HEALTH

Potent Compound Handling Operations

Introduction

Pharmacology is the study of interactions between a living organism and chemicals that affect their biochemical functions. In the field of pharmacology, potency is a measure of drug activity expressed in terms of the amount required to produce an effect of given intensity. A highly potent drug evokes a larger response at low concentrations, while a drug of lower potency evokes a smaller response at similar concentrations.

Occupational health professionals in the pharmaceutical industry have recognized the potential for occupational disease caused by overexposure to active pharmaceutical ingredients (APIs)[1]. Compounds that are routinely handled in the biotechnology, pharmaceutical, and medical device industries (from hereon called pharmaceutical industry) are unique in that they are designed to have an effect on the human body. Environmental, health, and safety professionals in the industry have responded to this risk by developing and implementing comprehensive programs for the anticipation, recognition, evaluation, and control of exposure to APIs. This is achieved by ensuring that employees are protected from exposure to potent APIs. The purpose of this technical brief is to provide an overview of the design and implementation of an effective and economical potent compound safety precautions for the industry.

The design and implementation of an effective potent compound safety program should follow the same basic process as traditional industrial hygiene programs – hazards should be anticipated, activities with drug exposure potential should be recognized and evaluated, and finally these exposures must be controlled. A comprehensive potent compound safety program is active at all stages of product development including research, discovery, pre-clinical development, pre-formulation, initial test batches, pilot plant, scale-up, and production.

Prior to the introduction of new APIs into the workplace, a thorough literature search on the specific or similar compounds should be conducted. While this may seem like a simple task, it often becomes challenging to find relevant hazard information for new discovery compounds. However, at this point, the primary focus should be to identify adequate information to allow preliminary classification or categorization of the compound into a control banding strategy, such as those proposed by Naumann et al.[1]. With a few minor revisions, this categorization scheme has been widely accepted across the pharmaceutical industry. The most common modification to the scheme described by Naumann and his colleagues is in the number of bands individual companies utilize for their compounds. Some companies use four bands while others use a five band system (Tables 1 and 2).

Table 1

FOUR BAND OCCUPATIONAL EXPOSURE BAND CONTROL TABLE

OEB	OEL	Suggested Design Controls	Properties
1	> 500 µg/m³	General room ventilation. Conventional open equipment with local exhaust ventilation (LEV).	Compounds that are not harmful, and/or have low pharmacological activity.
2	10 - 500 µg/m³	Semi-closed to closed material transfer; laminar flow/directionalized laminar flow, engineered LEV.	Compounds that are moderately toxic and/or have moderate pharmacological activity.
3	0.03 - 10 µg/m³	Transfer using direct coupling & closed systems. Selected use of unidirectional air flow booths.	Compounds that are toxic, and/or have high pharmacological activity. NOTE: Chemicals of unknown toxicity, which are believed to have the potential for high to extremely high toxicity or pharmacological activity based on its therapeutic class or other indicators, will be assigned to OEB 3 by default.
4	< 0.03 µg /m³	Totally enclosed processes; direct coupling transfer; barriers/isolation technology.	Compounds that are extremely toxic, and/or have very high pharmacological activity.

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Table 2

FIVE BAND OCCUPATIONAL EXPOSURE BAND CONTROL TABLE

OEB	OEL	Suggested Design Controls	Properties
1	> 1,000 µg/m³	General room ventilation. Conventional open equipment with LEV.	Compounds that have low pharmacological activity and are considered fairly safe to handle.
2	> 50 – 1,000 µg/m³	Semi closed to closed material transfer; laminar flow/directionalized laminar flow, engineered LEV.	Compounds that are harmful, and/or have low pharmacological activity.
3	> 20 – 50 µg/m³	Transfer using direct coupling & closed systems. Selected use of unidirectional air flow booths.	Compounds that are moderately toxic and/or have moderate pharmacological activity.
4	1 – 20 µg/m³	Totally enclosed processes; direct coupling transfer; barriers/isolation technology.	Compounds that are toxic, and/or have high pharmacological activity. NOTE: Chemicals of unknown toxicity, which are believed to have the potential for high to extremely high toxicity or pharmacological activity based on its therapeutic class or other indicators, will be assigned to OEB 4 by default.
5	< 1 µg/m³	Isolation technology; remote operations; fully automated.	Compounds that are extremely toxic, and/or have very high pharmacological activity.

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Recognition of Exposure Potential to APIs

A potent compound exposure control band provides an array of safety requirements for a specific category and a source of information to determine appropriate handling practices, industrial hygiene targets for air monitoring, and a starting point for final potent compound categorization by an occupational toxicologist. These bands are a concentration range of potent compounds where personnel exposure should be controlled. Naumann et al. discusses the basis for establishing occupational exposure levels (OELs) during the various stages of drug development as well as the criteria evaluated in determining occupational exposure bands (OEB). Toxicologists are frequently required to exercise professional judgment to properly complete a potent compound categorization.

Once a relevant dose has been determined, an estimated OEL, which is a contaminant concentration in a given volume of air, can be calculated using the methodologies such as those presented by Sargent (1988)[2]. After the potential hazards of the API have been identified and an estimated OEL has been calculated, the occupational health professional should identify the potential risk factors associated with its use.

These risk factors include:

- How the API is handled
- Form of the API (powder or liquid)
- Quantity of the API
- Exposure duration and frequency

In addition to routine laboratory and manufacturing processes, the environmental, health, and safety professional should have an understanding of potential exposure situations during non-routine activities, such as emergency repair activities.

OEBs that are utilized in discovery and early development are initially assigned based on:

- Toxicological assumptions about a compound based on limited data
- Analytical methods that may not be fully developed for a monitoring program

These bands are ranges of airborne concentrations of substances as 8-hour time-weighted averages (TWAs).

Evaluation of Occupational Exposure to APIs

In the initial exposure evaluation process, high priority activities are those where APIs are handled in powder form, such as weighing of powders in laboratories, dispensing, blending, dry granulation, and compression activities. Once the product is either in finished solid dosage or liquid form, the exposure risk is significantly reduced.

Monitoring methods for the APIs are then needed to establish the airborne and surface concentration of APIs. Alternatively, these evaluations may be performed using a surrogate powder such as sodium naproxen.

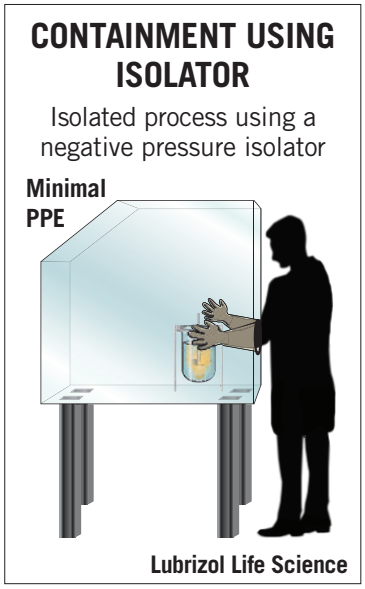
Control of Exposure to Potent Compounds

Employee exposure to potent compounds can be through:

- Ingestion through mouth or nose
- Transdermal through absorption through skin
- Intramuscular through accidental puncture
- Mechanical transfer through mucous membranes due to residues on clothing or equipment
- Ocular through airborne particles

The primary focus of a comprehensive potent compound safety program is to ensure employee safety through effective process containment. Containment is the design and implementation of engineering controls and personal protective equipment (PPE) for use with manufacturing, pilot plant, and laboratory operations with the goal of minimizing the emission of substances into the work environment and therefore limiting potential employee exposure. One example is the use of an isolator (Figure 1).

Figure 1



The pressure within the isolator is negative with respect to the environment which minimizes the contamination potential of the potent compound being manipulated in the isolator. Suggested activities for a successful implementation of a containment program are:

- Study and document containment requirements for a given activity
- Focus the same level of attention on personnel as the product for a given activity
- Involve the operator in selecting and testing containment system
- Consider the following in the system selection:
    - Peak and average containment levels expected for the operation
    - Operability and effects on productivity
    - Effect on product yield and material loss

- Portability or set up time
- Cleanability/maintainability/ durability
- Initial and operating cost
- Ability to test containment effectiveness and GMP

The activity to be contained needs to be studied and documented in detail. The goal is to control air and surface contamination. When handling highly potent compounds (i.e., OELs less than 1 µg/m^3) containment must be provided during all laboratory procedures or steps in the manufacturing process. The entire process must be considered including the potent chemical compounds that will be handled, the equipment used, and the hazards of those chemicals. Approaches can include modification of the engineering controls and employee interface. The engineering controls need to be ergonomically designed and user-friendly or there may personnel compliance issues. Minimizing the employee interface in a process will minimize exposure potential. In addition to engineering, administrative controls such as proper potent compound safety training is paramount and, if needed, product-specific medical surveillance may be implemented.

Summary of an Effective Potent Compound Safety Program

Design and implementation of an effective potent compound safety program requires that all elements be considered. Failure to adequately anticipate, recognize, evaluate, and control exposures to potent compounds can result in costly program missteps, delayed drug development schedules, or potentially hazardous exposures to workers. To be successful, a comprehensive potent compound safety program will have contributions from safety, engineering, toxicology, industrial hygiene, and operations.

References:

1. *Naumann, Bruce D., et. al., "Performance-Based Exposure Control Limits for Pharmaceutical Active Ingredients." American Industrial Hygiene Association Journal. 57: 33-42 (1996).*
2. *Sargent E.V., Kirk G.D., "Establishing Airborne Exposure Control Limits in the Pharmaceutical Industry." American Industrial Hygiene Association Journal 1988; 49(6): 309-313.*

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