PS 100 CARCINOGENIC RISK ASSESSMENT FOR THE USE OF METHYLENE BLUE IN DAIRY COWS.

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Methylene blue (MB), though not approved as an animal drug by FDA, is used as a food-animal antidote for nitrate poisoning because there is no viable alternative. CVM recommended in 1990s a 180-day preslaughter withdrawal period in ruminants. Since then, new information has emerged including total residue data and a 2008 NTP study report. Therefore, the purpose of this evaluation was to determine if the previously recommended 180-day withdrawal time for both edible tissue and milk could be reduced. To achieve such a goal, we followed a step-by-step approach. First, the NTP report (NTP TR 540) was evaluated and we concurred with the finding that MB is genotoxic and carcinogenic. Second, we calculated So, the concentration of total residue of carcinogenic concern of the test compound in the total diet of test animals that corresponds to a maximum lifetime risk of cancer in the test animals of 1 in 1 million. We allocated 70% and 30% of the So to tissue and milk, respectively. Third, we used the allocated So to derive Sm, the permitted concentration of residues of carcinogenic concern in a specific edible product. Fourth, we reviewed the available residue data for MB in tissues and milk, and found that neither the depletion rate of MB in tissues down to Sm concentration nor the depletion rate of MB in milk could be established. Based on the above assessment of the carcinogenic concern of MB and residue information, we conclude that (1) the available residue data are not sufficient to allow a shorter than 180-day withdrawal time for both tissue and milk, (2) a depletion study for total residues (typically 14C-radiolabel) with adequate sampling times and number of animals is needed in order to determine the depletion profile of MB in tissues and milk, and (3) the Food Animal Residue Avoidance & Depletion Program (FARAD) recommended 14-day withdrawal period for edible tissues and 4-day milk discard time for MB is not supported by the information available to CVM.

PS 101 CONSIDERING MODE OF ACTION IN ESTIMATING A NSRL FOR 3-MCPD.

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Pursuant to California's Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65), 3-monochloropropane-1,2-diol (3-MCPD) was listed as a carcinogen on October 8, 2010. As neither California EPA nor U.S. EPA has developed a cancer potency estimate (i.e., slope factor [SF*]) for 3-MCPD that could serve as a basis for a no-significant-risk level (NSRL), an independent risk assessment was conducted. SF*s for 3-MCPD were estimated using available experimental bioassay data for male and female Fischer 344 and Sprague-Dawley rats administered 3-MCPD for 2 years via drinking water. A multistage cancer risk extrapolation model was implemented by applying a bootstrap Monte Carlo procedure to the rat data. Based on information indicating a sole non-genotoxic mode of action (MOA) for 3-MCPD-induced killing of testicular cells, data pertaining to Leydig cell tumors were excluded for potency analysis. The highest plausible SF* estimate obtained was an aggregate value pertaining to mammary, renal tubule and pancreas islet cell tumors significantly elevated in male Fischer rats. However, available evidence clearly indicates that a non-genotoxic/nonlinear MOA either caused or at least contributed to some or most if not all of those elevated tumor risks. One way to reflect such evidence is to reduce the calculated SF* by a modifying factor that appropriately and explicitly expresses the expected or (in regulatory contexts) minimum magnitude by which the unmodified SF* value overestimates true cancer potency at relevant environmental levels of exposure. This approach is fully consistent with Proposition 65 requirements, insofar as they provide for modified risk-estimation procedures supported by strong metabolic and pharmacokinetic evidence on which there is a scientific consensus. All the modifying factors considered and the strength of the evidence will be discussed. This approach produces alternative NSRLs that appropriately reflect available MOA data for 3-MCPD clearly indicating a dual mode of action for induced tumors.

PS 102 DEATH BY CAFFEINE: INTENTIONAL POISONING OF A DOG.

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A 4 year old, 37 kg, male German Shepherd developed hyperthermia, tachycardia and agitation following consumption of ground meat found in the backyard. When presented to a veterinary clinic, plasma ethylene glycol testing was positive, and the dog was treated accordingly. Approximately 11 hours post-exposure, the dog died. Among tissues submitted for toxicological analysis, urine was negative for ethylene glycol, no drugs of abuse were detected in the source material (meat) and gastric contents were negative for phosphine and metaldehyde. GC/MS analysis of gastric contents confirmed the presence of caffeine. Caffeine concentration in the bait sample was estimated at 1%. Caffeine is a methylxanthine alkaloid with a reported canine oral median lethal dose (MLD50) of 140 mg/kg (range 120-200 mg/kg). Acute intoxication affects the cardiovascular (positive chronotropic and dromotropic effects), pulmonary, neurologic, gastrointestinal and metabolic systems. Commercially available 200 mg tablet formulations of caffeine were considered to be a possible source, based on the relative ease of bait formulation. Based on the oral MLD50, the dog would need to ingest approximately 500-550 g of bait to reach a potentially lethal dose. Although no tablet remnants were observed in the bait, tablets could have been crushed and/or dissolved. Other caffeine sources include guarana, brewed coffee and caffeine-containing beverages. Based on history, clinical signs, the detection of caffeine in the gastric contents and bait, a presumptive diagnosis of intentional caffeine poisoning was made. The lack of a full pathological evaluation limits the elimination of other causes of acute death. While few cases of accidental ingestion of caffeine by dogs have been described, the intentional use of a concentrated caffeine source to kill a dog has not been previously reported and warrants awareness by veterinarians and diagnostic professionals.

PS 103 A QUANTITATIVE RISK ASSESSMENT OF 2, 3-PENTANEDIONE, BASED ON PRELIMINARY DATA.

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Only preliminary (pilot study) toxicity data are currently available for the food flavoring 2,3-pentanedione (PD). However, it is possible to compare the pilot study data for PD to similar data for diacetyl and derive an estimate of the relative toxicities of PD and diacetyl in mice. PD data were taken from a study described by Morgan et al. [2010] (Toxicologist *114*(1):316) and compared to a diacetyl pilot study, Morgan et al [2008] (Tox. Sci. *103*(1):169-180. In the PD study, rats and mice (6/dose group) were exposed to 0, 50, 100, or 200 ppm for 2 weeks + 2days. In the diacetyl study, male C57Bl/6 mice (5/dose group) were exposed to 0, 25, 50, or 100 ppm for either 6 or 12 weeks. The pathology produced by both chemicals was very similar, affecting nasal tissue most severely but also the trachea, larynx, and bronchi. Benchmark dose analysis compared the BMD50s for nasal suppurative exudate in male mice, and for bronchial inflammation in male mice for diacetyl and female mice for PD. Comparing the PD data to the 6-week diacetyl data for the nasal suppurative exudate endpoint, PD appears to be 73% (95% CI 30-177%) as potent as diacetyl. Comparing the PD data to the 6-week diacetyl data for the bronchial inflammation endpoint, PD appears to be 53% (95% CI 18-158%) as potent as diacetyl. Comparisons to the combined 6 + 12-week diacetyl data yield toxicity ratios of 67% (95% CI 32-141%) for the nasal endpoint, and 58% (95% CI 22-153%) for the bronchial endpoint. Although the central estimates suggest that PD may be somewhat less potent than diacetyl for the endpoints in question, given the wide confidence limits equipotency of PD and diacetyl cannot be ruled out based on the current data. *The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health or the National Institute of Environmental Health Sciences.*

PS 104 US EPA'S PROPOSED TOXICITY VALUES FOR TCDD: IMPLICATIONS FOR DECISION-MAKING REGARDING THE SAFETY OF FOODS IN THE UNITED STATES.

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USEPA recently released a draft RfD (0.7 pg/kg-d) and oral CSF (0.001 pg/kg-d-1) for 2,3,7,8-TCDD. The CSF equates to intakes of 0.1–0.001 pg TEQ/kg-day at 10-4-10-6 risk levels, respectively. These intakes are substantially lower than tolerable daily intakes (TDIs) developed by other regulatory and public health agencies (eg, JECFA has established a provisional tolerable intake equivalent to 2.3 pg/kg-d), as well as considerably below estimated breastmilk intakes (242 pg/kg-d). Our objective was to compare intakes of dioxin-like compounds (DLCs) from US foods to intakes associated with the USEPA draft toxicity values as a means of assessing the implications of these values. Daily intakes were based on USFDA estimates of average total dietary intakes of DLCs, which were calculated using data from the Total Diet Study and consumption data from USDA. Risk and hazard were estimated using standard equations and exposure factors for child, adolescent, adult and age-adjusted scenarios. Daily intakes from food greatly exceeded the intakes associated with the CSF at all risk levels for all age groups. Daily intakes also exceeded the RfD for a number of infant, child and adolescent age groups. The cancer risk associated with lifetime dietary DLC exposure (3x10-4 to 9x10-4) was above USEPA's acceptable risk range. The noncancer hazard estimates were found to exceed the USEPA's target HQ of 1 for children (2.4), adolescents (1.4) and the age-adjusted group (1.3) when the full value of the detection limit was imputed for non-detects (NDs). In contrast, when intakes were compared to the JECFA value, which is protective of

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