used in formulations that are applied near the eye (highest concentration reported to be 19.6% HDI/Trimethylol Hexyllactone Crosspolymer in eye shadow).

Additionally, HDI/Trimethylol Hexyllactone Crosspolymer, Diethylene Glycol/DMAP Acrylamide/PEG-180/HDI Copolymer, HDI/PPG/Polycaprolactone Crosspolymer, PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether, and Steareth-100/PEG-136/HDI Copolymer were reported to be used in tonics, dressings and other hair grooming aids; face and neck products; body and hand products; and indoor tanning preparations that may be sprays and could possibly be inhaled. The highest maximum reported concentration of these ingredients in a likely aerosol product is 2.5% Steareth-100/PEG-136/ HDI Copolymer in tonics, dressings, and other hair grooming aids. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm.[37-40] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[37,39] HDI/Trimethylol Hexyllactone Crosspolymer and HDI/PPG/Polycaprolactone Crosspolymer were reported to be used in face powders at up to 12.6% and 11.8%, respectively, and could possibly be inhaled. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400- to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[41-43]

The European Union restricts the content of traces of diethylene glycol to a total of 0.1% in any cosmetic product, including the trace amount of diethylene glycol contained in polymers, such as Diethylene Glycol/DMAP Acrylamide/PEG-180/HDI Copolymer.[44]

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Data on toxicokinetics of HDI polymers were not found in the published literature and no unpublished data were provided.

TOXICOLOGICAL STUDIES

Single Dose (Acute) Toxicity

Oral – Non-Human

HDI/Trimethylol Hexyllactone Crosspolymer (5000 mg/kg) administered by gavage caused no clinical signs or mortalities to rats (Table 8).[15-17] The oral LD_{50} of Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer was reported to be >2000 mg/kg in rats.[33] The oral LD_{50} of PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether was reported to be >2000->2500 mg/kg in rats.[27] The oral LD_{50} for Steareth-100/PEG-136/HDI Copolymer was reported to be >10,000 mg/kg in rats; clinical signs included bristled fur, diarrhea and dirty fur around the anal region due to feces.[24]

The acute oral LD_{50} was >10,000 mg/kg in rats (n=5/sex) for a cosmetic ingredient mixture consisting of Bis-Cocaminopropylamine/HDI/ PEG-100 Copolymer (concentration not specified) and butylene glycol.[45]

Inhalation – Non-Human

Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer

The acute inhalation LC_{50} of Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer was reported to be >1.99 mg/L when administered in a dust/mist for 4 h in rats.[33] The test was conducted in accordance with the Organization for Economic Cooperation and Development Test Guideline (OECD TG) 403.

Repeated Dose Toxicity

Data on dermal, oral, or inhalation repeated dose toxicity of HDI polymers were not found in the published literature and no unpublished data were provided.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Data on the reproductive and developmental toxicity of HDI polymers were not found in the published literature and no unpublished data were provided.

GENOTOXICITY

Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer

Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer (concentration not specified) was not mutagenic in an Ames test, with or without metabolic activation.[33] No further details were provided.

PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether

PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether (concentration not specified) was not genotoxic when tested in accordance with OECD TG 471 (bacterial reverse-mutation test).[27] No further details were provided.

Steareth-100/PEG-136/HDI Copolymer

In an Ames test conducted according to OECD TG 471, Steareth-100/PEG-136/HDI Copolymer was not mutagenic to *Salmonella typhimurium* (strains TA98, TA100, TA1535, and TA1537) and *Escherichia coli* (strain WP2uvA) at up to 5000 µg/plate.[24]

CARCINOGENICITY

Data on the carcinogenicity of HDI polymers were not found in the published literature and no unpublished data were provided.

IRRITATION AND SENSITIZATION

Irritation

Dermal - In Vitro

Per the results of *in vitro* studies, Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer (concentration not specified), PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether, and a mixture containing 30% Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer were predicted to be non-irritating (Table 9).[20,27,33]

Dermal – Non-Human

HDI/Trimethylol Hexyllactone Crosspolymer (100%), Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate

Trimer Crosspolymer (concentration not specified), and Steareth-100/PEG-136/HDI Copolymer (100%; 0.5 g; dry) were not dermal irritants in rabbits (Table 9). [15-17,24,33] PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether was not a dermal irritant in guinea pigs when tested at concentrations at up to 30%.[27]

Dermal – Human

HDI/Trimethylol Hexyllactone Crosspolymer

HDI/Trimethylol Hexyllactone Crosspolymer (100% as a dry powder) was not a dermal irritant in a human patch test (Table 9).[15-17] Two foundations containing HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer (1.7% and 3.19%) were not irritating in human patch tests.[23]

Ocular – In Vitro

PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether

The RC_{50} (i.e., the concentration at which 50% of the treated eggs show a positive response) was reported to be >100 for PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether in a chorioallantoic membrane vascular assay (CAMVA).[27] No further details were provided.

The reported score for PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether in a bovine corneal opacity and permeability (BCOP) assay was calculated to be approximately 2.74.[27] A score of 0-3 does not require classifying the test substance as an ocular irritant or toxicant. No further details of the study were provided.

Ocular – Non-Human

In an eye irritation study of HDI/Trimethylol Hexyllactone Crosspolymer (100%), mild to moderate conjunctival redness and mild chemosis were observed in 4 of 6 rabbits 24 and 48 h after administration into the eyes (Table 10).[15-17] The authors considered the particle size (at least 92.9% >1 µm as shown in Table 4) and the water insolubility of the tested polymer and concluded that the eye irritation observed was likely attributable to mechanical abrasion rather than to chemical irritancy. Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer (concentration not specified) was a slight ocular irritant in rabbits.[33] PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether (up to 30%) was not an ocular irritant in rabbits.[27] Steareth-100/PEG-136/HDI Copolymer (100%) was classified as a non-irritant in the eyes of rabbits.[24]

Sensitization

Non-Human

In a Magnusson Kligman maximization test, Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer (concentration not specified) was not sensitizing in guinea pigs (Table 11).[33] In a skin sensitization assay (species not specified), PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether (30%) was not a dermal sensitizer.[27]

Human

In human repeated insult patch tests (HRIPT) of 2 foundations containing HDI/Trimethylol Hexyllactone Crosspolymer (30.7% and 10%), there were no signs of dermal irritation or allergic contact dermatitis observed (Table 11).[46,47] In an HRIPT of Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer (30%), one subject out of 48 exhibited barely perceptible erythema 48 h after the challenge.[20] In an HRIPT of PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether (concentration not specified) there was no evidence of dermal irritation or allergic contact sensitization.[27]

SUMMARY

This is a review of the scientific literature and unpublished data relevant for assessing the safety of 19 HDI polymers as used in cosmetics. These ingredients consist of copolymers, the monomers of which partially are comprised of HDI, or an analog thereof. The functions of HDI polymers include viscosity increasing agents-aqueous, anticaking agents, and film formers.

Exposure to diisocyanates, such as HDI, has caused occupational asthma, hypersensitivity pneumonitis, rhinitis, and accelerated lung deterioration.

The mean molecular weight of Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer is >7000 Da; 1.5% of the ingredient was reported to be <1000 Da and 1.2% was <500 Da. In an analysis of Bis-Lauryl Cocaminopropylamine/HDI/PEG-100 Copolymer, HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer, and Steareth-100/PEG-136/HDI Copolymer, no compounds of <1000 Da were detected. The molecular weight of HDI/PPG/Polycaprolactone Crosspolymer was reported to be >10,000 Da. The molecular weights of three batches of PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether were reported to range from approximately 4000-75,000 Da. Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer is reported to be fully crosslinked, and its molecular weight is reported to be infinite.

The residual amount of HDI in HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer was reported to be <0.5 ppm. The residual diisocyanate was reported to be below the limit of detection for Bis-Lauryl Cocaminopropylamine/HDI/PEG-100 Copolymer and Steareth-100/PEG-136/HDI Copolymer. Residual HDI was <100 ppm

in HDI/Trimethylol Hexyllactone Crosspolymer and HDI/PPG/Polycaprolactone Crosspolymer. In an analysis of 3 batches of PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether, no residual HDI was detected (detection limit <20 ppm).

In an analysis of a skin care cream and a makeup cream that contained HDI/Trimethylol Hexyllactone Copolymer and silica (5% as a plastic powder) and HDI/PPG/Polycaprolactone Crosspolymer and silica (2.4% as a plastic powder), respectively, the amount of HDI monomer was below the limits of detection in both of these products.

According to 2016 VCRP data, HDI/Trimethylol Hexyllactone Crosspolymer is used in 385 formulations, 378 of which are leave-on products and 7 of which are rinse-off products. The five other ingredients that had reported uses by the VCRP were used in 24 or fewer cosmetic formulations. The highest concentration of use was reported to be 31% for HDI/Trimethylol Hexyllactone Crosspolymer in leave-on products.

The acute oral LD_{50} was >10,000 mg/kg in rats for a product mixture consisting of Bis-Cocaminopropylamine/HDI/ PEG-100 Copolymer and butylene glycol. In an acute oral toxicity study using rats, a dose of 5000 mg/kg HDI/Trimethylol Hexyllactone Crosspolymer administered by gavage caused no clinical signs or mortalities. The oral LD_{50} of Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer was reported to be >2000 mg/kg in rats. The acute oral LD_{50} for PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether ranged from >2000->2500 mg/kg in rats. The oral LD_{50} for Steareth-100/PEG-136/HDI Copolymer was reported to be >10,000 mg/kg in rats.

The acute inhalation LC_{50} of Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer was reported to be >1.99 mg/L for a 4-h exposure.

Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer, Steareth-100/PEG-136/HDI Copolymer, and PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether were not mutagenic in Ames tests.

HDI/Trimethylol Hexyllactone Crosspolymer at 100% was not a dermal irritant on the intact or abraded skin of rabbits. Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer was reported to be dermally non-irritating in rabbits, and Steareth-100/PEG-136/HDI Copolymer at 100% was not dermally irritating to rabbits. PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether up to 30% was not a dermal irritant to guinea pigs in irritation assays.

Foundations containing HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer at 1.7% and 3.19% were not irritating in human primary skin irritation tests. In a human patch test of HDI/Trimethylol Hexyllactone Crosspolymer at 100% (as a dry powder), there were no effects observed when the patch was removed.

In an EpiDerm™ Skin Model *In Vitro* Toxicity Testing System, a mixture containing Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer at up to 30% was predicted to be non-irritating. Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer (concentration not specified) was predicted to be non-irritating in an in vitro test for corrosion of human skin and in an in vitro test for skin irritation using reconstructed human epidermis. The ET_{50} for PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether in an EpiDerm MTT Viability Assay was reported to be >24 h.

HDI/Trimethylol Hexyllactone Crosspolymer at 100% was a slight ocular irritant (thought to be due to mechanical abrasion) but was not an ocular irritant according to the approved criteria of the National Occupational Health and Safety Commission of Australia (NOHSC). Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer was a slight irritant in rabbits in an acute eye irritation/corrosion assay. PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether was not an ocular irritant up to 30% in rabbits. Steareth-100/PEG-136/HDI Copolymer at 100% was classified as a non-irritant in the eyes of rabbits.

The ocular RC_{50} was >100% in a CAMVA assay of PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether. In a BCOP assay, the test score of PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether did not require its classification as an ocular irritant or toxicant.

Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer was not sensitizing in guinea pigs in a Magnusson Kligman maximization test. PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether, up to 30%, was not a dermal sensitizer when challenged up to 30%.

In an HRIPT, Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer at 30% was not a dermal sensitizer. In HRIPTs of 2 foundations containing HDI/Trimethylol Hexyllactone Crosspolymer at 10% and 30.7%, there were no signs of dermal irritation or allergic contact dermatitis observed. In a HRIPT, PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether did not demonstrate any indication of dermal irritation or allergic contact sensitization.

DISCUSSION

The Panel examined the available data, which included method of manufacture and impurity data; acute oral, and inhalation toxicity; genotoxicity; dermal and ocular irritation data; and sensitization data. Three of these ingredients were not mutagenic in bacterial assays. Molecular weights for some of the ingredients were reported to range from <500 (a small percentage of the ingredient) to 75,000 Da. There were no toxicokinetic, repeated dermal toxicity, and reproductive/developmental data found in the published literature or submitted by Industry. The results of the assays for ocular and dermal irritation and dermal sensitization showed that there were no concerns that the tested ingredients would be irritating or sensitizing under the conditions of use.

The Panel recognizes that there are data gaps regarding use and concentration of these ingredients. However, the overall information available on the types of products in which these ingredients are used and at the concentrations provided indicate a pattern of use which was considered by the Expert Panel in assessing safety.

The Panel noted that the HDI monomer can cause occupational asthma, hypersensitivity pneumonitis, rhinitis, and accelerated lung deterioration. After examining the method of manufacture and impurity data, the Panel determined that

there would not be toxicologically significant levels of residual HDI (TMHDI, SMDI, or HDI isocyanurate trimer) monomers in these ingredients. Manufacturers and formulators should continue to use good manufacturing practices (GMPs) to minimize the monomer content to below toxicologically significant levels in these ingredients and in formulation.

Since the moieties of some these ingredients may be plant-derived, the Panel expressed concern regarding heavy metals that may be present in these ingredients. They stressed that the cosmetics industry should continue to use GMPs to limit these impurities in the ingredient before blending into cosmetic formulation.

These ingredients vary in size depending on the manufacturing process. Manufacturers and formulators should use GMPs to ensure that polymers with low molecular weights (<1000 Da) are minimized in cosmetic products and consistent with levels in materials (ingredients or formulations) for which direct safety test data are available.

Unpublished data on Steareth-100/PEG-136/HDI Copolymer were submitted with the suggestion that the data be used for read-across to HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer, Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer, and Bis-Lauryl Cocaminopropylamine/HDI/PEG-100 Copolymer. The Panel found the data to be appropriate for read across for these three ingredients.

Inspection of the chemical structural formulas of many, but not all, of these ingredients indicated that even the smallest possible polymers would have molecular weights >1000 Da, because at least one of the monomers was >1000 Da, and thus would have no significant dermal absorption. For example, it was noted that the PEG monomers (PEG-17 and PEG-11) were large, and that the resulting crosspolymer, Methoxy PEG-17/Methoxy PEG-11/HDI Crosspolymer, would therefore be large enough that it would not penetrate intact skin; accordingly, there is no concern about systemic exposure. GMPs should be followed to ensure that there are no low-molecular weight fractions or residual monomers (e.g., HDI) in these ingredients. This approach was not possible for Bis-Hydroxyethyl Acrylate Poly(1,4-Butanediol)-9/TMHDI Copolymer and 1,4-Butanediol/Succinic Acid/Adipic Acid/HDI Copolymer with the available chemical structural formulas.

The Panel discussed the issue of incidental inhalation exposure from products that may be sprays (e.g., tonics, dressings and other hair grooming aids; face and neck products; body and hand products; indoor tanning preparations and from face powders). These ingredients are reportedly used at concentrations at up to 2.5% in products that may be sprayed and aerosolized, and at up to 12.6% in cosmetic products that may become airborne. The molecular weight of several of these ingredients was reported to be 7000 Da or greater; some ingredients had no reported molecular weight data. Limited data available from an acute inhalation study of Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer suggest little potential for respiratory effects at concentration of use. The Panel noted that droplets/particles from spray and loose-powder cosmetic products would not be respirable to any appreciable amount. Furthermore, these ingredients are not likely to cause any direct toxic effects in the upper respiratory tract, based on the properties of the HDI polymers and on data that shows that these ingredients are not irritants. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. In addition, these ingredients are large macromolecules, insoluble in water, and chemically inert under physiological conditions or conditions of use, which supports the view that they are unlikely to be absorbed or cause local effects in the respiratory tract. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

Molecular weights were not provided for Bis-Hydroxyethyl Acrylate Poly(1,4-Butanediol)-9/TMHDI Copolymer and 1,4-Butanediol/Succinic Acid/Adipic Acid/HDI Copolymer. Therefore, it could not be concluded that these ingredients would not penetrate the skin, and the following data are needed for these two ingredients:

- Molecular weight distribution
- If the molecular weight is below 1000 Da, then solubility in formulation, dermal absorption, and/or 28-day dermal toxicity study
- If soluble or dermally absorbed, then systemic toxicity data including genotoxicity, carcinogenicity, and reproduction/developmental toxicity

CONCLUSION

The CIR Expert Panel concluded that the following 17 HDI polymers are safe in cosmetics in the present practices of use and concentration described in this safety assessment:

- HDI/Trimethylol Hexyllactone Crosspolymer
- Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer
- Bis-Isostearyl 1,4-Butanediol/HDI/Hydrogenated Dimer Dilinoleyl Alcohol Copolymer*
- Bis-Lauryl Cocaminopropylamine/HDI/PEG-100 Copolymer*
- Bis-Methoxy PEG-10 Dimethyl MEA/HDI/Bis-PEG-10 Dimethicone Copolymer*
- Cholesterol/HDI/Pullulan Copolymer*
- Decyl HDI/PEG-180 Crosspolymer*
- Diethylene Glycol/DMAP Acrylamide/ PEG-180/HDI Copolymer
- HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer
- HDI/PEI-45/SMDI Crosspolymer*
- HDI/PPG/Polycaprolactone Crosspolymer
- Methoxy PEG-17/Methoxy PEG-11/HDI Crosspolymer
- Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer
- PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether
- PPG-26/HDI Copolymer*
- Steareth-100/PEG-136/HDI Copolymer
- Stearyl HDI/PEG-50 Copolymer*

The available data are insufficient to make a determination that the following 2 ingredients are safe under the intended conditions of use:

- Bis-Hydroxyethyl Acrylate Poly(1,4-Butanediol)-9/TMHDI Copolymer*
- 1,4-Butanediol/Succinic Acid/Adipic Acid/HDI Copolymer*

*Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

TABLES

Table 1. Definitions, idealized structures, and functions of the HDI polymers in this safety assessment.[1,CIR Staff]

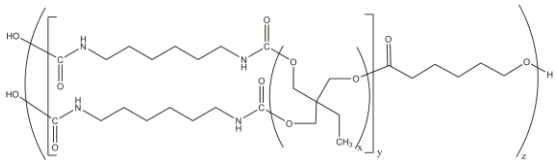
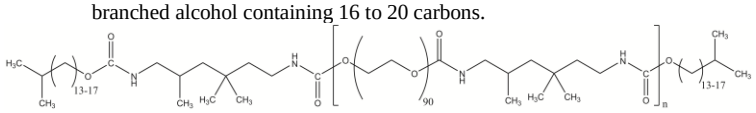
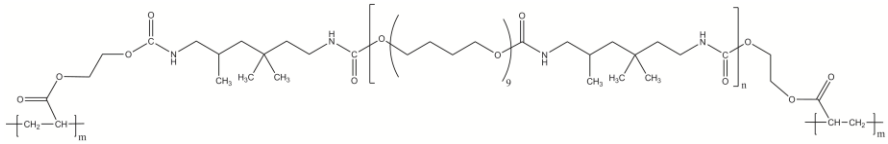
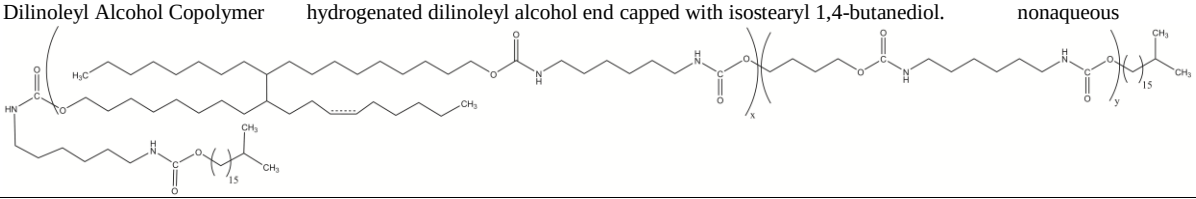
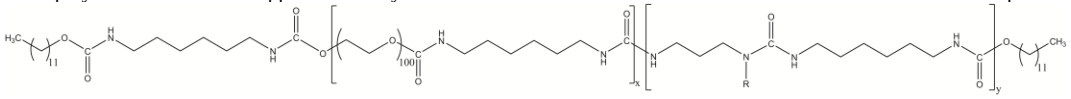
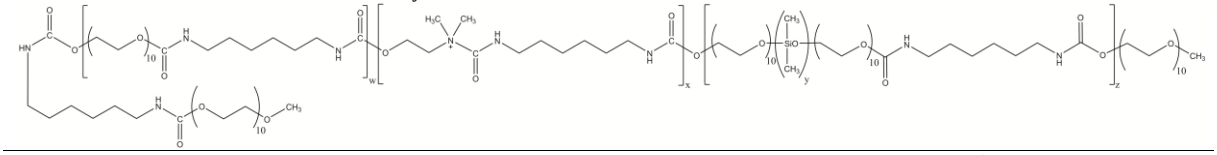
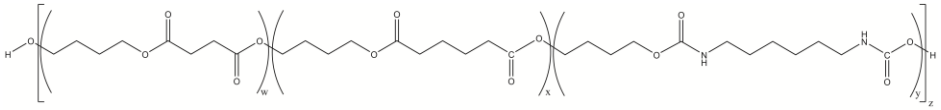
Ingredient/CAS No.	Definition	Function
HDI/Trimethylol Hexyllactone Crosspolymer	HDI/Trimethylol Hexyllactone Crosspolymer is a cross-linked condensation polymer formed from the reaction of hexamethylene diisocyanate (HDI) with the esterification product of trimethylolpropane with 6 to 7 ~~moles~~ [equivalents] of hexyllactone. 	Anticaking agent
Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer [one example of an "iso"]	Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer is a copolymer of trimethylhexanediisocyanate (TMHDI) and PEG-90 end capped with a branched alcohol containing 16 to 20 carbons. 	Viscosity increasing agent - aqueous
Bis-Hydroxyethyl Acrylate Poly(1,4-Butanediol)-9/TMHDI Copolymer	Bis-Hydroxyethyl Acrylate Poly(1,4-Butanediol)-9/TMHDI Copolymer is a copolymer of poly(1,4-butanediol)-9 and trimethylhexanediisocyanate (TMHDI) end capped with hydroxyethylacrylate. 	Film former
Bis-Isostearyl 1,4-Butanediol/ HDI/Hydrogenated Dimer Dilinoleyl Alcohol Copolymer	Bis-Isostearyl 1,4-Butanediol/HDI/Hydrogenated Dimer Dilinoleyl Alcohol Copolymer is a copolymer of hexamethylene diisocyanate (HDI), and hydrogenated dilinoleyl alcohol end capped with isostearyl 1,4-butanediol. 	Viscosity increasing agent - nonaqueous
Bis-Lauryl Cocaminopropylamine/HDI/ PEG-100 Copolymer [wherein R represents the fatty alkyl chain residues from coconut]	Bis-Lauryl Cocaminopropylamine/HDI/PEG-100 Copolymer is a copolymer of cocoaminopropylamine, PEG-100, and hexamethylene diisocyanate (HDI) end capped with lauryl alcohol. 	Viscosity increasing agent - nonaqueous
Bis-Methoxy PEG-10 Dimethyl MEA/HDI/bis-PEG-10 Dimethicone Copolymer	Bis-Methoxy PEG-10 Dimethyl MEA/HDI/Bis-PEG-10 Dimethicone Copolymer is a copolymer of hexamethylene diisocyanate (HDI), dimethylethanolamine and bis-PEG-10 dimethicone end capped with PEG-10 monomethyl ether. 	Hair conditioning agent
1,4-Butanediol/Succinic Acid/Adipic Acid/HDI Copolymer 119553-67-2	1,4-Butanediol/Succinic Acid/Adipic Acid/HDI Copolymer is a copolymer of 1,4-butanediol, succinic acid, adipic acid, and hexamethylene diisocyanate monomers. 	Abrasive, binder, film former
Cholesterol/HDI/Pullulan Copolymer	Cholesterol/HDI/Pullulan Copolymer is a copolymer of cholesterol, hexamethylene diisocyanate, and pullulan monomers.	Emulsion stabilizer, humectant, viscosity increasing agent - aqueous

Table 1. Definitions, idealized structures, and functions of the HDI polymers in this safety assessment.[1,CIR Staff]

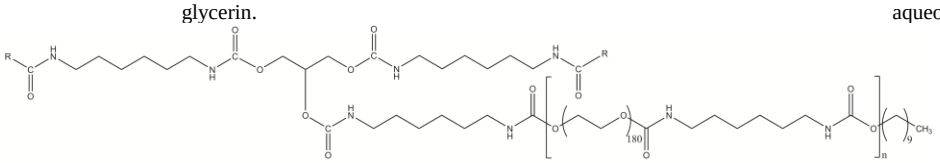
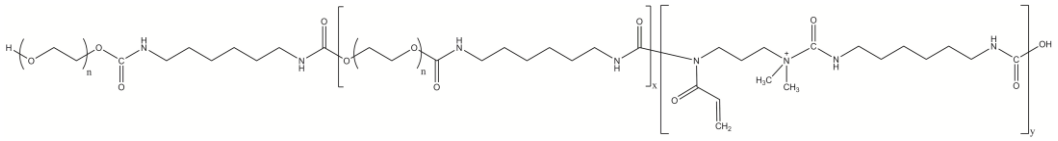
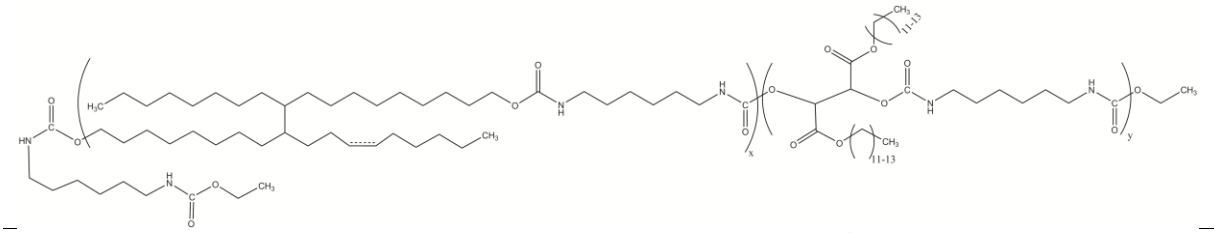
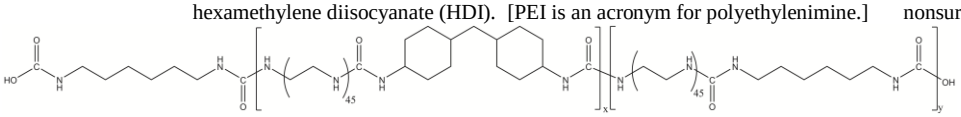
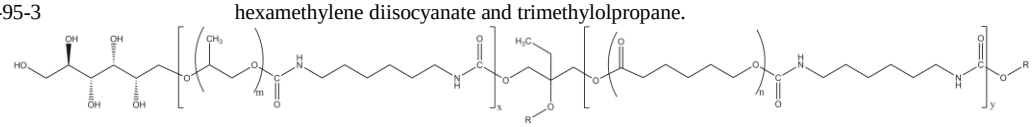
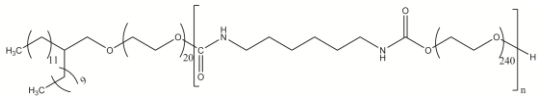
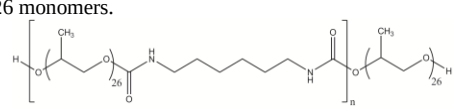
Ingredient/CAS No.	Definition	Function
Decyl HDI/PEG-180 Crosspolymer	Decyl HDI/PEG-180 Crosspolymer is a copolymer of hexylmethylene diisocyanate (HDI), PEG-180, and decyl alcohol monomers crosslinked with glycerin.	Viscosity increasing agent - aqueous
 [wherein R is glycerin, PEG-180, or decyl alcohol]		
Diethylene Glycol/DMAP Acrylamide/PEG-180/HDI Copolymer	Diethylene Glycol/DMAP Acrylamide/PEG-180/HDI Copolymer is a copolymer of diethylene glycol, dimethylaminopropyl (DMAP) acrylamide, PEG-180, and hexamethylene diisocyanate (HDI) monomers.	Hair conditioning agents/ skin protectants, skin-conditioning agent - miscellaneous
 [wherein n is 2 or 180]		
HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer 1268856-56-9	HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer is a copolymer of 1,6-hexamethylene diisocyanate (HDI), di-C12-14 alkyl tartrate, and hydrogenated dilinoleyl alcohol, chain-terminated by ethyl alcohol.	Film former
		
HDI/PEI-45/SMDI Crosspolymer	HDI/PEI-45/SMDI Crosspolymer is the crosslinked polymer formed by the reaction of PEI-45 with saturated methylene diphenyldiisocyanate (SMDI) and hexamethylene diisocyanate (HDI). [PEI is an acronym for polyethylenimine.]	Absorbent, dispersing agent - nonsurfactant
 [crosslinker/crosslinking is not defined]		
HDI/PPG/Polycaprolactone Crosspolymer 302791-95-3	HDI/PPG/Polycaprolactone Crosspolymer is a cross-linked condensation polymer of polycaprolactone, a sorbitol initiated polypropylene glycol with hexamethylene diisocyanate and trimethylolpropane.	Anticaking agents, bulking agent
 [wherein R is the residue of HDI and either PPG or Polycaprolactone]		
Methoxy PEG-17/Methoxy PEG-11/HDI Crosspolymer	Methoxy PEG-17/Methoxy PEG-11/HDI Crosspolymer is a copolymer of methoxy PEG-17, methoxy PEG-11, and hexamethylene diisocyanate (HDI) crosslinked by water and the addition of sodium hydroxide.	Anticaking agent
Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer	Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer is a copolymer of methoxy PEG-17, methoxy PEG-11, and hexamethylene diisocyanate (HDI) trimer in which the free isocyanate groups are crosslinked by water to form urea linkages.	Anticaking agent
PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether	PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether is a copolymer of PEG-240, decyltetradeceth-20, and hexamethylene diisocyanate monomers.	Viscosity increasing agent – aqueous
		
PPG-26/HDI Copolymer	PPG-26/HDI Copolymer is a copolymer of hexamethylene diisocyanate and PPG-26 monomers.	Film former, plasticizer
		

Table 1. Definitions, idealized structures, and functions of the HDI polymers in this safety assessment.[1,CIR Staff]

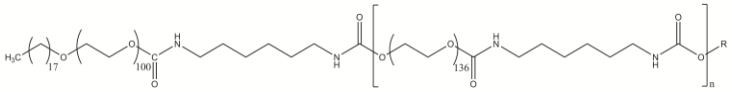
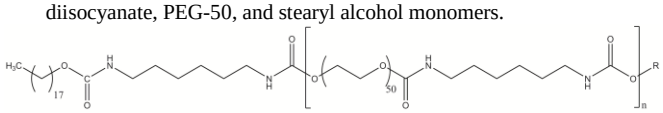
Ingredient/CAS No.	Definition	Function
Steareth-100/PEG-136/HDI Copolymer 103777-69-1	Steareth-100/PEG-136/HDI Copolymer is a copolymer of steareth-100, PEG-136, and hexamethylene diisocyanate monomers.  [wherein R is a residue of PEG-136 or steareth-100]	Viscosity increasing agent – aqueous
Stearyl HDI/PEG-50 Copolymer	Stearyl HDI/PEG-50 Copolymer is a copolymer of hexylmethylene diisocyanate, PEG-50, and stearyl alcohol monomers.  [wherein R is a residue of PEG-50 or stearyl alcohol]	Film former

Table 2. Previous safety assessments of components/monomers of HDI polymers in this safety assessment.

Constituent and ingredient group report	Conclusion	Maximum reported concentration of use reported for ingredients in the latest safety assessment or re-review	Reference
Polyethylene glycols (PEGs) - triethylene glycol and any PEGs ≥ 4	Safe for use in cosmetics in the present practices of use and concentration.	85%	2,4,7
PEG-10 dimethicone - polyoxyalkylene siloxane copolymers, alkyl-polyoxyalkylene siloxane copolymers, and related ingredients	Safe for use in cosmetics in the present practices of use and concentration.	22% hair; 15% dermal	3,5
Methoxy PEG-10, decyltetradeceth-20, steareth-100 - alkyl PEG ethers	Safe as used when formulated to be nonirritating	32% in a product to be diluted; 25%	9
Adipic acid, succinic acid - dicarboxylic acids, salts, and esters	Safe for use in cosmetics in the present practices of use and concentration.	26% in a product to be diluted; 0.4%	10
Cholesterol	Safe as used.	3%	8,48
Pullulan - microbial polysaccharide gums	Safe for use in cosmetics in the present practices of use and concentration.	12% hair; 17% in oral hygiene; biosaccharide gum-1 6% in dermal	11
Glycerin	Safe for use in cosmetics in the present practices of use and concentration.	99.4%	6
PPG-26 - propylene glycol, tripropylene glycol, and PPGs	Safe as used when formulated to be nonirritating.	99% in product to be diluted; 73% in dermal	12
Stearyl alcohol with oleyl alcohol and octyl dodecanol	Safe as used.	56%	6,48
Polyacrylamide	Safe as a cosmetic ingredient if the level of acrylamide monomer in formulation is not greater than 5 ppm	2.8%	13

Table 3. Chemical and physical properties of hexamethylene diisocyanate polymers.

Property	Value	Reference
HDI/Trimethylol Hexyllactone Crosspolymer		
Physical Form	Fine powder	15-17
Color	White to pale yellow	15-17
Molecular Weight g/mol	>10,000	15-17
Density @ 20°C kg/m^3	1100-1250	15-17
g/mL	0.6	18
Melting Point °C	>225	15-17
Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer		
Color	Translucent	32,49
Molecular Weight g/mol	Average >7000	20
Density g/mL @ 25°C	1.03-1.08	20
Viscosity kg/(s m)@ °C	3-10	20
Bis-Lauryl Cocaminopropylamine/HDI/PEG-100 Copolymer		
Color	Translucent	32
Molecular Weight g/mol	>10,000	22
Bis-Methoxy PEG-10 Dimethyl MEA/HDI/BIS-PEG-10 Dimethicone Copolymer		
Molecular Weight g/mol	>1000	21
HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer		
Physical Form	Viscous liquid	23
Color	Yellow	23
Odor	Characteristic	23
Molecular Weight g/mol	>25,000	23
Viscosity kg/(s m)@ 25°C	3-5	23
HDI/PPG/Polycaprolactone Crosspolymer		
Molecular Weight g/mol	>10,000	26
Density g/mL	0.6	19
Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer		
Physical Form	Solid, powder, granules	33
Color	White	33
Odor	Odorless	33
Molecular Weight g/mol	>1000	50
	Infinite	28
Density g/mL @ 20°C	~0.246	33
Melting Point °C	>200	33
PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether		
Molecular Weight g/mol	4000-75,000	27
Steareth-100/PEG-136/HDI Copolymer		
Physical Form	Powder	51
Color	White	51
Molecular Weight g/mol	>15,000	24
Melting Point °C	53-63	51
Water Solubility	Dispersible	51

Table 4. Reported particle size distribution for 2 grades of HDI/Trimethylol Hexyllactone Crosspolymer from 1 supplier and another sample from a second supplier.[15-17]

	<100 µm (%)	**<10 µm (%)**	**<1 µm (%)**	**Median diameter** (µm)
Grade 1	100	33.8	5.5	12.54
Grade 2	100	87.5	7.1	6.16
Second supplier	100	15.15*	0	12.0-18.0**

* ≤ 10.42 µm
** Average diameter

Table 5. Residual diisocyanate in HDI polymers.

Ingredient	Residual diisocyanate	Reference
HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer	<0.5 ppm	[23]
Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer	Below limit of detection (0.02%)[a]	[52]
Bis-Lauryl Cocaminopropylamine/HDI/PEG-100 Copolymer	Below limit of detection (0.017%)	[30]
Steareth-100/PEG-136/HDI Copolymer	Below limit of detection (0.017%)	[30]
HDI/Trimethylol Hexyllactone Crosspolymer	<100 ppm	[18]
HDI/PPG/Polycaprolactone Crosspolymer	<100 ppm	[19]
PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether	Below limit of detection (20 ppm)	[27]

[a] Trimethylhexanediisocyanate

Table 6. Frequency of use and concentration according to duration and exposure of HDI polymers.[34-36]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	HDI/Trimethylol Hexyllactone Crosspolymer		**Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer**		**Diethylene Glycol/DMAP Acrylamide/PEG-180/ HDI Copolymer**		**HDI/Di-C12-14 Alkyl Tartrate/Hydrogenated Dilinoleyl Alcohol Copolymer**	
Total/range	**385**	**0.0096-31**	**NR**	**0.6**	**6**	**NR**	**NR**	**0.026-7.6**
Duration of use								
Leave-on	378	0.0096-31	NR	0.6	1	NR	NR	0.026-7.6
Rinse-off	7	11.7	NR	NR	5	NR	NR	NR
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type[a]								
Eye area	139	0.049-19.6	NR	0.6	NR	NR	NR	1.2
Incidental ingestion	11	0.0096-15.1	NR	NR	NR	NR	NR	0.026-7.6
Incidental Inhalation-sprays	33[b]; 39[c]	NR	NR	NR	1[b]	NR	NR	NR
Incidental inhalation-powders	53; 39[c]	3-12.6; 0.78-14.4[d]	NR	NR	NR	NR	NR	NR
Dermal contact	360	0.059-31	NR	NR	NR	NR	NR	1.2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	NR	NR	NR	NR	6	NR	NR	NR
Hair-coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	1	0.21-0.96	NR	NR	NR	NR	NR	NR
Mucous Membrane	12	0.0096-15.1	NR	NR	NR	NR	NR	0.026-7.6
Baby	NR	NR	NR	NR	NR	NR	NR	NR

Table 6. Frequency of use and concentration according to duration and exposure of HDI polymers.[34-36]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	HDI/PPG/ Polycaprolactone Crosspolymer		Methoxy PEG-17/ Methoxy PEG-11/ HDI Crosspolymer		Methoxy PEG-17/ Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer		PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether	
Total/range	**24**	**2-11.8**	**3**	**NR**	**NR**	**0.025**	**4**	**1-2**
Duration of use								
Leave-on	24	2-11.8	1	NR	NR	0.025	4	1-2
Rinse-off	NR	NR	NR	NR	NR	NR	NR	1
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type								
Eye area	4	5-9.8	NR	NR	NR	NR	3	1.9-2
Incidental ingestion	NR	NR	1	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	6[b]; 3[c]	NR	NR	NR	NR	NR	1[b]	2[b]
Incidental inhalation-powders	3; 3[c]	3-11.8; 2-10.8[d]	NR	NR	NR	NR	NR	2[d]
Dermal contact	22	2-11.8	NR	NR	NR	0.025	4	1-2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	NR	NR	NR	NR	NR	NR	NR	1-2
Hair-coloring	NR	NR	NR	NR	NR	NR	NR	1
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	3	NR	NR	NR	NR	NR
Baby	NR	NR	NR	NR	NR	NR	NR	NR

	Steareth-100/PEG-136/ HDI Copolymer	
Total/range	**1**	**0.87-2.5**
Duration of use		
Leave-on	1	1.6-2.5
Rinse-off	NR	0.87
Diluted for (bath) use	NR	NR
Exposure type		
Eye area	NR	NR
Incidental ingestion	NR	NR
Incidental Inhalation-sprays	NR	2.5[b]
Incidental inhalation-powders	NR	NR
Dermal contact	NR	1.6
Deodorant (underarm)	NR	1.6[e]
Hair-noncoloring	1	2.5
Hair-coloring	NR	0.87
Nail	NR	NR
Mucous Membrane	NR	NR
Baby	NR	NR

NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted for Bath Product Uses.

[a] 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.

[b] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

[c] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

[d] It is possible these products may be powders, but it is not specified whether the reported uses are powders.

[e] Not spray products.

Table 7. HDI polymer ingredients that have no reported uses.[34-36]

Bis-Hydroxyethyl Acrylate Poly(1,4-Butanediol)-9/TMHDI Copolymer	Bis-Isostearyl 1,4-Butanediol/HDI/Hydrogenated Dimer Dilinoleyl Alcohol Copolymer
Bis-Lauryl Cocaminopropylamine/HDI/PEG-100 Copolymer	Bis-Methoxy PEG-10 Dimethyl MEA/HDI/Bis-PEG-10 Dimethicone Copolymer
1,4-Butanediol/Succinic Acid/Adipic Acid/HDI Copolymer	Cholesterol/HDI/Pullulan Copolymer
Decyl HDI/PEG-180 Crosspolymer	HDI/PEI-45/SMDI Crosspolymer
PPG-26/HDI Copolymer	Stearyl HDI/PEG-50 Copolymer

Table 8. Acute oral toxicity of HDI polymers in this safety assessment.

Ingredient	Animal; n	Results; Methods	Reference
HDI/Trimethylol Hexyllactone Crosspolymer	Wistar rats (n=5/sex),	5000 mg/kg administered by intragastric feeding caused no clinical signs or mortalities	15-17
Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer	Rats; not specified	LD_{50}=>2000 mg/kg. OECD TG 423	33
PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether	Rats; not specified	LD_{50}=>2500 mg/kg	27
PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether	Rats; not specified	LD_{50}=>2000 mg/kg	27
Steareth-100/PEG-136/HDI Copolymer	Rats; 5/sex	LD_{50}=>10 000 mg/kg. No mortalities during dosing and the observation period. At 24 h post dosing, 3 rats had bristled fur, diarrhea and dirty fur around the anal region due to feces; all of which resolved at 48 h after dosing. At necropsy, 2 rats had pinhead-sized, cartilaginous elevations on the forestomach mucous membrane; all other necropsies were unremarkable.	24

OECD TG= Organization for Economic Cooperation and Development Test Guideline

Table 9. Dermal irritation assays of HDI polymers.

Ingredient (concentration)	Assay	Results	Reference
Non-Human			
HDI/Trimethylol Hexyllactone Crosspolymer (100%)	Primary irritation study in rabbits (n=6); intact and abraded skin	Slight irritation of the skin was observed in 5 of 6 rabbits. 1 rabbit showed well-defined erythema and slight edema 24 and 72 h after administration. The irritation scores were below the threshold for classifying a test substance as an irritant according to the criteria of NOHSC.	15-17
Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer (concentration not specified)	OECD TG 404 in rabbits	Non-irritating	33
PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether (3%, 10%, or 30% in a PG solution)	Single dose in guinea pigs	Not a dermal irritant	27
PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether (3%, 10%, or 30% in a PG solution)	14-Day open-application cumulative assay in guinea pigs	Not a dermal irritant	27
Steareth-100/PEG-136/HDI Copolymer (100%; 0.5 g; dry)	OECD TG 404 in male rabbits (n=3)	Primary Irritation Index=0/8	24
Human			
HDI/Trimethylol Hexyllactone Crosspolymer (100% as a dry powder)	24-h Patch test (n=21 male, 23 female),	No effects observed. It was noted that this study may not be predictive of effects that may occur upon exposure to this substance in moist formulations.	15-17
HDI/Di-C12-14 Alkyl Tartrate/ Hydrogenated Dilinoleyl Alcohol Copolymer (1.7%) in a foundation product	Primary skin irritation test (n=20) under semi-occlusion.	Average irritation index was 0.0, the product was classified as non-irritating	23
HDI/Di-C12-14 Alkyl Tartrate/ Hydrogenated Dilinoleyl Alcohol Copolymer (3.19%) in a foundation product	Primary skin irritation test (n=20) under semi-occlusion.	Average irritation index was 0.05 at the first reading and 0.00 at the second reading. The product was classified as non-irritating.	23

Table 9. Dermal irritation assays of HDI polymers.

Ingredient (concentration)	Assay	Results	Reference
In Vitro			
Mixture containing 30% Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer (16.67%, 50%, and 100% in water; actual concentration: 5%, 15%, 30%)	EpiDerm™ Skin Model *In Vitro* Toxicity Testing System	The test substance is predicted to be non-irritating.	20
Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer (concentration not specified)	OECD TG 431, in vitro test for corrosion of human skin	Predicted to be non-irritating to the skin	33
Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer (concentration not specified)	OECD TG 439, in vitro test for skin irritation using reconstructed human epidermis	Predicted to be non-irritating	33
PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether	EpiDerm MTT Viability Assay	ET_{50}>24.0 h	27

ET_{50}= effective time of exposure to reduce tissue viability to 50%
NOHSC= National Occupational Health and Safety Commission of Australia
PG=propylene glycol

Table 10. Ocular irritation studies of HDI polymers using rabbits.

Ingredient (concentration)	Assay	Results	Reference
HDI/Trimethylol Hexyllactone Crosspolymer (100%)	Ocular irritation study (n=6)	Mild to moderate conjunctival redness and mild chemosis were observed in 4 of 6 rabbits 24 and 48 h after administration. 1 rabbit still showed redness 4 days after exposure, which was resolved 7 days after exposure. Mild chemosis was observed in 1 rabbit on day 1; this was resolved by day 2. The mean scores for observations 24, 48 and 72 h after exposure were 1.0 for redness and 0.1 for chemosis. It was concluded that the test substance was a slight ocular irritant but not classified as an ocular irritant according to the criteria of the NOHSC. The authors considered the particle size (at least 92.9% > 1 µm; Table 4) and the water insolubility of the tested polymer and concluded that the eye irritation observed was likely attributable to mechanical abrasion rather than to chemical irritancy.	15-17
Methoxy PEG-17/Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer (concentration not specified)	OECD TG 405	Slight irritant	33
PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether (3%, 10%, or 30% in PG solution)	Ocular irritation study	Not an ocular irritant	27
Steareth-100/PEG-136/HDI Copolymer (100%; 0.1 g)	OECD TG 405 (n=3)	Classified as a non-irritant	24

PG=propylene glycol

Table 11. Dermal sensitization studies of HDI polymers.

Ingredient (concentration)	Assay	Results	Reference
Non-Human			
Methoxy PEG-17Methoxy PEG-11/HDI Isocyanurate Trimer Crosspolymer (concentration not specified)	Magnusson Kligman maximization test using guinea pigs; OECD TG 406	Not sensitizing	33
PEG-240/HDI copolymer Bis-decyltetradeceth-20 ether (30% in PG solution)	Skin sensitization assay (species not specified); challenged at 3%, 10%, and 30%.	Not a dermal sensitizer	27
Human			
HDI/Trimethylol Hexyllactone Crosspolymer in a foundation product (30.7%; 0.1-0.15 g)	HRIPT (n=50)	No signs of dermal irritation or allergic contact dermatitis observed	46
HDI/Trimethylol Hexyllactone Crosspolymer in a foundation product (10%; 200 µL)	HRIPT (n=110)	No signs of dermal irritation or allergic contact dermatitis observed	47
Bis-C16-20 Isoalkoxy TMHDI/PEG-90 Copolymer (30% active in PG/water; 0.2 g)	HRIPT (n=48)	One subject exhibited barely perceptible (0.5) erythema 48 h after the challenge.	20
PEG-240/HDI Copolymer Bis-Decyltetradeceth-20 Ether (concentration not specified)	HRIPT (n not specified)	No evidence of dermal irritation or allergic contact sensitization.	27

HRIPT=human repeat insult patch test
PG=propylene glycol

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