An overview of setting occupational exposure limits (OELs) for pharmaceuticals

Setting appropriate occupational exposure limits is an integral component in assuring the health and safety of workers

By Robert H. Ku

INTRODUCTION

Occupational exposure limits (OELs)[1] for the protection of workers have been around at least since 1939 when the National (later changed to American) Conference of Governmental Industrial Hygienists (ACGIH) published its inaugural acceptable workplace exposure limits (now known as threshold limit values, or TLVs). In 1970, the U. S. Occupational Safety and Health Act incorporated by reference the 1968 ACGIH TLVs as enforceable limits. The Occupational Safety and Health Administration (OSHA) refers to these enforceable limits as permissible exposure limits (PELs).

Most TLVs and PELs are for commonly used industrial chemicals where a large number of workers potentially may be exposed. Very few pharmaceuticals fit this description, hence, very few pharmaceuticals are on the ACGIH list of TLVs or the OSHA list of PELs.

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Since adhering to OELs is considered an effective and proven way to protect workers from the deleterious health effects caused by chemicals, many pharmaceutical companies have opted to determine OELs for their drug substances for internal use.

OELs, if appropriately determined and periodically monitored in the workplace air, would offer a first line indication of whether exposures are acceptable or not. The challenge to toxicologists and other health professionals involved in setting OELs is to determine a value that has an adequate margin between a level that produces undesired health effects and one that does not. This is the safety margin. If an OEL is set with an inordinately large safety margin, then valuable resources may be expended unnecessarily in the form of extensive engineering containment equipment or overly protective personal protective equipment. If an OEL is set too high, then employee health may be compromised.

This article provides an overview of how OELs have been determined historically, new approaches that are on the horizon, and approaches that are unique to pharmaceuticals.

APPROACHES TO SETTING OELS

The historical approach used to set OELs was based on human experience in the workplace. If airborne levels of a chemical were causing adverse health effects, then these levels were reduced to a level that did not produce adverse health effects. In the latter half of the 1900s, as laboratory animal testing for the toxicity of chemicals became more common and more epidemiologic studies were done in workplaces, the approach used to set OELs was based on the "no-observed-effect-level/safety factor" (NOEL/SF) approach.[1] In this approach, all of the pertinent animal and human studies are reviewed and the highest dose that did not cause an effect in the most sensitive health end point (the NOEL) is identified.[2] Once a NOEL has been identified, a set of uncertainty (or safety) factors are applied to this value to accommodate limitations in the data and to try to assume that workers are protected.

The number and magnitude of these safety factors depend on the quality of the data. In general, some of these safety factors may include: (1) a factor from 1 to 10 for animal-to-human (interspecies) extrapolation (if the NOEL is based on animal data), (2) a factor from 1 to 10 for human-to-human intraspecies variability in response, (3) a factor from 1 to 10 to consider study duration (a long-term study being more helpful than a short-term study), (4) a factor to consider the persistence of the drug in the body (or elimination half-life), and (5) a factor to accommodate for absorption efficiency by different routes of exposure.[2–4]

If a NOEL is not available, then a lowest-observed-effect-level (LOEL) can be used The LOEL is the lowest level that causes an effect in the most sensitive end point.[3] A safety factor from 1 to 10 may be considered for extrapolating a LOEL to a NOEL. Whether the safety factor is closer to 1 or closer to 10 depends in part on the

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severity of the end point. For example, if the adverse health effect is considered serious (e.g., severe birth defect) then a factor closer to 10 may be more appropriate; if the adverse health effect is considered minor (e.g., decreased body weight) then a factor closer to 1 may be more appropriate.

The NOEL or LOEL is dependent on the number of test subjects used and the doses selected in the studies. The greater the number of test subjects per group, the greater the likelihood of observing an effect. The number of doses used per study is frequently limited, to 3 or 4 dose levels. If the doses are properly chosen, one of the doses will turn out to represent the NOEL, and another, the LOEL. However, the true NOEL or LOEL will probably be somewhere in between these two tested dose levels. If the gap between these two tested dose levels is large, then there could be greater uncertainty as to what the true NOEL or LOEL may be.

An equation that is used to determine an OEL for a chemical can be represented as follows[5]:

$$\text{OEL} = [(\text{NOEL}) \times (\text{human body weight})]/[(\text{safety factor})_n \times (\text{human breathing rate})]$$

NOEL usually is in units of milligram of chemical administered/kilogram of animal body weight/day.

Human body weight typically is assumed to be 70 kiligrams for an adult male.

Safety factors are numeric values for accomodating limitations in the data, as described above.

Breathing rate in workers typically is assumed to be 10 m^3/8-hour workday.

Here is an example of this approach for the synthetic estrogen, ethinyl estradiol. The NOEL in humans has been estimated to be around 3.5 μg/day. (Because it is reported in these units, there is no need to multiply by the human body weight). If one assumes a safety factor of 10 for the human variability in response and a breathing rate 10 m^3/8-hour workday, then the OEL is estimated to be 0.035 $\mu g/m^3$.

LINEARIZED MULTISTAGE (LMS) MODEL FOR CARCINOGENS

When the NOEL/SF approach was introduced, it was applied to all chemicals. This approach assumed that if exposure to a chemical was kept below some level (e.g., a threshold dose), no adverse effects would occur. However, as more information became available on the biologic mechanism of action of carcinogens (vs noncarcinogens), there was a concern that a cancer risk may exist at any level of exposure. In other words, contrary to noncarcinogens, where a threshold dose was believed to exist, there was no dose of a carcinogen that was considered without risk (i.e., no threshold dose). Because testing at very low doses and with a large number of animals was not possible or practicable, mathematical models were developed to try to predict the hypothetical incremental cancer rate at these very low doses. The model that was ultimately adopted by government agencies was the linearized multistage (LMS) model. This model essentially resulted in a linear dose-response relationship at very low doses while accomodating for the observable dose-response relationship at the high doses tested. All that was needed now was for government agencies to decide what the acceptable cancer risk should be. For the protection of public health, the U.S. Environmental Protection Agency has set the acceptable cancer risk at around 1×10^{-5} to 1×10^{-6} (one in one hundred thousand to one in one million) for potential exposure of individuals to chemical carcinogens in the environment. The dose that corresponded to the acceptable cancer risk based on the LMS model became the acceptable exposure limit.

Some researchers found that ACGIHs TLVs for carcinogens (determined by approaches other than the LMS approach) corresponded to approximately a 1×10^{-3} cancer risk using the LMS model.[6] Others have inferred that this cancer risk represented OSHA's acceptable cancer risk policy and believe this is the appropriate cancer risk level to use for workers.[7]

The pharmaceutical industry with some exceptions has not adopted the LMS or any other mathematical model for carcinogenic drugs when setting OELs. It has preferred to continue to use the NOEL/SF approach for all chemicals and simply considered cancer as a severe adverse health effect. Alternatively, some companies have adopted approaches to manage worker exposure by recommending specific personal protective equipment and requiring handling procedures be followed. This approach is based on the job assignment and potential for exposure (e.g., performance-based exposure control levels) in lieu of setting OELs.

BENCHMARK DOSE APPROACH

Recently, a new approach has been proposed for setting acceptable exposure limits called the benchmark dose approach.[8] For noncarcinogens, this approach attempts to identify a dose that corresponds to a measurable response rate (e.g., dose that results in a 10% response rate, or ED_{10}). This designated response rate also has been termed the "point of departure." In essence, the point of departure replaces the NOEL or LOEL. The point of departure is preferred over the NOEL or LOEL in that it represents a dose that corresponds to a specific and measurable response rate.

The benchmark dose approach then requires an estimation of exposure in the most heavily exposed individuals. The ratio of the dose corresponding to the point of departure and exposure estimate in the most heavily exposed individuals becomes an indicator of acceptability and has been termed the margin of exposure (MOE). The larger the MOE, the less likely that an adverse effect will occur. There is still debate over the upper limit of the MOE (e.g., 10, 100, 1000) to be considered acceptable.

One criticism of the LMS model is that all carcinogens are treated the same way. But as more became known about the mechanism of action of carcinogens, it appears that there may be at least two general groups, threshold dose and nonthreshold-dose carcinogens. Under the benchmark dose approach, threshold-dose carcinogens

are treated similarly to non-carcinogens.

For nonthreshold-dose carcinogens, a straight line is drawn from the point of departure to the origin. The acceptable exposure limit is determined for any acceptable response rate (e.g., 1×10^{-6}) below the point of departure. Thus, the benchmark approach attempts to address a major shortcoming of the LMS model, by treating threshold- and non-threshold-carcinogens differently.

APPROACHES SPECIFIC TO PHARMACEUTICALS

Pharmaceuticals are chemicals. However, they differ from most industrial chemicals because there often is a wealth of human data available on pharmaceuticals. In setting OELs for certain pharmaceuticals, some have proposed simply to divide the therapeutic dose by a safety factor. For certain pharmaceuticals that mimic some biologic activity of a chemical produced by the body, some have proposed limiting exposure to a fraction of this endogenous biologic activity. Both of these approaches actually are similar to the NOEL/SF approach described above.

THERAPEUTIC DOSE/SAFETY FACTOR APPROACH

In the therapeutic dose/safety factor approach, the lowest recommended therapeutic dose of the drug is identified. This therapeutic dose then is divided by a safety factor. A safety factor of 100 usually is suggested because it can be thought of as a factor of 10 for adjusting a therapeutic effective dose to a therapeutically noneffective dose (somewhat similar to adjusting a LOEL to a NOEL) and a factor of 10 to accommodate for individual variability in response.

For many drugs, this approach may be reasonable and has produced OELs similar to the traditional NOEL/SF approach described above. This approach cannot be used indiscriminately, however, for several reasons. First, is the drug administered through the respiratory tract, the route to which workers are exposed occupationally and for which an OEL is intended? If not, then one must consider the possible difference in bioavailability. For example, alendronate is a bisphosphonate drug approved for osteoporosis and for other bone diseases. It is administered orally and has a bioavailability of less than 1% orally. If this drug is readily absorbed through the respiratory tract, then the 100-fold safety factor may not be adequately protective. Unfortunately, it is often the case that for drugs that are not intended for administration by the inhalation route, no inhalation bioavailability data may be available. To be conservative (i.e., most health protective), one may assume that the inhalation bioavailability is complete (i.e., 100%). Then, if the oral bioavailability of the drug is 1%, an additional safety factor of 100 may be needed to accommodate for this difference in bioavailability by these two routes. If the oral bioavailability is closer to 100% (or closer to the inhalation bioavailability), then a smaller bioavailability adjustment factor may be considered.

A second issue to note when considering applying the 100-fold safety factor to the lowest recommended therapeutic dose is the intended use of the drug. If a drug is intended to be used in life-threatening diseases where significant toxicities may be considered acceptable, the 100-fold safety factor may not be adequately protective. Less than life-threatening side effects may be acceptable to the patient when trying to save the patient's life, but these same side effects are not acceptable to healthy workers. Clearly, the 100-fold safety factor approach for an anticancer drug where heroic doses may be needed to save the patient offers less protection than for an anticough drug where the effects of the disease are not life-threatening and may merely be a temporary nuisance. Whatever side effects are produced from an anticough medication ought not to cause any side effects more uncomfortable than the cough itself. In the case of anticough medication, the 100-fold safety factor approach may be overly conservative.

Another issue to consider is to determine whether the toxic effects of the drugs are related to its pharmacological mechanism of action. As the saying goes, "The dose makes the poison." What may be therapeutic at a low dose may cause serious toxicity at a high dose. For drugs where the mechanism of toxicity is related to exaggerated pharmacology, then by protecting a worker against the "normal" pharmacologic effects of the drug also will also protect against the "exaggerated" or adverse effects of the drug.

There are other drugs where toxic effects are unrelated to the mechanism of pharmacologic action. For instance, a drug may cause developmental toxicity (i.e., birth defects) or cancer by a mechanism unrelated to its pharmacologic effects. In these cases, using the 100-fold safety factor on the therapeutic dose may still be appropriate, but would need to be used with greater caution. If a promising drug causes birth defects near the therapeutic dose range, then its likelihood of ever reaching the marketplace (and thus manufactured in large quantities) is small. However, teratogenic drugs could make it into the marketplace if the drug is intended for older women (i.e., those past menopause) or for men.

In summary, applying the 100-fold safety factor to the lowest therapeutic dose is simple to do. However, there are a number of issues that must be considered to determine whether this method is appropriate. These include:

1. the difference in bioavailability between the route of drug administration and the inhalation route, the route by which workers are exposed;
2. the intended use of the drug or risk-benefit considerations (i.e., whether it is for serious or life-threatening situations or for less serious diseases); and
3. possible differences in the mechanism of action for the therapeutic effects versus the toxic effects.

Using ethinyl estradiol as an example here, the lowest therapeutic dose is around 20 μg/day. Dividing by the 100-fold safety factor and the breath-

ing rate of 10 m^3/8-hour workday, the estimated OEL is 0.02 $\mu g/m^3$.

INCREMENTAL INCREASE OF ENDOGENOUS BIOLOGICAL ACTIVITY

More and more frequently nowadays, drugs are being developed to replace or mimic the function of a substance naturally produced by the body. If the levels of these naturally occurring substances are decreased, the risk of certain diseases may increase. By supplementing the levels of these naturally occurring substances with an exogenous source, these diseases may be ameliorated or eliminated. This is the basis for hormone replacement therapy (HRT) in postmenopausal women. In these women, the levels of naturally occurring estrogens are reduced subjecting them to an elevated risk of certain types of diseases, e.g., osteoporosis. For individuals who do not have a reduced level of estrogens, additional exposure may be undesired and need to be controlled.

An approach that can be used for determining an OEL for these types of drugs is to limit exposure to a level where exposure contributes a small fraction, like 1%, of one's endogenous biological activity of that substance. For instance, if the daily production rate of 17-beta estradiol in the body is X mg/day, then the acceptable exposure could be set at 1% of that rate, or 0.01X mg/day. If the drug is not identical to the endogenous substance, then the relative potencies of the drug and the endogenous substance also must be determined to be able to limit exposure to a 1% increase in biologic activity. That is, if the limit is set at 1% of the endogenous biologic activity and the drug is 10 times more potent than the endogenous substance, then exposure to the drug must be limited to 0.1% of that of the endogenous substance.

Again, using ethinyl estradiol as an illustration, the production rate of endogenous estrogen, 17-beta estradiol, has been reported in men to be around 70 μg/day. (Using the production rate in men is more protective than using the production rate in women because the production rate in women is higher than the production rate in men.) The relative estrogenic potency of ethinyl estradiol to 17-beta estradiol is around 2. Assuming a 1% incremental increase in biologic activity from ethinyl estradiol is deemed acceptable and using a breathing rate of 10 m^3/8-hour workday, the estimated OEL for ethinyl estradiol is 0.035 $\mu g/m^3$.

SUMMARY

Setting appropriate OELs is an integral component in assuring the health and safety of workers. The approach proposed historically and still most commonly used is the NOEL/SF approach. In this approach, a NOEL for the most sensitive effect is identified and modified by safety factors to accommodate for uncertainties and data gaps. This approach presumes that both carcinogenic and noncarcinogenic effects do not occur if exposure is kept below the NOEL. As some evidence suggested that a finite risk for cancer may exist at any level of exposure to a carcinogen, the LMS model was developed and adopted for carcinogens. This mathematical model predicted the level of carcinogenic risk for any level of exposure. Once an acceptable risk level is specified, the acceptable exposure level could be determined. As further information about the mechanism of action of carcinogens became available, it became apparent that NOELs may indeed exist for some carcinogens. This resulted in the development of the benchmark dose approach. One of the major advantages of the benchmark dose approach is to allow for greater flexibility in the determination of acceptable exposure limits of carcinogens depending on what is known about the mechanism of action. For pharmaceuticals, in addition to the approaches described above, several other approaches have been used to set OELs. For instance, the use of the therapeutic dose and the use of an incremental increase in some level of endogenous biologic activity have been considered as approaches for OEL determination.

In the case where OELs can be estimated by several approaches, one may need to decide the most appropriate approach (i.e., the approach on which the underlying data are most solid) especially if the approaches result in OELs that vary significantly (e.g., by orders of magnitude). For the ethinyl estradiol example, the OEL estimated by the three approaches presented above varied by less than a factor of two. When they vary by such a small amount, the values essentially can be considered to be equivalent.

It should be kept in mind that the determination of an OEL for a pharmaceutical agent or for any other chemical entity is an inexact science. Each approach has its own set of assumptions and limitations. It often comes down to professional judgment as to which approach is preferred and how large the uncertainty factor should be. It is important for anyone who relies on OELs to understand the assumptions used in deriving the OEL. The real test for finding out whether an OEL has been appropriately set comes from actual workplace experience. The responsibility of toxicologists and other health professionals tasked with setting OELs is to estimate a value that is protective of workers yet without being so overly protective that resources are unnecessarily spent.

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