FEATURE

Occupational health categorization and compound handling practice systems—roots, application and future

Chemical categorization (or banding) of inherent toxicity and potency linked with defined engineering and work practice controls and personal protective equipment has become an integral component of assuring the health and safety of researchers and manufacturing personnel in the pharmaceutical industry.*

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INTRODUCTION

In the late 1980s, occupational health professionals within the pharmaceutical industry were faced with an issue that impacted the nature of worker protection and assessment of occupational health hazards, as well as risk communication needed to be provided. For many years, as pharmaceutical compounds were discovered that were therapeutic and efficacious but could potentially elicit human (and therefore potentially occupational) health effects at low levels, such as steroid hormones, opioids, peptide hormones and prostaglandins, guidelines could be provided on a compound-by-compound basis. This effort would include development of scientifically defensible Occupational Exposure Limits (OELs), similar to those set by the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs®) and US Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs) (see Ku),[1] and sensitive industrial hygiene sampling and analytical methods to monitor worker exposure to these individual substances.But the late 1980s and early 1990s saw an explosion of molecular biology, high through-put screening techniques, biotechnology, and diversity and an unprecedented increase in the nature and volume of new chemical entities that would enter the pharmaceutical research and manufacturing environments. Novel compounds of unknown toxicity and potency were being developed at a rate too fast for occupational health professionals to provide individual compound guidance. Additionally, pharmacological selectivity typically increased and more potent compounds were being developed. Correspondingly, there has been an increase in the occupational health risk associated with the handling of these increasingly potent drug entities in research, development, and manufacturing. The occupational health and safety professional was tasked with trying to communicate the risks of the compounds and to provide handling guidance to the employees in a timely and understandable manner.

BEGINNING OF THE OCCUPATIONAL HEALTH CATEGORIZATION AND COMPOUND HANDLING PRACTICE SYSTEM

Faced with this dilemma, occupational health representatives of five pharmaceutical companies who identified this as a major issue within their companies (Syntex (USA) Inc., Merck and Co., Inc., Eli Lilly and Co., Abbott Labs, and The Upjohn Co.) met to discuss how they could development a "potent compound safety management system" that would allow for appropriate handling of novel chemical entities and new pharmaceutical products. The five companies were part of a larger ad hoc group of pharmaceutical company health and safety professionals who periodically met to discuss solutions to common challenges they faced in providing health and safety services within the industry. Quarterly working group sessions were held over a two-year period. Each of the five

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*The terms categorization, banding, and performance-based exposure control limits (PB-ECLs) have all been applied to the concepts described in this paper. For the purposes of this paper, the term categorization will be used and should be considered to be equivalent to these other terms.

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individual companies assessed the types of risks and hazards they were facing and determined that an effective approach would be implementation of an appropriate compound categorization, exposure control and compound handling system. The approaches developed were similar to those developed by the Centers for Disease Control (CDC) for biosafety (Biosafety Levels or BSLs described in CDC/NIH).[2] The CDC BSLs, and occupational categorization systems are common in that they are both "hand in glove" systems, meaning that for a corresponding hazard determination, appropriate controls and work practices are developed and applied. In the case of the pharmaceutical compound categorization systems, the key task was to link pharmaceutical potency and toxicity to safe handling. Control recommendations were based on prior success with compounds having similar characteristics. Work environments, process controls, techniques, and personal protective equipment recommendations were based on data developed from historical industrial hygiene air monitoring results.

In the case of the authors, we could identify four work environments or degrees of containment (similar to the four BSL levels) in our laboratory and manufacturing facilities: low (e.g., open handling), intermediate (e.g., local exhaust ventilation with some limited open handling); high (e.g., containment at the source of dust generation through direct connection); and very high (e.g., isolation and glove box technology). The occupational toxicologist matched existing compounds and their toxicological characteristics of the compounds to the work environment descriptors developed by the industrial hygienist. This qualitative categorization criteria (rather than the OEL) became the "roots" of the system.

So, in summary, the initial approaches taken with occupational health categorization systems and their utility were to match toxicity and potency criteria with work environments in a qualitative manner. It was not and should not be used as a substitute for good industrial hygiene and safety practice, which would be to develop scientifically defensible Occupational Exposure Limits (OELs) and sensitive air sampling and analytical methods, followed by industrial hygiene monitoring of workers to verify control levels. Furthermore, once an OEL had been developed, it did not matter which "category" the material was in, as the OEL becomes the "target" for control measures within the workplace. Rather the system was designed to give guidance, based on experience, on safe handling until a meaningful quantitative task-oriented industrial hygiene exposure assessment could be conducted.

WHY IS THERE MORE THAN ONE OCCUPATIONAL BANDING AND HANDLING PRACTICE SYSTEM?

The original five companies attempted to create a "one size fits all" system to take back to the other companies of the ad hoc pharmaceutical safety group and found that this did not work for several reasons. Clearly the therapeutic substances were different in the five companies (and the other companies in the safety group that the concept was brought back to). Surprisingly it was found that the work environments, equipment and controls were also different. Due to these and other factors, each company developed company-specific systems which were based on the common themes developed by the initial group of five companies. Proper implementation would depend on customization to match each company's business and health and safety needs. Typically, four (SafeBridge Consultants, Inc.)[3] or five (Naumann et al.–the publication in this area derived from these meetings as applied to pharmaceuticals)[4] category systems were adopted based on these original discussions.

DESCRIPTION OF TOXICITY AND POTENCY CATEGORIES

The basic premise of the system is to place chemicals into categories based on their inherent toxicity and potency characteristics. These data are obtained from toxicological investigations that evaluate the effects of these substances in animals or *in silico* (predictive systems) and are inferred from application of specific dosing regimens during the course of human clinical trials (for pharmaceutical compounds). Mechanism of pharmacological action, therapeutic dose, and the spectrum and severity of clinically observed side effects of a specific drug substance, all provide the basis for the toxicity assessment. Ultimately, the assessment process involves placing a drug into one of four classification categories:

(1) Low Toxicity;
(2) Intermediate Toxicity;
(3) Potent/Toxic; or
(4) Highly Potent/Highly Toxic

Criteria used for each of these (in this case, four) categories are described in Table 1. A compound placed within either of the latter two categories of Potent or Highly Potent is typically associated with a comparatively low therapeutic dose (e.g., provides a therapeutic effect at a dose of approximately 10 mg or lower), and/or is believed to present the potential for '-genic' effects in individuals exposed to the compound (e.g., these compounds have typically been observed to induce carcinogenic, mutagenic, reproductive toxicity and/or developmental or teratogenic toxic effects in animal studies and/or human clinical trials).

Many of the novel compounds handled within the context of pharmaceutical research and development laboratories and clinical production environments frequently lack the data described above to sufficiently evaluate the occupational hazard posed to workers handling these substances. Yet, clearly these compounds are being developed for their targeted pharmacological potency and biological activity. In order to address possible adverse health effects of these types of pharmacologically active compounds to research and development laboratory workers, special care needs to be taken to avoid the potentially harmful consequences of underestimating risk. Generally, in situations where sufficient information is not

Table 1. Occupational Health Category Toxicity/Potency Criteria (SafeBridge[3])

Category 1	Category 2	Category 3	Category 4
• Irritant to the skin or eyes • Low acute or chronic system effects • Low potency (effects at 10–100 mg/kg or greater) • Effects that are reversible • Onset of symptoms is immediate • Not a mutagen, reproductive or developmental toxicant or carcinogen • Has good warning properties (odor threshold below a concentration which may cause toxic effects) • Occupational Exposure Limit (OEL) approximately 0.5 mg/m^3 or greater	• Moderate to high acute systemic toxicity such as cardiac or liver toxicity • Reversible systemic toxicity • Moderate chronic systemic toxicity with low severity (toxicity observed at approximately 1–10 mg/kg) • Corrosive • Weak (skin or respiratory) sensitizers • Moderately absorbed via inhalation or by dermal exposure • Onset of symptoms–may be immediate to delayed • Moderate degree of medical intervention (i.e., not life threatening) may be needed • May have poor or no warning properties • Not a mutagen, reproductive or developmental toxicant or carcinogen (see note[#]) • Occupational Exposure Limits (OEL) range from approximately 10 $\mu g/m^3$ to 0.5 mg/m^3	• Mutagenicity[##] • Carcinogenicity • Developmental and/or reproductive toxicity • Significant pharmacological potency (effects at approximately 0.01–1 mg/kg or 10 mg clinical dose) • Sensitizers • Well absorbed by occupational exposure routes • Irreversible effects • Severe acute systemic effects • Severe chronic systemic effects • Potential need for immediate medical intervention • Poor or no warning properties • Occupational Exposure Limits (OELs) range from approximately 30 ng/m^3 to 10 $\mu g/m^3$	• Highly potent pharmacological activity (observed at approximately 10 $\mu g/kg$) • Irreversible effects • Mutagenicity • Carcinogenicity • Developmental and/or reproductive toxicity • Well absorbed by occupational exposure routes • Severe acute or chronic systemic effects • May affect sensitive sub populations in a significant manner (e.g., asthmatics) • Occupational Exposure Limits are approximately 30 ng/m^3 or less

[#]In some cases, compound may produce chronic or "-genic" effects at high doses (usually >20 mg/kg/day); in these cases scientific judgment as to the likelihood of this occurring occupationally and classifying its inherent risk may be needed.

[##]Mutagenicity in the Ames assay alone without mammalian cell data or other endpoints may be an exception to classification in this category; in this case, a scientific judgment may also need to be made based on class of compound and "active moiety".

available to perform an assessment of a novel compound, it is strongly advisable to assume that it exhibits the characteristics of a potent compound, until proven otherwise. Therefore, it is recommended that Category 3 (Potent) be designated as a 'default' category, to which novel compounds are routinely assigned. This assumption is health-protective; as such, it incorporates a preventive approach to laboratory and clinical manufacturing worker safety, addressing potentially problematic situations before they actually occur.

However, to just "default" any "unknown" is not justifiable in all cases, so a thorough assessment should always be made. Data that should be employed to categorize the novel compounds are the pharmacological mechanism of action, structure–activity relationships, and therapeutic indication. Proper categorization will help to select appropriate resources and controls, and provide for appropriate risk communication as the compound is handled within research and manufacturing settings.

Lastly, in assessing compounds, one of the basic tenants of the categorization methodology is that *one or more of the characteristics may place a compound into a category*. For example, if a compound is given at a high therapeutic dose (especially for anti-cancer agents or immunosuppressive drugs), but has the property of teratogenicity at 0.5 mg/kg/day, then it should be placed in the potent/toxic category (Category 3) based on these data. The teratogenicity at 0.5 mg/kg/day may be the only property that causes the material to be placed into the category or band but it is the single characteristic which drives the categorization process in this case.

HANDLING PRACTICES LINKED TO POTENCY AND TOXICITY CATEGORIES

Pharmaceutical companies that have adopted a four or five category approach linked these compounds to work environments, engineering controls, work practices, and personal protective equipment to be used. The

recommendations are based on significant experience monitoring workplace exposures and successful containment and controls employed for compounds with the described potency and toxicity characteristics. Table 2 presents an example of recommended controls for each category in pharmaceutical manufacturing and pilot plant operations handling kilogram quantities of active pharmaceutical ingredients. A similar matrix for laboratory operations is available in most companies using these systems.

FURTHER DEVELOPMENTS AND ADOPTION OF CATEGORIZATION AND HANDLING PRACTICE SYSTEMS

Occupational health categorization and compound handling practice systems are considered "standard practice" throughout the industry in both research and manufacturing operations.

As with the initial approaches, further modifications have been made to "customize" the systems for the types of compounds handled by various companies, as well the types and degree of work environment and containment and control features (see Heidel).[5] The Association of the British Pharmaceutical Industry (ABPI) supported the categorization approach in their publication on this subject.[6]

The pharmaceutical industry approach has been expanded to other industries and workplaces by the UK Health and Safety Executive (HSE) and International Labour Organization (ILO). As part of the Control of Substances Hazardous to Health (COSHH) regulations in the UK, the HSE has developed a five-category system, most recently described in COSHH Essentials (2003).[7] The HSE COSHH Essentials system was developed to assess the risks to health from chemicals and to decide what controls are needed to help firms comply with the COSHH regulation. By applying a categorization approach to chemical hazards linked to prescriptive control strategies for specific industries, both small and medium sized companies can address their issues without the need for complete risk assessment capabilities by an occupational health professional. Additionally the International Labor Organization (ILO) has adopted a similar approach, and like the HSE, applied R (Risk) and S (Safety) phrases to each of five categories.[8] In 2004, ACGIH and NIOSH, as well as other international organizations sponsored the first US-based and second international control banding workshop on these approaches to chemical hazards in the pharmaceutical and other industries. Both the HSE COSHH and ILO approaches were prominently featured.

IMPACT OF A CATEGORIZATION/ BANDING AND HANDLING PRACTICE SYSTEM

An occupational health categorization and compound handling practice system if applied appropriately will raise employee awareness of the potential hazards in the workplace. Understanding the nature of the hazard goes a long way to respecting the chemicals being handled and adoption of appropriate techniques and controls. However, such systems require training so that employees understand the nature of the risks surrounding use of the toxic chemicals or potent pharmaceuticals that they may be handling. This program should not be an exercise in "MSDS review" but should be extended to factors that may contribute to exposure and instruct employees as to why good technique and sophisticated containment measures may be necessary in some cases. Use of good work practices does not come automatically; it comes from proper attitudes, having a clear understanding of the hazard potential of the materials involved, detailed evaluation of the process steps and determining the best way to accomplish each step efficiently and safely with minimal risk of a spill or exposure.

TRENDS AND MISCONCEPTIONS OF THE SYSTEM

The systems that have evolved over the more than 15 years of application in the pharmaceutical industry have had some "drift" from the original intent. These include the following:

(1) Many systems apply the order of magnitude (10-fold differential) between categories or bands. While this may be relatively convenient, control technologies and toxicity and potency characteristics may not be in order of magnitude "buckets". For example, air concentrations generated from use of a containment valve may have more than an order of magnitude difference in industrial hygiene air monitoring results depending on worker-to-worker as well as equipment-to-equipment variability. Companies using customized systems should consider modifying their bands or categories based on their industrial hygiene air monitoring experience for the particular toxicity and potency characteristics of the drugs or chemicals they are handling.

(2) OELs are sometimes being used as the sole determinant of the category, i.e., there appears to be a strong reliance on the quantitative rather than qualitative aspects of the system, which was originally designed more as a qualitative tool than a quantitative tool. The OEL should not be the primary basis for the determination of the category. If an OEL has been established and the company chooses to also categorize the compound, it should be used as one (but not the primary) criteria along with the qualitative criteria to determine the category for a chemical or pharmaceutical substance. Use of just the OEL for categorization purposes may not be completely indicative of hazard or risk. For example, there are several compounds now used in "patch" technology (delivery of drugs via the dermal route), which have recommended limits in lower/less toxic categories (Category 1 or 2), but the "driver" for determining their occupational health handling practices is that they are well absorbed through the skin, requiring handling practices for more

Table 2. Recommended Work Environments and Handling Practices For Pilot Plant and Production Scale for Each Occupational Health Category (SafeBridge[3])

Category 1	Category 2	Category 3	Category 4
• Open handling is acceptable for low dust-generating operations or solutions. • Wear appropriate gloves; lab coat, nylon coveralls or disposable Tyvek suit; safety glasses and safety shoes. Use good manufacturing practices (e.g., cGMPs). • Wear a N95 filtering facepiece respirator or a higher level of respiratory protection for high dust-generating operations. If exposure monitoring indicates exposures are below the OEL, respiratory protection may not be required. • Use local exhaust ventilation and/or enclosure at dust-generating points in the process.	• Wear appropriate gloves; lab coat, nylon coveralls or disposable Tyvek suit; safety glasses and safety shoes. Use good manufacturing practices (i.e., cGMPs). • Use a powered, air-purifying respirator (PAPR) with HEPA cartridges or a supplied-air respirator (SAR), unless air-monitoring data has shown that a lower level of respiratory protection is adequate. • Protective garment (coveralls, Tyveks, lab coat) is not to be worn in common areas (e.g., cafeterias) or out-of-doors. • Use local exhaust and/or enclosure at dust-generating points. Emphasis is to be placed on closed material transfer systems and process containment, with limited open handling of powders. • High-energy operations such as milling, particle sizing, spraying or fluidizing should be done within an approved emission control or containment system. • Develop cleaning procedures and techniques that limit potential exposure.	• Wear appropriate gloves; lab coat, nylon coveralls or disposable Tyvek suit; safety glasses, safety shoes, and disposable booties. Use good manufacturing practices (i.e., cGMPs). • Protective garment (coveralls, Tyvek, lab coat) is not to be worn outside the work area. • Clean/dirty/decontamination areas are to be established. • Negative/positive air pressure relationships and buffer zones required (i.e., ante-room/ degowning room/airlock). • Area access is to be restricted. • High-energy operations such as milling, particle sizing, spraying or fluidizing should only be done within an approved emission control or containment system. • Develop cleaning procedures and techniques that limit potential exposure. • *Powders Handling* - Emphasis is to be placed on closed material transfer systems and process containment, with no open handling of powders. Use enclosures and containment measures to reduce potential exposures. - Use a powered, air-purifying respirator (PAPR) with HEPA cartridges or a supplied-air respirator (SAR) until processes have been monitored to show that respiratory protection is not required.	• Wear appropriate gloves; lab coat, nylon coveralls or disposable Tyvek suit; safety glasses, safety shoes, and disposable booties. Use good manufacturing practices (i.e., cGMPs). • Protective garment (coveralls, Tyvek, lab coat) is not to be worn outside the work area. • Clean/dirty/decontamination areas are to be established. • Negative/positive air pressure relationships and buffer zones required (i.e., ante-room/ degowning room/airlock). • Area access is to be secured and restricted. • Separate and dedicated work areas should be established. • A highly specialized ventilation system should be installed with failure protection. • High-energy operations such as milling, particle sizing, spraying or fluidizing must be done within an approved emission control or containment system. • Clean-in–place systems should be in place. • An emphasis on process automation and fail-safe systems should be employed. • Develop cleaning procedures and techniques that limit potential exposure.

- *Solutions Handling*
  - Enclose systems where possible. Processing tanks are to be kept covered. Process samples should be taken from sample ports if feasible.
  - Wear a N95 filtering facepiece respirator or a respirator supplying a higher level of protection until processes have been monitored to show that respiratory protection is not required.
  - Ensure gloves are protective against solvents in use.

- *Powders Handling*
  - Emphasis is to be placed on closed material transfer systems and total process containment, with no open handling of powders. Use enclosures and containment measures to reduce potential exposures.
  - Use a powered, air-purifying respirator (PAPR) with HEPA cartridges or a supplied-air respirator (SAR) until processes have been monitored to show that respiratory protection is not required.
- *Solutions Handling*
  - Enclose systems where possible. Processing tanks are to be kept covered. Process samples should be taken from sample ports if feasible.
  - Wear a N95 filtering facepiece respirator or a respirator supplying a higher level of protection until processes have been monitored to show that respiratory protection is not required.
  - Ensure gloves are protective against solvents in use.

potent (Category 3) compounds (i.e., this one characteristic may place the compound into the more potent or toxic category).

(3) The system was designed as a continuum of potency and toxicity, with increasing levels of control using good scientific judgment. The system is sometimes applied too rigidly, especially when the compound "just falls short" of being considered potent or toxic compound (Category 3). In this case, the more toxic Category 2 compound may need handling practices more akin to the Category 3 handling practices but its toxicity or potency characteristics don't quite meet the Category 3 criteria.

SUMMARY AND CONCLUSION

The occupational health categorization and compound handling practice system presented herein is directed to formulation of distinct control strategies and is designed specifically for pharmaceutical compounds of varying potency, including highly potent materials. Successful incorporation of such a system into the research and development and clinical production processes characteristic of drug discovery and development can effectively control the workplace hazards associated with novel and potentially potent new pharmaceuticals. This approach accomplishes reduction of risk and provides substantial dividends in terms of protection of worker health and increased productivity with the side benefit of assisting in speeding new therapies to market. There is a potential for similar systems to be applied to other chemicals, industries, processes and equipment. As with the pharmaceutical industry approach, this would require knowledge of containment and control approaches that successfully worked for the hazards (and their related potency and toxicity characteristics) that occur in the particular industry.

References

1. Ku, R. H. An overview of setting occupational exposure limits (OELs) for pharmaceuticals. *Chem. Health Safety*, **2000**, *7*(1), 34–37.
2. Centers for Disease Control and Prevention and National Institutes of Health (May 1999). *Biosafety in Microbiological and Biomedical Laboratories. 4th ed.* United States Government Printing Office.
3. SafeBridge Consultants, Inc. "Occupational Health Toxicity/Potency Categorization and Handling Practices"–SafeBridge, Fifth Revision–January 2002, 12 pp.
4. Naumann, B. D.; et al. Performance-based exposure control limits for pharmaceutical active ingredients. *Am. Ind. Hyg. Assn. J.* **1996**, *57*(1), 33–42.
5. Heidel, D. Industrial hygiene aspects of pharmaceutical manufacturing, In J. Wood (Ed.), *Containment in the Pharmaceutical Industry*. Marcel Dekker, 2001 p. 19 [chapter 3].
6. Association of the British Pharmaceutical Industry, "Guidance on Setting In-House Occupational Exposure Limits for Airborne Therapeutic Substances and their Intermediates"–ABPI Publication, October 1995.
7. UK Health and Safety Executive "Control of Substances Hazardous to Health Essentials", HSE 1999, 2000. 2003. COSHH Essentials, 2003 (url: http://www.coshh-essentials.org.uk/assets/live/CETB.pdf). Accessed January 2005.
8. International Labor Organization, Chemical Control Toolkit, Draft Guidelines, International Labor Office, Geneva, Switzerland (url: http://www.ilo.org/public/english/protection/safework/ctrl_banding/toolkit/main_guide.pdf). Accessed January 2005.