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Methods for Setting Limits for Acute and Chronic Toxic Ambient Air Contaminants

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Over the past 10 years there has been increasing interest in understanding the amount of emissions of nonpriority pollutants to the ambient air and the degree of control needed to achieve acceptable (safe) levels of exposure. These chemicals, which have often been called air toxics, are present as a result of combustion, various fugitive and point source emissions, and mobile sources. In an attempt to understand the airborne concentrations at which some chemicals might pose a health hazard, a number of approaches have been proposed and used. These safe concentrations are often called ambient air limits (AALs). This article presents the ten different methods by which AALs have been or could be calculated. Historically, the vast majority of AALs established by regulatory agencies have been derived from occupational exposure limits, such as the American Conference of Governmental Industrial Hygienists Threshold Limit Values® (TLV®) and the Occupational Safety and Health Administration's Permissible Exposure Limits. The advantages and disadvantages of the various approaches are discussed. About 50 references are cited.

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In the United States, from 1970 to about 1985, only seven chemicals emitted to ambient air were regulated on a national basis.[1] These were known as National Ambient Air Quality Standards (NAAQS). The substances regulated included particulates, nitrogen dioxide, carbon monoxide, sulfur dioxide, ozone, lead, and total hydrocarbons.

Beginning in about 1985, following the episode in Bhopal, there began to be growing public concern that many of the other 600 or so chemicals frequently used in industry might also pose a public health hazard if present in ambient air.[2] These non-NAAQS chemicals became known as air toxics because they weren't typical ambient air contaminants caused by combustion from power plants, yet they clearly possessed some health hazard at sufficiently high concentrations. Over the past decade there has been a major effort at the state level to develop what are now called air toxics programs and to promulgate a number of regulations to control emissions of these chemicals (Table 1). Some of the regulatory initiatives addressed the health risks of episodic events like the immediate release of volatiles from a ruptured tank or from a railroad tank car involved in an accident. More often, the interest was in preventing the ongoing release of toxic (rather than irritant) nicals from point sources, mobile sources, and fugitive ssions. All of these regulatory efforts have been essentially designed to address health concerns resulting from exposure to contaminants other than the original seven that the Environmental Protection Agency (EPA) regulated more than 20 years ago.[3]

Since about 1990 the public has called for additional regulatory action to control the release of fugitive and point source toxic air pollutants. Their concern has been based on a number of arguments. One of the most frequently cited reasons is the claim that there is a higher incidence of lung cancer in urban than in rural areas, and that a large number of contaminants, including carcinogens such as benzene, vinyl chloride, and chloroform have been measured there.[4] Another is that we cannot predict or measure most adverse effects in humans that may be occurring due to ambient air contaminants because their cause cannot be distinguished from other background illnesses. Lastly, it has been claimed that the incidence of childhood asthma has been increasing in recent years and that this could be due to certain ambient air contaminants.

In general, the scientific basis for these concerns has not been compelling. For example, as noted by Calabrese and Kenyan,[5] the attribution of the higher incidence of lung cancer in urban settings to air pollution is controversial given the multifactorial nature of complex diseases such as cancer. Factors such as dietary differences, stress, smoking patterns, indoor air pollutant levels, and other important independent variables that may vary between urban and rural areas make it difficult to establish a casual link. However, in the most widely respected study which has yet been conducted, Doll and Peto[6] estimated that the contribution of all forms of pollution (air, water, and food) to cancer incidence is 2 percent, with a range of 1 to 5 percent. They also indicated that the contribution of air pollution to the observed incidence of lung cancer after correction for smoking is minimal and that it does not account, to a large extent, for differences in observed lung cancer rates between rural and urban areas. Lastly, the concern about childhood asthma is real, but the current data are not conclusive, and if the incidence is greater than in the past, it may well be due to indoor air pollution, food allergies, or other factors. Consequently, the focus on air toxics appears to have been due as much to public concern as to the documented adverse health hazards.

The way state agencies charged with regulating air contaminants evaluate the severity of the ambient air hazard involves four steps. First, they assemble information regarding the amount of chemicals purchased by various users and manufacturers. Second, major users are expected to estimate the likely loss of these chemicals from their facilities to the ambient air using simple measurements or mathematical formulas. Third, models are used to predict the aerial distribution of the con-

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TABLE 3. Various Toxicologic Endpoints Upon Which OELs May Be Based

- Systemic effects
- Irritant effects (eye, nose, throat)
- Odors
- Cancer
- Nuisance
- Neurological effects
- Esthetics (blue skin, yellow eyes)
- Local effects (perforated septum)
- Reproductive/developmental effects

hours of exposure each week. These limits were intended to prevent adverse health effects for an exposure period of 8 hours per day, but it is assumed that at some lower concentration they should not pose a hazard when persons are exposed up to 24 hours per day.[19]

The formula for identifying the AAL is straightforward:

$$AAL = \frac{OEL}{(4.2)(UF_1)(UF_2)} \quad (1)$$

where:

AAL = ambient air limit ($\mu g/m^3$)
OEL = occupational exposure limit ($\mu g/m^3$)
4.2 = adjust for difference in weekly duration of exposure (168 h/40 h)
UF_1 = uncertainty factor to adjust for possible increased susceptibility of some people in the public versus the relatively healthy worker (usually 5 to 10)
UF_2 = uncertainty factor to adjust for small margin of safety inherent in the OEL

Most frequently, UF_1 times UF_2 yields a value of 100, which is applied to the TLV and multiplied by the 4.2 adjustment for duration (e.g., many AALs are based on dividing the OEL by 420). The advantage of this approach is that it is simple and can be used to readily set an AAL for as many as 700 chemicals for which OELs are currently available.

There are at least four disadvantages to this approach. First, the toxicologic rationale for setting the OEL can be one of nine different adverse effects (see Table 3), so any generic approach will inherently have some shortcomings. Second, the scientific basis and the inherent margin of safety within each of the various OELs (including the TLVs) varies significantly from chemical to chemical,[20] in part because they were set at different times over the past 40 years. Third, the severity of the toxic effect to be avoided varies for each OEL, and this should influence the size of the overall UF (Table 3). For example, the size of these modifiers is often small for an eye or respiratory tract irritant (perhaps as small as two or three), whereas each modifier for a chemical like lead would be much greater, depending on the endpoint and quality of data. As noted by Calabrese and Gilbert,[22] these UFs are not independent of one another and therefore some modification from multiplicity is appropriate. Fourth, one has to be relatively thoughtful when attempting to adjust for pharmacokinetic considerations. For example, some chemicals have biologic half-lives as short as 20 minutes, while others have half-lives as long as 7 to 10 years.[9] Calabrese and Kenyan[5] have described these and other disadvantages to using OELs to derive AALs (Table 4).

In spite of the scientific pitfalls associated with using OELs as a starting point in AAL derivation, it remains an attractive option for many agencies for several good reasons. For example, TLVs and their documentation constitute the largest database available on toxic substances in air that has been peer-reviewed by highly qualified professionals representing a number of relevant disciplines. Thus, they are an extremely valuable resource for agencies with limited staff and fiscal resources. As noted by Calabrese and Kenyan,[5] to completely ignore this wealth of data which have been collected, analyzed, and critiqued would be inappropriate. If for no other reason, the existence of a large number of OELs provides a convenient starting point for agencies faced with the need to regulate a large number of chemicals in a relatively short period of time.

One caveat is that there is less than broad support for using TLVs, for example, as the basis for deriving AALs when the critical toxic effect is carcinogenicity. The primary reason is that for regulatory purposes there is usually presumed to be no safe level of exposure to genotoxic carcinogenic chemicals,

TABLE 4. Disadvantages in the Use of OELs for AAL Derivation

1. As typically used by regulatory agencies, it is implicitly assumed that OELs are the equivalent of human NOAELs, when in fact many OELs may be based on human or animal experimental data, industrial experience, or chemical analogy based on similar structure. The degree to which the type and quality of data are factored into the limit is inherently variable (thereby implying a variable margin of safety) since the final TLV, for example, is based on consensus judgment by the Chemical Agents TLV Committee.
2. OELs are intended to prevent or minimize a given effect in workers who are generally healthy individuals between the ages of 18 and 65. However, the health effect of major concern in workers may not be the same as that for the general population, which contains high risk subpopulations (e.g., individuals who are very old or young or those with preexisting disease states, particularly respiratory disease).
3. OELs are set assuming a zero-exposure 16 hr recovery period (i.e., a time period during which there is no exposure). While it is possible that correction factors (e.g., 4.2, 10, or 100) may correct for this in the case of certain cumulative effects, it may be overly conservative for noncumulative threshold activity agents such as primary irritants. In addition, recovery times allowed by different OELs vary (e.g., TLVs allow 16 hours between workdays and 64 hours on weekends, and NIOSH RELs allow 14 hours between workdays and 68 hours on weekends).
4. It is difficult when using TLVs or other OELs to account for the influence of factors such as multiple sources of exposure and exposure to multiple agents, which may be important considerations in setting a final limit.
5. Use of some OELs, like the PELs, does not give the regulatory agency the flexibility to change AALs to reflect new data until the PEL is changed, and substances for which PELs have not been set cannot be dealt with.

Source: This table was assembled from material in References 13 and 18, and was presented in Reference 5.

BLE 6. Rules of Thumb for Adjusting OELs to Derive AALs for Those Who Are Continuously Exposed to an Air Contaminant

1. Where the goal of the OELs is to minimize the likelihood of a systemic effect, the concentration of the toxicant to which persons can be exposed 24 hours/day, if it has a half-life between 4 and 400 hours. A conservative approach is to set the AAL at 1/100 the OEL.
2. Exposure limits whose goal is to avoid excessive irritation or odor will, in general, not require much modification to protect people exposed 24 hours/day.
3. Adjustments to TLVs or PELs to set AALs are usually modest (under 20) if the biological half-life of the toxicant is less than 3 hours or greater than 400 hours.
4. The biologic half-life of a chemical in humans can often be estimated by extrapolation from animal data.

Source: Modified from a table presented in Paustenbach.[9]

problem in setting an OEL, but when one extrapolates them to predict acceptable levels of exposure for people in the community, this issue needs to be considered. For example, a chemical with a biologic half-life of 3 to 6 hours will only cumulate modest quantities of the chemical in the person between Monday and Friday afternoon for typical occupational exposures of 8 hours per day. By the following Monday (after a weekend of nonexposure) the body and blood levels will return to background.[9] On the other hand, a chemical that has a biologic half-life greater than 14 hours will produce increasing body burdens of the chemical each day of the week and will not return to background blood levels by the following Monday. This tendency for certain chemicals to cumulate and reach a higher steady-state blood or whole-body concentration following continuous exposure needs to be considered when setting an AAL.

An approach to account for the pharmacokinetics of a chemical with respect to modifying OELs was first discussed by Mason and Dershin.[29] Its importance was recognized in the 1960s and 1970s when workers in the pharmaceutical and petroleum industries began to extend the workday to 12 hours and the workweek to 4 or 5 days per week.[9,30,31] Due to the questions raised about whether and how to adjust standard OELs (intended for 8-hour workdays) to protect persons who would be exposed 12 hours per day, a series of articles was published which explained how such adjustments should be conducted using pharmacokinetic principles. Much of this work was conducted primarily by Dr. John Hickey.[19] The guidance offered is applicable to setting AALs based on OELs.

The basis of all of the pharmacokinetic approaches is to determine a special exposure limit for people exposed during extraordinarily long work shifts (or continuously), which will prevent peak tissue or body burdens from being greater than those observed during standard work shifts. This special limit is expressed as a decimal adjustment factor which, when multiplied by the appropriate exposure limit, would yield the modified limit. It was worthwhile to note that researchers in this area did not assert that currently prescribed or recommended occupational health limits are safe, but only that the special limit that can be predicted from models should yield equal protection during a special exposure situation! As noted by Hickey,[19] this approach to adjusting OELs for people who work more than 8 hours per day can also be applied to protect those who are continuously exposed, such as in the ambient environment.

The general formula for adjusting OELs is as follows:

$$AAL = (Fp)OEL \tag{3}$$

where:

Fp = pharmacokinetic reduction factor
OEL = occupational exposure limit

The following general equation for regular repetitive schedules can be used to estimate an Fp for continuous exposure:

$$Fp = \frac{[1 - e^{-kt_{1n}}][1 - e^{-k(t_{1n}+t_{2n})n}][1 - e^{-kT_s}][1 - e^{-k(t_{1s}+t_{2s})}]}{[1 - e^{-kt_{1s}}][1 - e^{-k(t_{1s}+t_{2s})m}][1 - e^{-kT_n}][1 - e^{-k(t_{1n}+t_{2n})}]} \tag{4}$$

where:

Fp = TLV or PEL reduction factor
k = rate content for uptake and excretion rate of the substance in the body (e.g., $k = \ln 2/t_{1/2}$)
t_{1n} = length of normal daily work shift (8 hours)
t_{2n} = length of normal daily nonexposure periods (16 hours)
$t_{1n} + t_{2n}$ = length of normal day (24 hours)
T_n = length of normal week (168 hours)
n = number of workdays per normal week (5)
t_{1s} = length of special daily work shift (hours)
t_{2s} = length of special nonexposure periods between shifts (hours)
$t_{1s} + t_{2s}$ = length of basic work cycle, analogous to the day (hours)
T_s = length of periodic work cycle, analogous to the day (hours)
m = number of work days per work week in the special schedule

The above formula can be used to predict the permissible level and duration of exposure necessary to avoid exceeding the normal peak body burden during other exposure scenarios, including environmental exposure:

$$Fp = \frac{(1 - e^{-8k})(1 - e^{-120k})}{(1 - e^{-hk})(1 - e^{-dhk})} \tag{5}$$

where:

h = hours per day exposed
d = days per week exposed

Some rules of thumb for when and how to adjust OELs are presented in Table 6.

When attempting to set limits for continuous exposure, such as for ambient air contaminants, one must use the general equation (Equation 4). As noted by Hickey and Reist,[19] the one-compartment model, which is usually acceptable for adjusting OELs, predicts that no adjustment (except for the total

their correlation with toxicity further complicates selection of an appropriate NOAEL. For example, is liver enzyme induction a toxic effect?

3. It is difficult to precisely incorporate factors which account for the differential quality of various studies (e.g., experimental design).

It should be noted that the EPA, in recent years, has established various working groups to address these issues.

Method V: Fixed Generic Approach Using Animal Data

Another approach based on animal data is to simply divide any NOEL by a factor of 70 to derive preliminary AALs. The rationale is that 1.75 is an appropriate body weight scaling factor for animals to humans (if the TLV is based on animal data), the duration is 4.2-fold longer, and a factor of 10 should account for differences in susceptibility between people in the public versus those at work.

$$AAL = \frac{\text{animal NOEL}}{(42.)(1.75)(10)} = \frac{\text{animal NOEL}}{70} \quad (8)$$

where:

NOEL = no observed effect level in animals
4.2 = adjust for difference in weekly duration (168 h/40 h)
1.75 = body weight scaling difference
10 = adjustment for differences in susceptibility between humans

This method was first proposed in 1977 and is one way to quickly identify preliminary AALs. For the reasons discussed previously, its simplicity has the same shortcomings as method I.

Method VI: Extrapolating from the ADI or Reference Dose (for Noncarcinogens)

The reference dose (RfD) is defined by the EPA as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." The RfD supplants the earlier concept of the ADI, although it is derived operationally in much the same manner (i.e., division of a NOEL or other appropriate response by a series of independent multiplicative UFs).[5,12] However, the methodology for the development of RfDs is more rigorously defined and applied within the EPA, particularly with respect to dosimetry issues, than was the ADI. The inhalation RfD, which is called a reference concentration in air (RfC), is used for those situations where there is continuous lifetime exposure to an ambient air contaminant. A feature of the RfC is the refined dosimetric adjustments which are used to convert an animal inhalation NOAEL or LOAEL to an appropriate human equivalent concentration. This approach has been discussed in several articles, including those by Weil,[34] Dourson and Stara,[27] Dourson *et al.*,[32] and others.

Using this method, an AAL can be derived by selecting an appropriate ADI or EPA RfD or an EPA RfC and adding conversion factors. In short, the dose units need to be converted (if necessary) to an airborne concentration.

$$AAL = \frac{(RfD)(BW)}{IR} \quad (9)$$

where:

RfD = EPA reference dose (μg/kg-day)
BW = body weight (kg) for humans
IR = inhalation rate (m^3/day)

Example:
To estimate an AAL for chloroform based on the EPA's RfD, the following approach could be used:

Given:

RfD = 10 g/kg-day (based on a 90-day study in rats)
BW = 70 kg
adverse effect = liver toxicity
IR = 20 m^3/day

$$AAL = \frac{(RfD)(BW)}{IR}$$

$$AAL = \frac{(10\ \mu g/kg\text{-}day)(70\ kg)}{20\ m^3/day}$$

Therefore:

$$AAL = 35\ \mu g/m^3$$

Method VII: Physiologically Based Pharmacokinetic Method

In the early 1980s, physiologically based pharmacokinetic (PB-PK) models were available for perhaps six chemicals. By 1995 PB-PK models for more than 40 chemicals had been developed and validated.[35,36] Basically, the method involves describing the absorption, metabolism, and excretion of an agent in an animal using differential equations, and then using these, plus scale-up techniques, to predict the human response. If the computer model properly predicts the animal's treatment of the chemical, then one tests the model's applicability to humans by scaling up the physiologic parameters and then checking the model prediction versus data collected in humans. If the human response is accurately predicted from the scaled-up animal data, then the model is considered valid.[37,38]

A PB-PK model can be used to identify the adjustment factor needed for an unusual exposure schedule (such as 24 hours per day). The benefit of this approach is that it is considered the most precise and accurate way to scale up animal data to predict the likely human response. These models require data on the blood–air and tissue–blood partition coefficients, the rate of metabolism of the chemical, organ volumes, organ blood flows, and ventilation rates in humans. Andersen *et al.*[39] have illustrated how to use this approach to protect workers exposed to styrene and methylene chloride for extraordinarily long exposure schedules. This methodology can be altered to address continuous exposure to chemicals in the ambient air. The authors noted that pharmacokinetic approaches alone should not be relied on for exposure periods greater than 16 hours/day or less than 4 hours/day because the mechanisms of toxicity for some chemicals may vary for very short or very long-term exposure. However, with proper understanding of the toxicology of the chemical and the ap-

n:

$$RsD = 1.0\ \mu g/kg\text{-}day\ (10^{-5}\ risk)$$
$$BW = 70\ kg$$
$$IR = 20\ m^3/day$$

$$AAL = \frac{(1.0\ \mu g/kg\text{-}day)(70\ kg)}{20\ m^3/day}$$

$$AAL = 3.5\ \mu g/m^3$$

One perceived problem with this approach is that it can yield AALs so low as to be either impossible to measure or too low to reasonably achieve.[47] In addition, sometimes the values are below concentrations already present in the ambient air (e.g., background). For example, in many urban areas, background ambient air concentrations of benzene exceed these concentrations.[48] In an effort to set more achievable standards, and because they perceive the models to be conservative (overpredicting risk), some states have adopted a risk criterion of 10^{-4} or 10^{-5}, rather than the more widely cited 10^{-6} value.

Method IX: Monte Carlo of Several Approaches

An approach that is receiving consideration in setting AALs is the use of Monte Carlo techniques to identify a best estimate of the CPF for carcinogens and the RfD for noncarcinogens. In this approach, one places a weight on each plausible toxicity value. These values are then placed in a probability density function (PDF) such as a square distribution or other relevant distribution. This is then combined with distributions for the other exposure parameters to yield a family of values.[49,50] Monte Carlo techniques have been applied to the exposure assessment phase of risk assessment for several years,[50] but only to the dose–response assessment for a few chemicals.[51]

There is a cost, however, to incorporating all relevant scientific information into decision making to capture the current state of knowledge in the expert community, since the distributional method requires more time and resources to perform than does a standard potency assessment. For example, the tasks of developing probability trees, probability training, and eliciting judgmental probabilities from the experts are not elements of a standard potency assessment. Consistent with recent recommendations (e.g., Reference 52), one can envision the distributional approach used in those cases where the stakes are high and screening or default risk assessments are judged to be inordinately imprecise.[53,54]

A strength of the distributional method is the assessor's ability to incorporate new mechanistic data while taking into account technical reservations about the quality, relevance, and uncertainty of such information. As long as several expert scientists are consulted, this method allows risk managers to see how differences in scientific judgment translate into different quantitative risk estimates.

As has been discussed in the literature, when one relies upon the EPA CPF, only a single point estimate of cancer risk is presented along with a qualitative statement about the uncertainty in the estimate (including the fact that there could be no risk at all). This limited description fails to convey a large amount about what is known about a chemical. It is also now widely recognized that point estimates convey a false degree of precision about risk to the risk manager, and narrative statements of uncertainty are rarely considered by risk managers, journalists, or the public. Some have suggested that risk managers be presented with multiple risk estimates based on different assumptions and data. However, it is unclear how a risk manager would know how to use this information. Probability distributions, on the other hand, have the benefit of conveying both the range of possible risk values and the relative likelihood that each is correct. Even though a single summary statistic can be reported from the probability distributions, there is no strong technical rationale for reporting one summary statistic as opposed to another. It can be expected that more experience with the distributional method, including collaboration with risk managers on how to interpret and use the results, will help put these quantitative characterizations of uncertainty into their proper perspective in the years ahead.

Method X: Monte Carlo of Expert Opinions

This last approach is a variation of the Monte Carlo method. It involves relying upon expert panels to identify the most scientifically valid CPF, RfD, or RfC. Specifically, one identifies a chemical that deserves attention, and all reasonable approaches to extrapolating the dose–response relationship are evaluated.[53,54] Then the carcinogenic risk posed by a specific dose is characterized by a probabilistic distribution, where each expert offers his estimate of the relative likelihood of different risk estimates. The approach utilizes expert judgment and a probability tree.

The use of the methodology has been illustrated in a case study of chloroform exposure.[54] In this example, experts in cancer biology/toxicology, pharmacokinetics, and dose–response modeling were identified by a panel of science policy specialists. These experts were then convened and each expert quantitatively rated the probability that a given approach was likely to be accurate, considering biological and epidemiology data. All expert views were consolidated and a weighing of opinions regarding the best response curve was provided using a PDF. Distributions of carcinogenic risk were developed based on the probability tree, chloroform data, judgmental probability proved by the experts, and classical statistical techniques. Another benefit of this approach is that issues of scientific disagreement leading to different risk distributions between experts are discussed in an open forum.

Discussion

As shown, there are quite a number of approaches that can be used to identify an AAL for the more than 500 so-called toxic ambient air contaminants. All of the approaches should yield results that are health protective if adequate professional judgment is incorporated into the process. The primary difference between the various methods is the amount of information that is considered in the assessment. Generally, it is expected that the more complex approaches, such as incorporating expert opinion into a PDF and PB-PK model estimates, will yield results that are more precise than those which simply apply a series of UFs to a specific value.

One issue that is not addressed in this article is society's ever-changing expectations about the degree of risk that is considered acceptable. This issue is particularly relevant and timely with respect to occupational standards. For example, in recent years it has been recognized that the theoretical in-

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