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- 794 INTEGRATING CRITICAL SCIENTIFIC DATA INTO REGULATORY EXPOSURE LIMITS: A CASE STUDY WITH HYDROGEN SULFIDE. L B Walker, B D Kerger, and D J Paustenbach. ChemRisk Division of McLaren/Hart Environmental Engineering Corporation, Irvine, CA.

Exposure to hydrogen sulfide has been a well recognized acute inhalation health hazard for decades, and there is a good understanding of the acute responses in both humans and in experimentally exposed animals. The animal and human literature show a steep concentration-response curve with well-delineated thresholds for both localized eye and respiratory tract injury occurring at moderate concentrations, and a systemic tissue hypoxia that results from inhibition of cytochrome oxidase at higher exposure concentrations. Most of the community ambient air standards have been derived by applying a range of subjective uncertainty factors to occupational exposure limits. These uncertainty factors are presumably justified by the lack of chronic animal studies and human epidemiology studies of persons exposed to low exposure concentrations. However, additional mechanistic studies demonstrating that hydrogen sulfide is produced endogenously and is rapidly metabolized support the premise that compensatory mechanisms exist to protect against chronic toxicity at low concentrations. Our analysis integrates these important mechanistic and pharmacokinetic aspects in deriving health-based ambient air limits for hydrogen sulfide. The results of our analysis emphasize that evaluating the full breadth and weight of relevant scientific data can help identify a valid ambient air standard.

- 795 A MODEL FOR SUCCESSFUL ADVERSE EFFECTS REPORTING. M O Tisdell, J H Gillis, K S Stumpf, and J A Stone. Ciba-Geigy Corporation, Plant Protection Division, Greensboro, NC.

Reporting of potential adverse toxicological effects is regulated by EPA under Section 8(e) of TSCA and Section 6(a)(2) of FIFRA, which dictate reporting requirements during different stages of a pesticide's development, yet often overlap; criteria for reportable effects, reporting time frames, branch of EPA concerned, and penalties are different under the two sets of laws. Specific scientific interpretation and mechanisms for monitoring and reporting information are the responsibilities of agricultural chemical companies. The Toxicology Department of Ciba-Geigy Plant Protection has developed a successful program (AESOP) for timely review, decision making, tracking and reporting of information to fulfill these requirements. This system includes reviews, checklists, standard forms/letters, and information transfer schemes which are closely monitored by trained toxicology personnel. The initial review uses a checklist approach, which may be followed by consultation with additional toxicologists or committees. Records of all reviews (for both reportable and non-reportable studies/information) are maintained in a central location, and follow-up actions are monitored. This approach to adverse effects reporting is efficient in terms of use of professional time, ensures compliance and avoidance of penalties, yields consistent judgments, and is adaptable to changes that may be made in regulations.

- 796 PROPOSED SAFETY EVALUATION GUIDELINES FOR NEW EXCIPIENTS. M L Weiner, M Steinberg, J F Borzelleca, E K Enters, D F Hager, F K Kinoshita, A Loper, D B Mitchell, C B Tamulinas. International Pharmaceutical Excipients Council Safety Committee

There are currently no regulations governing the approval of new excipients, independent of formulated drug products. The International Pharmaceutical Excipients Council (IPEC) Safety Evaluation Committee has developed guidelines for new excipients to assure their safe use in drug products. Background information on chemical/physical properties; purity/specifications; exposure/use conditions; manufacture process and biological activity is compiled and reviewed. A base set of toxicology data is generated to support limited human exposure. The base set includes acute toxicity; 28-day toxicity studies (1 rodent & 1 non-rodent species) by oral and intended exposure routes; genotoxicity and metabolism/pharmacokinetics studies. Evaluation of the base set could allow a single exposure in man. Additional studies are recommended for repeated (2-6 wks) use in man: 90-day toxicity study in an appropriate species; developmental toxicity study (2 species) and additional genotoxicity studies. For extended human exposure (> 6 wk), chronic and reproductive toxicity tests should be considered, based on scientific review of all of the studies. Special studies for specific routes are also included, i.e. skin sensitization for dermal exposure.

- 797 THE CMR INTERNATIONAL TOXICOLOGY DATABASE 1981-1993: CRITICAL EVALUATION OF SAFETY TESTING ISSUES. C Parkinson, S A Griffiths, J A N McAuslane and C E Lumley. Centre for Medicines Research, Woodmansterne Road, Carshalton, Surrey, UK. Sponsor: B Lake

Repeat dose toxicity studies are a regulatory requirement and play an essential part in the non clinical safety evaluation of pharmaceutical compounds. However regulatory procedures need to keep pace with the advances being made in the science. To help rationalise the design and interpretation of repeat dose toxicity studies the Centre for Medicines Research established the International Toxicology Database (ITD) which has been updated and maintained since 1981. This database currently contains data obtained from 34 companies on 226 pharmaceutical compounds. Of these, 198 have been studied in the rat, 178 in the dog, 39 in primates and 10 in other species. Other details include therapeutic class, study design, and all salient toxicology findings. The data has been used for numerous analyses including the minimum duration of chronic toxicity studies and the use of two species. Data from the ITD has recently been used in the harmonisation discussions that have led to the adoption by the regulators in Japan and the USA of 6 month rodent studies for pharmaceuticals. In over a decade of use this database has shown that retrospective analyses can allow both critical evaluation of issues relating to safety testing of pharmaceuticals and provide a historical background against which individual companies can evaluate their own findings.