

In this evaluation, physiologically based pharmacokinetic modeling was used to predict tissue doses from acceptable/safe exposures as established by different organizations and agencies. Internal doses calculated for an agency's acceptable/safe exposures via oral and inhalation routes may differ substantially, but are sometimes in excellent agreement. Based on the 14 compounds modeled in this effort, acceptable occupational exposures almost always produce greater internal doses than acceptable environmental exposures. This finding suggests different mindsets among these groups regarding how safe is "safe." (This work was supported by Contract No. DAAA21-93-C-0046 (Task No. N.113, Subtask R1-4) to the National Defense Center for Environmental Excellence, operated by Concurrent Technologies Corporation.)

372 COMPARISON OF ACUTE INHALATION EXPOSURE LEVELS FOR CHEMICAL IRRITANTS AMONG FIVE AGENCIES IN THE UNITED STATES.

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Acute inhalation exposure limits have recently been developed by various agencies to protect the community. Many of the chemicals for which limits have been set are sensory irritants. In general, these limits have been established to give guidance regarding the need to evacuate following accidental releases. The purpose of this paper was to compare the various scientific approaches used to set these limits. Proposed one-hour exposure limits intended to prevent sensory irritation for the chemicals formaldehyde, xylene, toluene, methyl ethyl ketone and hydrogen sulfide were evaluated. Comparisons between the AIHA Emergency Response Planning Guideline (ERPG), EPA Acute Reference Exposure (ARE), Minnesota Health Risk Value (HRV), New York Air Guide-1 (AG-1), and California Acute Reference Exposure Level (REL) were made. A set of recommended criteria for calculating alternative one-hour exposure limits for these chemicals was developed. These criteria included the use of specific toxic endpoint selection, correction for short-term experimental exposure duration, and a recommendation to build a dose-response curve based on the a collection of the best published sources. Our analysis indicated that there was significant variability between short-term ambient air exposure limits developed by the five different agencies and that these were often different from our recommended values. The selection of the most sensitive adverse effect, the application of default uncertainty factors and the identification of a NOEL from a single study rather than a "blended" NOEL based on the weight of evidence accounted for the differences among the agencies. Disparities in the methodologies used to establish exposure limits will likely be resolved as more experience is accumulated.

373 VALIDATION STUDY OF AN OCCUPATIONAL EXPOSURE BAND (OEB) CLASSIFICATION SYSTEM.

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The purpose of an OEB Classification / Handling Guideline System is to provide an exposure control and containment strategy for handling substances when the available data are insufficient to establish a numerical Occupational Exposure Limit (OEL). In such a system, substances are assigned to one of several bands (OEBs) based upon the substance's presumed hazard and/or whatever limited toxicological and hazard data may be available at the time the classification is made. For each OEB there is then a general containment philosophy, a Handling Guideline (HG), specific for differing scales of operations. The HG identifies engineering controls, personal protective equipment, administrative controls, waste disposal methods, and decontamination practices generically appropriate for limiting exposure to materials with the designated level of hazard. In order to validate the OEB Classification Scheme used by Pfizer, we examined certain information contained in 29 drug substance OEL monographs approved by the corporation's Technical Review Committee (TRC) and, independent of the TRC's OEL, cast each compound into one of the 5 OEBs described by the Classification Scheme. The data considered for the banding exercise were limited to those generally available early in product development, and consisted of: clinical potency, acute toxicity, irritation / corrosion, sensitization, mutagenicity, and ≤ 30 -day repeat-dose toxicity. In 27 of 29 instances, the OEB Criteria caused the compound to be classified at the same or a more conservative Band than that called for by the OEL. Indeed, in 12 of the 27 "correct" cases, the OEB and the OEL were in concurrence. In the 2 cases of non-concurrence, the cause of the failure was judged to be rounding error inherent in the OEL set-

ting process. Based upon the high level of concordance and low failure rate in this study, the Pfizer OEB Classification Criteria have been successfully validated and adopted for corporate application worldwide.

374 DETERMINATION OF ACCEPTABLE EXPOSURE LIMITS FOR THE ANTI-VIRAL AGENT RIBAVIRIN.

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Ribavirin is a potent and broad spectrum antiviral agent commonly given in aerosol form to treat respiratory syncytial virus infections in children. Oral administration of ribavirin has been tested for teratogenicity in rats, mice, rabbits and baboons. The most susceptible test species for reproductive effects was the rabbit, with a no observable adverse effect level (NOAEL) of 1 mg/kg/day (Huntington Laboratories). Even though no adverse health effects have been reported in patients treated with ribavirin, potential fetal toxicity is a major concern among occupationally exposed health care professionals, since many of these workers are women of child-bearing age. Previous approaches to calculating a permissible exposure limit (EL) in humans were based on pharmacokinetic studies reporting an oral bioavailability of about 45%. However, a recent human study provides more relevant bioavailability data for inhalation exposures received by medical personnel. In this study, we used this recent human data that demonstrates that ribavirin bioavailability following inhalation exposure is only 0.5% of the total inhaled dose (Linn et al., 1995). We then used this human bioavailability data together with plasma and red blood cell (RBC) concentrations of ribavirin in pregnant rabbits administered a NOAEL dose of ribavirin during organogenesis. The rabbit teratology study showed that plasma and RBC ribavirin levels at the NOAEL are 2.4 and 23.6 $\mu\text{mol/l}$, respectively. An upper limit of an inhaled dose for occupational exposure was then derived using a 100-fold uncertainty factor applied to blood ribavirin levels at the rabbit NOAEL. Assuming an average female worker of 60 kg, a ventilation rate of 25 l/min, and continuous exposure during an 8-hr shift, the calculated 8-hr EL for inhalation of ribavirin was 7.4 mg/m^3 .

375 THE CONCENTRATION-EXPOSURE DURATION RELATIONSHIP FOR INHALED TOXICANTS.

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When desired exposure-duration data are lacking for an assessment of acute inhalation toxicants, scaling across time may be based on the relationship between exposure concentration and exposure duration for a specific response such as lethality (LC_{50}). A log-log regression analysis similar to the probit analysis described by ten Berge et al. (1986, *J. Hazard. Mat.* 13:301-309) was used to extrapolate concentration-response data across different exposure times. The regression analysis by ten Berge et al. resulted in the following equation: $C^n \times t = k$, where C = concentration, t = exposure time, k = a constant, and the exponent n is $= b_1/b_2$ (probit regression coefficients) or the negative reciprocal of the slope of the log-log regression analysis. Data sets were evaluated for 40 different inhalation toxicants including respiratory tract irritants such as ammonia and hydrogen fluoride, systemic toxicants such as hydrogen cyanide, and combined respiratory tract irritant and systemic toxicants such as ethylene oxide. All data sets were not sufficient to conduct a regression analysis. The results showed that n fell between 0.8 and 2.5 for almost all data sets. This evaluation suggests that a default n between 1.5 and 1.7 (mid point) may be a good estimate for chemicals with insufficient data. Evaluation of these data sets also suggests that n may be based on data for a breakdown product (HCl for chloromethylsilanes) or a structurally/mechanistically similar chemical (ethylenimine for propylenimine) for chemicals with insufficient data.