SafeBridge
CONSULTANTS, INC.

Developing Occupational Exposure Limits (OELs) for Pharmaceutical Substances

Developed by Allan W. Ader, Ph.D., DABT, Principal Toxicologist

1. Description of the Issue

Occupational exposure limits have been employed as a means to define "acceptable" limits for occupational exposure to workers for many years. The American Conference of Governmental Industrial Hygienists (ACGIH), a consensus organization has established exposure limits, termed Threshold Limit Values (TLVs) based on a number of approaches, including worker experience and extrapolation of effects in laboratory animals to man. The U.S. Occupational Safety and Health Administration (OSHA) was formed in 1970 and adopted the 1968 ACGIH TLV list as enforceable workplace standards contained in the U.S. Code of Federal Regulations (CFR) (29 CFR 1910,1000). OSHA refers to these standards as Permissible Exposure Limits (PELs). Since then, OSHA has promulgated standards on a chemical by chemical basis, which includes a PEL as the primary basis for assessing the acceptability of exposure to hazardous materials, e.g., benzene, in the workplace. In addition, the American Industrial Hygiene Association (AIHA) has developed Workplace Environmental Exposure Limits (WEELs) for compounds identified by the organization and its members to need occupational exposure limits.

Most, if not all, of the compounds for which exposure limits have been established by consensus or regulatory agencies are for commodity industrial chemicals, such as methanol and chlorine. In some cases, a TLV or PEL has been established on a non-commodity chemical when a significant biological effect has been observed, e.g., dibromochloropropane or DBCP and decreased fertility. Even though pharmaceutical compounds are widely used, manufactured and have significant biological effects, few, if any pharmaceutical compounds have had TLVs or PELs established on them. This task has been performed by the pharmaceutical companies themselves.

Pharmaceutical compounds inherently have pharmacological activity or potency and are toxic at some dose. The gap between an efficacious pharmacological dose and toxic dose in part determines a drug's effectiveness and viability as a candidate for drug development. The trend in the pharmaceutical industry is towards the development of more potent drugs that are efficacious at lower dose levels. Such drugs often exhibit toxic effects at low (potent) doses including reproductive and developmental toxicity and in some cases, carcinogenicity. These effects potentially pose a risk to occupationally exposed employees.

Workers involved in the synthesis and handling of these compounds need to be protected from excessive exposures. One approach to protect against possible adverse effects in employees who handle these drugs is to establish an exposure assessment and control program. An important element of this program is to determine an "acceptable" airborne level for the compound in the workplace, i.e., an internal occupational exposure limit or OEL, using scientifically defensible risk assessment methodologies. The types of risk assessment methodologies are numerous and depend on the information available on the compound. The assessments could include the following:

1. Safety factor extrapolation from animal toxicology data
2. Benchmark dose determination based on animal toxicity data
3. Acceptable daily intake determinations based on extrapolation from human clinical experience
4. Extrapolation using carcinogenicity models (e.g., multistage) to determine a significantly low (1 in 1,000 to 1 in a million) increased risk of cancer in the worker population
5. Structure activity relationships

In addition to an OEL, an industrial hygiene air monitoring and analytical method for sample analysis is needed. Comparing workplace exposures to the OEL provide management with a valuable tool in evaluating workplace safety.

The staff of SafeBridge Consultants, Inc. has been involved in the development of OELs and air sampling and analytical methods for drug substance and intermediates for over 15 years. OELs developed by SafeBridge Consultants, Inc. will have sufficient and defensible safety or uncertainty factors applied to effect levels observed in humans or laboratory animals. The OELs will be like PELs and TLVs in that the recommended number will be at a concentration at which it is expected nearly all workers could be exposed without suffering ill effects either on a time-weighted or short-term basis (whichever is considered the most appropriate endpoint).

2. Description of Tasks and Estimated Hours

Development of an OEL requires the review of available data, determining its relevance and applicability to developing an OEL, and then applying risk assessment methodologies to the data to arrive at a scientifically defensible value. The time to perform each of these tasks is very dependent on the amount and quality of information available on the compound and its stage of pharmaceutical development. The tasks and estimated hours, based on past experience, are as follows.

<u>Task One: Obtain and Review Available Data</u>

This task would involve the review of all available data/information on the compound. Data provided by the company, as well as independent search of data bases (if necessary) would be undertaken. The available data may include pharmacologic activity in laboratory animals and humans, pharmacokinetics, non-clinical (toxicological) data in laboratory animals, human clinical experience and adverse reaction reports in humans.

Estimated Hours to Complete Task: 8-16 hours

Task Two: Evaluation of the Data to Determine Relevance to an Occupational Exposure Limit (OEL)

This task would include a critical evaluation of the data and its application to OEL development. The most relevant study or studies on which to base an OEL will be identified.

Estimated Hours to Complete Task: 3-5 hours

Task Three: Prepare OEL Documentation, including Internal/External Review

This task would include preparing a draft OEL documentation of the relevant pharmacological and toxicological properties of the compound, as well as relevant human clinical experience, and preparing a scientific rationale for the OEL.

The OEL documentation will be finalized by incorporating comments received from the client.

Estimated Hours to Complete Task: 16-20 hours

Comments and questions can be directed to:

Allan W. Ader, Ph.D., DABT
SafeBridge Consultants, Inc.
1924 Old Middlefield Way
Mountain View, CA 94043-2503
Phone: (650) 961-4820 ext. 228
Fax: (650) 623-0096
allan.ader@safebridge.com