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History, implementation and evolution of the pharmaceutical hazard categorization and control system

ABSTRACT

Chemical categorization (or banding) of inherent toxicity and potency linked with defined safe work environments including exposure controls has become an integral component of assuring the health and safety of research workers and manufacturing personnel in the pharmaceutical industry but is not a substitute for quantitative risk assessment in the workplace.

INTRODUCTION: THE SOLUTION TO A PROBLEM

In the late 1980's at a pharmaceutical safety meeting that included the safety directors of 15 of the largest integrated multi-national pharmaceutical companies, the issue of the challenge of how to protect research and development scientists was discussed. The occupational health challenge was identified because of repeated experiences with health effects in R&D staff when handling newer chemical entities and pharmaceutical products and when these materials moved "off the bench". Process scale up and process optimization in synthetic chemistry kilo labs, operations in chemical and pharmaceutical pilot plants and formulation development activities where up to kilo quantities of newer active pharmaceutical ingredients (APIs) were handled presented potential worker exposure situations where standard quantitative occupational health tools were unavailable. To this point in time most large R&D-based pharmaceutical companies ("Big Pharma") were routinely establishing scientifically defensible occupational exposure limits (OELs) for the APIs in their products. OELs by convention are usually eight-hour time-weighted average limits (8-hour TWAs) that are intended to be airborne levels that healthy workers could safely inhale up to forty hours per week over a working lifetime. This is a similar definition to regulatory limits (e.g. U.S. OSHA Permissible Exposure Limits or PELs) and limits set by the American Conference of Governmental Industrial Hygienists (Threshold Limit Values or TLVs®). Once OELs are set, air sampling analytical methods are developed to allow for proper industrial hygiene (known as occupational hygiene in Europe) studies to be conducted. These technical tools are required to do quantitative industrial hygiene properly. Toxicologists experienced in risk assessment limit-setting techniques and pharmaceutical science set OELs based on toxicology and pharmacology studies conducted by the pharmaceutical companies as part of the drug development process.

Analytical chemists use the OEL as a target to determine the appropriate sensitivity needed in developing an air sampling and analytical method. Without established limits or air monitoring methods that are not adequately sensitive, meaningful occupational health determinations cannot be made with respect to actual worker exposures and effectiveness of control approaches.

A dilemma arises when a new API is being developed and processed for which toxicity and potency data are not yet available to set OELs. Exposures can be significant, especially if the compound is potent, in chemical and pharmaceutical development operations such as filtering, drying, weighing, milling, blending and tablet and capsule manufacturing. Many of these processes require "open" handling of powder and can release material into the air at concentrations of concern when the batch size approaches the kilo scale. Pharmaceutical compounds range in potency from lower potency non-steroid anti-inflammatory drugs to highly potent steroid and peptide hormones, cytotoxic drugs and prostaglandins. How does a company or individual know how to handle these materials when data are limited?

DEVELOPMENT OF A CONCEPT

Five companies volunteered to work on this problem and report possible solutions to the larger group of 15. Occupational health and safety professionals of Syntex, Merck, Abbott, Upjohn and Lilly agreed to meet quarterly to develop a way forward. Two of the authors participated in these meetings as they worked at Syntex in Palo Alto, California at that time. The sub-group met over a two-year period alternating between host facilities. One concept that emerged was based on the biosafety level approach developed by the U.S. Centers for Disease Control (CDC) where four levels or categories of microorganisms (viruses and bacteria) were established based on an ascending order of pathogenicity and virulence of the microorganisms (Biosafety Level 1 being the least pathogenic and virulent microorganisms and Biosafety Level 4 being the most) (1). These levels were linked to descriptors of safe laboratory work environments and work practices ranging from working on the open bench with good laboratory technique to working inside sophisticated isolators while wearing air suits. The idea that pharmaceutical compounds could be put into such a system based on the characteristics of compound toxicity and potency and then linked to safe work environments and work practices emerged by comparing

drug substances and drug products that were well known and studied. The toxicologists in the group described the characteristics in a matrix of increasing severity and lower dosages and the industrial hygienists in the group linked these to descriptions of work environments where air monitoring studies supported operations that were considered safe and acceptable. This has been described as the "hand-in-glove" system where compound characteristics (the hand) are matched to safe work environment descriptors (the glove). An additional concept utilized by safety professionals worldwide is to assume something is hazardous until it is demonstrated not to be (i.e. to err on the side of conservatism). This concept resulted in establishment of a "default" category for substances that were brand new or novel and for which very little information was known about them.

During this brainstorming phase of concept development, variations on this theme were considered and companies evaluated three, four and five tiered systems. Soon it was identified that one could establish an almost infinite number of categories or tiers based on toxicity and pharmacological potency data; however, only a limited number of workplace environments and associated controls could be described in which the compounds could be safely handled. This is a critical factor in categorization system development. For example open handling of powder can generate milligrams of material per cubic meter of air, a chemical bench hood may control airborne powder down to a hundred micrograms per cubic meter of air, a closed transfer device with special valves may control down to a microgram per cubic meter of air and an isolator may control down to several nanograms per cubic meter of air. One is always limited by the workplace descriptors and will be limited in the number of categories for any given system by this feature. This type of system is known as a "banding", performance-based exposure control level (PB-ECL) and/or "categorization" system through the industry. For the purposes of this discussion the term "categorization" is used to describe all such similar systems.

ONE SIZE DOESN'T FIT ALL: WHY THERE ARE SEVERAL DIFFERENT SYSTEMS

The original intent of the sub-group was to develop a single safety system to be brought back to the other ten companies which could be a model for the whole pharmaceutical industry. This objective faded quickly when it became clear that each company had its own set of therapeutic areas and compounds of interest (this was no surprise), and became crystal clear upon touring company manufacturing facilities. It was a surprise that the equipment, layout, construction and procedures differed

significantly from company to company. The revised objective became establishing a general concept that each company would customize for its own needs. The customization idea is encouraged from company to company and has been suggested in various documents including the Association of British Pharmaceutical Industries (ABPI) publications entitled "Guidance on Setting In-House Occupational Exposure Limits for Airborne Therapeutic Substances and their Intermediates" and "Guidelines for the Control of Occupational Exposure to Therapeutic Substances" (both published in October 1995) (2). To date there are at least sixteen variations on this theme within Big Pharma alone in addition to numerous other systems that have evolved within contract manufacturers, biotechnology companies and generic pharmaceutical companies. Most systems are either four category systems (similar to the SafeBridge system described below) or five category systems (as described by Naumann et al in the paper describing the Merck system entitled "Performance-Based Exposure Control Limits for Pharmaceutical Active Ingredients", *AIHA Journal*, January 1996) (3). Three and six category systems are also known to be in practice.

The development of a number of systems is reasonable due to the differences in a company's products, facilities, equipment and processes. What is fundamental, however, is the need to share the system description with other interested parties (for example between drug innovator and contract manufacturer) along with the documentation of the categorization decision for the compound and related handling practices. With this information, knowledgeable health and safety professionals can "translate" from one system to another.

WHERE IT STANDS NOW: A USEFUL QUALITATIVE TOOL

The categorization approach for the safe handling of APIs has been demonstrated to be an effective stop-gap or interim measure to provide initial guidance during the early stages of drug development. The concept has been almost universally accepted and adopted throughout the pharmaceutical, and now biotechnology industry, in its various forms. The importance of the system has grown due to the rapid development of candidate drug substances and the increasing trend toward higher potency. Other groups have implemented similar systems to address other issues the most notable of which may be the UK Health and Safety Executive (HSE) system for controlling occupational health hazards in small and medium sized businesses. This useful system is called "Control of Substances Hazardous to Health Essentials" (or COSHH Essentials: HSE 1999, 2000) (4). Similar to the pharmaceutical categorization system, COSHH Essentials was developed to address a specific need. In this case, the provision of sound health hazard exposure control advice to industrial organizations without easy access to occupational health and safety professionals.

THE SAFEBRIDGE SYSTEM

The SafeBridge "Occupational Health Toxicity / Potency Categorization and Handling Practices" system (copyright SafeBridge Consultants, Inc., Fifth Revision – January 2002) (5, 6) is a four-category system that has proven useful for a number of organizations over the past nine years. The characteristics of compound potency and toxicity by category are described in Table 1. It is critical

to understand that placing a compound into a category should be based on analysis of data and professional judgment regarding the most important factors to consider. It is common that only one or two criteria or characteristics are used to place a compound into a category, and it is not expected that all the listed criteria in the table will be relevant. To properly categorize a compound a document should be developed that establishes the criteria that was reviewed and that clearly states the basis for the categorization. This becomes an important record for justifying the choice of category and potentially for transferring information to another party. In broad terms Category 1 materials may have irritating qualities but limited or no systemic organ effects and no permanent or "genic" effects. Genic effects include mutagenicity, carcinogenicity, developmental effects (which may include teratogenicity) and reproductive system effects. Category 2 includes a wide variety of pharmaceutical substances and can be characterized by materials that have organ system effects such as effects on the heart, liver, lung etc. but limited or no genic effects at doses expected to be encountered in the workplace. Category 3 materials are considered potent and/or toxic and include substances that can elicit health effects at low doses (i.e., potent) and may have permanent and potentially severe effects such as genic effects (i.e., toxic). Category 4 is reserved for the small but very real class of ultra-potent and/or ultra-toxic materials that have permanent and potentially severe effects at extremely low doses. Category 4 also includes materials that may have a severe effect at low doses on sub-populations of the workforce such as women of child bearing potential, asthmatics and workers with minor blood or liver ailments that may be at increased risk when working with these materials. Category 3 is the default category in this system. The handling recommendations and basic descriptors of safe work environments can be found in Table 2. Again professional judgment is necessary to decide if the guidance is applicable and correct for a given situation. In addition to the potency and toxicity characteristics, other factors such as the volume, concentration, physical form of the material and process involved must be considered when selecting control approaches. These factors do not change the inherent potency and toxicity of the material (and therefore do not change the category) but they may change the handling

requirements. In general, Category 1 allows for open handling of materials with well-applied traditional control technology such as local exhaust ventilation. Category 2 requires basic process containment such as gravity feeding systems and direct connections and/or custom designed local exhaust ventilation at process emission points. Category 3 prohibits open handling and requires closed systems, direct connections, isolation and/or combinations of controls such as direct connections with local exhaust ventilation support. Category 4 requires complete containment, closed systems and/or isolation. Each category in the SafeBridge system describes laboratory and pilot plant/production work environment controls and work practices.

The SafeBridge system differs from some of the other systems in use in the industry particularly in some of the airborne concentration "cut-offs" that are used to establish the break points between categories. The SafeBridge system is based on years of sampling pharmaceutical, chemical and laboratory processes using ultra-sensitive analytical methods such as radioimmunoassay (RIA) and enzyme immunoassay (EIA) that are capable of detecting 100 picograms of API on an air monitoring filter. This kind of sensitivity allows for very short sampling times consistent with short term operations such as small quantity weighings and material transfers. This has resulted in the SafeBridge Category 3 being broader than many other systems (some systems split the SafeBridge Category 3 into two subcategories such as 3A and 3B). Other systems start the most toxic or potent category at <1 microgram per cubic meter of air and require isolation of all operations where materials in this category are used. It is our experience that a combination of controls can be used down below one microgram per cubic meter and be protective.

The SafeBridge system does not strictly use order of magnitude cut-offs that are common to other systems. Air monitoring conducted over many years indicates that control approaches do not necessarily conform to order of magnitude numbers (e.g., 1000 $\mu\text{g}/\text{m}^3$, 100 $\mu\text{g}/\text{m}^3$, 10 $\mu\text{g}/\text{m}^3$ and 1 $\mu\text{g}/\text{m}^3$).

The most important advice is to build a system based on solid air monitoring studies using APIs of interest to the company in question in their facilities on their equipment and comparing air monitoring data to justifiable OELs for those compounds. This experience and data

Category 1	Category 2	Category 3	Category 4
<ul style="list-style-type: none"> 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/m³ or greater 	<ul style="list-style-type: none"> 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 $\mu\text{g}/\text{m}^3$ to 0.5 mg/m³ 	<ul style="list-style-type: none"> Mutagenicity** Carcinogenicity Developmental and/or reproductive toxicity Significant pharmacological potency (effects at or below approximately 0.01 - 1 mg/kg) 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/m³ to 10 $\mu\text{g}/\text{m}^3$ 	<ul style="list-style-type: none"> Highly potent pharmacological activity (observed at approximately 10 $\mu\text{g}/\text{kg}$ or less in animals or humans) 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/m³ 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 be made based on class of compound and "active moiety"

Table 1

Category 1	Category 3	Category 4
<ul style="list-style-type: none"> 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 certified Dust/Mist 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. 	<ul style="list-style-type: none"> 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. Establish a means of personnel decontamination prior to entering the degowning room such as a misting shower. 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. <ul style="list-style-type: none"> 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. <ul style="list-style-type: none"> Wear a certified Dust/Mist 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. 	<ul style="list-style-type: none"> 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. Establish a means of personnel decontamination prior to entering the degowning room such as a misting shower. 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. 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. <ul style="list-style-type: none"> 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. <ul style="list-style-type: none"> Wear a certified Dust/Mist 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.
Category 2		
<ul style="list-style-type: none"> 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. 		

Table 2

demonstrating where operations are safe can then be compared to operations with new compounds to make good judgments about safety in advance of activities.

in a large multi-site organization where technology transfers take place and APIs and processes move around the company.

IMPLEMENTATION AND BENEFITS OF THE SYSTEM

Communication of the categorization system for a company is critical to the proper implementation of the system and, if done well, can yield great benefits. One of the key elements is to keep the system simple and straightforward. This results in the greatest understanding and acceptance of the system. A categorization system should not be limited in scope to the health and safety staff. It should be rolled out to the entire organization involved in API handling. For contract manufacturing organizations, such a system should be understood by the business development staff as well as the operations, laboratory and health and safety staff. A process for categorizing APIs accurately can assist in the bidding process such that the contract manufacturing organization understands what facility controls and process equipment will be necessary for safe handling. The bidding process can be made more effective if a thorough compound questionnaire is used to gather all the available health, safety and environmental data from the prospective client. Once the categorization system is well understood by the whole organization, the meaning of a Category 1, 2, 3, 4 etc. becomes a new language and quickly communicates potential risk and required controls throughout the workforce. This can be especially effective

LIMITATIONS: IT IS NOT A REPLACEMENT FOR QUANTITATIVE RISK ASSESSMENT

One serious consideration and negative aspect of the development of the pharmaceutical compound categorization system is the assumption that the implementation of such a system removes the requirement for quantitative risk assessment and good industrial hygiene practice. Specifically the development of OELs and validated air monitoring methods is essential to understand potential exposure to workers and to prevent impacts to their health. The basis for development of the categorization system in the pharmaceutical industry was the documented prevention of health effects when working with APIs including the range of performance of engineering controls and containment equipment through industrial hygiene air monitoring studies. To continue to apply the categorization system as new compounds are developed and new manufacturing technologies evolve, the setting of OELs and conduct of industrial hygiene measurements is essential.

The separating points or lines between the categories should be considered as "soft" lines rather than "hard" lines. The categorization system was developed with the intent that health and safety professionals would apply sound judgment to particular situations using the system as a guide. It was never intended to be a "cookbook"

solution to every problem. It is also interesting to note that we have been informed that some regulatory agencies in the EU will not accept a “banding control” approach by itself for large chemical and pharmaceutical companies. Proper limit setting and measurement are the standard expectation of these agencies in companies where occupational health resources should be available.

FUTURE USES, SUMMARY AND CONCLUSION

It has been over seventeen years since the group of five pharmaceutical companies began meeting to address the challenge of handling new potent pharmaceutical materials safely and the categorization system that has evolved has gone around the world with wide acceptance as a concept. Health and safety regulators have adopted the concept and wider applications are being investigated in areas such as noise control, mining hazard mitigation and general chemical exposure control. While this is gratifying to the creators of the system, it should be understood that the system was designed to address a particular problem – health protection of pharmaceutical workers in the absence of traditional occupational health quantitative tools. Other potential applications are possible but first the problem that such a system is trying to address needs clear definition to evaluate if a categorization system is appropriate.

The potential trend to move away from quantitative risk assessment through the development of scientifically defensible limits, validated air sampling methodologies and proper industrial hygiene monitoring studies was not the intended consequence of the categorization system. This trend is not recommended and could lead to misunderstanding of real worker exposure potentials. The

proper use of a categorization system for chemical exposure control is as a “stepping stone” along the way to quantitative risk assessment, an effective risk communication tool and a means of providing guidance for working safely with new materials.

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