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Developing Acceptable Surface Limits for Occupational Exposure to Pharmaceutical Substances

ABSTRACT: Acceptable surface limits (ASLs) are developed in order to establish a quantitative measure for the potential risk from exposure by dermal contact. In the pharmaceuticals industry, ASLs are used for protection against active pharmaceutical ingredients that are known to cause pharmacological or toxicological effects. An ASL can be used, together with appropriate analytical methods and industrial hygiene monitoring, to assess workplaces for potential dermal exposure and to protect the health and safety of individuals who might come in direct contact with contaminated surfaces in the workplace. ASLs are also used to evaluate the adequacy of housekeeping measures and the effectiveness of engineering containment approaches, or to determine whether a chemical is present on surfaces where it is not intended to be (e.g., in lunch rooms or offices, or on the outside surfaces of packaging materials). However, they should not be confused with cleaning limits for the surfaces of manufacturing devices that might come into contact with the drug product, which are set to minimize cross contamination between drug products and to protect end-users (e.g., patients taking drug products) as opposed to workers. A number of parameters must be evaluated in order to accurately develop appropriate and scientifically supportable limits. These include the dose or concentration that will cause the potential effect, the degree of chemical transfer from contaminated surfaces to the skin, and the rate or amount of percutaneous absorption. In practice, this information is usually limited or unavailable. Additionally, there has been very little regulatory guidance on the setting of ASLs. Consequently, in order to calculate an ASL, various assumptions must be made by health and safety professionals regarding how dermal exposures might occur. As quantitative data become available, the ASL can be adjusted accordingly. An overview of the setting of health-based and performance-based ASLs for pharmaceutical substances from animal and human toxicological data is provided.

KEYWORDS: surface limit, occupational, pharmaceuticals

Introduction

In the workplace, systemic exposure to chemical substances occurs primarily via the inhalation route. However, another important route of occupational exposure is through dermal contact. During manufacturing operations, surfaces can become contaminated for several reasons, including inadequate containment and/or cleanup processes following spills, ineffective enclosures and engineering controls, poor employee training on industrial hygiene practices, inadequate and/or improper housekeeping practices, and specific physicochemical processes of the chemical(s) being handled. During the manufacture of active pharmaceutical ingredients (APIs), there are additional challenges related to a known or predicted pharmacological response following a systemic exposure, which, regardless of its nature, would be considered deleterious to a healthy worker population. Moreover, certain APIs that are developed for transdermal administration have inherent dermal absorptive properties or are mixed with permeation-enhancing chemicals in topical formulations in order to facilitate systemic exposure. Consideration must also be given to potency, which is becoming increasingly high as new drugs are being investigated/ marketed that are pharmacologically active at low therapeutic doses. As a result, even the smallest exposures to these novel APIs via any route can potentially present a serious health risk.

As mentioned previously, APIs are intended to be pharmacologically active, but there are also other characteristics that distinguish APIs from commodity chemicals. APIs, although biologically reactive, tend to be chemically stable (note: the same might not be true of their synthetic intermediates). In addition, most APIs are solids and as such are readily deposited on surfaces, whereas commodity chemicals might

Manuscript received October 12, 2010; accepted for publication June 26, 2011; published online August 2011.

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be solid, liquid, or gas. APIs tend to have more robust toxicokinetic/toxicodynamic profiles than commodity chemicals. These data are collected as part of the drug research and development process and include critical information such as the systemic bioavailability and bioaccumulation potential. Frequently, there is a wealth of human data available for an API, whereas for other chemicals the human data are often limited to accidental (over)exposures with resultant toxicities. Overall, the data set that is routinely assembled for an API is better suited for performing human health risk assessments.

Factors Influencing Dermal Absorption

The process of chemical migration from the surface of the skin to the systemic circulation is a complex one [1,2]. There are many factors that contribute to the dermal absorption potential of a chemical, including the following:

- *ability to penetrate the skin*, determined by such factors as physical adherence to skin, the condition and thickness of the contacted skin, the number of sweat glands and hair follicles at the site of contact (even though these make very small contributions to the exposure), the ambient temperature in the work area, occlusion of the exposed area by clothing or other personal protective equipment (which might prolong the contact between the chemical and the skin), and inherent physicochemical properties such as the molecular size (smaller molecules are more likely to penetrate the skin) and lipophilicity (a log P_{ow} between +1 and +2 is the most favorable for dermal absorption);
- *amount of chemical that contacts the skin*, referring to the chemical concentration on the surface;
- *amount of skin that contacts the chemical*, referring to the surface area of the skin that contacts the chemical;
- *frequency and duration of the contact event*;
- *concomitant exposure to multiple chemicals*—e.g., in drug formulations (which might include permeation-enhancers); and
- *interindividual variability*.

Each of these parameters must be considered when assessing the potential for skin absorption.

Setting Dermal Exposure Limits for APIs in the Workplace

Occupational dermal exposure limits, hereinafter referred to as acceptable surface limits (ASLs), are risk assessment tools used for worker safety. Similar to occupational exposure limits, which set acceptable airborne concentrations for inhalation exposure to chemicals, the ASL is considered as a surface concentration that is “reasonably” safe to individuals following contact with unprotected skin. It is used by health and safety professionals to help determine whether it is safe for workers to re-enter a previously contaminated work area without personal protective equipment, as well as for risk communication purposes. It must be emphasized that an ASL is not equivalent to an equipment cleaning limit: ASLs are set for worker safety, whereas equipment cleaning limits (used to minimize product cross-contamination between batches of two different drug products sharing the same equipment) are intended to protect patients as opposed to workers.

An ASL cannot be properly used without the development of validated analytical methods for monitoring specific surfaces, as different surfaces might not be equally suitable for recovery of the material. A validated method requires putting a known amount on the surface, using a collection technique (sometimes called a wipe or surface sampling method) for taking the sample, and quantitatively measuring the recovered amount from that surface.

With an ASL and a validated surface sampling and analytical method, an industrial hygienist or other trained occupational health professional can conduct a workplace exposure assessment. This involves developing a plan to determine sites at which dermal contact is most likely to occur, based on the nature of the task and work patterns, and selecting appropriate areas and surfaces to be sampled.

Methodology

The pivotal step when performing a proper risk assessment for setting an ASL is to know, or be able to predict, the systemic bioavailability of a chemical via the dermal route. Limited regulatory guidance on dermal exposures is readily found in the public domain; the Environmental Protection Agency has

published guidelines for estimating dermal exposures to pesticides and contaminated soil/water [2–5], and the European Union has issued a guidance document for predicting dermal exposure (with proposed revisions submitted by the UK Health & Safety Executive) that focuses on agrochemical scenarios [6,7]. Exposures in workplace settings are not expressly covered by these documents. Moreover, information on dermal absorption found in the public domain is usually compound-specific and cannot be used to extrapolate to other chemicals. Although there are new methods published for the theoretical or practical determination of individual parameters contributing to absorption (such as the flux rate and permeation coefficient), there still remains a shortage of overall guidance on understanding the entirety of the dermal absorption process. This presents a tremendous challenge in performing risk assessments.

Another difficulty in establishing quantitative dermal exposure limits for an occupational setting is that wherever exposure via the dermal route is possible, exposure via ingestion (e.g. following incidental hand-to-mouth contact) and/or inhalation is also possible. Consequently, if workers experience an adverse effect, the relative contribution of dermal exposure is unknown. For simplicity, it is assumed in this paper that dermal exposure is the only route of exposure.

Despite the lack of guidance, it is necessary for industry to develop approaches to ASL setting in order to properly protect workers. Within the pharmaceuticals industry, a common practice is to develop ASLs by performing a health-based risk assessment using readily available data and calculate an “occupational acceptable daily exposure” (ADE_{occ}) as follows:

$$ADE_{occ} (\mu\text{g}/\text{day}) = \frac{(\text{NOAEL})(\text{BW})}{(\text{UF}_{1,2,3})(\alpha)} \quad (1)$$

where:

NOAEL = no-observed-adverse-effect level for the critical endpoint of concern (if a NOAEL is not identified, a lowest-observed-adverse-effect level [LOAEL] may be selected instead),

BW = body weight (50 kg for an adult worker),

$\text{UF}_{1,2,3}$ = composite uncertainty factors for considerations such as inter-individual variability, inter-species variability, pharmacokinetic variability, extrapolation from a LOAEL to a NOAEL, severity of adverse effects, sensitive subpopulations, and robustness of the data set, and

α = adjustment factor for bioavailability via the route of administration by which the critical effect was observed.

For APIs, ADE_{occ} may also be derived using a low therapeutic dose, expressed in mg/day or $\mu\text{g}/\text{day}$. Because a pharmacological effect in healthy workers is considered to be adverse, this dose is considered to be a LOAEL.

The ASL is then derived from the ADE_{occ} as follows:

$$\text{ASL} (\mu\text{g}/\text{cm}^2) = \frac{ADE_{occ}(\mu\text{g}/\text{day})}{(\text{SA})(\alpha_d)} \quad (2)$$

where:

SA = surface area of the skin that comes into contact with the API each day, and

α_d = adjustment factor for bioavailability via the dermal route of exposure.

For this approach, it is assumed that the average surface area of each palm is 100 cm^2 , the total area of contact is equivalent on average to two palms (200 cm^2), and, in the absence of data to suggest otherwise, dermal transfer (adherence and absorption) is complete (100%). These assumptions reflect the highly conservative and protective nature of this approach, which is needed given that the process of dermal absorption remains poorly characterized. The area that is typically sampled by the industrial hygienist when monitoring potential surface contamination is 100 cm^2 . However, when the surface does not lend itself to using a $10 \text{ cm} \times 10 \text{ cm}$ template (e.g., sampling a door handle or product vial), the surface area sampled is estimated. ASLs are expressed as mass units per square centimeter in order to account for this variability in sampled surfaces. The sampling results are compared to the ASL for the purpose of allowing workers to use less, or remove, dermal protection.

An alternative approach to the above-described health-based approach in the setting of ASLs for pharmaceuticals is to “align” the ASL with an occupational health categorization (“banding”) system used for

both hazard characterization and exposure control. Each category is determined by toxicological and potency criteria for the intrinsic hazard of an API; the category to which an API is assigned increases relative to the degree of hazard. Categories can also be associated with a range of (inhalation) occupational exposure limit values, within which a value is likely to be calculated for the API and similarly may be linked to ASLs; higher categories correspond to lower exposure limits. As an example, a 4-band categorization system is described as follows:

- category 1 is assigned to APIs of low toxicity and/or potency.
- category 2 is assigned to APIs of low-to-moderate toxicity and/or potency.
- category 3 is assigned to APIs of high toxicity and/or potency.
- category 4 is assigned to APIs of very high toxicity and/or potency.

Although “potency” is a relative term (“potent” APIs are those that exert their effect at “low” dosages), a general rule used in the industry is that an API is considered to be potent if it has a pharmacologically effective or therapeutic dosage of ≤ 10 mg/day. Exposure controls and handling practices are established based on the categorization of an API and the task(s) being performed. (For a more detailed, general discussion of the principles of a banding and handling practice system described above, the reader is referred to Ader et al. [8], Farris et al. [9], and/or Naumann et al. [10].)

According to this approach, which may be described as “performance-based” rather than health-based, ASLs may then be assigned as follows:

- For category 1 and category 2 APIs, surfaces should be sufficiently clean such that there is no visible dustiness (corresponding to an ASL of 1 to 5 $\mu\text{g}/\text{cm}^2$ [11]).
- For category 3 APIs, the ASL is an order of magnitude lower than that for category 1 or 2 APIs (0.1 to 0.5 $\mu\text{g}/\text{cm}^2$).
- For category 4 APIs, the ASL is an order of magnitude lower than that for band 3 APIs (0.01 to 0.05 $\mu\text{g}/\text{cm}^2$).

In addition, up to tenfold adjustments to the ASL for category 2 through category 4 APIs may be made based on special considerations for the API in question and/or the application of professional judgment by a properly trained occupational toxicologist. Category 2 ASLs may be adjusted downward only, whereas category 3 or 4 ASLs may be adjusted upward or downward. Some factors that contribute to the adjustment of ASLs are outlined in Table 1.

As an example, if an API is considered to fall into category 3 with an ASL of 0.1 to 0.5 $\mu\text{g}/\text{cm}^2$ but there are ancillary skin absorption data that generally support the likelihood for significant systemic absorption, then the ASL might be reduced to 0.05 $\mu\text{g}/\text{cm}^2$.

It should be noted that the purpose of the performance-based ASL (PB-ASL) system is to assign ASLs for compounds with limited data or with only a band. It is not intended to be used as a tool for determining the band based on an existing ASL. For instance, if an API is categorized in band 4, it would be assigned a PB-ASL of between 0.01 and 0.05 $\mu\text{g}/\text{cm}^2$, depending on the other variables listed in the table. It should also be noted that other factors such as chemical-to-skin contact, the frequency/duration of the contact event, and interindividual variability are not considered in either the health-based or the performance-based approach because conservative assumptions are made during the derivation (e.g., skin permeability is complete in the absence of quantitative data) and/or appropriate data are unavailable for making scientifically defensible adjustments (e.g., to account for interindividual variability). Mathematical models are

TABLE 1—Some parameters that might be considered when adjusting a performance-based ASL.

Criterion	May increase PB-ASL if...	May decrease PB-ASL if...
Ancillary skin absorption data ^a	Suggest that absorption is poor	Suggest that absorption is good
Molecular weight (MW)	>1000 Dalton ^b	<500 Dalton ^c
Octanol:water partition coefficient (log P_{ow})	Less than +1 or greater than +2 ^b	Between +1 and +2 ^c
Nature of observed toxic or adverse effects	Mild/moderate in severity and/or reversible	Severe and/or irreversible
Banding characteristics	Closer to Band 2 than 4	Closer to Band 4 than 2

^aMay include animal data, human cadaver data, experience with related compounds, predictive modeling, workplace case reports, etc.

^bDermal absorption is less favorable.

^cDermal absorption is more favorable.

available for the prediction of dermal absorption; however, they are highly complex and difficult to incorporate as part of the ASL-setting process [2,3,12–14].

Both the health-based and the performance-based ASL approaches have strengths and limitations. The health-based approach is based on a more comprehensive evaluation of the data; however, it frequently carries a high degree of uncertainty, necessitating the use of very conservative safety factors. The performance-based approach bypasses the above-mentioned conservatism by using “fixed” values based on a hazard category; however, the ASLs are assigned as ranges of values, and professional toxicological judgment is required in order to choose an appropriate limit. To the knowledge of the authors, at present there is no known “complete” approach to setting ASLs within the pharmaceutical industry or within other industries.

Summary

The potential for systemic toxicity following dermal exposure is an important consideration when assessing the hazards of a workplace setting. Active pharmaceutical ingredients have characteristics that, compared to other chemicals, can make it easier for the occupational health professional to perform a risk assessment for dermal exposure. However, the complexity of the dermal absorption process, along with limited regulatory guidance, presents challenges. At the present time, the setting of acceptable surface levels for active pharmaceutical ingredients relies on approaches that are highly conservative and/or only partially health-based. As our overall knowledge increases and reliable/validated tools for predicting or quantifying skin absorption are developed, it is anticipated that these approaches will be modified so as to increase their accuracy, appropriateness, and scientific supportability.

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