Safety Assessment of Trimellitic Anhydride Copolymers as Used in Cosmetics

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date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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

The 2015 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Monice M. Fiume, Assistant Director/Senior Scientific Analyst/Writer and Bart Heldreth, Ph.D., Chemist.

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INTRODUCTION

This scientific literature review is the initial step in preparing a safety assessment of the following 6 trimellitic anhydride copolymers as used in cosmetic formulations:

- Adipic Acid/CHDM/MA/Neopentyl Glycol/Trimellitic Anhydride Copolymer
- Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer
- Isostearoyl Trimellitic Anhydride/Trimethylolpropane Copolymer
- Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer
- Propylene Glycol/Sebacic Acid/Trimellitic Anhydride Copolymer
- Trimethylpentanediol/Isophthalic Acid/Trimellitic Anhydride Copolymer

Most of the trimellitic anhydride copolymers are reported to function as film formers in cosmetic formulations[1] (Table 1).

The ingredients in this report are related as copolymers in that they all share in common trimellitic anhydride (aka 1,2,4-benzenetricarboxylic acid anhydride) as a monomer. Each copolymer is also composed of 1 to 5 of the following additional monomers: adipic acid, cyclohexanedimethanol (CHDM), ethylene glycol, isophthalic acid, maleic anhydride, neopentyl glycol, phthalic anhydride, propylene glycol, sebacic acid, trimethylpentanediol, or trimethylolpropane (chain-terminated by isostearic acid).[1] No information has been submitted regarding the amount of each residual monomer present in these copolymer ingredients, and it is therefore possible that these monomers could be present in the copolymers. Accordingly, relevant information on the toxicity of these monomers is presented in Table 2.[2-31] This information is not intended to be exhaustive or complete, but purely summary to provide insight as to any possible toxicity concerns for these monomers. (If data are submitted that show that no residual monomers are present, or that those residual monomers are entrapped in such a way that they cannot have an effect, then these data can be deleted.)

The anhydride monomers herein (e.g., trimellitic anhydride) can be respiratory sensory irritants, and exposures in the work-place to the anhydrides that are used in the production of these copolymers have resulted in numerous adverse effects. Symptoms such as asthma, allergic rhinitis, bronchitis, conjunctivitis, rhinoconjunctivitis, and elevated antibody levels have been associated with occupational exposures (Table 2).

The safety of several of the non-anhydride monomers as used in cosmetics has previously been reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel (Panel). In 2012, the Panel concluded that adipic acid and sebacic acid are safe in the present practices of use and concentration,[8] and that propylene glycol is safe as used in cosmetic formulations at the present practices of use and concentration when formulated to be non-irritating.[26] In 1999, the Panel published a special report on the reproductive and developmental toxicity of ethylene glycol and its ethers, concluding that the metabolites of ethylene glycol monoalkyl ethers are reproductive and developmental toxins, but in general, these metabolites of concern are not expected to be formed in cosmetic formulations that contain polymers of ethylene glycol.[11]

CHEMISTRY

Definition and Structure

The ingredients in this report are related as copolymers that share in common trimellitic anhydride as a monomer. The monomers of these copolymers are interconnected via ester bonds to form highly branched polymeric (polyester) networks. For example, propylene glycol/sebacic acid/trimellitic anhydride copolymer is the result of the polymerization of propylene glycol, sebacic acid, and trimellitic anhydride. In this case, there are two acidic monomers (sebacic acid and trimellitic anhydride) and one alcohol monomer (propylene glycol). This means that to form a polyester copolymer, every other repeat unit must be propylene glycol. Whether the repeat unit on either end of propylene glycol is the residue of sebacic acid or the residue of trimellitic acid is dependent on the polymerization conditions. Since trimellitic anhydride serves as a ridged, non-linear, tri-functional (trivalent) monomer, these polymers are branched, if not highly-branched in a manner similar to dendrimers.

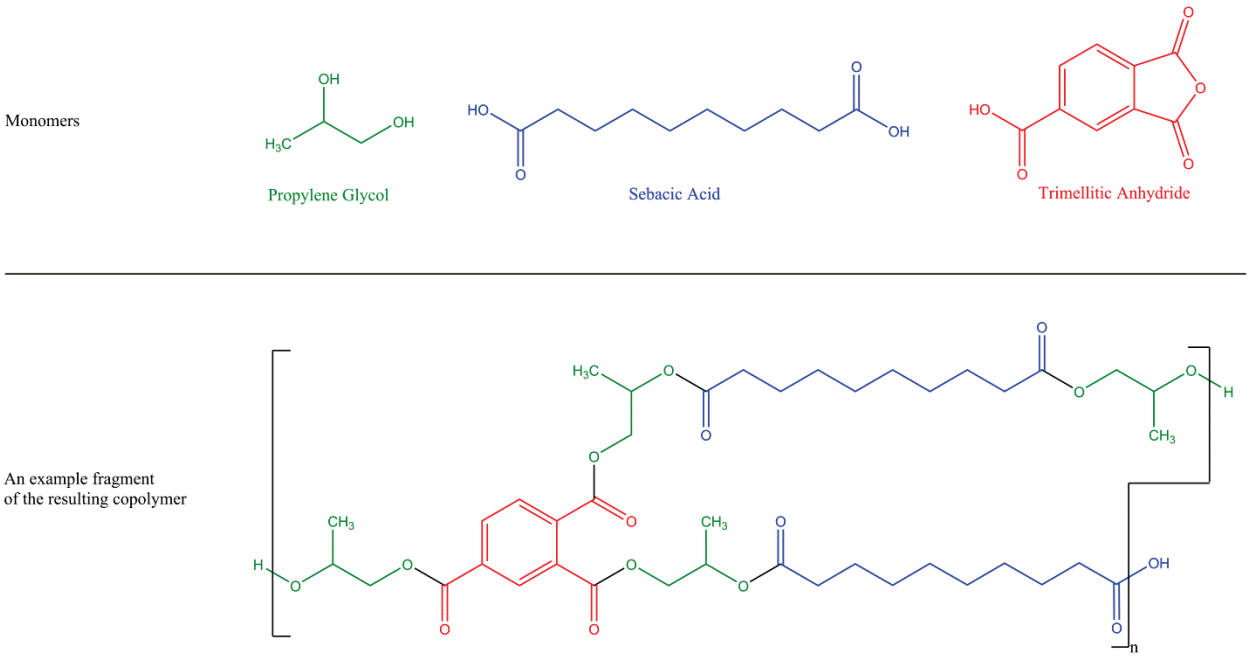


Figure 1. propylene glycol/sebacic acid/trimellitic anhydride copolymer – the connectivity between alcohols (propylene glycol, in this case) and which acids (sebacic acid and trimellitic anhydride, in this case) can vary; this is just one theoretical example of a fragment within a polymeric network

The definitions and structures of the ingredients included in this review are provided in Table 1.

Physical and Chemical Properties

Very little physical and chemical properties data on the trimellitic anhydride copolymers as cosmetic ingredients were found in the published literature, and unpublished data were not provided. The property information that was found is presented in Table 3.[32-34]

Method of Manufacture

The manufacture of each of these trimellitic anhydride copolymers begins with trimellitic anhydride (an activated form of trimellitic acid). No ingredient-specific manufacture flow charts or synthetic schemes have been submitted. However, general polyester synthetic techniques common in the art can be described.[35] For example, synthesis would start by dissolving trimellitic anhydride in a dry solvent, such as dimethylformamide, under an inert gas, such as nitrogen. Next, whatever polyol monomer (e.g., propylene glycol, neopentyl glycol, cyclohexanedimethanol, trimethylolpropane, ethylene glycol, or trimethylpentanediol) is to be used would be added to the solution and distilled under reduced pressure. In a second step, the resultant terminal alcohol groups may be further esterified with appropriate mono- or multi-functional carboxylic acids (e.g., sebacic acid, adipic acid, maleic anhydride, isostearic acid, phthalic anhydride, sebacic acid, or isophthalic acid), and likely a catalyst. This two-step methodology would result in dendrimer-like copolymers, with trimellitic acid as the central core in each. Alternatively, trimellitic anhydride, a polyol, and whatever additional carboxylic acid of choice could be reacted together in one step, under similar conditions, to form more random structured copolymers. Due to the trivalent nature of trimellitic acid, however, the resultant polymers from either of these two methodologies would be non-linear.

Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer

Phthalic anhydride/trimellitic anhydride/glycols copolymer results from condensation of phthalic anhydride, trimellitic anhydride, ethylene glycol and neopentyl glycol monomers.[36]

Impurities/Constituents

Very little impurities data on the trimellitic anhydride copolymers as cosmetic ingredients were found in the published literature, and unpublished data were not provided. The reactions used to manufacture the copolymers can be designed to result in little to no residual monomer, but information on the exact manufacturing process was not available. Without having a precise manufacturing method, the amount of monomer present in the copolymer is unknown. Therefore, it is possible that residual amounts of the following monomers (used in the production of these copolymers) could be present in these ingredients: adipic acid, cyclohexanedimethanol, ethylene glycol, isophthalic acid, maleic anhydride (or maleic acid),

neopentyl glycol, phthalic anhydride (or phthalic acid), trimellitic anhydride (or trimellitic acid), trimethylpentanediol, trimethylolpropane, and isostearic acid.

One supplier has reported that adipic acid/neopentyl glycol/trimellitic anhydride copolymer is sold in butyl acetate, and does not contain formaldehyde, toluene, or xylene.[33]

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated on the basis of the expected use in cosmetics. The Panel utilizes data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry in determining the expected cosmetic use. The data received from the FDA are those it collects 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 product category.

According to the 2015 VCRP survey data, adipic acid/neopentyl glycol/trimellitic anhydride copolymer is reported to be used in 411 cosmetic formulations, and phthalic anhydride/ trimellitic anhydride/glycols copolymer is reported to be used in 74 cosmetic formulations, and both of these ingredients are reported to be used almost exclusively in nail formulations[37] (Table 4). The results of the concentration of use survey conducted by the Council in 2015 indicate that the highest maximum concentration of use for both of these ingredients is in nail polish and enamel; in this product category, adipic acid/neopentyl glycol/trimellitic anhydride copolymer is reported to be used at up to 32.8%, and phthalic anhydride/trimellitic anhydride/ glycols copolymer is reported to be used at up to 12%.[38] According to the Council survey, adipic acid/neopentyl glycol/trimellitic anhydride copolymer has a reported use in one product category that results in dermal exposure, i.e., it is used in face and neck products with a reported maximum concentration of use of 1%.

None of the other trimellitic anhydride copolymers (i.e., adipic acid/CHDM/MA/neopentyl glycol/ trimellitic anhydride copolymer; isostearoyl trimellitic anhydride/ trimethylolpropane copolymer; propylene glycol/sebacic acid/trimellitic anhydride copolymer; or trimethylpentanediol/isophthalic acid/trimellitic anhydride copolymer) are reported to be in use.

All of the trimellitic anhydride copolymers named in the report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[39]

Non-Cosmetic

Adipic acid/CHDM/MA/neopentyl glycol/trimellitic anhydride copolymer is used in preparation of glass fiber reinforced plastic.[32] Phthalic anhydride/trimellitic anhydride/glycols copolymer is used in the manufacture or dyes, pharmaceuticals, insecticides, and as a hardener for resins.[40]

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Toxicokinetics studies on the trimellitic anhydride copolymers were not found in the published literature, nor were unpublished data provided.

TOXICOLOGICAL STUDIES

Toxicological studies on the trimellitic anhydride copolymers were not found in the published literature, nor were unpublished data provided.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Reproductive and developmental toxicity data on the trimellitic anhydride copolymers were not found in the published literature, nor were unpublished data provided.

GENOTOXICITY

Genotoxicity data on the trimellitic anhydride copolymers were not found in the published literature, nor were unpublished data provided.

CARCINOGENICITY

Carcinogenicity data on the trimellitic anhydride copolymers were not found in the published literature, nor were unpublished data provided.

IRRITATION AND SENSITIZATION

Dermal

Skin Irritation and Sensitization

Dermal irritation and/or sensitization test data on the trimellitic anhydride copolymers were not found in the published literature, nor were unpublished data provided. However, several case reports describing allergic reactions to phthalic anhydride/trimellitic anhydride/ glycols copolymer were available.[36,40,41] Details from these case reports are summarized in Table 5.

Ocular

Ocular irritation data on the trimellitic anhydride copolymers were not found in the published literature, nor were unpublished data provided.

INFORMATION SOUGHT

The CIR is seeking the following information on trimellitic anhydride copolymers for use in the resulting safety assessment:

1. information on the amount of residual monomers remaining in the copolymer ingredients;
2. method of manufacture;
3. toxicokinetics and dermal penetration data; if absorbed, the following data may be needed:
    a. oral toxicity data
    b. reproductive and developmental toxicity data
4. dermal toxicity;
5. inhalation toxicity;
6. genotoxicity data; if positive, carcinogenicity data are needed;
7. dermal irritation and sensitization data; and
8. any other data relevant to the determination of safety of these ingredients as used in cosmetics.

SUMMARY

This report addresses the safety of 6 trimellitic anhydride copolymers as used in cosmetics. According to the *International Cosmetic Ingredient Dictionary and Handbook*, these ingredients are reported to function as film formers. The trimellitic anhydride copolymers are related as they all share a common monomer, i.e., trimellitic anhydride; each copolymer is also composed of another 1 to 5 monomers. The monomers that comprise these copolymers are interconnected via ester bonds to form highly branched polymeric (polyester) networks. Currently, no information is available regarding the amount of residual monomer in these copolymers.

VCRP data obtained from the FDA, and data received in response to a survey of the maximum reported use concentration by product category conducted by the Council, indicate that 2 of the 6 ingredients included in this safety assessment are used in cosmetic formulations. Adipic acid/neopentyl glycol/trimellitic anhydride copolymer is reported to be used in 411 cosmetic formulations, with a reported maximum use concentration of 32.8%, and phthalic anhydride/trimellitic anhydride/glycols co-polymer is reported to be used in 74 cosmetic formulations, with a reported maximum use concentration of 12%.

Dermal irritation and/or sensitization test data on the trimellitic anhydride copolymers were neither found in the published literature, nor were unpublished data provided. However, several case reports described allergic reactions to phthalic anhydride/ trimellitic anhydride/ glycols copolymer.

Toxicokinetics, toxicological, genotoxicity, or ocular irritation data were neither found in the published literature, nor were unpublished data provided.

TABLES

Table 1. Definitions and Functions[1] ,CIR Staff

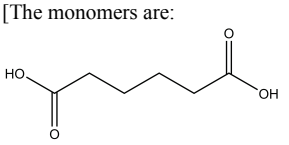
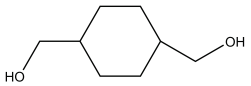
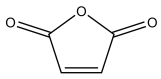
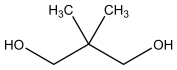
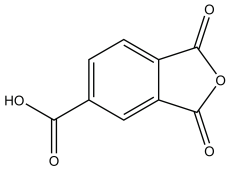
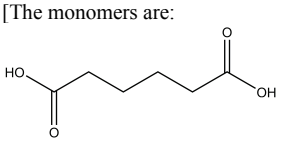
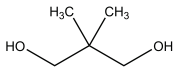
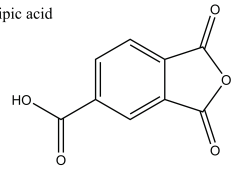
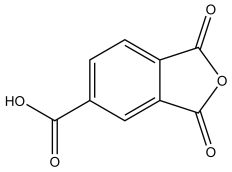
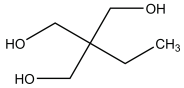
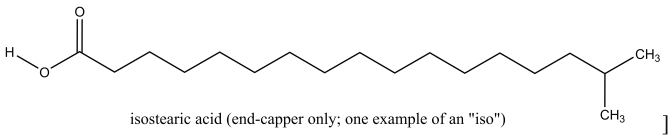
Ingredient (CAS No., if available)	Definition	Function(s)
Adipic Acid/CHDM/MA/Neopentyl Glycol/Trimellitic Anhydride Copolymer [67970-02-9]	a copolymer of adipic acid, cyclohexanedimethanol (CHDM), maleic anhydride (MA), neopentyl glycol and trimellitic anhydride monomers [The monomers are:  adipic acid  cyclohexanedimethanol  maleic anhydride  neopentyl glycol  trimellitic anhydride]	film former
Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer (28407-73-0)	a copolymer of adipic acid, neopentyl glycol and trimellitic anhydride monomers [The monomers are:  adipic acid  neopentyl glycol  trimellitic anhydride]	film former
Isostearoyl Trimellitic Anhydride/Trimethylolpropane Copolymer (1190965-82-2)	a copolymer of trimellitic anhydride and trimethyl[ol]propane chain-terminated by isostearic acid. [The monomers are:  trimellitic anhydride  trimethylolpropane  isostearic acid (end-capper only; one example of an "iso")]	skin protectant; skin-conditioning agent - emollient; skin-conditioning agent - miscellaneous

Table 1. Definitions and Functions[1] ,CIR Staff

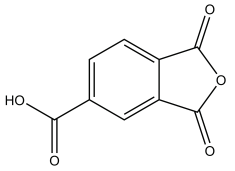
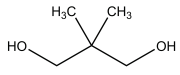
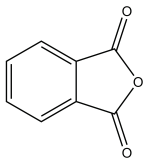
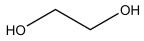
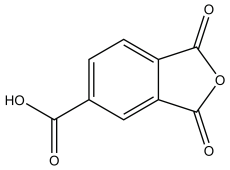
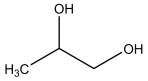
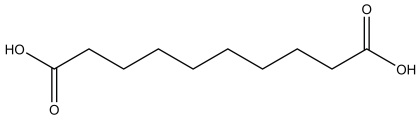
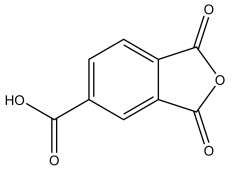
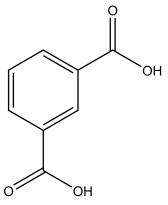
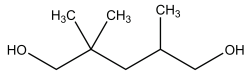
Ingredient (CAS No., if available)	Definition	Function(s)
Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer (186688-25-5)	a copolymer of phthalic anhydride, trimellitic anhydride, ethylene glycol, and neopentyl glycol monomers [The monomers of are:  trimellitic anhydride  neopentyl glycol  phthalic anhydride  ethylene glycol]	film former; viscosity increasing agent – non-aqueous
Propylene Glycol/Sebacic Acid/Trimellitic Anhydride Copolymer	a copolymer of propylene glycol, sebacic acid and trimellitic anhydride [The monomers are:  trimellitic anhydride  propylene glycol  sebacic acid]	film former
Trimethylpentanediol/Isophthalic Acid/Trimellitic Anhydride Copolymer	a copolymer of trimethylpentanediol, isophthalic acid and trimellitic anhydride monomers [The monomers are:  trimellitic anhydride  isophthalic acid  trimethylpentanediol]	film former; viscosity increasing agent – non-aqueous

Table 2. Monomer safety data

Monomer (CAS No.)	Toxicity Data	Reference
trimellitic anhydride (552-30-7)	molecular weight: 192.13 g/mol toxicokinetics: rapidly converted to acid trimellitic in the body (complete hydrolysis likely occurs in <10 min); in rats exposed to 0.95 mg/m^3 for 45 min and killed 3 hr or 1, 2, 4, 8, 16, and 32 days following exposure, in general, the highest tissue concentrations were obtained at the first time point (T-max<3 hr), and a second T-max of 8 days was reported for lung lymph nodes in male rats, suggesting a possible role in the gender differences observed for lung toxicity; the biological half-life in the lungs was estimated to be 21 days in male rats and 16 days in female rats, and in lung associated lymph nodes, half-lives of 13 and 33 days were estimated for male and female rats, respectively; some of the rats became sensitized oral toxicity: the oral LD_{50} has been reported to range from 2,030 to 3,340 mg/kg in male and female rats, with stomach lesions appearing as the most consistent lesion upon necropsy; no adverse effects were observed in rats in a 90-day feed study with 1000- 10,000 ppm (50-500 mg/kg/day) dermal toxicity: the dermal LD_{50} was >2000 mg/kg in rabbits after a 24-h occlusive application inhalation toxicity: the LC_{50} in rats was reported to exceed a concentration of 2,330 mg/m^3, with lung lesions appearing as the most consistent lesion upon necropsy numerous studies were conducted in rats, and in each of the following studies, the exposure was 6 h/day, 5 days/wk: in 2-wks studies, no adverse effects were observed with 0.3 mg/m^3; in rats exposed to 0.1 mg/m^3, lung injury was absent after 2 days of exposure, minimal after 6 days of exposure, and marked after 10 days of exposure; a dose-dependent increase in antibody levels and lung foci was observed in rats exposed to up to 0.30 mg/m^3 for 1-2 wks, and the lung foci completely resolved within 12 days after the last exposure, but reappeared following exposure to a single challenge concentration; exposure to 0.5 mg/m^3 produced hemorrhagic foci of the lung and increased antibody levels, and treatment with estrogen but not testosterone reduced the number of lung foci in both male and female rats; in a 13-wk study, a dose-dependent increase in lung lesions (hemorrhagic foci, inflammatory cell infiltration, bronchoalveoloar pneumonia) and antibody levels was observed in rats exposed to ≤0.054 mg/m^3, and these effects were more pronounced in rats following 6.5 weeks of exposure than observed in animals following 13 wks of exposure, and a NOEL was not identified in 5-day inhalation study in mice with a 14-day recovery period, decreased time of inspiration and expiration and increased length of apneic periods were observed, and the LOEL was 0.01 mg/m^3 reproductive and developmental toxicity: not teratogenic effects or fetal deaths in rats or guinea pigs exposed to 500 µg/m^3 via inhalation on days 6-15 of gestation, however lung foci and TMA-specific antibody were observed in exposed dams and TMA-specific antibody was also noted in neonatal rats and in fetal but not neonatal guinea pigs, lung foci were only observed in the challenged offspring of rats whose mothers had not completely recovered from the original TMA exposure, but lung foci were not observed in adult rat offspring or in neonatal or adult guinea pig offspring; histopathological changes to reproductive tissues have not been observed in rats following subchronic exposures genotoxicity: not genotoxic with or without metabolic activation in 2 Ames tests (≤10,000 µg/plate), in a CHO/HGPRT mutation assay (≤2000µg/ml), or a chromosomal aberration assay in CHO cells (≤2080 µg/ml) dermal irritation/sensitizer: mild skin irritation potential; was a dermal sensitizer in guinea pigs with induction with a 30% solution in DMSO and challenge with 5% in acetone, but 300 mg of powder was not a sensitizer in guinea pigs; sensitizer in rats with 25-50% solutions in acetone/corn oil; sensitizer in mice with 10-50% solutions in acetone/olive oil ocular irritation: highly irritating to rabbit eyes when instilled undiluted effects with occupational exposure: may be a respiratory sensory irritant; elevated antibody levels, asthma, allergic rhinitis, and a late respiratory systemic syndrome are associated with occupational exposures in some workers immunologic response: TMA-induced syndromes are related to high chemical reactivity, which couples to human serum albumin and other proteins to form trimellitate protein conjugates, and some of the TMA syndromes have been correlated to immunologic responses to trimellitate haptenic groups; in TNF-$\alpha^{+/+}$ mice, in the late phase of TMA-induced contact hypersensitivity, the peak of ear swelling responses occurred at 24 h with single challenge and at 8 h after repeated challenge recommended limits: REL (U.S. NIOSH) – TWA 0.04 mg/m^3 (0.005 ppm)	2-7
adipic acid (124-04-9)	**CIR Conclusion: safe in the present practices of use and concentration; reported to be used at a maximum of 0.000001% in leave-on formulations and 18% in rinse-off formulations** molecular weight: 146.14 toxicokinetics: under normal physiological conditions, dicarboxylic acids are rapidly β-oxidized, resulting in very low cellular concentrations and practically non-detectable concentrations in the plasma, and oxidation of odd- and even-numbered chains proceeds to different end points with even chains completely, and odd-number chains not completely, oxidized; recovered unchanged in the urine of rats: with oral and i.v. dosing, approximately 53-67% and 59-71% was recovered, respectively; in humans, 6.76-61% was found in the urine after dosing oral toxicity: oral LD_{50} in rats ranged from 0.94 g/kg to greater than the highest dose tested (11 g/kg); in feeding studies in rats, the NOAEL was >435 mg/kg bw/day in a 4 wk study; with ≤34000 mg/kg bw/day sodium adipate in a protein-deficient diet, the NOAEL was 3333 mg/kg bw in a 19-wk study; 10/14 rats fed a diet containing 3200 mg/kg bw/day died during wks 0-4 of a 33 wk study, body weights of the surviving animals in that group were similar to controls at study termination, and slight effects were seen in the liver; in a 2-yr study, the NOAEL was 1%; slight decreases in weight gains were observed with 3 and 5% inhalation toxicity: in mice exposed to 13 or 129 mg/m^3 adipic acid via inhalation for 4 mos, decreased weight gain, altered oxidase activity, and upper respiratory tract, liver, kidney, and central nervous system effects were observed	8

Table 2. Monomer safety data

Monomer (CAS No.)	Toxicity Data	Reference
	reproductive and developmental toxicity: NOAELs for maternal and developmental toxicity were 288 mg/kg bw in CD-1 mice (highest dose given orally on days 6-15 of gestation) and 288 mg/kg bw in Wistar rats (highest dose given orally on days 6-15 of gestation); NOAELs for maternal toxicity and developmental toxicity were ≥250 mg/kg bw and 250 mg/kg bw, respectively, in Dutch-belted rabbits (maximum dose given by gavage on days 6-18 of gestation); a genotoxicity: not genotoxic in vitro in the Ames tests (concentrations up to 10,000 mg/plate), yeast gene mutation assay (concentrations ≤200 mg/l), mouse lymphoma assay (concentrations of ≤2000 µg/plate), or cytogenetic assay (human embryonic lung fibroblast cells, ≤200 mg/l), or in vivo in a cytogenetics assay (chromosomes from rats dosed by gavage with 5000 mg/kg bw (single dose) or 2500 mg/kg bw (1x/day for 5 days)) or in a dominant lethal assay (up to 5000 mg/kg bw); a significant increase in resorption per implant site was observed in hamsters with 205 mg/kg bw adipic acid, resulting in a decreased number of live fetuses (this decrease was not evaluated statistically, and no effects were reported at this or the other doses (≤44 mg/kg bw)) carcinogenicity: not carcinogenic in a 2-yr chronic study in rats fed up to 5% adipic acid dermal irritation: occlusive application of a 50% aq. solution to intact and abraded rabbit skin for 24 h produced an erythema score of 2-3/4 for intact skin, with clearing by day 3, and mild to severe erythema and edema, for abraded skin, which cleared by day 7; when applied undiluted or as an 80% aq. paste to the backs or ears of rabbits for 24 h, no irritation was observed on the backs and erythema was observed on the ear, with clearing by 72 h; no irritation was observed with a 24 h application (not details provided; semi-occlusive application of a 50% paste in propylene glycol produced slight to mild irritation in 3/6 rabbits; a semi-occlusive application of undiluted adipic acid was not corrosive; 50% in propylene glycol, was not irritating to guinea pigs dermal sensitization: not a sensitizer (1% for intradermal induction, up to 50% in propylene glycol for derma challenge) and produced very mild or no irritation ocular irritation: mild to severe ocular irritant in rabbit eyes; irritation was dose-dependent peroxisome proliferation: did not induce peroxisome proliferation and did not affect relative liver to body weights in rats fed 2% dissolved in alcohol for 3 wks	
cyclohexanedimethanol (CAS No. 105-08-8)	molecular weight: 144.21 g/mol toxicokinetics: when rats were dosed by gavage with 40 or 400 mg/kg/bw (^{14}C; 70% trans-, 30% cis-isomers), there was rapid absorption from the GI tract and after 48 hr, 95% of dose was excreted in urine, 2.5% in feces, 0.03% respired as $^{14}CO_2$, and 0.4% remained in carcass, recovery of radioactivity averaged 98.9% of dose, and the half-life in plasma from rats dosed with 400 mg/kg was about 13 min; the test article and 4-hydroxymethyl-cyclohexanecarboxylic acid were detected in plasma, unchanged test article was not detected in urine and the major metabolites identified in urine were cyclohexanedicarboxylic acid (68%) and 4-hydroxymethylcyclo-hexanecarboxylic acid (31%), <2% of radioactivity in urine was not fully characterized, and the cis-trans ratio of metabolites excreted in urine was the same as that of original dose oral toxicity: observations in rats given a single oral dose by gavage of 400-6400 mg/kg bw ranged from normal to very weak with prostration and vasodilatation; the oral LD_{50} is reported to be >3200-6400 mg/kg in rats; in a 13-wk study in which rats were given 4-12.5 mg/l (i.e., 256-861 mg./kg bw/day for males and 440-1754 mg/kg bw/day for females) in drinking water, the LOAELs were 861 and 1754 mg/kg bw/day for males and females, respectively, based on decreased survival, abnormal urine and feces, reduced body weights and weight gains, decreased feed consumption and increased urinary protein levels, and the NOAELs were 479 and 754 mg/kg bw/day for males and females, respectively reproductive and developmental toxicity: in male and female rats were given 4-12.5 mg/l (i.e., 256-861 mg./kg bw/day for males and 440-1754 mg/kg bw/day for females) in drinking water prior to and during mating and until day 4 of lactation, for systemic toxicity, the LOAELs were 861 and 1360 mg/kg bw/day (based on bloody or discolored urine, reductions in body weights and weight gains and decreased feed consumption) and the NOAELs were 479 and 854 mg/kg bw/day for males and females, respectively, for developmental toxicity the LOAEL was 1360 mg/kg bw/day (based on decreased fetal weight and postnatal survival) and the NOAEL was 854 mg/kg bw/day, and for reproductive toxicity the LOAEL was greater than the highest dose tested and the NOAEL was 1360 mg/kg bw/day genotoxicity: not genotoxic in vitro in an Ames test at ≤5000 µg/plate without and with activation, in a chromosomal aberration assay in human lymphocytes at ≤10 mM with or without metabolic activation, or in vivo in a mammalian bone marrow chromosomal aberration test in which rats and a mouse micronucleus test at doses up to 2000 mg/kg dermal irritation/sensitization: not irritating to rat skin when applied undiluted with a semi-occlusive patch; not a sensitizer in a guinea pig maximization test with 1% at intradermal induction at neat, applied neat for topical induction, and neat and at 50% for challenge ocular irritation: moderately irritating to rabbit eyes	9,10
ethylene glycol (107-21-1)	**CIR Conclusion (Special Report on reproductive and developmental toxicity): the metabolites of ethylene glycol monoalkyl ethers are reproductive and developmental toxins, but in general, these metabolites of concern are not expected to be formed in cosmetic formulations that contain polymers of ethylene glycol** molecular weight: 62.07 g/mol	11

Table 2. Monomer safety data

Monomer (CAS No.)	Toxicity Data	Reference
isophthalic acid (121-91-5)	molecular weight: 166.13 g/mol toxicokinetics: readily eliminated from the body, largely unchanged, thru the urine; in a 13-wk feed study in rats, levels of test article in the blood increased in a dose-dependent manner, and 24-h urinary excretion samples collected on days 7, 30, 60, 90 indicate that urinary excretion, presumably as the unchanged chemical, is the primary route of excretion.; exposure of rats to 10 mg/m^3 for 6 h/day resulted in immediate detection of the test article in the blood, serum levels were 5.3-9.3 ug/ml in females and 1.4-3.4 ug/ml for males, but no test article was detected in the blood 1 wk following exposure oral toxicity: reported oral LD_{50}s have been reported in the range >5000 to 13,000 mg/kg in rats; in a 13-wk feeding study in rats with 800 mg/kg/day, a slight increase in the incidence of and renal pathology (mild hydro-nephrosis, pelvic calcification) were observed, the NOAEL was 250 mg/kg/day, and the LOAEL was 800 mg/kg/day dermal toxicity: no mortality was observed in rabbits following acute exposure to 23,000 mg/kg; in a study with a 24 h occlusive application, the oral LD_{50} was >2000 mg/kg bw inhalation toxicity: no mortality was observed in rats following acute inhalation exposures to 11,400 mg/m^3 ; in a 4-wk study in which rats were exposed 6h/day 5 days/wk, no significant effects were observed with up to 10 mg/m^3, and the NOAEL was 10 mg/m^3 reproductive and developmental toxicity: no maternal or developmental toxicity at inhalation exposures up to 10 mg/m^3 in rats on days 6-15 of gestation genotoxicity: mixed results were reported in 3 Ames tests; negative in a chromosomal aberration assay in CHO cells at up to 5000 µg/ml with and without metabolic activation, in an HGPRT assay, and a mouse lymphoma mutation assay dermal irritation/sensitization: no dermal irritation with application of a single dermal dose to rabbits; a 4-h semi-occlusive application and a 24-h occlusive application of undiluted test material was not irritating to rabbit skin; mild dermal irritation with application of 2000 mg/kg; a 30% solution was not a skin sensitizer in guinea pigs (a reaction were observed in 1/10 of the guinea pigs) ocular irritation: non- to slightly irritating to rabbit eyes	12-14
maleic anhydride (108-31-6)	toxicokinetics: readily hydrolyzed to maleic acid under aqueous conditions oral toxicity: according to the OECD summary, relatively low acute toxicity, with the oral LD_{50} of about 1.0 g/kg in rats, but according to the EPA summary, acute oral studies in rats, mice, rabbits, and guinea pigs have demonstrated moderate to high acute toxicity by ingestion; oral feeding studies have resulted in kidney damage in rats at relatively high doses (> 100 mg/kg/day after 90 days of exposure), with the effects (which were more severe in males than in females) likely due to maleic acid; no kidney effects were observed in rats that were fed diets containing 32 and 100 mg/kg/day maleic anhydride for 2 yrs; a dietary study in dogs dosed with up to 60 mg/kg for 7days/wk for 90 days, showed no adverse effects related to maleic anhydride exposure dermal toxicity: according to the OECD summary, relatively low acute toxicity, with a dermal LD_{50} in the range of 1.6 - 2.6 g/kg in rabbit, but according to the EPA summary, moderate acute dermal toxicity inhalation toxicity: bronchial asthma was observed with acute exposure in guinea pigs; possible respiratory sensitizer to rats; repeated exposure by inhalation to rats, hamsters, and monkeys resulted in effects that were limited to the respiratory tract and eye irritation; in a 4-wk study in rats exposed 6 hours/day to up to 84 mg/m^3 (21 ppm), evidence of nasal, trachea, and lung irritation was observed at all exposure levels, and the effects were concentration-related and included epithelial hyperplasia and the presence of inflammatory exudates in the nasal turbinates and trachea; and epithelia hyperplasia, squamous metaplasia, and intra-alveolar hemorrhage in the lung, with a LOAEL of 12 mg/m^3 (3 ppm); in a 6-month inhalation study in which rats, hamsters, and monkeys were exposed to up to 9.8 mg/m^3 (2.4 ppm), respiratory tract and eye irritation were observed, hyperplastic and metaplastic changes in the nasal passages were considered indicative of irritation and judged to be reversible, and the NOAEL for rats was 3.3 mg/m^3 (0.8 ppm) and the NOAEL for hamsters and monkeys was 9.8 mg/m^3 (2.4 ppm) reproductive and developmental toxicity: in a 2-generation reproductive toxicity study in which rats were dosed via gavage with up to 150 mg/kg/day, the NOAEL for reproductive effects was 55 mg/kg/day (highest dose tested due to parental death at 150 mg/kg/day), but in the parental group adverse effects (mortality, body weight changes, and respiratory irritation) were observed at 150 mg/kg/day and there were histopathological effects in the kidneys and bladder of the parental animals (first generation only) in all treated dose groups, and the LOAEL for parental effects was 20 mg/kg/day; no developmental toxicity was observed when pregnant rats were dosed via gavage with up to 140 mg/kg/day, but the dams in all dose groups either lost weight or failed to gain weight between days 6 and 9 of gestation (effect was not statistically significant at any interval and was reversible), and the NOAEL (maternal) was determined to be 140 mg/kg/day genotoxicity: negative in bacterial gene mutation tests; in a single in vitro chromosomal aberration test with and without S-9 was positive (due to inadequate documentation on this study, it is unclear whether the results were due to the test material itself or a change in pH to an acidic environment, which could have resulted in a non-specific effect); exposure of Sprague-Dawley rats of up to 100 mg/m^3 (25 ppm) did not increase chromosomal aberrations in the bone marrow carcinogenicity: not carcinogenic when given to rats in their diets for 2 yrs at doses up to 100 mg/kg/day; the EPA has not classified maleic anhydride for carcinogenicity dermal irritation/sensitization: severely irritating to the skin of rabbits after application of 0.5 g to the skin for 4 hours (mean irritation score of 3.67 – 4.00 during the 7-day observation period); shown to be a skin sensitizer to guinea pigs ocular irritation: severely irritating to the eyes of rabbits (eye irritation score was 106.7/110); in humans,	15-18

Table 2. Monomer safety data

Monomer (CAS No.)	Toxicity Data	Reference
	exposure to 0.25 - 0.38 ppm (1- 1.6 mg/m3) produced eye irritation, no irritation was reported at 0.22 ppm respiratory effects (human): exposure to 0.25 - 0.38 ppm (1- 1.6 mg/m3) produced respiratory tract irritation, no irritation was reported at 0.22 ppm effects with occupational exposure: according to the OECD summary, there have been a few published human cases suggesting that maleic anhydride provokes asthma in a relatively small proportion of exposed workers, however, questions have been raised whether the asthma was actually related to maleic anhydride exposure; according to the EPA summary, chronic (long-term) exposure has been observed to cause chronic bronchitis, asthma-like attacks, and upper respiratory tract and eye irritation in workers, and in some people, allergies have developed so that lower concentrations can no longer be tolerated recommended limits; the EPA RfD is 0.1 mg/kg bw/d based on renal lesions in rats (the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious noncancer effects during a lifetime; it is not a direct estimator of risk but rather a reference point to gauge the potential effects); OEHHA inhalation REL is 0.7 $\mu g/m^3$ (2.5 ppb) **Maleic Acid - CIR Conclusion: safe for use in cosmetic formulations as a pH adjustor in the practices of use described in the safety assessment (only use as a pH adjustor was evaluated) ; was reported to be used at 0.004% in "other" bath products; used in hair straighteners, other hair-coloring preparations, and shaving cream according to VCRP data, but no concentration data were reported for these uses** according to the Discussion of the report, the Panel recognized that maleic acid itself may be a dermal and/or ocular irritant, but its use as a pH adjustor in cosmetic formulations dictates that most of the acid would be neutralized into various maleate salts; additionally, the concentration of maleic acid would be dependent on the alkaline content of the formulation; the Panel also stated that safety of maleic acid as a pH adjustor should be based on the amount of free maleic acid remaining after neutralizing the formulations	[19]
neopentyl glycol (126-30-7)	molecular weight: 104.15 toxicokinetics: after rabbits were dosed with 1-1.5 g/kg bw (unlabeled) by gavage, 62% of the dose was found in the 24-h urine as the conjugate of glucuronic acid, indicating rapid absorption, 1.9% was recovered as the metabolite 3-hydroxy-2,2-dimethylpropionic acid, and only 0.7% of the dose was present unchanged oral toxicity: oral LD_{50} in rats reported as 3200 mg/kg to 6920 mg/kg; with repeated dosing with up to 1000 mg/kg/day by gavage, the NOAEL for males and females were 300 and 1000 mg/kg/day, respectively; in a 90-day gavage study, no adverse effects were observed at doses up to 1000 mg/kg dermal toxicity: the dermal LD_{50} was >4000 mg/kg bw in guinea pigs with a 24-h occlusive application to a 20% solution in acetone/corn oil vehicle inhalation toxicity: there was no mortality in rats exposed to a saturated vapor for 8 h (the calculated nominal concentration was 140 mg/m^3); rats exposed for 6 h to 39,400 ppm (168 mg/l) showed symptoms of irritation of the respiratory tract, 1/3 died within 24 h; 3 rats were exposed to 4000 ppm, 6 h/day for 10 days, and irritation of the respiratory tract and dilatation of the skin blood vessels were detected, but no evidence f toxic effects on internal organs was observed at necropsy reproductive and developmental toxicity: the NOAEL f or maternal and prenatal developmental toxicity was 1000 mg/kg with dosing with ≤1000 mg/kg on days 6-19 of gestation; in a reproductive toxicity study in which rats were dosed with up to 1000 mg/kg/day by gavage before and during mating and through day 3 of lactation, the NOAEL was 1000 mg/kg for the parent and F_1 generation genotoxicity: not genotoxic in an Ames test (up to 5000 µg/plate) or to Chinese hamster ovary cells (up to 1 mg/ml) dermal irritation/sensitization: an 80% aq. solution was not an irritant to rabbit skin with a 20-h -occlusive exposure; slightly irritating to rabbit skin with a 4-h exposure to undiluted test material; not a sensitizer in a mouse LLNA ocular irritation: instillation of crystalline test substance resulted in serious damage to rabbit eyes in one study, and instillation of neat test article in rabbits resulted in irreversible damage in one study and slight to moderate irritation in another study	[20,21]
phthalic anhydride (85-44-9)	molecular weight: 148.12 g/mol toxicokinetics: rapidly hydrolyzed to phthalic acid upon contact with water; half-life was 30.5 sec at pH 7.24. and 61 sec at pH 6.8; unconjugated compound was found in the urine of humans exposed by inhalation, demonstrating systemic absorption and elimination via the urine and the existence as a hydrolysis product in vivo oral toxicity: oral LD_{50} of 1530 mg/kg bw in rats; low repeated dose toxicity in rats; in a 7-wk feed study in which mice were given up to 7140 and rats up to 3330 mg/kg bw/day, there were no effects in mice, but there was a significant reduction in body weight gains in rats of the high dose group and centrilobular cytoplasmic vacuolation were seen in the livers in most of the male rats fed 1660 mg/kg bw/day; in male and female mice fed 4670 and 3430 mg/kg bw/day, respectively, for 105 wks, significantly increased incidences of lung and kidney lymphocytosis in the low- and high-dose males and females, chronic bile duct inflammation in the high-dose males and females, and dose-related adrenal atrophy and mineralization of the thalamus in the low-and high-dose males were observed, and the time weighted LOAELs were approximately 1717and 2340 mg/kg bw/day in female and male mice, respectively, and no NOAEL was obtained dermal toxicity: the dermal LD_{50} was >10,000 mg/kg bw in rabbits inhalation toxicity: the LC_{50} was >2.14 mg/l following a 4-h nose-only exposure; respiratory sensitization potential in guinea pigs, and animals exposed to and challenged with 5.0 mg/m^3 phthalic anhydride dust had	[22-25]

Table 2. Monomer safety data

Monomer (CAS No.)	Toxicity Data	Reference
	significant numbers of hemorrhagic lung foci reproductive and developmental toxicity: no evidence of toxicity to reproductive organs was observed in comprehensive carcinogenicity studies in rats and mice, as no treatment-related changes were observed for any reproductive organ investigated during macroscopic and microscopic examination; decreased spermatozoa motility time was reported in one study in which male rats were exposed via inhalation genotoxicity: not mutagenic in the Ames test (up to 5000 μg/plate); induced chromosomal aberrations in mammalian cells only at the high concentration of 10 mM without metabolic activation; not genotoxic in a sister chromatid exchange assay (10-300 μg/ml with and without metabolic activation) carcinogenicity: no evidence of carcinogenicity in rats fed 1000 mg/kg bw/day or in in male and female mice fed 4670 and 3430 mg/kg bw/day, respectively, 105 wks dermal irritation/sensitization (animal): mild irritation was observed when 550 mg of flakes were applied to rabbits for 4 h, the average dermal irritation index after semi-occlusive exposure was 1.21/8, and observed effects were reversible; semi-occlusive application of 500 mg (moistened with water) on the ear for 24 h was not an irritant; sensitizer in the GPMT and at a concentration of 10% in the LLNA in mice dermal irritation (humans): contact with either the solid or a vapor has been reported to cause skin irritation after occupational exposure; erythema, blistering, ulceration and necrosis have been reported following skin contact ocular irritation: slightly to moderately irritating to rabbit eyes mucous membrane irritation: a primary irritant in humans when in the form of vapor, fumes, or dust respiratory effects (humans): a primary irritant to the upper respiratory tract when in the form of vapor, fumes, or dust effects with occupational exposure: conjunctivitis, rhinitis, rhinoconjunctivitis, bronchitis, and irritation of the skin and mucous membranes of the respiratory tract have been observed in exposed workers; initial exposure produces coughing, sneezing, burning sensations in the nose and throat, and increased mucous secretion; occasional bloody sputum, emphysema, lower blood pressure, and minor signs of central nervous system excitation has been observed in chronically-exposed workers recommended limits: the EPA has calculated a provisional RfC of 0.12 mg/m^3 (the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious noncancer effects during a lifetime. It is not a direct estimator of risk but rather a reference point to gauge the potential effects); the EPA has established a RfD of 2.0 mg/kg bw/day	
propylene glycol (57-55-6)	**CIR Conclusion: safe in the present practices of use and concentration when formulated to be non-irritating; reported to be used at up to 73% in leave-on formulations** molecular weight: 76.09 g/mol toxicokinetics: the major route of metabolism is to lactaldehyde and then lactate via hepatic alcohol and aldehyde dehydrogenases dermal absorption: penetration from a ternary cosolvent solution through hairless mouse skin was 57% over a 24-h period, and it appears that it does not reach the dermis; it can act as a penetration enhancer oral toxicity: the oral LD_{50} was 21 g/kg in rats; no mortality in mice given 10% in drinking water for 14 days; lesions were not observed in rats that were fed diets containing 50,000 ppm (2.5 g/kg/day) for 15 wks or up to 50,000 ppm in the diet for 2 yrs; similar results were reported in a study in which dogs were fed 2 or 5 g/kg in the diet for 103 wks; in dogs given 5% in drinking water for 5-9 mos, no hepatic or renal impairment was noted inhalation toxicity: some effects in rats due to exposure of 2.2 mg/L air for 6 h/day, 5 days/wk, for 13 wks, but these effects were inconsistent and without dose-response trends reproductive and developmental toxicity: not teratogenic in female CD-1 mice when administered at a concentration of 10,000 ppm on days 8-12 of gestation; no reproductive effects in a continuous breeding reproduction study in albino mice with up to 5% administered in feed or water; no adverse effects on reproduction or development when given orally at at doses up to 1600 mg/kg in mice and rats, 1230 mg/kg in rabbits, or 1550 mg/kg in hamsters genotoxicity: no mutagenic in an Ames test at up to 10,000 μg/plate with or without metabolic activation; caused a dose-dependent increase in the frequency of SCEs in a Chinese hamster cell line and was classified as a weak inducer of SCEs, but in another SCE study, it was not genotoxic in human cultured fibroblasts or a cultured Chinese hamster cell line with or without metabolic activation; chromosomal aberrations were induced in Chinese hamster fibroblasts in another assay; was not genotoxic in additional tests for chromosomal aberrations, mitotic recombination, or basepair substitution, or DNA damage or a micronucleus test carcinogenicity: not carcinogenic in a 2-yr feeding study at up to 50,000 ppm in rats; did not induce skin tumors and was not carcinogenic in a lifetime dermal study at concentrations up to 100% in mice dermal irritation/sensitization (animal): 10% was not a dermal irritant in a 24-h test in nude mice, but hyper-trophy, dermal inflammation, and proliferation were observed at a concentration of 50%; not an irritant to intact or abraded skin of rabbits in a Draize test, to guinea pig or rabbit skin when applied for 48 h using open and occlusive patches, or to swine skin in 48-h and 21-day open and occlusive patch tests; not a sensitizer in a mouse external ear swelling sensitization test undiluted), in a GPMT, OET, or chamber (Finn chamber) test (at 70%); was a potentially weak sensitizer in one maximization test, but the results of 6 other guinea pig sensitization indicated it was not an allergen dermal irritation/sensitization (human): induced skin irritation and sensitization reactions in normal subjects and patients in studies with test concentrations ranged from 2 - 100%, and reactions were observed at concentrations as low as 10% in predictive tests and as low as 2% in provocative tests; however, the dermal irritation potentials	[26,27]

Table 2. Monomer safety data

Monomer (CAS No.)	Toxicity Data	Reference
	of deodorant formulations containing 68.06% or 69.15% were evaluated in an SIOPT and compared to a reference in-use control formulation, and the formulations containing propylene glycol were no more irritating or even less irritating than the reference control; use studies of deodorant formulations containing 35%-73% did not report any potential for eliciting irritation or sensitization; deodorant formulations containing 69.15% or 86% did not induce sensitization reactions; questionable results were obtained in an RIPT of a deodorant containing 73%; retrospective analysis of pools of patient patch test data indicated that ≤6.0% of patients tested had positive reactions to a 30% aq. solution; increased the allergic responses in 43 patients patch tested with 50 µg 1% nickel sulfate solution photoallergenicity: did not produce a photoallergic response in a provocative photopatch test (concentration not specified) ocular irritation: did not induce corneal damage in rabbit eyes in one study; was a slight ocular irritant in another	
sebacic acid (111-20-6)	**CIR Conclusion: safe in the present practices of use and concentration; reported to be used at a maximum of 0.03% in leave-on formulations and 1% in rinse-off formulations** molecular weight: 202.25 toxicokinetics: oxidized to water and carbon dioxide, passing through acetyl-CoA and succinyl-CoA formation; under normal physiological conditions, dicarboxylic acids are rapidly β-oxidized, resulting in very low cellular concentrations and practically non-detectable concentrations in the plasma, and oxidation of odd- and even-numbered chains proceeds to different end points with even chains completely, and odd-number chains not completely, oxidized; recovered unchanged in the urine of rats: with i.v. dosing, approximately 35% sebacate was recovered oral toxicity: . disodium sebacate was not toxic to rats or rabbits fed up to 1000 mg/kg bw for 6 mos reproductive and developmental toxicity: in dietary studies, disodium sebacate was not a developmental toxicant in rats (500 mg/kg bw day; days of dosing not stated) or rabbits (1000 mg/kg bw)	[8]
trimethylpentanediol (144-19-4)	molecular weight: 146.23 oral toxicity: oral LD_{50} was 1800 mg/kg bw and >2000 mg/kg bw in male mice and female rats, respectively; in rats fed ≤2% for 57 days, the NOAEL for males and females was 0.5% (376 mg/kg bw/day) because of changes in organ wts at higher doses dermal toxicity: in a study in guinea pigs (1 animal/dose), the dermal LD_{50} was >1 g/kg bw inhalation toxicity: the LC_{50} was >4.5 mg/l in rats with a 6-h exposure period (the respirable concentration of the test substance was 1.43 mg/l and the calculated exposure to the respirable portion of the test substance was 2.8 g/kg bw) reproductive and developmental toxicity: in a 3-generation dietary study in rats at concentrations up to 1% in feed, the NOAEL was 1% for both parental and for reproductive and developmental toxicity genotoxicity: not genotoxic, with or without metabolic activation, in an Ames test at concentrations up to 5000 µg/plate, in a mammalian cell assay at concentrations up to 1462.3 µg/mL in mouse lymphoma cells, or in a chromosomal aberration assay at concentrations up to 1500 µg/ml in CHO cells irritation/sensitization: an occlusive 4-h exposure was not irritating to intact or abraded rabbit skin; 0.1 M was not a sensitizer in guinea pigs ocular irritation: undiluted test material was a slight irritant to rabbit eyes	[28,29]
trimethylolpropane (77-99-6)	molecular weight: 134.17 g/mol oral toxicity: in a gavage study, the LD_{50} was ~14,700 mg/kg in male rats; in a 90 day feeding study with up to 1.0% (667 mg/kg bw/d) in rats, the NOAEL was 0.1% (67 mg/kg bw/d) based on significant changes of clinical chemistry or hematological data (at ≥0.3 %) and histopathological changes, mainly in liver and spleen (at 1%) dermal toxicity: the dermal LD_{50} was >10,000 mg/kg bw in rabbits with a 24-h occlusive application inhalation toxicity: the LC_{50} was >850 mg/m^3 (vehicle, ethanol/lutrol 1:1) in rats with a 4-h exposure period reproductive and developmental toxicity: in rats dosed by gavage with up to 1000 mg/kg/day on days 6-20 of gestation, the NOAEL was 100 mg/kg bw/day for developmental toxicity due to decreases in fetal weight and 100 mg/kg bw/day for maternal toxicity due to decreased body weight and weight gains; in a study in which male and female rats were dosed by gavage with up to 800 mg/kg bw/day before, during, and after mating, the NOAEL was 800 mg/kg bw/day for reproductive and developmental toxicity and 200 mg/kg bw/day for general toxicity genotoxicity: not genotoxic, with or without metabolic activation, in an Ames test at concentrations up to 5000 µg/plate, in a mammalian cell assay at concentrations up to 1400 µg/mL in Chinese hamster lung fibroblasts, or in a chromosomal aberration assay at concentrations up to 1340 µg/ml in Chinese hamster lung cells dermal irritation/sensitization: application to the inner ear of rabbits did not produce irritation; not sensitization in a mouse LLNA at concentrations up to 50% ocular irritation: not irritating to rabbit eyes when instilled undiluted or melted	[30,31]

Abbreviations: DMSO – dimethyl sulfoxide; EPA – Environmental Protection Agency; CHO – Chinese hamster ovary; GPMT – guinea pig maximization test; HGPRT - hypoxanthine-guanine phosphoribosyltransferase; LLNA – local lymph node assay; LOAEL – lowest observable adverse effect level; NIOSH – National Institute for Occupational Safety and Health; NOAEL – no-observable adverse effect level; OECD – Organisation for Economic Co-operation and Development; OEHHA - Office of Environmental Health Hazard Assessment; OET – open epicutaneous test; REL – reference exposure level; RfC – reference concentration; RfD - reference dose; RIPT – repeated insult patch test; SCE – sister chromatid exchange; SIOPT – single insult occlusive patch test; TMA – trimellitic anhydride; TWA – time-weighted average

Table 3. Physical and chemical properties

Property	Description	Reference
Adipic Acid/CHDM/MA/Neopentyl Glycol/ Trimellitic Anhydride Copolymer		
physical characteristics	liquid or solid	[32]
solubility	insoluble in water	[32]
Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer		
physical characteristics	clear liquid	[33]
molecular weight	442.41g/mol	[34]
solubility	low solubility in cold water; soluble in all "common solvents"	[33]
acid number	10-20 mg KOH/g	[33]

Table 4. Frequency and concentration of use according to duration and type of exposure

	# of Uses[37]	*Max Conc of Use (%)*[38]	*# of Uses*[37]	*Max Conc of Use (%)*[38]	*# of Uses*	*Max Conc of Use (%)*
	Adipic Acid/Neopentyl Glycol/Trimellitic Anhydride Copolymer		**Phthalic Anhydride/ Trimellitic Anhydride/Glycols Copolymer**			
Totals*	**411**	**1-32.8**	**74**	**1.8-12**		
Duration of Use						
Leave-On	*410*	*1-32.8*	*74*	*1.8-12*		
Rinse-Off	*1*	*NR*	*NR*	*NR*		
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*		
Exposure Type						
Eye Area	NR	NR	NR	NR		
Incidental Ingestion	NR	NR	NR	NR		
Incidental Inhalation-Spray	NR	NR	NR	NR		
Incidental Inhalation-Powder	NR	NR	NR	NR		
Dermal Contact	1	1	2	NE		
Deodorant (underarm)	NR	NR	NR	NR		
Hair - Non-Coloring	NR	NR	NR	NR		
Hair-Coloring	NR	NR	NR	NR		
Nail	410	5.4-32.8	72	1.8-12		
Mucous Membrane	NR	NR	NR	NR		
Baby Products	NR	NR	NR	NR		

* Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may or may not equal the sum of total uses.

Table 5. Case reports

Case History	Patch Testing	Reference
Phthalic Anhydride/Trimellitic Anhydride/Glycols Copolymer		
a female subject had a 2-mo history of an intermittent itchy rash on the neck and around the eyes, associated with episodes of swelling of the eyelids; mild erythema and scaling were present the upper eyelids and neck	- Patch testing was performed with the British standard series, a modified cosmetic series, a modified plant series, with her cosmetics, and her nail varnish (which was applied to a Finn Chamber and allowed to dry before application); a positive reaction (+) was observed with the nail varnish at days 2 and 4; there was no reaction to tosylamide/formaldehyde resin - Patch testing with the nail varnish components resulted in a positive reaction (++) to 1% phthalic anhydride/trimellitic anhydride/glycols copolymer in petrolatum was observed at days 2 and 4; a + reaction was also observed to the 5 coloring bases that contained this ingredient - testing in 12 control subjects had negative results	41
a female subject had a 12-mo history of periorbital and fingertip eczema	- the subject was patch-tested with the BCDSB, a cosmetic and medicament series, and her own cosmetics; a positive reaction (+) was observed with her nail varnish (which was applied to a Finn Chamber and allowed to dry before application) on day 4 - Patch testing with the nail varnish components resulted in a positive reaction (++) to 1% phthalic anhydride/trimellitic anhydride/glycols copolymer in petrolatum at day 4	40
a female subject had a 6-mo history of perioral eczema and dry, fissured lips	- the subject was patch-tested with the BCDSB, a cosmetic and dental series, and her own cosmetics; a positive reaction (+) was observed with her nail varnish (which was applied to a Finn Chamber and allowed to dry before application) on day 4	40
a female subject had a 6-mo history of intermittent eczema of her face and fingers	- the subject was patch-tested with the BCDSB, a cosmetic series, and her own cosmetics; positive reactions (+) were observed with her nail varnish (which was applied to a Finn Chamber and allowed to dry before application) on days 2 and 4 - patch testing with the nail varnish components resulted in a positive reaction (+) to 1% phthalic anhydride/trimellitic anhydride/glycols copolymer in butyl acetate on day 4	40
a female subject had periungual dermatitis affecting all her fingers; she had been wearing nail varnish and acrylic nails for several years	- the subject was patch-tested with the BCDSB and acrylic series; she had positive reactions to several compounds, including 1% phthalic anhydride/trimellitic anhydride/glycols copolymer in butyl acetate on day 4on days 2 and 4	40
Three case reports were described: an atopic female subject presented with generalized eczema and major lichenification of lips and eyelids progressively worsening during the past 4 yrs; recent patch testing with the standard ICDRG series (2) was negative a female subject had recurrent eyelid and neck dermatitis, with severe nail dystrophy; patch testing with a standard series, toluene sulfonamide formaldehyde resin, and her own nail polishes were negative; the lesions persisted for several mos, and she was referred again a female subject had a history of occupational contact dermatitis and asthma due to glutaraldehyde presented with head and neck eczema lasting for 3 mos	- patch testing with all nail polish formulations resulted in positive reactions to a few of the polishes; patch testing with toluene sulfonamide formaldehyde resin was negative - patch testing with the nail varnish components identified phthalic anhydride/trimellitic anhydride/glycols copolymer (tested at 1% and 5% in petrolatum) as the allergen in all 3 subjects - subsequent patch testing with the raw monomers, i.e. phthalic anhydride, trimellitic anhydride and glycols was performed in 2 subjects; the results were negative	36

Abbreviations: BCDSB - British Contact Dermatitis Society Standard Battery; ICDRG - International Contact Dermatitis Research Group

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