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Performance-Based Exposure Control Limits for Pharmaceutical Active Ingredients

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For many years pharmaceutical companies have established employee exposure limits for the active ingredients used in their products. Historically these limits were derived using traditional risk assessment methods. Because the trend in the pharmaceutical industry is to identify and develop more selective drugs of increasing potency, and because of the difficulty in identifying no-effect levels for certain drugs, a new performance-based approach for setting limits was developed. This method involves assigning materials into one of five hazard categories according to their inherent toxicological and pharmacological properties. The criteria used to assign compounds into performance-based exposure control limit (PB-ECL) categories focus on the degree to which exposure impacts human health. These assignments dictate the level of containment required to assure employee safety that is achieved through the use of engineering controls and safe handling practices. Several matrices were developed to specify general design concepts and controls for unit operations in laboratory and manufacturing operations. Containment options range from conventional handling practices for low potency (PB-ECL Category 1) materials, to technologically advanced systems that result in essentially no open handling for potent or toxic (PB-ECL Category 3) materials, to state-of-the-art facilities employing closed processes and use of robotics for extremely potent (PB-ECL Category 5) materials.

Key words: exposure control, pharmaceuticals, engineering controls, safe handling practices

Pharmaceutical companies have long recognized that the active ingredients used in their products, which are specifically designed to modify biological function, can place employees at risk of experiencing pharmacological effects if exposures are not adequately controlled.[1] While these effects are considered desirable in patients being treated for a particular medical condition under the supervision of a physician, any clinically significant pharmacological effect occurring as a result of work exposure, whether considered beneficial or not, is unacceptable.

Historically numerical exposure control limits (ECLs) have been established to provide the guidance necessary to industrial hygienists, engineers, and line management to maintain exposures low enough to prevent adverse effects in workers. The procedure used to establish numerical ECLs for pharmaceutical active ingredients has been described elsewhere.[2–5] In general, a no-effect level is identified for the most sensitive endpoint and, after correction for body weight, is divided by a safety factor (or a combination of uncertainty and modifying factors) and the volume of air breathed during an 8-hour work shift (10 m^3) to yield an airborne time-weighted average concentration (TWA). The ECL may also be adjusted to reflect information on bioavailability and pharmacokinetic considerations.[2] In practice, the ECL should not be exceeded on a TWA basis. Exposure control limits for some drugs are established as ceiling values, or 15-minute short-term exposure limits, and some carry a skin notation because of the potential for significant amounts to be absorbed through the skin based on the underlying supporting data.

With a better understanding of specific underlying disease mechanisms, many new pharmaceuticals are being developed to be more selective,

i.e., to bind to specific receptors or inhibit specific enzymes. Increased specificity means increased potency and, therefore, lower exposure control limits. Low exposure control limits present a number of problems for the industrial hygienist. Exposure control limits established at or below 1 $\mu g/m^3$ are difficult to evaluate, because sampling and analytical methods often lack the necessary sensitivity, especially for short-term samples that are often used to characterize the brief substep operations common in the pharmaceutical industry. The following are a few classes of compounds that, by virtue of their inherent pharmacological or toxicological properties, typically have very low exposure control limits: antineoplastic agents that can cause DNA damage; opioid analgesics and neuromuscular depolarizing agents that can cause respiratory paralysis; Class III antiarrhythmics and ergot alkaloids that produce cardiovascular effects at low dosages; and receptor-mediated drugs like prostaglandins, estrogens, or gonadotropin-releasing hormone analogs that can cause endocrine-mediated reproductive and development effects.[6]

For some materials the toxicological or pharmacological properties of a compound make it difficult for the occupational toxicologist to establish a numerical limit.[7-8] In the case of antineoplastic agents or potent receptor-mediated drugs, it is often very difficult to identify a clear no-effect level on which to base an ECL.

This trend toward increasingly potent drugs and the inability to establish numerical exposure limits for some materials has led to a search for an alternative approach to control exposures to pharmaceutical active ingredients. Consequently, a new performance-based approach was developed. This approach relies more on qualitative or semiquantitative criteria for assessing compounds and knowledge of the effectiveness of the containment technologies. It was developed to identify the design features necessary to afford the proper overlapping layers of protection.

The evolution of the performance-based concept began with the realization that the increased level of containment required to control dusts of potent compounds was analogous to the Biosafety Level (BSL 1–4) practices and techniques, safety equipment and facilities used by research facilities that handle microorganisms of increasing pathogenicity.[9] The engineering approaches developed to create physical barriers to preclude the escape of even a single highly pathogenic organism (which might theoretically result in fatal consequences) were very similar conceptually to the control strategies being implemented within the industry for potent drugs. In addition to personal experience applying new technologies to deal with potent drugs, the authors have also drawn on experience from other industries. For example, clean room technology used in the semiconductor industry, isolation technology used to maintain sterility, barrier technology used by breeders of specific pathogen-free animals, and the "containment" of proteolytic enzymes within coated prills utilized by the manufacturers of detergents have all been sources of ideas.

This article describes a performance-based approach for setting exposure control limits that, like numerical limits, relies on the specific properties of pharmaceutical active ingredients, but places a compound into a specific category taking into consideration the engineering controls and administrative procedures known to control employee exposure to a prespecified level. That this approach may be useful in other industries having the opportunity to collect similar data was a key motive for publishing this paper.

The performance-based exposure control limit (PB-ECL) category dictates the level of control necessary for given operations to maintain risks at acceptable levels. In other words, the level of containment or exposure control is commensurate with the risk. Once a compound is enrolled in a PB-ECL category, the level of containment required to assure employee safety is achieved through a combination of engineering controls, administrative procedures, and safe handling practices. Personal protective equipment is only used to provide redundant protection.

An implementation strategy will be presented utilizing matrices for general design and examples of acceptable handling technologies to assist industrial hygienists, engineers, and line management in developing procedures and specifying equipment for the safe handling of compounds in laboratories, pilot plant, and manufacturing areas. The approach is particularly useful very early in the drug development process when insufficient data may be available to firmly establish numerical limits.

BACKGROUND

Assignment of Compounds to PB-ECL Categories

As shown in Figure 1, compounds in development are assigned to a preliminary PB-ECL category as early as possible in the drug discovery process based on an initial review of available data. PB-ECL assignments are made by a multidisciplinary panel of scientists with expertise in the areas of toxicology, medicine, chemistry, pharmacology, pharmacy, industrial hygiene, and chemical engineering. Preliminary PB-ECL category assignments, designated with the prefix "P," are established first and are intended primarily for use in laboratories. At this stage in development the available preclinical safety information is typically insufficient to support the establishment of a numerical ECL. Unstudied compounds are automatically assigned to PB-ECL Category P-3 unless there are data (e.g., mechanistic data or extensive experience with a similar compound) that would support a higher or lower assignment.

Although preliminary PB-ECLs provide important guidance, especially for laboratory operations, numerical ECLs or final PB-ECL categories are derived as soon as sufficient data become available. Typically this is when the first definitive repeat-dose (e.g., 90-day) toxicology studies are completed. At this time the preliminary "P" designation is removed. PB-ECL assignments provide industrial hygienists and engineers the guidance necessary during process scale-up to ensure that appropriate engineering solutions are developed in pilot plant areas to control exposures to acceptable levels. For some compounds, a no-effect level may not be available or the potential adverse effects are truly not quantifiable. In these cases a numerical limit cannot be derived, and only a PB-ECL assignment will be made. Numerical ECLs and PB-ECLs are

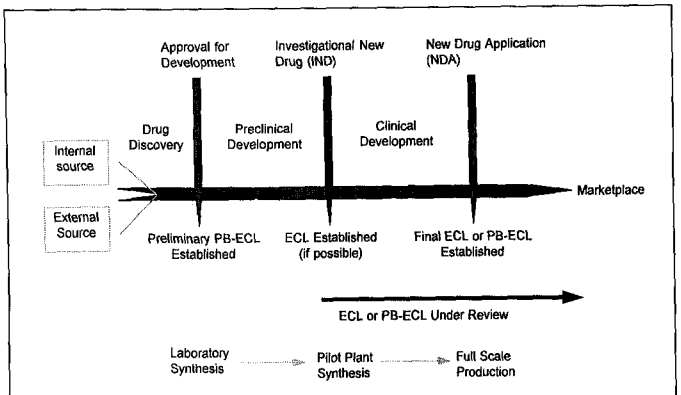

FIGURE 1. Timeline for evaluation of development compounds

reevaluated as new data become available and at significant milestones in the drug development process (e.g., at the time of Investigational New Drug and New Drug Application filings) and are modified as necessary.

Data Collection and Evaluation

The first step in assigning a compound to a PB-ECL category is a comprehensive evaluation of all available data on the compound, most of which is generated during the normal course of drug discovery and development. Data are derived from the areas of pharmacology, medicinal chemistry, safety assessment, and clinical research and are used to identify potential adverse effects, including pharmacological effects, and the dosages required to produce these effects. When preliminary PB-ECLs are established, the only information available is the intended use of the drug, the mechanism of action, the pharmacological activity/potency of the compound, some measure of its acute toxicity in animals, and its mutagenic potential. Additional useful information, when it becomes available later in drug development, includes the anticipated clinical dose, results of preclinical and clinical studies, the probable route(s) of entry, and identification of possible adverse effects in workers.

Data are evaluated with respect to a number of factors regarding the inherent hazardous properties of the material and characterized with respect to the severity of each in general accordance with the criteria shown in Table I. The classification scheme is similar to that used to support hazard communication labeling systems.[10–13] Descriptions for enrollment criteria, which take into consideration effects following acute and chronic exposure, are given below. These criteria are subjective in nature, but show the range of effects that are considered in the evaluation process. Obviously, the assignment of a material to a PB-ECL category involves more than the literal application of the criteria given in the table, since for most criteria a general continuum is depicted. The assignment always relies heavily on professional judgment and reflects an overall, collective assessment of each of the enrollment criteria.

In general practice, for both ECLs and PB-ECLs, the evaluation often focuses on one or more primary health concern(s) or lead endpoint(s) potentially associated with acute or chronic exposure, as well as the reversibility and severity of these effects. Most often, the limits/categories will be conservatively based on the most sensitive endpoint, especially when there is concern for acute life-threatening effects or disabling, irreversible, chronic effects. In most cases the endpoint resulting in the highest category will drive the overall assignment. Thus, by protecting against the most sensitive endpoint identified, whether qualitative or quantitative in nature, protection is afforded against all known endpoints.

Acute Effects

To assess potential acute effects, both the activity and potency of the drug candidate are evaluated. The type of pharmacological effect(s) expected, the mechanism of action, and the dosage required to produce these pharmacological effects are important considerations. The severity of acute (life-threatening) effects is assessed in a qualitative manner to determine the likelihood that the anticipated pharmacological or toxicological effects may result in serious injury or death. An integral part of the evaluation is a determination of whether medical intervention might be required if an overexposure occurs, and how rapid the response must be. Consideration is also given to the availability of a specific antidote, whether the potential adverse effects are medically treatable, and the adequacy of symptomatic/supportive care.

The compound may or may not have acute warning properties such as odor, irritancy, or rapidly occurring nonserious pharmacological effects that might alert an individual to the presence of the material and/or a potential overexposure. Collectively, the more subtle the warning signs, the higher the protection category. The timing of the onset of symptoms of overexposure relative to the appearance of more serious effects is also an important consideration.

Results of acute toxicity studies in animals can also provide information on the ability of the compounds to produce immediate adverse effects, serious injury, or death. Acute toxicity values

TABLE I. PB-ECL Category Enrollment Criteria

	PB-ECL Category				
Enrollment Criteria	**1**	**2**	**3**	**4**	**5**
Potency (mg/day)	>100	>10–100	0.1–10	<0.1	<0.1
Severity of acute (life-threatening) effects	low	low/mod	moderate	mod/high	high
Acute warning symptoms	good	fair	fair/poor	poor	none
Onset of warning symptoms	immediate	immediate	may be delayed	delayed	none
Medically treatable	yes	yes	yes	yes	yes/no
Need for medical intervention	not required	not required	may be required	may be required immediately	required immediately
Acute toxicity	slightly toxic	moderately toxic	highly toxic	extremely toxic	super toxic
Sensitization	not a sensitizer	mild sensitizer	moderate sensitizer	strong sensitizer	extreme sensitizer
Likelihood of chronic effects (e.g., cancer, repro, systemic)	unlikely	unlikely	possible	probable	known
Severity of chronic (life-shortening) effects	none	none	slight	moderate	severe
Cumulative effects	none	none	low	moderate	high
Reversibility	reversible	reversible	may not be reversible	may not be reversible	irreversible
Alteration of quality of life (disability)	no	no	yes/no	yes	yes

may be available for various routes of administration. These may include the median lethal dose (LD50), approximate lethal dose, or median lethal concentration (LC50). Compounds with a high order of acute toxicity and poor or delayed warning properties are of greatest concern. Skin sensitization studies are commonly performed in guinea pigs to evaluate the potential for a material to produce delayed contact hypersensitivity. The dosages required to induce sensitization or to elicit an allergic response in previously sensitized animals are considered. In addition, the percentage of animals responding positively is also taken into consideration. Occasionally, results of patch tests in humans are also available.

Chronic Effects

A determination is also made on the likelihood and severity of possible chronic effects. This weight-of-evidence evaluation is performed on the results of genotoxicity assays, *in vitro* experiments, and preclinical and clinical studies to determine the potential for the material to produce target organ effects, reproductive or developmental toxicity, cancer, or other adverse chronic effects. A key piece of information is the dosage required to produce these effects, or preferably, the highest dosage that does not produce these effects (i.e., the overall no-observed-adverse-effect level). A judgment is made regarding the severity of chronic effects and whether they may have disabling consequences or the potential to cause early death. An estimate is also made of the potential for the material (or the damage it produces) to accumulate. A very important factor is whether effects are transient in nature (reversible) or permanent (irreversible). The reversibility of effects following both chronic and acute exposure are evaluated. Finally, a subjective determination is made of how exposure to the compound could have disabling consequences or impact on an individual's lifestyle, general well being, and quality of life.

Examples of PB-ECL Assignments

PB-ECL Category 1

Compounds assigned to PB-ECL Category 1 are relatively nontoxic or nonpotent and produce no systemic effects. Exposure limits for these materials typically range from 1 to 5 mg/m^3 on an 8-hour TWA basis.

Methyldopa, a relatively nonpotent antihypertensive agent, is an example of a PB-ECL Category 1 material. In clinical use the usual daily dosage of methyldopa is between 500 mg and 2 g. It has the potential to produce a transient, reversible decrease in blood pressure. Other possible effects include sedation, headache, numbness, and weakness, none of which are considered serious effects.

PB-ECL Category 2

Compounds assigned to PB-ECL Category 2 also have low pharmacological potency and generally have little or no systemic toxicity. Overexposure to these materials requires only first-aid or simple medical treatment. Exposure limits for these materials typically range from 0.1 to 1 mg/m^3.

Omeprazole, a gastric acid secretion inhibitor, is considered a PB-ECL Category 2 material, because the effects on acid production are reversible, and because side effects—including, diarrhea, constipation, rash, and headache—are rarely observed in clinical use. Therapeutic doses range from 20 to 60 mg/day. Cases of contact skin sensitization have been reported in workers handling this compound.

PB-ECL Category 3

Compounds assigned to PB-ECL Category 3 begin to require significant containment. Typically they have short-term effects that are normally reversible, but may produce effects that are slowly or not completely reversible, especially following prolonged exposure. These effects are generally not life-threatening or incapacitating, and overexposures can be satisfactorily managed medically. Typical exposure limits tend to be in the range of 1 to 100 μg/m^3.

Simvastatin, a potent cholesterol-lowering agent, was assigned to PB-ECL Category 3. The drug inhibits HMG-CoA reductase, an enzyme that catalyzes an early and rate-limiting step in the biosynthesis of cholesterol. The usual starting clinical dose ranges from 5 to 20 mg/day. Adverse effects to therapy are generally mild and transient, although some patients may experience changes in liver function tests that should be monitored periodically for this reason. Myopathy has been reported rarely. In preclinical studies in animals simvastatin produced a spectrum of changes in several tissues that represent an exaggeration of the biochemical effect of the drug at the high end of the dose-response curve. HMG-CoA reductase inhibitors as a class have the potential to cause fetal harm.

PB-ECL Category 4

PB-ECL Category 4 compounds are those that can produce life-threatening effects, with symptoms that may be incapacitating and may require immediate medical intervention. They may also have short-term or long-term effects that are not reversible and could have disabling consequences. Exposure limits are expected to be below 1 μg/m^3, if they can be established at all, and a total containment approach is used to control exposures.

Mechlorethamine is an example of a PB-ECL Category 4 material. It is an antineoplastic agent (nitrogen mustard) that acts as a biological alkylating agent and is effective against a number of lymphatic cancers. Normal rapidly dividing cells are also susceptible to the cytotoxic effects of mechlorethamine. It has a high order of acute toxicity, is corrosive to soft tissue, and causes bone marrow suppression, toxic effects on the GI tract, developmental toxicity, and an increased incidence of malignant tumors in animals at relatively low dosages. In clinical use serious toxicities associated with therapy include nausea, vomiting, bone marrow suppression, infertility, and an increased incidence of secondary malignancies.

PB-ECL Category 5

PB-ECL Category 5 compounds represent the most toxic substances known. As described in Table I, candidates for this level of containment would be extremely potent and/or toxic, with single doses producing life-threatening effects that would require immediate, heroic medical intervention. They might also produce irreversible health effects that may be severely disabling or significantly shorten life-expectancy. No drugs have been assigned to this category yet.

Implementation of PB-ECLs

In general, PB-ECLs represent a classification system for assigning compounds to one of five health hazard categories of increasing severity based on their inherent pharmacological and toxicological properties. The categories correspond to predefined strategies known to provide the necessary degree of control to protect employees and the environment. These range from conventional handling to situations where open handling is kept to a minimum, to closed systems where no open handling is permitted and robotics may be employed. Table II shows the general level of containment for PB-ECL Categories 1 through 5.

Several matrices have been developed by industrial hygiene professionals and engineers that translate these assignments into general recommendations for real-life actions and practices that, when used effectively, achieve the necessary level of control. Several matrices have been developed to provide guidance on various subjects. Each of these is discussed below.

General Design Concepts Matrix

A basic "General Design Concepts Matrix" is presented in Table III. A host of basic requirements are defined in this table that must be followed whenever building or renovating a facility to house a particular category of compound. The matrix is intended to give a description of the overall intent and goals of the various control strategies.

Laboratory Matrix

A specific matrix was developed for laboratory operations including research and quality control that defines a specific set of criteria for operations involving very small quantities of compounds under controlled conditions. In the laboratory setting, Categories 1 and 2 are combined, since the same basic laboratory practice covers both. The Laboratory Matrix incorporates many of the provisions of the General Design Concepts Matrix but reflects an overall exposure assessment based on laboratory-scale operations.

A very large number of PB-ECL Category 3 (or P-3) compounds are handled in the laboratory setting. This is because very little information is available on the toxicity of these compounds until they are formally approved as drug candidates. Typically these compounds represent a class referred to as "unstudied compounds." Compounds in this class may not be handled on the open bench top. They must be handled within a basic containment device such as a fume hood or, preferably, a glove box or ventilated enclosure, if available.

Unit Operations Matrix

The Unit Operations Matrix was developed to guide the engineering design team in the appropriate types of manufacturing technologies based on our historic ability to control employee exposure through engineering design.

An excerpt from the Unit Operations Matrix is shown in Table IV to provide an example of how guidance is given on the types of operations and equipment in manufacturing areas permitted for each category. The full matrix deals with all possible operations in chemical and pharmaceutical manufacturing, but is not presented here because of its complexity, and because the specifics may vary from company to company. This "yes/no" matrix was designed to give process engineers a framework for development or modification of processes. Deciding whether or not a compound can be handled in given equipment depends on the category it is assigned to and an exposure assessment of that operation. For example, scooping of a wet cake from a centrifuge is allowed for PB-ECL Category 1, 2, and 3 materials, because there is little dust generated during that operation. It is not allowed for Level 4 and 5 materials, because even the small amount of material that may become airborne during this operation could represent an unacceptable risk to employee health. An example of a half-suit isolator, which is used primarily for PB-ECL Category 4 compounds, is shown in Figure 2. The design of this containment device is similar to the "negative pressure" modified glove bag techniques described recently for asbestos removal,[14] but the goal is to achieve total containment rather than controlling exposures below a prespecified level.

In addition to the matrix for solids charging, unit operations matrices were prepared for the following operations: solids handling, pharmaceutical granulating, liquid handling, solid/liquid separations, liquid/liquid separations, particle size reduction and control, solids drying, dosage form operations, coating operations, packaging operations, and quality control sampling.

Teams of engineers developed the full Unit Operations Matrix based on their experience. Both industrial hygiene monitoring data and professional judgment were used to develop the matrix. Since the matrix was developed from a historical perspective, it is assumed that new or modified applications of existing technologies or new technologies may also provide adequate protection. The guidelines provide a basis for design and known acceptable methods only. Alternate approaches and solutions are acceptable as long as they achieve the same level of control and containment.

Validation of PB-ECL Category Control Strategies

Air monitoring and wipe test data are used to evaluate the effectiveness of performance-based controls. Where numerical exposure control limits can be derived, these provide the basis of the validation program. Wipe test criteria are also provided for materials in PB-ECL Categories 3, 4, and 5 to evaluate external surface contamination and validate the adequacy of engineering controls. Wipe test criteria are usually not necessary for PB-ECL Category 1 and 2 materials, because validation of traditional control technologies is no longer necessary. Wipe test criteria, expressed as a mass per unit surface area (usually 100 cm^2), are primarily intended to provide guidance on the required level of analytical sensitivity of the wipe test methods. For PB-ECL Category 3 materials, the wipe test criteria can also be used to approximate a "safe" level of exposure via external surface contamination. For PB-ECL Category 4 and 5 materials any detectable surface contamination indicates that the goal of total containment (no open handling) has not been achieved.

Within the General Design Concepts Matrix, the field industrial hygienist is provided with general guidance on the sampling strategy necessary to validate the performance of the engineering design. Validation of the matrix-specified operations with industrial hygiene monitoring data is a continuing process and is required before new technologies can be added to the matrix. One approach to validating the effectiveness of new controls for a new compound in a PB-ECL 3, 4, or 5 category is to use a compound assigned to a lower PB-ECL category (with an appropriately low detection limit) in a trial run. An example of this approach was the use of acetaminophen as a surrogate compound to validate the effectiveness of controls in a new Level 3 facility. Ongoing monitoring is also required to detect breaches in a previously validated containment system.

The PB-ECL Category is an essential piece of information used to guide facility design. Past experience dictates that PB-ECL

TABLE II. General Containment Levels

PB-ECL Category	Containment Level
1	good manufacturing practices
2	good manufacturing practices (with more stringent controls)
3	essentially no open handling (closed systems should be used)
4	no open handling (closed systems must be used)
5	no manual operations/human intervention (robotics/remote operations encouraged)

TABLE III. General Design Concepts Matrix

Design Consideration	PB-ECL Category 1	2	3	4	5
General concept	Unauthorized personnel must not be permitted to enter the area. Work surfaces are cleaned after each day and after major spills. Eating, drinking, smoking, and applying cosmetics are not permitted in the work area. All procedures must be carefully performed to minimize exposure through all potential routes of exposure. The wearing of laboratory coats, gowns, or work uniforms is recommended.	Unauthorized personnel must not be permitted to enter the area. Work surfaces are cleaned after each day and after major spills. Eating, drinking, smoking, and applying cosmetics are not permitted in the work area. All procedures must be carefully performed to minimize exposure through all potential routes of exposure. The wearing of laboratory coats, gowns, or work uniforms is strongly recommended.	Controlled access to the work area is strongly recommended. Only those persons who have received training specific to the compound shall be admitted. Work surfaces are to be decontaminated after all potentially high-risk activities. Eating, drinking, smoking, and applying cosmetics are not permitted in the work area. Excellent work practices must be established, taught, and enforced. Deviations from established practices cannot be tolerated. Signs shall be posted indicating the compound in question and its associated hazards.	Controlled access to the work area is required. Only those persons who have received training specific to the compound shall be admitted. Work surfaces are to be decontaminated after all potentially high-risk activities. Eating, drinking, smoking, and applying cosmetics are not permitted in the work area. Excellent work practices must be established, taught, and enforced. Deviations from established practices cannot be tolerated. Signs shall be posted indicating the compound in question and its associated hazards.	Controlled access to the work area is required. Only those persons who have received training specific to the compound shall be admitted. Work surfaces are to be decontaminated after all potentially high-risk activities. Eating, drinking, smoking, and applying cosmetics are not permitted in the work area. Excellent work practices must be established, taught, and enforced. Deviations from established practices cannot be tolerated. Signs shall be posted indicating the compound in question and its associated hazards.
Containment level	No special containment technologies are required. Local exhaust ventilation should be provided based on ACGIH ventilation design standards.	No special containment technologies are required. Local exhaust ventilation should be provided based on ACGIH ventilation design standards.	Open handling must be limited to only very small quantities. Fume hoods and other open-face containment devices are acceptable when face velocities of at least 80 lfpm are achieved. Partitions, barriers, and other partial containment technologies are required to prevent migration of the compound to uncontrolled areas.	Open handling is not permitted under any circumstances. All operations require the use of an appropriate containment technology designed to prevent leakage to the workplace. In general, glove boxes, totally enclosed processes, and materials transport systems would be expected.	Open handling is not permitted under any circumstances. All operations require the use of an appropriate containment technology designed to prevent leakage to the workplace. In general, glove boxes, totally enclosed processes, and materials transport systems would be expected. All containment systems require leakage testing and must meet zero leakage criteria. Remote operations should be encouraged wherever possible. Minimizing human interactions must be the goal.

continued

TABLE III. General Design Concepts Matrix (continued)

Design Consideration	PB-ECL Category 1	2	3	4	5
General ventilation	A minimum of 7 air changes per hour is required. Air recirculation is permitted if adequate scrubbing/filtration is provided to maintain exposure levels below 50% of the numerical exposure limit within the production area. No recirculation is permitted into nonproduction areas.	A minimum of 7 air changes per hour is required. Air recirculation is permitted if adequate scrubbing/filtration is provided to maintain exposure levels below 50% of the numerical exposure limit within the production area. No recirculation is permitted into nonproduction areas.	A minimum of 10 air changes per hour is required. Air recirculation is permitted in limited situations. Air flow must be directed away from the operator's breathing zone. Air pressure must be negative relative to surrounding areas.	A minimum of 12 air changes per hour is required. Air recirculation is not permitted. Air flow must be directed away from the operator's breathing zone. Air pressure must be negative relative to surrounding areas. Air locks with interlocked doors are required to the processing areas.	A minimum of 12 air changes per hour is required. Air recirculation is not permitted. Air flow must be directed away from the operator's breathing zone. Air pressure must be negative relative to surrounding areas. Double air locks with interlocked doors are required.
Local exhaust ventilation (LEV)	LEV must be provided at the sources of contamination using ACGIH ventilation design criteria. Recirculation of LEV exhaust is permitted only through HEPA filters.	LEV must be provided at the sources of contamination using ACGIH ventilation design criteria. Recirculation of LEV exhaust is not permitted.	LEV must be provided at the sources of contamination using ACGIH ventilation design criteria. Exhaust must be HEPA filtered to the outside.	LEV must be provided at the sources of contamination using ACGIH ventilation design criteria. Exhaust must be HEPA filtered to the outside.	LEV must be provided at the sources of contamination using ACGIH ventilation design criteria. Exhaust must be HEPA filtered to the outside.
Surfaces	No special requirements	Easily cleanable surfaces required	Smooth, nonporous, minimal ledges, easily cleaned	Smooth, nonporous, minimal ledges, easily cleaned. Surfaces must be contiguous.	Smooth, nonporous, minimal ledges, easily cleaned. Surfaces must be contiguous.
Maintenance, cleaning, waste disposal, and decontamination	Floor sweeping is not recommended for cleaning powders. Only vacuum systems should be used prior to wet mopping/cleaning. Chemical decontamination is not required nor is validated surface contamination testing. All waste material must be double bagged and clearly labeled according to applicable standards. Material may not be crushed or shredded prior to final disposal.	Floor sweeping is not permitted for cleaning powders. Only HEPA vacuum systems are to be used prior to wet mopping/cleaning. Chemical decontamination is not required nor is validated surface contamination testing. All waste material must be double bagged and clearly labeled according to applicable standards. Material may not be crushed or shredded prior to final disposal.	Floor sweeping is not permitted for cleaning powders. Only HEPA vacuum systems are used prior to wet mopping/cleaning. Chemical decontamination is not required nor is validated surface contamination testing. All waste material must be double bagged and clearly labeled according to applicable standards. Material may not be crushed or shredded prior to final disposal. Clean-in-place systems for equipment are	Floor sweeping is not permitted for cleaning powders. Only HEPA vacuum systems are used prior to wet mopping/cleaning. Chemical decontamination is recommended if possible. Surface contamination testing is required for deregulation of the facility and equipment. All waste material must be double bagged, placed in a rigid container, and labeled according to applicable standards. Material may not be crushed or shredded prior to final	Floor sweeping is not permitted for cleaning powders. Only HEPA vacuum systems are used prior to wet mopping/cleaning. Chemical decontamination is recommended if possible. Surface contamination testing is required for deregulation of the facility and equipment. All waste material must be double bagged, placed in a rigid container, and labeled according to applicable standards. Material may not be crushed or shredded prior to final

continued

TABLE III. General Design Concepts Matrix (continued)

Design Consideration	PB-ECL Category 1	2	3	4	5
Maintenance, cleaning, waste disposal, and decontamination (continued)			recommended wherever possible. Safe change filters are required for all ventilation systems. Wherever possible equipment should be accessed for maintenance from outside of the containment area.	disposal. Clean-in-place systems for equipment are required wherever possible. Safe change filters are required for all ventilation systems. Wherever possible equipment should be accessed for maintenance from outside of the containment area.	disposal. Clean-in-place systems for equipment are required wherever possible. Safe change filters are required for all ventilation systems. Wherever possible equipment should be accessed for maintenance from outside of the containment area.
Personal protective equipment (PPE)	Appropriate respiratory protection is required based on air sampling data. No restriction on the type of respiratory protection as long as protection factors are not being exceeded. Qualitative respirator fit-testing is required for negative pressure respirators. Effective gloves should be worn by all operators. Appropriate eye protection is required.	Appropriate respiratory protection is required based on air sampling data. No restriction on the type of respiratory protection as long as protection factors are not being exceeded. Qualitative respirator fit-testing is required for negative pressure respirators. Effective gloves are required for all operators. Appropriate eye protection is required.	Only powered air purifying respirators or air supplied respirators are permitted. For dusts, only HEPA filters are permitted. Effective gloves are required for all personnel entering the area. Appropriate eye protection is required. Tyvek or an equivalent outer protective garment is required. Garment must be impervious to the chemicals involved.	Only powered air purifying respirators or air supplied respirators are permitted. For dusts, only HEPA filters are permitted. Double gloves are encouraged for all personnel entering the area. Appropriate eye protection is required. Tyvek or an equivalent outer protective garment is required. Double Tyvek is recommended. Garment must be impervious to the chemicals involved.	Only powered air purifying respirators or air supplied respirators are permitted. For dusts, only HEPA filters are permitted. Double gloves are required for all personnel entering the area. Appropriate eye protection is required. Double Tyvek or an equivalent outer protective garment is required. Garment must be impervious to the chemicals involved.
IH monitoring	Breathing zone TWA samples are required for an initial exposure assessment to fully characterize the workplace. Routine monitoring is not required unless the action limit is exceeded.	Breathing zone TWA samples are required for an initial exposure assessment. The sampling strategy should be based on a statistically valid number of samples. Routine monitoring is required to assure compliance with accepted work practices and that engineering controls are being used effectively. Ventilation testing is required.	Breathing zone TWA samples are required for an initial exposure assessment. The sampling strategy should be based on a statistically valid number of samples. Routine monitoring is required to assure compliance with accepted work practices and that engineering controls are being used effectively. Ventilation testing is required.	Breathing zone TWA samples are required for an initial exposure assessment. The sampling strategy should be based on a statistically valid number of samples. Routine monitoring is required to assure compliance with accepted work practices and that engineering controls are being used effectively. Ventilation testing is required.	Breathing zone TWA samples are required for an initial exposure assessment. The sampling strategy should be based on a statistically valid number of samples. Routine monitoring is required to assure compliance with accepted work practices and that engineering controls are being used effectively. Ventilation testing is required.
Medical surveillance	General chemical/ pharmaceutical operator surveillance should be performed as determined by health services.	Surveillance should be based on anticipated health effects of the compound in question, the potential for exposure, and the availability of objective test criteria.	Surveillance should be based on anticipated health effects of the compound in question, the potential for exposure, and the availability of objective test criteria.	Surveillance should be based on anticipated health effects of the compound in question, the potential for exposure, and the availability of objective test criteria.	Surveillance should be based on anticipated health effects of the compound in question, the potential for exposure, and the availability of objective test criteria.

TABLE IV. An Excerpt from the Unit Operations Matrix

	PB-ECL Category				
Solids Charging/Transfers	**1**	**2**	**3**	**4**	**5**
Vacuum convey (closed system)	yes	yes	yes	yes	yes
Half-suit isolator	yes	yes	yes	yes	yes
Glove box	yes	yes	yes	yes	yes
Iris valve	yes	yes	yes	yes	no
Open screw convey	yes	yes	yes	no	no
Open scooping (wet)	yes	yes	yes	no	no
Gravity (totes/drum dumping)	yes	yes	no	no	no
Open scooping with LEV[A] (dry)	yes	yes	no	no	no

[A] LEV = local exhaust ventilation

categories specify controls that are generally capable of controlling exposures to the ranges of ECL values and wipe test criteria given in Figure 3. It should be recognized that, because numerical limits are quantitative in nature and PB-ECL categories are more subjective, the latter may not always conform exactly to the corresponding range of ECL values or wipe test criteria. This is most likely to occur at the borderline between categories.

DISCUSSION

The development of performance-based control strategy matrices was made possible by a large database containing industrial hygiene monitoring data for various pharmaceutical unit operations. These data enabled an evaluation of the suitability of various equipment and techniques to handle compounds in each category. It is important to note that the higher PB-ECL categories incorporate increasing levels of redundancy in protection and provide a greater margin of safety for increasingly potent or toxic compounds.

With implementation of the PB-ECL matrices, the design team now has a rational basis for planning, costing, and constructing processes and facilities. There is much less debate among parties on basic design concepts, and focus is now drawn toward assuring that performance criteria are met and assuring that all design criteria are satisfied. Use of the matrices also helps greatly in negotiations with vendors, because it allows one to clearly define expectations.

Line management, laboratory workers, and operators all have clear expectations both from an equipment performance perspective and about how their work practices will be designed. One benefit of the matrix concept is that line management, engineers, and the field industrial hygienists agree on the design strategies beforehand, because these strategies were based in large part on their own historic data. The real key to the success of this program is a predefined, tangible, understandable, real-world interpretation of hazard information for persons with limited knowledge of toxicology that can be applied easily to provide proper protection.

Although the PB-ECL concept was initially developed for use in the pharmaceutical industry, it may have general applicability in other industries. For example, in the chemical industry this system could be applied to the handling of carcinogens, mutagens, and potent reproductive or developmental toxins. In the agricultural chemical industry such a system might be applied to potent pesticides. Finally, such a system is certainly applicable to the handling of genetically engineered materials.

FIGURE 2. Half-suit isolator used primarily for PB-ECL Catergory 4 compounds

CONCLUSIONS

Pharmaceutical active ingredients are assigned to one of five PB-ECL categories based on their inherent pharmacological and toxicological properties regardless of whether numerical limits can be established. Preliminary assignments are made very early in the drug development process.

Assignment of materials into PB-ECL categories relies heavily on professional judgment and reflects an overall assessment of all the available data, but emphasizes potential immediate, life-threatening effects and delayed or chronic, irreversible effects. PB-ECL assignments are used, either alone or in conjunction with numerical ECLs, to identify predefined strategies known to

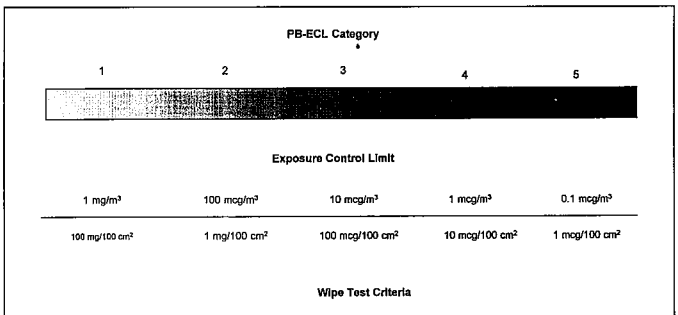

FIGURE 3. General correspondence between numerical and performance-based exposure control limits

provide the necessary degree of control to protect employees and the environment.

For materials assigned to PB-ECL Categories 1, 2, and 3, the PB-ECL matrices can be a useful tool to help define technologies and procedures known to control exposures to the corresponding numerical ECL value. For PB-ECL Category 4 and 5 materials, the level of control must be accomplished via matrix specified or equivalent control technologies. Industrial hygiene monitoring must be performed on an ongoing basis to continually validate containment technologies implemented to meet matrix defined levels of control.

A dialogue is necessary between industrial hygiene professionals, project engineers, and line management to ensure that the rationale for the establishment of the numerical ECL, if available, and for the assignment of the PB-ECL category is understood, and that the facility design and safe handling recommendations properly reflect these limits/categories.

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