1676 Safety Assessment of Acacia Seyal Gum for Use in Mascaras

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Acacia gums are edible ingredients used in foods and cosmetics. Acacia Seyal Gum (CAS# 9000-01-5) is an ingredient of interest for use in cosmetics (eye products/mascara). A typical pre-market safety review of cosmetics includes: 1) a public literature and vendor information review and 2) a test battery to fill any data gaps. Public toxicology-related literature was limited for Acacia Seyal gum. The literature review indicated that the Cosmetic Ingredient Review panel (CIR) has evaluated similar ingredients (Acacia Senegal gum and Acacia Senegal gum extract) and declared them safe as used in cosmetics (up to 9% in mascaras). However, Acacia Seyal gum was not specifically included in this review. The literature review also indicated that there were similarities between the previously CIR-reviewed Acacia Senegal gum and Acacia Seyal gum in terms of chemical, biochemical and structural characteristics. Acacia Senegal and Acacia Seyal gums are hyperbranched polysaccharide biopolymers rich in arabinose and galactose, similar in global biochemical and structural properties and somewhat different in the macromolecular conformation. Both are structured into polyproline type II helices. Both ingredients have high molecular weights (> 10^5 Da) and, thus, negligible potential for dermal absorption. Data from the CIR review have been incorporated into weight of evidence review and contributed to substantiating the safety of this botanical ingredient. However, to further substantiate the safe use of this ingredient in mascaras up to 1% at the final formula level, a robust test battery was designed to include chemical characterization (elemental impurities analysis), microbiological characterization, *in vitro* eye irritation (BCOP/CAMVA), clinical skin irritation (48-Hour Patch Test), clinical skin sensitization (Human Repeat Insult Patch Test), *in vitro* phototoxicity (UV spectrum, 3T3 assay). Results indicated that this ingredient conformed with Shiseido standards for elemental impurities, was of appropriate microbiological formula quality (met USP 51 criteria), was not an eye irritant, not a skin irritant, not a skin sensitizer, and not phototoxic. Consequently, Acacia Seyal Gum is safe for consumer use in the tested mascara formula up to 1% maximum use level under normal use conditions.

1677 The Toxicological Profile of Reklemel: A Reduced Risk Nematicide

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Reklemel™ is the commercial name for fluazaindolizine (CAS # 1254304-22-7), a new crop protection active ingredient for control of parasitic nematodes in various vegetable and fruit crops. Reklemel belongs to the sulfonamide class of chemistry and acts through a mode of action distinct from other commercial nematicides. Currently, fumigant products requiring specialized handling and stewardship approaches are highly represented in this market segment; thus, there is a significant opportunity to bring forward new products that will reduce human risk both from a hazard and exposure perspective. During development, the mammalian toxicology and human risk profile of Reklemel was compared to that of six registered nematicide active ingredients. Reklemel has a favorable acute toxicity profile (Oral LD_{50} = 1187 mg/kg; Dermal LD_{50} <5000 mg/kg; Inhalation LD_{50} > 5.8 mg/L), is not a dermal irritant nor sensitizer and is a moderate eye irritant. This profile was more favorable relative to two competitors and similar to the other four. When comparing end-use formulations, the profile of the product containing Reklemel was more favorable when compared to four out of six competitor end-use products. Reklemel was non-genotoxic based on the outcome of *in vitro* and *in vivo* assays which was a similar profile to competitors. Reklemel was shown to be non-carcinogenic in rats and mice. This profile was more favorable compared to four of six competitors. In the rat two-generation study there were no effects on fertility or other reproductive parameters nor did Reklemel cause developmental toxicity in rats or rabbits. The other active ingredients were similarly not specific reproductive or developmental toxicants. When comparing toxicity endpoints derived from sub-chronic and chronic toxicity studies, Reklemel had higher NOAEL values compared to all competitors. In summary, Reklemel has a favorable toxicity and reduced risk profile relative to several existing nematicides.

1678 A 13-Week Rat Inhalation Study of Aerosols Generated from Two Flavor Mixtures

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Two nicotine-free flavor mixtures (one containing 10.76% w/w menthol flavors and the other containing 1.15% non-menthol flavors) and a carrier mixture (glycerin and propylene glycol [PG]) were evaluated via a 13-week rat inhalation study in general accordance with OECD TG 413. Male and female Sprague Dawley rats were randomly assigned to groups for exposure to 1, 3, or 5 mg/L of aerosols of each flavor mixture, 5 mg/L carrier, or filtered air for up to 6 hours per day on a 5-day per week basis for 13 weeks, followed by a 6-week recovery. In addition, a satellite group of male rats were exposed on a comparable regimen to evaluate micronuclei (MN) in bone marrow (mammalian erythrocyte micronucleus test; OECD 474) and potential DNA damage in liver, lung, and nasal tissue (mammalian alkaline Comet assay; OECD 489). Plasma PG, a marker of exposure, increased with the increased aerosol exposure in both males and females at both weeks 4 and 11. There were no flavor- or carrier-related effects on survival, clinical observations, ophthalmic findings, or respiratory physiology after 13 weeks of exposure. In addition, no flavor- or carrier-related alterations in hematology, coagulation, serum chemistry, urinalysis parameters, or bronchoalveolar lavage fluid chemistry values and cytology were observed. Non-adverse, minimally lower mean body weights were noted in males and females exposed to 5 mg/L menthol flavor as compared to the filtered air groups, which correlated to slightly lower food consumption. Thymus weights in females exposed to 3 and 5 mg/L menthol flavor were lower than the 1 mg/L group and marginally lower (not statistically significant) than the filtered air and carrier groups. The decreased thymus weights were considered non-adverse given the lack of correlating histologic observations and the reversibility suggested at the recovery necropsy and may have represented a secondary stress response. Non-degenerative histologic changes of minimal to mild severity grades were observed in various nasal levels of males and females in all flavor and carrier groups at both the terminal and recovery necropsies. Both flavor mixtures and carrier were negative for the induction of MN in bone marrow and DNA damage in liver, lung and nasal tissue. Based on these findings, the no-observed-adverse-effect-concentration (NOAEC) was established to be 5 mg/L (the high-dose level) for each flavor mixture and the carrier.

1679 Toxicological Evaluation of Acrylonitrile Butadiene Styrene (ABS) 3D Printer Emissions

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Fused filament fabrication 3D printing with acrylonitrile butadiene styrene (ABS) filament emits billions of particles and numerous volatile organic compounds (VOCs). This study sought to investigate the toxicity of ABS emissions from a 3D printer both *in vivo* and *in vitro*. For the *in vivo* studies, Sprague Dawley rats were exposed to real-time ABS printing emissions or air (control) for 4 h/day, 4 days/week for 1, 4, 8, 15, and 30 days. The average aerosolized particle concentration was 0.24 ± 0.09 mg/m^3, and the average median particle electric mobility diameter was 85 nm with an average geometric standard deviation of 1.6. Benzene was the predominant VOC released during printing. At 24 h after the last exposure, rats were assessed for pulmonary injury, inflammation, and oxidative stress as well as systemic and other organ toxicity. Results showed that among the measured cytokines in bronchoalveolar lavage, only IL-10 and IFN-γ at day 1 and 4, and IL-13 at day 30 of the exposure were increased when compared to the air-control. Moreover, neither pulmonary oxidative stress responses nor histopathological changes of the lungs were found among the exposed rats. There were no significant differences in serum cytokines levels or hematological indices, except for an increase in platelets and monocytes at day 15. Several serum biomarkers involved in liver damage were significantly higher at day 1 of the exposure. For the *in vitro* study, both particles and VOCs were collected into serum-free cell culture medium using an impinger sampler inside a chamber while printing for 1.5 h, followed by characterization of the physicochemical properties, as well as assessment of cytotoxicity, oxidative stress, and cytokine production in human small airway epithelial cells (SAEC). Results showed that particle numbers and VOC concentrations varied between print runs. The particle dose range was 1.42 x 10^6 - 4.72 x 10^6 particles/cm^2, and the average median hydrodynamic particle diameter was 168 nm with an average arithmetic standard deviation of 53. Styrene was the predominant VOC collected in the medium. Based on mixed model regression analyses, at 24 h post-exposure, ABS emissions in-

duced significant dose-dependent cytotoxicity, oxidative stress, and production of pro-inflammatory cytokines in SAEC. In conclusion, our *in vitro* studies indicated that the emissions from ABS 3D printing induced toxicological effects, which were not substantiated by the *in vivo* studies with the current low exposure concentrations. Thus, more *in vivo* studies with higher dose-response are needed to verify the *in vitro* findings.

1680 Retrospective Review of Safety Data for the Vehicle Sulfobutyl-ether-β-cyclodextrin (SBE-β-CD) in the Nonclinical Studies

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Sulfobutyl-ether-β-cyclodextrin (SBE-β-CD), also known as Captisol. SBE-β-CD is used in several commercial drugs and also as a common vehicle in non-clinical studies. Sixteen studies involved SBE-β-CD in mice, rats, dogs and monkeys were reviewed and the data analyzed to further evaluate the safety of Captisol when used as part of the vehicle formulation. In eleven studies (5 rat studies; 4 dog studies; and 2 monkey studies) 198 mg/kg/day to 1000 mg/kg/day SBE-β-CD was dosed for 28 consecutive days. No vehicle related adverse effects were noted up to 1000 mg/kg/day oral dose in rats, dogs and monkeys in all above studies. Base on the study results the NOEL of SBE-β-CD for oral dose in rats, dogs and monkey was considered as 1000 mg/kg/day. Mice were more sensitive to the oral exposure to the SBE-β-CD in three exploratory studies. The duration was from 5 days to 28 days and the dosages were from 850mg/kg/day to 1960 mg/kg/day. Increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL) were noted in these studies along with histopathology changes as hepatocellular necrosis accompanied by neutrophilic infiltration. In two GLP studies when SBE-β-CD (from 960 to 4800mg/kg/day) was administered by intravenous in rats and dogs, vacuolations and foamy macrophases in various tissues or organs were noted in the histopathology. In the dosing phase, histopathologic findings associated with the SBE-β-CD included vacuolation of the renal tubular epithelial cells and epididymis along with an infiltrate of foamy macrophages in a variety of lymphoid organs, spleen, liver, lungs, cecum, heart, urinary bladder and uterus. The histopathological changes in morphology due to SBE-β-CD were not associated with any cellular degeneration and/or necrosis. Histopathologic findings associated with SBE-β-CD in the heart, cecum, lungs, spleen urinary bladder, kidney, epididymis, mandibular lymph node and mesenteric lymph node were revisable. There was no recovery of the histopathologic findings in the liver and uterus. In conclusion the toxicity of SBE-β-CD is dependent on the species and route of administration in the non-clinical studies. Oral dose was safe for most of the species such as rats, dogs and monkey but except for mice which could induce liver related changes in both clinical pathology and histopathology data. Intravenous infusion administration resulted vacuolations and foamy macrophages in various tissues or organs but not associated with any cellular degeneration and/or necrosis.

1681 Hazard Potential of Perfume Products Assessed by a Combination of *In Vitro* Methods and Chemical Analysis

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Alternative *in vitro* methods and studies on human volunteers are the only hazard assessment approaches available, as animal testing is prohibited in the EU for cosmetic ingredients and final products. In our study we tested 10 samples of deodorants, EDT and EDP and combined results from biassays, suitable for detection of cytotoxicity (ISO EN 10993-5), skin sensitization *in chemico* (OECD TG 442C) and *in vitro* (OECD TG 442D), genotoxicity (Comet assay on 3T3 Balb/c fibroblasts) and endocrine activity (YES/YAS assay; Xenometrix®). Samples 1, 2, 3, 5 exhibited the highest cytotoxicity. The skin sensitization was identified by a method *in chemico* for samples 5, 6, 7, 8 and a method *in vitro* at 12.5 µg/ml for sample 6, resp. at 100 µg/ml for samples 7, 8, 9. Comet assay detected no genotoxicity at 250 µg/ml, however, a concentration dependent DNA fragmentation was observed (samples 6, 8, 9, 10). Samples 1, 2, 5, 6, 7, 8, 9, 10 exhibited endocrine activity. 24 allergens (INCI names: D-limonene, linalool, benzyl alcohol, citronellol, methyl 2-octynoate, geraniol, citral, hydroxycitronellal, cinnamal, anise alcohol, cinnamyl alcohol, eugenol, alpha-isomethyl ionone, isoeugenol, butylphenyl methylpropional, coumarin, farnesol, amyl cinnamal, hydroxyisohexyl 3-cyclohexene carboxaldehyde, amylcinnamyl alcohol, hexyl cinnamal, benzyl benzoate, benzyl salicylate, benzyl cinnamate) were determined by GC/MS. Although the hazard of individual components is known, the hazard of the final mixture may be variable, depending on either total load of ingredients or the content of specific active substances. Combination of bioassays and chemical analysis seems to be promising for risk assessment of cosmetics. *The work was supported from ERDF/ESF project "International competitiveness of NIPH in research, development and education in alternative toxicological methods" (No. CZ.02.1.01/0.0/0.0/16_019/0000860).*

1682 Comparative Subchronic Inhalation Toxicity 2-Pentanoneoxime

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Oximes are formed by the reaction of hydroxylamine with the carbonyl group of either an aldehyde or a ketone. In the body, the reaction reverses and the hydroxylamine is released. Hydroxylamine then causes hemolysis of the red blood cells resulting in the release of hemoglobin and an increase in platelets. As the liver and spleen filter the hemolyzed red blood cells, this can cause an increase in cell turnover. The carcinogenic potential of 2-pentanoneoxime (2-PO) was evaluated in a genomics study following a 90-Day exposure study. Groups of 10 male and 10 female Sprague Dawley rats were exposed to levels of 0 (control), 50, 150 and 300 ppm of 2-PO 6 hours/day, 5 days/week for 13 weeks and then sacrificed. Two recovery groups of 5 male and 5 female rats were also included. They were exposed to 0 and 300 ppm of 2-PO for 13 weeks and then held for a 4 week recovery period. 2-PO was metabolized to methylpropylketone (MPK). Clearance from the body was rapid. At 6 hours post exposure, neither 2-PO nor MPK was seen in the blood. Hemoglobin levels showed a slight decrease (4.4%), reticulocytes showed a increase (31,3%) and platelets showed an increase (27.9%) in the high exposure level males, no differences were seen in females. In the rats sacrificed at the end of the 13 week exposure period, increases were seen in the relative kidney weights in both male and female rats exposed to 300 ppm. Also relative spleen weights were increased in female rats exposed to 300 ppm. All organ weight effects were reversible following the 4 week recovery period. No treatment related histopathological alterations were seen in any of the organs evaluated. Since the changes were minimal, only seen in one sex and fully reversible in the rats held for the 4 week recovery period, they were considered to be non-adverse. It was therefore concluded that the No Adverse Effect Level for a 13-week exposure to 2-PO was 300 ppm. In the 2-PO exposed rats, there were no observations of treatment related effects during necropsy. In the microscopic examination of tissues from the 300 ppm exposure level group, the only observation that may have been related to the exposure was a reversable increased frequency of mild mononuclear inflammation of the liver in the female rats. This would not have caused a significant increase in apoptosis. 2-PO was evaluated in a genomics assay by a highly competent laboratory and found to not activate the genes associated with liver cancer. This assay has been used for over a decade and found to accurately predict carcinogenic potential. The results from this assay should be trusted for the safety evaluation of 2-PO.

1683 Comparing Cytokine Data to In-Life Parameters on Nonhuman Primates in Nonclinical Toxicology Studies

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Cytokines are important immunoregulatory proteins that have gained attention in safety assessment associated with innate or adaptive immune responses. Interpreting cytokine data comes with challenges due to the variable nature of their stimuli and responses. Contributing factors to the variability in cytokine expression include species-specific reactions, individual variations, dose-response relationships, and unanticipated immunotoxicity. For these reasons, cytokine measurements should not be used as standalone biomarkers for immunotoxicity assessment. However, in conjunction with additional parameters such as clinical observations, body weights, and clinical pathology data, cytokine interpretation can be used to provide more definitive assessments in nonclinical safety studies. In several case studies, cytokines were evaluated for a dose response relationship. Multiplex platforms such as Luminex or MSD® were used to determine cytokine levels in non-human primates including IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12/IL-23p40, MCP-1, IFN-γ, and TNF-α. In several instances, measurable levels of IL-6 or IL-12 correlated with clinical observations of bruising, injury, or abnormal feces, not necessarily considered test article-related. Elevated TNF- α and IL-6, pro-inflammatory cytokines, were detected in animals observed as dehydrated with elevated BUN, creatine, and decreased electrolytes. In cases of test article-related effects, animals becoming moribund also had elevated TNF-α and IL-6 levels. Increased levels of MCP-1, a monocyte chemotactic factor, was observed in one study with an animal with petechial bruising, and another study with a cohort with test-article associated renal failure, characterized by hypoproteinemia, azotemia, and hyperkalemia. In conclusion, cytokines are useful markers

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Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and Scientific Sessions of the 59th Annual Meeting of the Society of Toxicology, held at the Anaheim Convention Center, Anaheim, California, March 15–19, 2020.

An alphabetical Author Index, cross-referencing the corresponding abstract number(s), begins on page 542.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 580.

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