17/229 (7%) patients receiving 20 mg/kg-day versus 1/67 (1.5%) patients receiving 10 mg/kg-day and 2/220 (1%) patients receiving placebo. Based on these data, a human no observed adverse effect level (NOAEL) of 10 mg/kg-day was identified, which served as the POD for the assessment. The use of human clinical data instead of animal data to derive the POD is supported by toxicokinetic data, which indicate considerable interspecies differences in metabolism and internal exposures to the CBD parent compound and its metabolites. Most notably, the internal dose of the 7-COOH-CBD metabolite appears to be much higher in humans compared to rats, mice and dogs, whereas the internal dose of the 7-OH-CBD metabolite appears to be much higher in mice compared to the other species, including humans. Although it is unknown whether the parent compound or one or more metabolite(s) are the toxic moieties, these differences suggest uncertainty in the human relevance of toxicity observed in animals administered oral doses of CBD, including recent studies reporting Sertoli cell toxicity in male mice exposed to 30 mg/kg-day CBD for approximately five weeks. A total uncertainty factor of 100 was applied to the human NOAEL to account for inter-individual differences in sensitivity to liver effects (10x), extrapolation to a lifetime exposure duration (3x), and uncertainty in the selection of the critical effect due to a lack of sufficient reproduction and developmental toxicity data relevant to humans (3x). This results in an ADI of 10 mg/kg-day / 100, or 0.1 mg/kg-day (7 mg/day for a 70 kg adult). In addition, alternate ADIs consisting of revised uncertainty factors that consider the use of product labeling to restrict use of CBD in pregnant women or to a maximum use duration of 14 weeks are also proposed in this assessment. The ADI of 7 mg/day is less than 2-fold higher than the ADI of 4 mg/day derived from the COT evaluation. Although the ADI proposed in the COT assessment was similarly based on elevated liver enzyme activities in human patients treated with CBD, the difference between the COT ADI and the currently proposed ADI are related to differences in the selection of the POD and the uncertainty factors.

PS 4490 Acute Exposures to Acetone and Developing an Immediately Dangerous to Life or Health (IDLH) Value in Occupational Settings

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Acetone is a colorless water-soluble liquid that is used as an industrial solvent in chemical production. The primary route of exposure to acetone in occupational settings is inhalation. Acute exposures to acetone have been reported to elicit neurological effects, irritation, and respiratory effects, which could impair a worker's ability to escape from a contaminated environment. The National Institute for Occupational Safety and Health (NIOSH) develops immediately dangerous to life or health (IDLH) values to identify air concentration levels that cause severe irreversible adverse health effects, impairment of escape from the exposure environment, and in extreme cases, death. NIOSH guidelines for deriving IDLH values include an evaluation of toxicological data from human and animal studies, including dose-response information, if available. At exposure levels of several thousand parts per million (ppm), acetone is associated with neurological effects like dizziness, headache, and loss of coordination in human studies, and narcosis and decreased visual vigilance in animal studies. Acetone has a current IDLH value of 2,500 ppm. NIOSH-sponsored human experimental studies reported that exposure to a concentration of 1,000 ppm acetone for 4 to 8 hours did not result in neurobehavioral effects in humans. However, these studies identified mild irritation of the eyes and upper respiratory tract. Animal studies have reported loss of reflex, ataxia, decreased response, and narcosis at exposure concentrations greater than 10,000 ppm for 3-8 hours. Certain studies reported a 50% decrease in respiration rate (RD_{50}) in mice exposed to concentrations ranging from 77,500 ppm for 10 minutes to >84,000 ppm for 4 hours. These data are a measure of respiratory irritation. Lethal concentration in 50% (LC_{50}) of rats exposed to acetone for 4-8 hours ranged from 16,000 ppm to 50,000 ppm. NIOSH will continue to evaluate these data in the development of a draft updated IDLH value for acetone based on neurological and irritation endpoints from findings from both animal and human studies.

PS 4491 Probabilistic Exposure Modeling as a Key Tool for Refining Cosmetic Assessments

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Cosmetic risk assessment includes many default assumptions that build an intrinsic conservatism to ensure consumer safety. These default assumptions can be refined when data (exposure data, endpoint-specific toxicity data) are available without compromising safety. Refining the toxicity assessment aspect of risk assessment has become more challenging in the cosmetics industry following introduction of animal testing bans. Exposure calculation inputs are one aspect of the risk assessment that can often be more readily refined. Most deterministic exposure models intentionally overestimate consumer exposure, adding an additional layer of conservatism to the cosmetic risk assessment. However, significant overestimation of consumer exposure can result in unfavorable risk assessment outcomes and ultimately in unnecessary restrictions on the use of key ingredients. This does not afford additional consumer protection and can hinder product innovation. To overcome this challenge, risk assessments can rely on probabilistic exposure modeling to estimate the variety of products consumers use, product volumes, and use frequencies. This still includes enough conservatism to result in an acceptable margin of safety and reduces unnecessary ingredient restrictions. To demonstrate the impact of refinement to exposure calculations, aggregate exposure calculations were carried out using both deterministic and probabilistic models for a selection of important materials in the cosmetics industry. The SCCS Notes of Guidance (11th Ed.) calculations and default assumptions were selected as the conservative deterministic model, and the refined approach was carried out using the Crème RIFM aggregate exposure probabilistic model. A case study of Ethylhexylglycerin (EHG) will be discussed in detail. Comparing the results of the two models' predicted consumer exposure values demonstrates use of the Crème RIFM probabilistic model can consistently support significantly higher ingredient levels (in wt% formula) while still assuring safe use of multiple cosmetic ingredients. The Crème RIFM model has some limitations, including no data for UV products, minimal habits and practices data for Asian markets, and no available data to assess certain unique sub-populations. However, use of this probabilistic model is an important and impactful tool for refining estimated cosmetic exposures in risk assessments. Future improvements to this model will ideally address some of the limitations.

PS 4492 Identification of Direct and Specific Inhibition of Fatty Acid Oxidation on Isolated Hepatic Mitochondria to Investigate Drug-Induced Steatosis

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Drug-induced liver injury (DILI) is one of the major causes of premature termination of drug development, or marketing. Among DILI, macrovacuolar steatosis is a common and benign lesion characterized by lipid accretion (mostly triglycerides), although it can slowly progress in some patients to steatohepatitis or cirrhosis. In rare cases, drugs can also induce microvesicular steatosis, a severe form of DILI associated with hepatic cytolysis and hypoglycemia. Impairment of mitochondrial fatty acid oxidation (mtFAO) is a key mechanism whereby drugs can induce steatosis, with the most severe mtFAO alterations leading to microvesicular steatosis. In a screening study showing high relationship between steatosis and mtFAO inhibition (positive predictive value 91%, specificity 77%), the steatogenic drugs dexamethasone, olanzapine, ritonavir and zidovudine inhibited fatty acid-driven oxygen consumption in mouse liver mitochondria (with IC_{20} below 100 µM) but not complex I- and complex II-driven oxygen consumption (with glutamate/malate and succinate as respiratory substrates, respectively). Hence, results indicate that these drugs likely inhibit mtFAO via a direct mechanism and not via an impairment of the mitochondrial respiratory chain (MRC). This represents a new mechanism for the antiretroviral drug zidovudine since mitochondrial DNA (mtDNA) depletion was deemed to be the unique mechanism whereby this drug can induce hepatic mitochondrial toxicity and steatosis. Notably, three types of substrates (palmitoyl-L-carnitine, palmitoyl-CoA + L-carnitine and octanoyl-L-carnitine) were used in our assay in order to determine whether drug-induced inhibition of mtFAO is involving carnitine palmitoyltransferase 1 (CPT-1, an enzyme located at the outer membrane and allowing the formation of palmitoyl-L-carnitine from palmitoyl-CoA and L-carnitine) and/or other enzymes involved in the oxidation of long-chain and medium-chain fatty acids within the mitochondrial matrix. Thanks to this methodology, we uncovered that the four aforementioned drugs inhibited mtFAO of both medium and long-chain fatty acids and that CPT-1 was not impaired. On the contrary, other steatogenic drugs such as doxycycline, indomethacin, rifampicin and troglitazone inhibited complex II- and complex I-driven oxygen consumption and mtFAO at similar concentrations (with IC_{20} below 25 µM), suggesting that mtFAO inhibition was secondary to an impairment of MRC. Finally, our study demonstrates the usefulness to test drug-induced alteration of mtFAO and MRC in isolated mitochondria incubated with different respiratory substrates to better understand the mechanism whereby drugs can induce mitochondrial dysfunction and liver injury including steatosis and hepatic cytolysis. In addition, because severe mitochondrial dysfunction can cause drug withdrawal during clinical trials or after marketing (e.g. pirprofen, fialuridine, troglitazone), our methodology might be helpful during drug development to avoid such major misadventures.

PS 4493 Chemical Mixtures: The Science of Skin Deep

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The US personal care product industry mostly regulates itself, with limited oversight from the Food and Drug Administration. Without a standardized approach to formulation, the industry is replete with product ingredients that vary in quality and in their potential risks to human health and the environment. Although the potential risks posed by personal care products are well-documented, the standard single chemical risk assessment approach used in the personal care sector limits the ability of consumers, regulators, and formulators to accurately assess the safety of their products. The Environmental Working Group's Skin Deep database utilizes a weighted hazard stacking approach to approximate cumulative risk from the complex mixtures that comprise personal care products. Skin Deep hazard stacking

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