

## CONTROL BANDING IN THE PHARMACEUTICAL INDUSTRY

BRUCE D. NAUMANN, Ph.D., DABT  
Merck & Co., Inc.

### Summary

The pharmaceutical industry embraced the concept of control banding many years ago. Control banding is a process of assigning a compound to a hazard category that corresponds to a range of airborne concentrations – and the engineering controls, administrative controls, and personal protective equipment – needed to ensure safe handling. While the terminology used was different, the high potency of some pharmaceutical compounds required the use of alternatives to setting numerical occupational exposure limits (OELs), e.g., performance-based exposure control limits (PB-ECLs) or occupational exposure bands (OEBs), especially for early development compounds with limited information. The long experience in setting OELs for active pharmaceutical ingredients, and the myriad of engineering solutions required to achieve these internal exposure standards, paved the way for a more performance-based approach. Enrolment criteria were developed that were more descriptive than the prescriptive risk phrases used in the UK's COSHH Essentials. The latter do not adequately address the types of effects potentially produced by pharmaceuticals, especially highly potent compounds. Internal experts are available in pharmaceutical companies to interpret the preclinical and clinical data for new drug products, including those with novel therapeutic mechanisms, against technical enrolment criteria that require more professional judgment.

The range of concentrations covered by control bands used in the industry is fairly consistent and generally reflects full log intervals. The boundaries differ slightly in some cases because verification studies have identified different break points for various new control technologies employed. There are also “semantic” differences in how control bands are named – most use numbers but these may point to different ranges. There has been no attempt to harmonize these designations so it is important for companies to clearly define the range of concentrations associated with each band when communicating to outside interests.

The pharmaceutical industry has begun conducting verification studies on the effectiveness of engineering controls and some attempt has been made, through the International Society for Pharmaceutical Engineers (ISPE) to standardize these assessments. Benchmarking has shown some variability in verification data; however, many design choices are available, whether used alone or in combination with other control technologies (e.g., alpha/beta valve used inside a down flow booth), that allow companies to meet specified design targets.

Control banding is just one part, although an important one, of a comprehensive occupational health program. In fact, the performance-based approach used in the industry combines engineering controls with administrative and procedural controls, which overlap to achieve the desired level of employee protection. Other aspects of the program – ranging from hazard communication to compliance monitoring strategies – are inextricably linked to the control banding system.

Occupational hygienists play a critical roll in verifying the effectiveness of engineering controls and, ultimately, the success of the control banding concept. Many more verification studies are needed and should be published to ensure that a consistent and robust database is developed to support control banding recommendations. Occupational toxicologists must continue to set

scientifically defensible OELs that provide adequate protection of workers. Assigning the same compounds to control bands using existing categorization schemes will provide prospective verification that the existing control banding criteria are categorizing compounds appropriately. Occupational hygienists, occupational toxicologists and occupational physicians need to work together as a team to continue to ensure that occupational health risk assessments and medical surveillance programs are focused on verifying that control banding practices are achieving the desired level of worker protection.

## **Introduction**

The term “Control Banding” was rapidly adopted, after it was introduced a few years ago, as the preferred description of a chemical classification/exposure control strategy for chemicals. The banding concept and approach are very similar to what has been used for many years in the pharmaceutical industry in the US and in the EU.

The value of classifying chemicals according to their hazards to ensure proper handling has been recognized for many years and is the basis for schemes used by most developed countries for labeling containers of chemicals. The concept of using categorization schemes for managing chemical handling is also decades old (Henry and Schaper 1990; Money 1992). The system developed by a number of major pharmaceutical companies in the late 1980s to classify compounds based on the severity of hazard, and the controls required to reduce exposures to acceptable levels, was later described in an AIHAJ article (Naumann et al. 1996). About the same time “banding schemes” were being discussed in the US, the Association of the British Pharmaceutical Industry published a similar hazard categorization scheme (ABPI 1995), but did not include a linkage to associated control recommendations. Meanwhile, the Health and Safety Executive (HSE) in the UK was developing a user-friendly scheme called COSHH Essentials (Brooke 1998; Gardener and Oldershaw 1991; HSE 1999; Maidment 1998), primarily for the benefit of small and medium sized enterprises that may not have the benefit of expertise from a resident occupational hygienist. The International Labor Organization is also supporting the use of control banding throughout the world, especially in less-developed countries. There have been series of national and international workshops in the last 3 years sponsored by ACGIH, AIHA, ILO, IOHA, NIOSH, OSHA and WHO to increase the visibility and encourage the use of control banding. While other descriptions have been used in the past (e.g., performance-based exposure control limits, occupational exposure bands), “Control Banding” is the term most widely known today and appears to be here to stay.

In the following I will briefly describe the establishment and use of control banding at Merck and the rest of the pharmaceutical industry. I will focus on the unique nature of pharmaceutical products, verification of the effectiveness of controls, and the integration of banding strategies within comprehensive occupational health programs.

## **Control Banding at Merck**

Merck has had a program in place since 1979 – the year the Industrial Toxicology Advisor Committee (ITAC) was chartered – to set occupational exposure limits (OELs) for pharmaceuticals and to provide specific guidance for so called CMTR agents (carcinogens, mutagens, teratogens and reproductive toxicants). The early work of the committee was summarized in a seminal paper on setting occupational exposure limits for pharmaceuticals (Sargent and Kirk 1988). Most pharmaceutical companies set OELs for their active pharmaceutical ingredients (APIs) using this method, through their own internal committees or with the assistance of consulting toxicologists. Essentially, the no-effect level for the critical endpoint (the effect that occurs at the lowest part of the dose-response curve) is divided by a series of “safety factors” – that address various

uncertainties and pharmacokinetic considerations – and the volume of air breathed by a worker during a typical work shift. We continue to try to improve the limit setting process by discussing the scientific basis for the uncertainty factors used (Naumann and Weideman, 1995), refinements in the methodology (Naumann and Sargent 1997), and the replacement of default uncertainty factors with chemical-specific adjustment factors (CSAFs) (Silverman et al. 1999).

It is important to discuss setting numerical limits within the context of control banding because, without them, there is no assurance that the levels associated with different bands provide the necessary degree of protection. Within Merck, and the other pharmaceutical companies that set their own OELs, the establishment of performance-based exposure control limits (PB-ECLs) (Merck's term for control bands) was only possible because we spent years designing processes and identifying engineering controls that were necessary to achieve those numerical exposure control limits (ECLs). It was only after we had sufficient experience in setting ECLs (and coming up with associated design strategies) over the course of 10 years that we were in a position to develop a more generic system, or performance-based approach. This is applied to new compounds, typically early in the drug development timeline, with similar or equivalent hazards and exposure control requirements.

The need for a system to categorize early compounds was also heightened by the recognition that new compounds coming out of drug discovery had novel therapeutic mechanisms, for which we had no experience, and were becoming more and more potent. For some classes of compounds, our ability to clearly define a no-effect level was difficult. A few compounds had pharmacologic properties that could have immediate life-threatening effects at doses that were achievable in the workplace. Others, such as cytotoxic antineoplastic agents, had the potential to cause genotoxic effects at low levels of exposure that might not become evident for many years. These agents were likened to pathogenic organisms, whereby exposure to a single organism could theoretically lead to severe illness or death. The approach used to manage organisms of varying pathogenicity (i.e., Biosafety Levels) was very intriguing to the early developers of the PB-ECL program at Merck.

The performance-based approach is predicated by the inextricable association of two components:

- 1) A hazard classification scheme used to assign compounds into one of a series of health hazard categories of increasing severity based on their inherent pharmacological and toxicological properties, and
- 2) The existence of corresponding predefined strategies known to provide the necessary degree of control to employees and the environment for compounds in those categories.

The enrolment criteria used to assign compounds into PB-ECL categories are listed in Table I.

<b>Table I. Enrolment criteria for Performance-Based Exposure Control Limits (PB-ECLs)</b>						
<b>Enrolment Criteria</b>	<b>PB-ECL Category</b>					
	<b>1</b>	<b>2</b>	<b>3</b>	<b>3+</b>	<b>4</b>	<b>5</b>
Potency (mg/day)	>100	10-100	1-10	0.1-1	<0.01	<0.01
Severity of Acute (Life-Threatening) Effects	Low	Low/Moderate	Moderate	Moderate/High	High	Extreme
Acute Warning Properties	Excellent	Good	Fair	Fair/Poor	Poor	None
Onset of Warning Symptoms	Immediate	Immediate	Immediate	May Be Delayed	Delayed	None
Medically Treatable	Yes	Yes	Yes	Yes	Yes/No	No
Need for Medical Intervention	Not Required	Not Required	May be Required	May Be Required	Required	Required Immediately
Acute Toxicity Oral LD50 (mg/kg)	Slight >500	Moderate 50-500	High 5-50	Very High 0.5-5	Extreme 0.05-0.5	Super <0.05
Irritation	Not an Irritant	Slight to Moderate	Moderate Irritant	Severe Irritant	Corrosive	Extreme Corrosive
Sensitization	Not a Sensitizer	Mild Sensitizer	Moderate Sensitizer	Strong Sensitizer	Extreme Sensitizer	Extreme Sensitizer
Likelihood of Chronic Effects (e.g., Cancer, Repro)	Unlikely	Unlikely	Possible	Probable	Known	Known
Severity of Chronic (Life-Shortening) Effects	None	None	Low	Moderate	High	Extreme
Cumulative Effects	None	None	Low	Moderate	High	Extreme
Reversibility	Reversible	Reversible	Reversible	Slowly Reversible	Irreversible	Irreversible
Alternation of Quality Of Life (Disability)	Unlikely	Unlikely	Possible	Probable	Known	Known

It should be noted that the major pharmaceutical companies, and many toll manufacturers and other contractors that serve the industry, use a similar system for classifying their compounds and identifying appropriate facilities and equipment to manufacture them. The ranges of concentrations in each band are generally consistent, although the boundaries may differ slightly based on perception of where the technology breaks are. The actual designations for a given band may also differ. For example, Merck's PB-ECL Category 3+ corresponds to OEB 4 at several other companies. This is why it is important to include the range of concentrations in connection with the control band when communicating outside the company. For example, in Section 8 of our safety

data sheets (SDS) we now include the following for PB-ECL Category 3 compounds to avoid confusion by outside users:

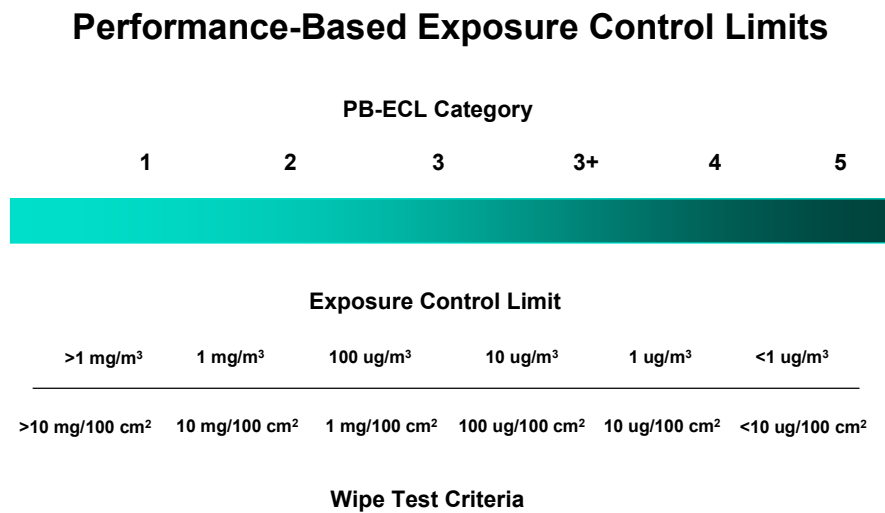
“PB-ECL Category 3 (Corresponds to 10-100  $\mu\text{g}/\text{m}^3$  as an 8-hr TWA). The PB-ECL category is an internal Merck control band.”

For those familiar with COSHH Essentials, it is readily apparent that there are no EU Risk Phrases included in the scheme and the criteria appear to be much more subjective. When the enrolment criteria were developed, a more flexible system was chosen because of the nature of the compounds we needed to address. While some have oral LD50s below the typical cut-offs and some may cause eye or skin irritation, target organ or reproductive effects, the activity and potency of these pharmaceutical agents (and some process intermediates) required use of criteria that captured all of the preclinical and clinical data generated during development. The criteria also enabled the use of professional judgment to properly interpret these data, since each are not weighted equally. Fortunately, the major pharmaceutical companies have experts that are capable of making those assessments.

One of the biggest challenges in the pharmaceutical industry, as well as other industries, is how to categorize compounds with little or no information. In other words, what should be the default control band for relatively unstudied compounds? At Merck, the default PB-ECL category is P-3 (the “P” denotes a preliminary assignment), which corresponds to 10-100  $\mu\text{g}/\text{m}^3$  as an 8-hr TWA. This allows a total daily dose of 100-1000  $\mu\text{g}$  for a worker breathing 10  $\text{m}^3$ . Merck’s default category was viewed as adequately protective for relatively unstudied compounds, even if they were later shown to have some health concerns. This early decision is supported by a recent analysis we conducted on the application of the threshold of toxicological concerns to pharmaceutical manufacturing operations (Dolan et al. 2005). The primary purpose of this publication was to document the scientific rationale for recommended acceptable daily intake (ADI) values to support quality operations and good manufacturing practices (e.g., cleaning validation and atypical investigations). The same rationale extrapolating from large databases of well-studied compounds, and the safe exposure limits established for these compounds, to chemicals of different structural classes with little or no toxicity data also validated our earlier choice for a default category (i.e., PB-ECL P-3). In the absence of any data suggesting a chemical might be unusually toxic or potent, the analysis showed that an ADI of 100  $\mu\text{g}/\text{day}$  (equivalent to 10  $\mu\text{g}/\text{m}^3$ ) was considered adequately protective (Dolan et al., 2005). As discussed below, average exposures need to be at the low end of the band to ensure that the majority of personal sample results remain within the band. Additional ADIs of 10  $\mu\text{g}/\text{day}$  and 1  $\mu\text{g}/\text{day}$  were recommended for compounds with limited data suggesting they may either be toxic/potent or carcinogenic, respectively (Dolan et al. 2005).

The correspondence between numerical and performance-based exposure control limits is shown in Figure 1. Wipe test criteria values are also included. The PB-ECL categories are “centered” over the range of concentrations that generally correspond to that category (e.g., PB-ECL 3 spans 10-100  $\mu\text{g}/\text{m}^3$ , an as 8-hr TWA). These are presented as a continuum and not bright lines since they represent a qualitative or semi-quantitative description of the toxicological and pharmacological properties of the compound.

**Figure 1. Alignment of Numerical and Performance-Based Exposure Control Limits**



As mentioned, each PB-ECL category is associated with controls, whether engineering, administrative or procedure-related, that affords the desired level of protection. As described in the earlier article (Naumann et al. 1996), several exposure control matrices were developed that provide specific recommendations for each PB-ECL category: 1) a general design concepts matrix, 2) a laboratory matrix and, 3) a manufacturing unit operations matrix. Table II shows an excerpt from the unit operations matrix, which was created using available industrial hygiene data and application of professional judgment. The engineering standard for facility design also includes an appendix that summarizes the verification data for some of the newer containment technologies and serves as a repository for results of exposure control verification studies.

**Table II. Excerpt from the Unit Operations Matrix**

Solids Charging/Transfers	PB-ECL Category					
	1	2	3	3 +	4	5
Vacuum Convey (Closed)	yes	yes	yes	yes	yes	yes
Half-Suit Isolator	yes	yes	yes	yes	yes	yes
Glove Box	yes	yes	yes	yes	yes	yes
Alpha-Beta Valve	yes	yes	yes	yes	no	no
Iris Valve	yes	yes	yes	yes	no	no
Down flow Booth	yes	yes	yes	no	no	no
FIBC with Slot Box	yes	yes	yes	no	no	no
Continuous Liner	yes	yes	yes	no	no	no
Open Screw Convey	yes	yes	yes	no	no	no
Open Scooping (Wet)	yes	yes	yes	no	no	no
FIBC without Slot Box	yes	yes	no	no	no	no
Kleissler Ring	yes	yes	no	no	no	no
Gravity (Totes/Drum Dumping)	yes	yes	no	no	no	no
Open Scooping with LEV (Dry)	yes	yes	no	no	no	no

As mentioned earlier, the PB-ECL categories and associated control recommendations are based on our past experience with similar compounds. What worked well in the past is expected to perform similarly with other compounds in the same hazard category, assuming the physical characteristics are also comparable. The unit operations matrix indicates which control strategies (e.g., butterfly valves, flexible intermediate bag containers (FIBCs), down flow booths, glove boxes, etc.) can be used for a given PB-ECL category. The health hazard level is combined with the inherent exposure potential for an operation (without controls) to determine the level of risk, and consequently, the level of containment required.

The PB-ECL program therefore works the same as COSHH Essentials in that a risk assessment is performed, combining hazard with exposure potential to estimate the risk and level of control required. The yes/no entries in the unit operations matrix reflect the exposure assessment inherent to that piece of equipment. Table III shows a comparison of the HSE and Merck “banding” schemes and the descriptive language used for each band. As you can see the Merck bands extend into much lower concentration ranges, owing to the potent nature of an increasing number of active pharmaceutical ingredients (APIs).

<b>Table III. Comparison of HSE Hazard Categories and Merck PB-ECL Categories</b>		
Control Bank	HSE Hazard Group	Merck PB-ECL Category
>1-10 mg/m <sup>3</sup>	A – Use Good Industrial Hygiene Practice	1 – Good manufacturing practices
>0.1-1 mg/m <sup>3</sup>	B – Use local exhaust ventilation	2 – Good manufacturing practices (with local exhaust ventilation)
>0.01-0.1 mg/m <sup>3</sup>	C – Enclose process	3 – Essentially no open handling (ventilated enclosures required)
>0.001-0.01 mg/m <sup>3</sup>	D – Seek specialist advice	3+ – Virtually no open handling (containment systems required)
≤0.001 mg/m <sup>3</sup>	D – Seek specialist advice	4 – No open handling (closed systems required)
≤0.001 mg/m <sup>3</sup>	D – Seek specialist advice	5 – No manual operations/human intervention (robotics or remote operations required)

### **Design Target Verification and Exposure Assessment Strategies**

There has been much debate within the pharmaceutical industry on the appropriate guidance to support facility design and verification of the effectiveness of identified exposure control technologies. Historically, companies have designed facilities to “achieve” the numerical OEL. A benchmarking survey was conducted prior to a recent Occupational Toxicology Roundtable (OTR) meeting to define the range of approaches pharmaceutical companies use to establish design targets and the range of concentrations achieved through verification studies of their design choices. Typically, data are collected as part of factory acceptance testing (FAT).

Based on the survey of 16 pharmaceutical companies, the design targets for situations where a numerical OEL was available were (no. of companies in parentheses): the OEL (N=5), 0.5 x OEL (N=3), 0.25 x OEL (N=2), 0.1 x OEL (N=1), and dispersion potential (e.g., dustiness) (N=1). For

situations where only a control band or OEB was available, 2 used the upper end of the band, 2 used the arithmetic mean of the band, one used the geometric mean of the band, 7 used the lower end of the band (also to reduce or eliminate PPE and increase plant flexibility), and one indicated they would design to ensure that exposures remained anywhere in the band.

Verification data routinely collected and reported included area samples to initially assess migration and personal samples to interpret potential exposures relative to the OEL. Other samples taken include air monitoring used for leak testing, wipe sampling to assess external surface contamination, and real-time particle counting used for trouble-shooting and training operators. Verification data were collected for equipment “as manufactured”, “as installed” and “as used” and were presented in a variety of different ways: arithmetic mean (with or without the standard deviation), geometric mean and geometric standard deviation, ranges and percent exceeding the OEL.

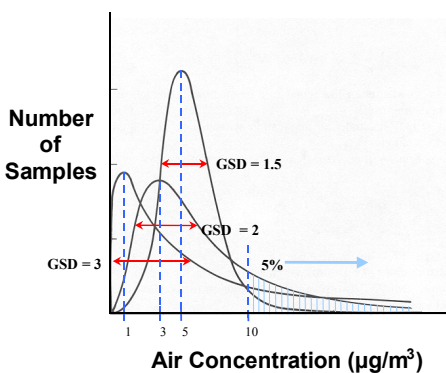
Table IV lists the benchmarking survey results for the expected range of concentrations for different control technologies used in the pharmaceutical industry. The disparity in some of the results is due to the unique circumstances, equipment design, use of hybrid approaches (i.e., combining several containment strategies) and variations in operator technique. Clearly, much work still needs to be done to verify which approaches perform best for different manufacturing configurations. For the manufacturer, the key is to determine what works best for them.

<b>Table IV. Benchmarking survey results of verification assessments from 16 pharmaceutical companies</b>	
<b>Control Technology</b>	<b>Expected Range (ug/m<sup>3</sup>)</b>
General Ventilation	>100, >10,000
LEV (elephant trunks)	>100-5000, 500-1000, >1000
Engineered LEV (enclosures)	>20, >30, 100-5000
Down-Flow Booths	1-20, 10-20, 300-500, 100-1000
Engineered Hoods	>20, 100-1000
Ventilated Enclosures	>1, 100-1000
FIBCs (w/o enclosures)	1, 1-20, <100, <200, 100-5000
FIBCs (w/ enclosures)	1-20, 25, 10-1000
Continuous Liners	1, 1-5, 10-100, 50-100, 100-1000
Split-Butterfly Valves	1, 1-10, 1-20, 10, 10-20
Isolators/Glove Boxes	0.01, <1, <1-10, <10
Barrier Isolators (filling)	0.1
Bag w/in bag	1, <10, 1-20
Charging Canisters	1-20
Direct Connections	10
Vertical Process Trains	1-20, 10

At Merck, like other pharmaceutical companies, we have comprehensive internal exposure assessment and monitoring policies, procedures and guidelines. The approach we use to evaluate employee exposures using personal monitoring results is essentially the same, regardless of whether a compound has a numerical exposure control limit (ECL) or performance-based exposure control limit (PB-ECL). The criteria used to determine if an operation has “achieved” the ECL, is that the 95<sup>th</sup> percentile point estimate of the exposure distribution is below the applicable ECL.

Conceptually, the same approach is used to set design targets and to assess whether exposures are maintained within the PB-ECL category or band. As illustrated in Figure 2 for PB-ECL Category 3+, depending on how well a process is controlled – and the resulting variability in the results of verification sampling reflected in the geometric standard deviation – a design target may be close to the lower end of the control band (i.e., the lower concentration in the range). From a compliance monitoring standpoint, however, the upper end of the band (i.e., the higher concentration in the range) is used as a surrogate for the ECL and the same acceptance criteria mentioned above applies.

**Figure 2. Design Targets and Verification Criteria**



### **Integration into Occupational Health Programs**

The assignment of a compound to a control band involves a number of considerations. Inherent to its success is the integration of exposure control recommendations within a comprehensive occupational health program. The PB-ECL categories at Merck dictate much more than engineering equipment choices. In addition to the containment level, the matrices include detailed design considerations for general ventilation; local exhaust ventilation; surfaces; maintenance, cleaning, waste disposal and decontamination; personal hygiene; personal protective equipment; IH monitoring; hazard communication; and medical surveillance. Medical surveillance programs are important to verify, as a secondary means following personal monitoring, that overexposures are not occurring. It also serves as a useful tool for ongoing verification of the success of the overall control banding scheme as it has been proposed and implemented world wide.

In the laboratories, numerical limits are not very meaningful. Consequently, in order to control exposures, departmental compound handling procedures are tied to the PB-ECL category. To ensure proper handling for all compounds, we have retrospectively assigned PB-ECL categories to all older compounds with numerical limits that preceded the initiation of the PB-ECL concept.

It should also be noted that the PB-ECL enrollment criteria, originally developed for assessment of Merck compounds, were recently merged with the risk phrases used in COSHH Essentials and the Risk Control Program developed by Monash University in Australia to create a separate internal hazard category for non-Merck compounds called the Health Effects Rating (HER). The HER is used, along with several exposure criteria, to help industrial and occupational hygienists prioritize qualitative and quantitative assessments for all chemicals handled at their sites.

## Future Needs and Directions

Control banding, regardless of what it is called in different companies and countries, has demonstrated great value in communicating, in simple well-understood terms, what controls are needed to protect workers from chemical hazards. Its success will likely cause it to be considered for application in other areas of occupational hygiene (e.g., physical agents, ergonomics, and biotechnology products) and development of separate categorization schemes, with stressor-specific enrolment criteria and control strategies, will also require verification (Nelson 2005).

The initial validation work of Brooke (1998) and Maidment (1998), along with the efforts within the pharmaceutical industry should be acknowledged; however, much work still needs to be done to verify the effectiveness of control banding recommendations. Air monitoring should be focused on verifying and documenting the effectiveness of control band-specific engineering equipment recommendations. Efforts should also continue to confirm that the hazard-based enrolment criteria, whether descriptive (as used in the pharmaceutical industry) or prescriptive (as used in COSHH Essentials), are accurately assigning compounds to the “correct” categories or hazard groups. Analyses should continue to be performed on large numbers of compounds from different chemical classes using risk phrases as the primary criteria, and comparing them to published OELs, for example. A recommended approach would be for various OEL setting bodies to band chemicals prospectively at the same time they are making numerical OEL recommendations to look for concordance. Over time, the correspondence between numerical limits and control bands would be firmly established, and any inconsistencies that become apparent could be addressed on a case-by-case basis. Continued scrutiny will reduce (or at least quantify) the uncertainties in categorizing compounds and identifying appropriate control strategies. Finally, as alluded to above, the ultimate verification of the effectiveness of these programs is through medical surveillance and the generation of a negative database documenting the lack of adverse effects in workers in areas guided by control banding recommendations.

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