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Modeling framework for human exposure assessment

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We are at the dawn of a new era of quantitative consumer exposure and risk assessment of chemicals driven by regulatory mandates. This remarkable development also signals the beginning of a dramatic resurgence in the need for and development of human exposure models. This paper presents some of the philosophical background underlying exposure modeling in the context of human health risk assessment. The basic types of and structure of inhalation exposure models are discussed, as well as the research needed to move us forward into this exciting new period of development.
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Background and introduction

Exposure modeling represents the essence of the science of exposure assessment and should be considered the primary stock-in-trade of the active professionals within this field. The prime function of human exposure assessment is to evaluate scientifically the potential risk of chemical exposure to the health of people. The human exposure modeling framework has the following features:

- Human Health Risk is driven equally by the actual exposure experience and the health effects per unit exposure for any particular agent or mixture.
- Historically, the essence of the human health risk assessment process in most settings is simply the comparison of estimated human exposure to an exposure limit(s).
- When faced with scientific uncertainty a precautionary approach is typically applied, which advises practitioners to err on the side of safety and thus overestimate risk or obtain more information to lower the uncertainty.
- Risk is thus estimated (typically overestimated) versus the true risk, and the true risk is never known.
- Risk assessment is typically a tiered or iterative approach starting with relatively inexpensive evaluations that generally overestimate, and proceeding to more expensive but more accurate analytical tools.

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It should be reasonably obvious from the above that exposure assessors measure or otherwise estimate human exposure, and this exposure has no contextual meaning without a valid toxicological benchmark (e.g., an exposure limit) with which to compare it. Thus, whenever term ''exposure assessment'' is used in this paper it should be understood that this evaluation always occurs within this exposure, exposure limit and risk framework. Also, it should be noted that these toxicological benchmarks are critical to the determination or estimation of risk. They are not the subject of this paper but are mentioned here to remind the reader of their critical role in the overall process.

Reason or need — why do exposure modeling?

If one is committed to conducting a comprehensive and scientifically valid and rational evaluation of human exposure to substances, (then) modeling is an indispensable element of that assessment. It can be argued, however, that this level of comprehensive assessment of human exposure to chemicals has not occurred and that the vast majority of exposures have not been systematically and proactively addressed (USEPA, 2006). Indeed, it is reasonably well established that the risks of most types of personal chemical exposures to consumers in modern society are not assessed at this point. These are the exposures that result predominately from residential sources. Today, we are on the cusp of a change in which regulatory mandates playing out in the world that are driving the overall scientific development of human health exposure assessment for the multitude of common and relatively unstudied substances to which humans are exposed. Given this

commitment to assessment, model utilization and development should come to the forefront.

Exposure models are critical to any commitment for comprehensive exposure assessment because we will never be able to monitor or measure every exposure everywhere. The need for models increases proportionally with the growing universe of chemicals under consideration. Also, as a technical expert, an exposure assessor has a critical need for objective and rational scientific tools for analysis. This need requires ongoing scientific development of the discipline. In situations where he or she does or decides not to do specific measures or other direct evaluations of exposure, models can provide the explicit rationale(s) for why he or she arrived at any particular conclusion and took whatever actions that he or she did. Exposure assessors can also use the modeling constructs to posit testable hypotheses to enhance our basic understanding or ability to estimate real exposures.

Consider an example in Occupational Hygiene as an important subset of exposure assessment; within a typical large modern manufacturing plant in which there are hundreds of workers performing perhaps thousands of tasks. It is probably safe to say that under the current operating system the exposure associated with a majority of tasks are never monitored because the occupational hygienist judges them to be safe (Mulhausen, 2005, 2006). In the current situation he or she is not required to present a formalized or systematic analysis in support of these decisions. That is, he or she has observed the universe of situation and has, for the most part and probably correctly, concluded that the exposure limit is not exceeded. When asked how that determination was arrived at, the typical answer is that he or she applied expert judgment. That is, the occupational hygienist uses his or her combined experience to make this decision. When pressed further, the hygienist might say that it is because the system or scenario under consideration is relatively closed, that the vapor pressure is low; the exposure limit is relatively high, etc. This combination of factors tell an experienced occupational hygienist that overexposure will not occur. Some threshold must exist for these skilled estimators where conditions are such that predicted concentrations and exposures approach or exceed the exposure limit. At this point, the occupational hygienist typically moves to action and monitors the scenario in question. The results of that monitoring determine whether controls are implemented.

Reactive, reflective and relatively undefined expert judgment as described above is the way much of exposure assessment in general and occupational hygiene in particular have been practiced in the past. Within the occupational hygiene world this manner and technique of working has done much good to workers and protected them from overexposure and subsequent adverse health effects; however, it has a number of serious flaws: (1) it is difficult or impossible to explain objectively; (2) it is typically not supported by explicit quantified facts relating specific cause and effect and (3) as such it is not amenable to technology transfer (i.e., those who are new to the field find it hard to learn); and finally (4) it may not be useful or sufficient in the defense against litigation or other legal challenges.

The same general situation currently exists and is even more undefined and uncertain for human exposure to consumer products that here-to-fore were essentially unexamined or simply assumed to be ''safe''. Indeed, under the previous somewhat casual scheme, concerted exposure assessments in either the occupational or consumer areas were typically done only when one of the following circumstances occurred:

- An untoward health effect had already occurred that might be attributed to the specific exposure (e.g., formaldehyde from foam insulation).

or

- New toxicology indicated that the substance (or structurally analogous materials) to which persons are exposed has new and potentially dreaded adverse health effects (e.g., phthalates).

In most cases, an obvious danger associated with a consumer exposure needed to ''present itself'' after the fact before any focused evaluation was enacted.

Thus, until recently there has been little need for model development to address a dramatically large universe of exposure possibilities. Specifically, the new and substantially increased call for modeling has been tied to the need for conducting explicit and pro-active exposure assessment which in turn is being driven by pending regulations in the European Union.

The scientific method and models

Simply stated, models are the business of science. This becomes obvious when one considers the basic elements of the scientific method:

1. State the problem or premise
2. Form a hypothesis
3. Experiment and observe
4. Interpret the data
5. Draw conclusions and make predictions (form new hypotheses or go back to 2)

In exposure assessment the hypothesis is the ''model'' or our technical portrayal of what we think is happening in the world relative to cause and effect. Consider again the example considered above in the world of occupational hygiene. In many (indeed most) instances, the hypothesis is formed (for any number of reasons) that an exposure to an agent in a particular situation or job is not above the occupational exposure limit. To test that hypothesis, the occupational hygienist observes the workers and then may

conduct the experiments (i.e., physically measures or monitors their exposures). These monitoring results provide objective experimental evidence to accept or reject the hypothesis and to draw conclusions about the potential consequences of this exposure. Perhaps more important, this process feeds the hygienist's internal database (i.e., it increases experience) and makes predictions possible about similar situations in the future. That is, it builds the ability to apply expert judgment.

The point of learning here is that there was clearly some model in mind when the hypothesis was formed. There was a mathematical relationship or an algorithm that hypothesized, ''given the characteristics of all the causes of exposure in this situation, the resulting exposure will be less than the exposure limit.'' As mentioned above, much more often than not the hygienist is so sure of the hypothesis (the model) that he or she does not do the ''experiment''; that is, he or she does not physically measure the exposure. If this important discretionary decision was not made, then everything everywhere would have to be monitored, which, of course, is not possible. Because every exposure possibility cannot be monitored, the occupational hygienist must choose where to spend resources.

Sometimes monitoring proves the hypothesis wrong. This unpleasant reality has probably happened to most people who have been in the field for some time. However, those who do not learn from their mistakes are doomed to repeat them. Thus, at the point when the model or hypothesis is proven wrong, it needs to be readjusted and refined. Note, however, that even a false hypothesis will never be proven wrong in the vast majority of exposure scenarios where monitoring is not conducted.

Some choose to call this typical hypothesis forming process of the occupational hygienist ''qualitative exposure assessment,'' when in fact it involves the comparison of a quantitative estimate of the exposure (however unconsciously formulated) with a numerical exposure limit. The point here is that there is a quantitative model present and operating, if only subconsciously, and occupational hygienists need to have a more conscious understanding and explanation of the technical details of the decision-making process. Specifically, a formal model needs to be defined and forwarded. This conscious treatment and identification will help identify and fix a broken or defective model, and it will also allow for a rational explanation as to how occupational hygienists operate professionally. Rather than simply invoking a claim of unsubstantiated professional judgment relative to their decisions, the use of explicit models enables the occupational hygienist to understand and display the scientific rationale behind those decisions.

As mentioned above, the same basic lack of rational and positive science-based examination also currently exists in the realm of consumer exposure assessment. In both situations, there is a general but somewhat undefined responsibility to ensure the relative safety of workers and consumers. However, as previously indicated, regulatory mandates are requiring changes in these safety practices. These changes requiring a proactive approach should force paradigm development, which will dramatically impact the entire science and practice of human exposure assessment. Given this commitment to explicit exposure assessment the need to use and develop exposure models will become increasingly critical.

Human exposures can be understood only to the extent that the physical world and the entities within it that cause exposures (i.e., the independent or predictor variables) are identified and defined. Even given a rich database of monitored airborne concentrations (i.e., dependent variable data), one must relate these quantitative outcomes to the determinants (i.e., predictors or drivers) within the environment that produced those exposures. The conceptualization of these relationships is necessary both to assure the continued validity of the predicted exposures for this and similar scenarios in the future and to facilitate accurate forecasts or at least hypothesis formation for different scenarios.

Thus, the construction and use of exposure models is relatively straightforward science. In the context of modeling human exposure this effort can be thought of as investigating and seeking to understand the determinants of contaminant source contact, generation and control. As the critical variables governing exposure are discerned, the tools are formed that will build experience, knowledge bases, and confidence to simulate scenarios that will predict actual concentrations and exposures in the real world. Model development consists of formulating hypotheses about the predictors of exposure and then testing them with data from experiments examining cause and effect. As such, it is the scientific method.

As understanding of why and how models are developed grows, it also becomes clear that the models represent a principal structural basis for the science of exposure assessment. These models, along with the statistical modeling of monitoring data, form the scientific foundation for characterizing human exposure.

Models are not perfect, but they present an evergreen possibility at any stage in their development of refining our understanding and knowledge. Also, physical–chemical exposure models are not limited to predicting present exposures. They can be used to estimate historical exposures that cannot be re-created easily and, of course, as mentioned above, possible future exposures in hypothetical situations or scenarios. By employing a model, an exposure assessor's insight about possible exposures is enhanced, even if the model is not perfectly accurate. A noted and wise statistician, GWE Box, has been credited with the profound observation that ''all models are wrong, but some are useful.''

What Dr. Box knew and the rest of us should keep in mind is that all scientific models, including exposure models, are more or less generalized (and therefore crude) representations

of reality. Even remarkably elegant and presumably complete and correct basic scientific models such as those devised by Sir Isaac Newton to describe the laws of motion are wrong under certain conditions as described by Einstein. Thus, predictions from exposure models can be extremely valuable; however, at this point these models are far from being considered elegant or complete. As such, they need be interpreted with caution and the usual judgment and intelligence that a competent exposure assessor brings to his or her craft.

Almost all of the discussion of exposure modeling within this paper is centered on inhalation. It should be noted that physical–chemical models of dermal exposure and models of ingestion exposure are also available as valuable tools. They are simply not covered in any detail in the interest of available space.

Elements of concentration exposure models (assumptions, tiered approach, model hierarchy)

Assumptions in Concentration Exposure Modeling

Most exposure models do not estimate human exposure directly. For example, in the area of inhalation exposure, models estimate the concentration of toxicant in the air and assume that the person is breathing air with this concentration. The use of this and other assumptions is important and necessary in exposure assessment. It has been said of many activities that ''the devil is in the details.'' It could also be said of exposure assessment that ''the devil is in the assumptions.'' In order for those who view the output of these tools to understand it, they need to be able to review the assumptions of the assessor. Indeed, it is vital to the integrity of the process to sort out and identify each and every assumption used in the modeling and estimation of exposure.

Tiered Approach to Exposure Modeling

It is typical to start with relatively simple models that have overestimating assumptions because these models require relatively little in the way of resources and thus are simple and quick to run. The downside is that these simple models can dramatically overestimate the exposure potential of the scenario under investigation. As such, depending on the conclusions of the predicted level of exposure compared to the exposure limit (i.e., the exposure/exposure limit ratio), it may be necessary to use more sophisticated modeling tools. These more complicated models cost more time, effort and money but they render answers that if properly applied are less overestimating.

During the typically tiered approach to exposure assessment discussed in detail below, it is not unusual to run out of modeling resources before gaining a definitive answer, and in this case either a better model needs to be developed or representative air monitoring is performed. Unfortunately, for the general development of exposure models the second solution (monitoring) has historically been chosen almost invariably because it is relatively inexpensive and answers the question at hand expeditiously. Thus, even though exposure models are most cost effective in the long run, they have not been reasonably evaluated or developed to provide more precisely accurate portrayals of reality. Instead, they exist today in many areas as somewhat underdeveloped (albeit still useful) tools for the over-estimation of contact concentrations and exposure. It is the authors' belief and assertion that the true promise of exposure assessment as a science will not be realized until resources are allocated to appropriately evaluate and develop these models in a standard development cycle.

Hierarchy of Modeling Estimation Techniques (Toluene Inhalation Example)

Below is a consolidated discussion and presentation of inhalation exposure modeling techniques. It is provided to introduce these tools, show their operational elements and demonstrate the general progression from simple to sophisticated techniques.

For purposes of exposition a case study of the inhalation exposure potential to toluene from an aqueous solution containing 1 ppm (1 weight part per million weight parts, or w/w) of toluene will be considered. Most of the details of this analysis are left out, and the reader is encouraged to go to a detailed development of the various models and inputs used in this case presented elsewhere (Jayjock, 2003). In this example the models are shown in order of increasing sophistication and level of information needed to use them appropriately and successfully. Thus, the first model one might think of using is the simple saturation model, followed by the box and dispersion models. More sophistication is brought into the investigation only if the overestimation cannot be tolerated in the subsequent evaluation of the risk.

Given minimal information about the use scenario and physical properties of a material, one can estimate the saturation concentration as an estimation of worst case airborne exposure to vapors in a Tier 1 analysis.

Tier 1: Saturation or Zeroventilation Model

This very basic and typically very conservative inhalation exposure model calculates the maximum possible concentration of vapor (i.e., saturation) in air. It is best used for gases and vapors emitted without mist formation with no information on ventilation or details of use. For any liquid, saturation will eventually occur in the air above a liquid surface if no ventilation is present and the evaporation rate ultimately overwhelms any removal mechanism such as absorption, adsorption or chemical transformation.

The equilibrium saturation concentration (C_{sat}) in volume parts of contaminant per million volume parts of air (ppm,

v/v) will be

$$C_{sat} = \frac{(10^6)\,(\text{vapor pressure})}{(\text{atmospheric pressure})} \quad (1)$$

Units: Vapor pressure and atmospheric pressure can be in any units (mm Hg, atmospheres, Pascals, etc.) as long as both are expressed in the same units.

Vapor pressure at any ambient temperature is an experimentally determined quantity; however, it can also be estimated for any class of liquids from boiling point data either at atmospheric pressure or under vacuum (Haas and Newton, 1978) The vapor pressure of components within mixtures can also be estimated using established procedures (Lyman et al., 1982) such as Henry's law constant (ratio of vapor to solution concentration) or Raoult's law (portion of a substance's pure vapor pressure in the headspace is the same as is mole fraction in solution).

This saturation model is usually conservative for the prediction of workroom air concentrations. It has been our experience that it overestimates workroom air concentrations of vapor (i.e., non-particulate) in all but the worst-case scenarios (e.g., large spills indoors with poor ventilation) by a factor ranging over four orders of magnitude (10 to 10,000-fold). This observation is the result of comparing scores of measured concentrations of organic air contaminants in occupational settings with their saturation concentrations calculated from vapor pressure or boiling point data. Worst-case scenarios include those in which significant aerosol is released or there is a relatively large area (greater than a few square meters) of evaporating liquid. In these situations the saturation model is often not very overestimating.

This model's value lies in its simplicity as a screen with only a few basic physicochemical properties required as input. As a typically very conservative estimate, it represents a good "first step" in a tiered exposure assessment. If exposure levels determined by the model are below the compound's ascribed toxic exposure level (e.g., an occupational exposure limit or OEL), a high degree of confidence exists that actual vapor concentrations do not pose an unacceptable risk to worker health via inhalation exposure. Of course, other routes of potential exposure (e.g., dermal or oral) and aerosol generation are not considered in this method.

A reasonable worst-case estimate provided by this model in our example is 61 ppm (v/v) toluene. This value came from estimating the headspace concentration of toluene above an aqueous solution containing 1 ppm (1 weight part per million weight parts, or w/w) of this compound using Henry's law constant. This concentration (61 ppm) is above the American Conference of Governmental Industrial Hygienists (ACGIH) Exposure Limit of 50 ppm (v/v) as an 8 h time-weighted concentration.

Tier 2: General Ventilation Model

One of the oldest and most used models in inhalation exposure modeling is the "box" or general ventilation model. It relies on the simple concept of the conservation of mass. Imagine a box of air, any box of air. Now imagine it is a black box; that is, you cannot go into it and you cannot look into it. Now consider that as you begin to put an airborne contaminant into the box you will constantly measure any contaminant that subsequently comes out. The average concentration in the box can be described as

$$\text{Concentration} = \frac{(\text{amount going into the box}) - (\text{amount coming out of the box})}{\text{volume of the box}} \quad (2)$$

Units: Concentration (mass/volume)
Amounts going into and out or the box (mass)

If the contaminant is going into the box at a steady rate and leaving with the outgoing air at the same rate, then we know that the system is at "steady state" and that the average concentration in the box is constant. This is actually a relatively simple and very useful mathematical relationship given by Eq. (3) below.

If we are to believe that the concentration in the box is the same or homogeneous throughout the volume of the box then we need to make the assumptions that the contaminant:

- remains airborne (does not absorb onto surfaces) air
- does not change chemically within the box and
- upon entering the box is instantly and completely mixed with the air in the box.

This is the so-called well-mixed box construct.

Using this simple steady-state model and assumptions a general ventilation equation for this situation is

$$C_{eq} = G/Q \quad (3)$$

Where C_{eq} is the steady-state concentration (mg/m^3), G is the rate going into the box (mg/h) and Q is the ventilation rate of air leaving the box (m^3/h).

Of course, the real world is often much more complicated. The mixing of airborne contaminants is often not at equilibrium nor is it complete and instantaneous. Also, some substances of interest are removed by non-ventilatory mechanisms such as adsorption or chemical reaction. Also, the nonsteady-state situation is significantly more complicated to describe mathematically. A differential equation that attempts to take all of these factors into account can be written for the pollutant concentration within the box for any time (Tichenor et al., 1991):

$$V\,dC = G\,dt - (C)\,(Q)\,(m)\,dt - (C)\,(k)\,dt \quad (4)$$

In Eq. (4), V is the assumed volume of the box (m^3), t is the time variable (h), C is the concentration in the box at any

given time (mg/m^3), G is the constant rate of generation of pollutant within the box (mg/h), Q is the constant volumetric flow rate of air exchange in the box (m^3/h), m is the dimensionless mixing efficiency of ventilation in the assumed box (Brief, 1960), and k (m^3/h) and the removal rate from mechanisms other than ventilation and filtration.

Typically, we do not have specific information on non-ventilatory loss rate (k), the mixing efficiency (m) or on the time course of exposure. Thus, we assume values for these factors and for the ventilation (Q) and generation rate (G) that render a reasonable upper bound estimate of C. Indeed, we often default to the steady-state condition for our analysis.

Using these assumptions, our general ventilation model that incorporates the mixing factor and ignore "k" (i.e., set $k = 0$) is

$$C_{eq} = \frac{G}{(Q)(m) + k} = \frac{G}{(Q)(m)} \tag{5}$$

where C_{eq} is the equilibrium concentration (mg/m^3)

In this case study, we have previously estimated the headspace concentration (from its concentration and water and Henry's law constant) and the worst-case exposure potential associated with it. We did this with only information on the concentration of toluene in the product and some available data on its vapor pressure over aqueous solution. To carry out a more detailed analysis in our case study, we need to get more information about the actual exposure scenario to use this model. We find that this aqueous product is typically used in light industrial settings in which the primary off gassing and exposure comes from an open container of the product. The open surface area is 100 cm^2 and the workroom is maintained at 25°C. It is also determined that the workers are often in the room but very rarely immediately proximate to the open container. That is, we are interested in average room concentrations and not near field concentrations and exposures very close to the open drum. Using the above information and an early evaporative source model developed by the EPA (USEPA, 1984) a source rate (G) of 40 mg/h into this room volume is estimated. Please note there are later and more accurate evaporative source rate models available (Fehrenbacher and Hummel, 1996; Sparks et al., 1996) than the early EPA model used in this example. The old model was used here because of its relative simplicity to explain the point.

The general ventilation rate has not been specifically determined for this example but it is known that there is typically no local exhaust ventilation.

The ventilation rate Q is equal to the room volume times the air change rate per hour:

$$\begin{aligned} Q &= (V)(\text{air change/h}) \\ Q &= (50)(0.1) = 5\,\text{m}^3/\text{h} \end{aligned} \tag{6}$$

Air change/hour = mixing exchange rate of air into and out of V (1/h)

Using various worst reasonable worst-case assumptions (air change per hour = 0.1 and $m = 0.3$) this model predicts an average air concentration in the workroom of about 27 mg/m^3 (7 ppm, v/v) in the room. This is below the current 188 mg/m^3 (50 ppm, v/v) exposure limit.

Tier 2a: Dispersion Model

The general ventilation model avoids the question of contaminant mixing in the volume by assuming that it is well mixed. It also ignores near field exposure or sharp gradients of concentration for workers close to the source. A diffusion model that is more sophisticated in that it does not rely on this assumption has been developed for heat flow (Carslaw and Jaeger, 1959) and applied to indoor air modeling (Roach, 1981; Wadden et al., 1991). The equation for a continuous point source is presented in the references to predict concentration at position r and time t.

$$C = \frac{G}{240\pi Dr}\left[1 - \text{erf}\left(\frac{r}{\sqrt{4tD}}\right)\right] \tag{7}$$

where erf represents the error function. (The error function is related to the normal or Gaussian distribution. This is the bell-shaped curve described by the function $\phi(x) = (1/\sqrt{2\pi})e^{-(x^2/2)}$. This curve is called the normal curve of error and the area under this curve represents probability integrals such that $\int_0^x \phi(x)dx = \frac{1}{2}\text{erf}(x/\sqrt{2})$. To evaluate erf(2.3) proceed as follows: Since $x/\sqrt{2} = 2.3$, one finds $x = (2.3)\sqrt{2} = (2.3)(1.1414) = 3.25$. In the normal table entry for area opposite $x = 3.25$, the value of 0.4994 is given. Thus erf (2.3) = 2 (0.4494) = 0.9988. Modern PCs and software (e.g., EXCEL and Mathcad) can do this without effort). In the above equation, C is the concentration, mass/volume (mg/m^3), G is the steady-state emission rate, mass/time (mg/h), r is the distance from the source to the worker (m), D the effective or eddy diffusivity, area/time (m^2/h) and t is elapsed time (h).

Diffusion of contaminants in workroom air occurs principally because of the turbulent motion of the air (Keil, 2000). In most industrial and residential environments, molecular diffusion is not significant between the emission source and the person's breathing zone. Instead, the normal "turbulence" of typical indoor air causes eddys (or packet-like motions) that have the effect of breaking up the contaminant cloud and hastening its mixing with the workroom air. Therefore, applications of diffusion models in industrial environments use experimentally determined diffusion coefficients (D) called eddy or effective diffusivities. These eddy diffusivity coefficients are 3–5 orders of magnitude larger than molecular diffusivity.

The eddy diffusivity term (D) can be based on experimental measurements at the site being modeled. Some eddy diffusivity values are also available in the literature (Wadden et al., 1989; Scheff et al., 1992). Measurements of D in

indoor industrial environments have ranged from 3 to 690 m^2/h with 10 m^2/h being a typical value.

Plotting the predicted airborne concentration (C) at one position, r, for many values of time, t, gives an increasing curve of concentration that approaches a steady-state level.

For sources (emitting into a hemisphere) on a surface and at equilibrium, Eq. (7) simplifies to

$$C_{eq} = \frac{G}{120\pi Dr} \quad (8)$$

Consider our example with $G = 40$ mg/h. Consider a person working within 1 m of the source ($r = 1$ m). We know that the lowest D measured in a very limited database was 3 m^2/h. If we use this value then the estimated equilibrium airborne concentration of toluene is about 2 mg/m^3. This is less than 1/10th the amount predicted with the box model; however, the worst-case ventilation could be very low and this could result in very little mixing and a true D value that is much lower than 3 m^2/h. The fact of the matter is that we simply do not have enough data to use this model with much confidence. It is useful, however, in that it allows us to estimate the effect of distance from the source on worker exposure. It predicts that it is a straight inverse relationship with the exposure going down two-fold for every doubling of distance from a theoretic point source.

There is little doubt that the eddy–diffusivity model could be a very valuable tool that can potentially provide near and far field exposure estimations; however, this approach in general suffers because it lacks the reasonable characterization of the primary predictor variable, eddy diffusivity.

The point of this case study is to show the hierarchy of available inhalation exposure models and the iterative nature of the exposure assessment process. It is also intended to introduce some of the technical details extant within these tools.

Structure of exposure models and modeling

All of the models considered above can be classified as concentration models in that they predict the concentration of toxicant in the media (air in this case) potentially contacting the human.

Their basic structure can be shown as

$$\text{Concentration} = f(\text{Source Strength}, \text{Transport}, \text{Fate}, \text{Penetration})$$

These models do not place or time the individual in the concentration field and assumptions are needed to fill in the gaps associated with this critical element of activity. Indeed, any of these concentration models can be fit into more sophisticated higher level models that include variable activity and contact over any part or all of a lifetime (Price et al., 2001). A more general description of these relatively high level exposure models has been developed elsewhere along with criteria for evaluating these tools (Jayjock et al., 2004).

On the other side, the critical elements within each of these concentration models (e.g., source strength, transport, fate or penetration) can be comprised of very sophisticated and complex submodels. On 20 and 21 June 2005 a workshop was held on "source characterization and transport and fate source" submodels under the auspices of the European Commission — Joint Research Centre, Institute for Health and Consumer Protection Physical and Chemical Exposure Unit in Intra (Italy). In this workshop, the primary organizer Dr. Stylianos Kephalopoulos, brought together human exposure modeling experts and model users from Europe, America and Asia in an effort to identify and characterize the state-of-the-science and point to the most expeditious and cost-effective path for future advancements. Every effort was made to network within the team to recognize and invite additional experts or users to this workshop. Indeed, distribution of the workshop report (JRC, 2005) and other work products from this workshop to further engage the worldwide scientific community in this effort is fully encouraged.

The participants of the workshop rendered the following conclusions and work products:

1. Development of a complete taxonomy of indoor pollution sources and sinks that would have a major impact on the appropriate evaluation of indoor air, surface concentrations, exposure and subsequent risk to human health.
2. The decision was made by the participants not to outline, characterize or explicitly build upon the currently available source submodels beyond the draft workshop report done before the meeting. Instead the workshop participants endeavored to build a framework for this body of scientific work from "the ground up". Existing models, where available, were mentioned or otherwise used to fill in this framework.
3. Identification of specific operational model elements in the above taxonomy in a progressive tiered approach for each comprising zero tier, first tier and n-tier mechanistic source models.
4. The same general type of framework was outlined for transport and fate models.
5. It was anticipated that given this comprehensive framework, practitioners will be able to match up potentially the elements of each with existing model tools. However, in many cases, the specific submodels do not exist and will require focused research and development.

It is the recommendation of the workshop participants that the work products of that gathering be used in the systematic development of human exposure models for their use in a tiered approach to exposure assessment.

Hybrid models for prioritization

Clearly, new regulations that require the estimation of exposure and human health risk posed by large numbers of substances will present regulatory managers with a significant challenge. Indeed, logically and in the interest of cost-effective resource allocation and regulation one would typically and naturally first attempt to rank-order or prioritize the substances according to the human exposure potential that each might pose. In the past, models that evaluated exposure to substances in consumer products were divided into two categories (surrogate models and quantitative dose models). The surrogate models address a large number of substances and used measures of exposure related properties (use codes, nature of the use codes, physical chemical properties, production volumes and release volumes) as surrogates for exposure. Because such models require minimal information on each substance, they can be applied to large numbers of substances.

While the surrogate models do not actually estimate exposure associated with the substances, these models are useful for the segregation and ordinal binning of substances into high and low priority categories prior to the performance of quantitative assessments.

The second type of exposure model is the quantitative dose models which have been discussed above. These focus on a single substance and the quantitative modeling of exposures and doses of a substance that occur as a result of the interaction of individuals and the products. These dose estimates are in turn used to estimate the potential risks offered by the substance. These models focus on one substance and one product at a time. They have to deal with issues such as the large number of products that may contain a substance, the various routes of exposure by which an exposure can occur, and the variation in doses received across the population of users of a product. They use relatively sophisticated algorithms requiring large amounts of substance-specific information and are labor intensive. As a result, they can only be applied to a relatively small number of substances. However, these quantitative dose models provide relatively accurate actual estimates of dose for each source of exposure and are powerful tools for regulatory decision-making.

A hybrid of the two types of models is being developed and is intended to be used as an improved screening model and, under certain circumstances, to eliminate the need for additional quantitative modeling. Like the quantitative dose models this tool, entitled ComET/CEPST (Jayjock et al., 2007), is based on quantitative models of exposure. Combined with substance-specific toxicological benchmarks it will render ordered estimates of risk for a large number of compounds. It is, however, designed to require less detailed information on the substance's uses and thus can be applied to a larger numbers of substances.

Conclusions

Exposure modeling represents the best hope and means of understanding the exposure and ultimately managing the risk to humans from the myriad of chemicals we encounter everyday in our natural environment. The models and modeling framework as currently extant are "useful" but their utility and value as optimally cost-effective tools within any comprehensive regulatory mandate awaits the necessary resources and research to feed and otherwise develop them.

Thus, the specific work as outlined and prescribed in JRC Workshop 2005 "source characterization and transport and fate source sub models" should be implemented as a public works project funded by the primary stakeholders, namely, the effected industrial concerns and the scientific regulatory community.

Furthermore, hybrid models as exemplified by ComET/CEPST should be fully developed as a critical step forward to provide a rational way forward to effectively dealing with the multitude of substances under consideration.

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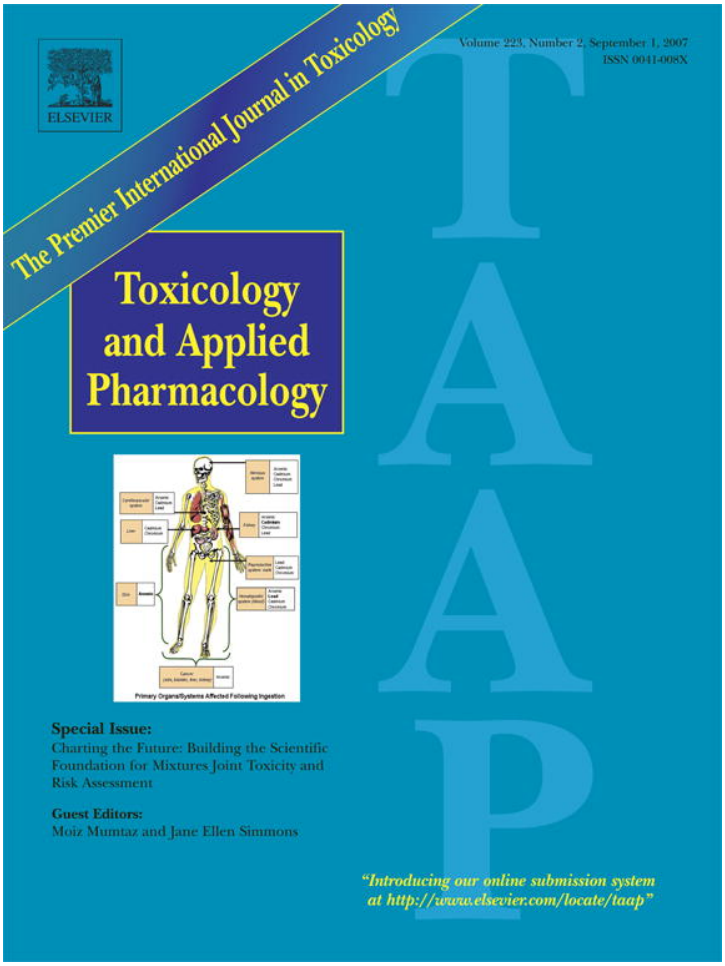

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Modeling mixtures resulting from concurrent exposures to multiple sources

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Abstract

There is a growing recognition of the need to identify when exposures to specific combinations of chemicals result in toxicological effects of concern. In order to meet this need new tools are required to evaluate the doses of multiple chemicals that occur from the concurrent exposures to multiple sources of the chemicals. Limitations associated with the traditional approach for exposure modeling (source-to-dose models) have led to the development of a new approach that focuses on the person. These Person Oriented Models (POMs) use available data on personal characteristics that are statistically representative of the population receiving an exposure. Once the person's characteristics are defined, the information is ued to model the probability of being exposed durinf a particular period of time. This process is repeated for different time periods and for hundreds or thousands of persons to produce a description of longitudinal exposures across a population. This approach allows the modeling of route-specific doses from multiple concurrent exposures; allows the modeling of doses from time varying exposures across, individuals, and provides a basis for modeling the person-related charactersitics in subsequent steps in the process of assessing risks from mixtures.
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Keywords: Person-oriented models; Exposure assessment; Multiple chemicals; Longitudinal; Mixtures

Introduction

Humans live in a sea of chemicals and life is a function of the exchange of chemicals between our bodies and the environment. There is a growing recognition of the need to identify when exposures to specific combinations of chemicals result in toxicological effects of concern. In order to meet this need new tools are required to evaluate the toxicological effects associated with concurrent exposures to multiple substances (hazard assessment) and the potential for concurrent exposures to those substances (exposure assessment). The tools needed to assess these exposures must allow the determination of doses of multiple substances that occur by multiple pathways from multiple sources, and how these exposures vary over time and across individuals (EPA, 2000a,b, 2001; ILSI, 1998, 1999).

The need for these tools is not a recent phenomenon; the goal of assessing total exposure to a chemical or multiple chemicals has existed since the passage of TSCA in the late 1970s. The passage of the Food Quality Protection Act of 1996 and newer programs focused on exposures to children has focused renewed attention on this need. Moreover, programs that focus on a single source such as the Safe Drinking Water Act, Clean Water Act, and Clean Air Act require the consideration of "other" sources of exposure to regulated chemicals.

There are two types of exposure to mixtures; one type is the exposure to discrete complex mixtures. Examples of this type of exposure include consumption of fish containing multiple PCBs, incidental ingestion of soil containing multiple PAHs, and inhalation of complex mixtures from specific sources such as diesel exhaust. The other type of exposure to mixtures, and the one discussed in this paper, is the concurrent exposures to multiple chemicals from multiple sources. An example of such exposures would be the doses of a set of substances where an exposure for one substance could be an oral dose from a dietary source, for a second substance a dermal dose from use

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of a consumer product, and an inhalation dose from an environmental source such as air pollution for a third substance. Is should be noted that exposure approaches developed for the second type of exposure to mixtures is also applicable to the simpler first type of exposures to mixtures.

The first step in any assessment of risk from mixtures is the basic characterization of the toxicology of the substances of concern and the risks posed by concurrent exposures to such substances (mixtures). The exposure assessor is therefore dependent on the toxicologist to identify the models of the interaction of substances that are of concern that define the relevant substances. Once these are identified, then the likelihood of the appropriate concurrent exposures of the substances can be investigated.

As with the field of toxicology, the field of exposure assessment is being redefined by advances in technology. Better analytical tools result in better and more cost effective monitoring. Studies that will automatically track location, exposure relevant behaviors (breathing rates), use of products and air monitoring are being developed. Faster computers have enabled this data to be used in the construction of simulation modeling of concurrent exposures.

Because of limitations in monitoring, exposure assessors have focused on simulation models as the tool for modeling exposure. The traditional exposure models have started with a source of exposure and modeled the movement of the substance through the environment and then determined the amount that actually enters the person's body (dose). This methodology has its limitations; it does not readily allow for the assessment of concomitant exposures from multiple sources or the assessment of the cumulative effects of exposure to multiple chemicals. To assess these more complex scenarios, the traditional approach has been replaced with one that enables the exposure assessor to overcome these limitations; one that focuses on the person (Price and Chaisson, 2005).

Person-oriented models

Person-oriented models (POM) begin by defining the characteristics of a person that is statistically representative of a population of interest of receiving or potentially receiving an exposure. Once this is defined the information is used to model the probability of being exposed during a particular period of time. This process is repeated for hundreds or thousands of individuals to produce a description of exposures across a population (Price et al., 1996; Zartarian et al., 2000; and EPA, 2003).

Fig. 1 presents the flow chart for a simple POM. The model first assigns the person's relevant characteristics. For example if the source of exposure was diet then the age of the person and the season of the year might be important to define since diet varies with age and season.

Once these characteristics are defined, the model determines, based on the person's characteristics, if they are exposed to a source. If the person is not exposed then the dose is set at zero. The person's characteristics are also used not only to define if the person is exposed but also to define how large a dose is

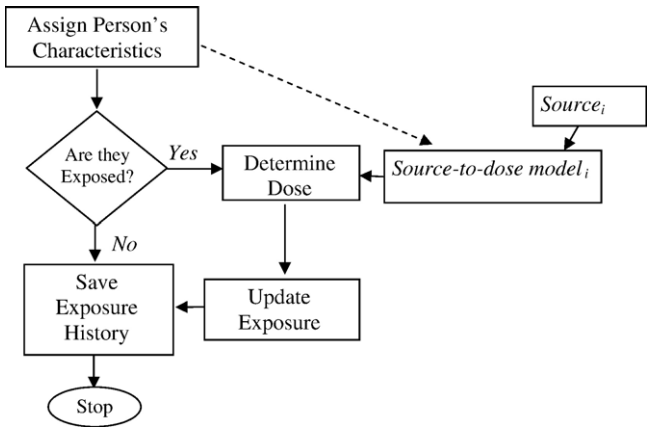

Fig. 1. Person-oriented modeling.

received (dotted arrow). For example if the exposure was from a carbonated beverage then the age of the person will influence the consumption rate (small in infants and large in young adults).

Fig. 2 demonstrates how a more complex structure can support an assessment of one or more substances. The modeling approach can be extended to deal with modeling multiple sources using an exposure event loop, modeling exposure sources that change over time using a time step loop, and modeling multiple individuals with an individual loop. The ability of using nested loops is a hallmark of these models.

As before, the model begins by defining the person, then using that information to define the potential exposure to a source in a given period of time (such as a year, a day, an hour, or a shorter period of time. If the exposure occurs then the model records the dose. The model then goes to the next source. The next source may be for the same substance or a different substance in the mixture of concern. This process of cycling through each of the possible sources is called the "exposure event loop". The model then moves to the next time period in the person's life and repeats the exposure event process. The cycling through the time periods is the time step loop. Once the process has reached the last time step, the model moves to the next person in the simulated population in the individual loop. The result of this modeling is a set of dose estimates for each time step for each individual in a simulated population.

The LifeLine Group, Inc. currently is developing POM models for exposures to mixtures. Current versions of the software focus on dietary, water, and residential exposures to substances that operate by a common mechanism of action. LifeLine software have been used to model risks from exposures to multiple pesticides operating by a common mechanism of action such as organo-phosphorous and methyl carbamates that occur on the same day. The software is freely available to the scientific community and the public. Additional information on these models can be found at www.thelifelinegroup.org. Case studies in which the LifeLine software was used are also available at this site.

The software is capable of modeling several hundred sources, modeling the dose received on each day in the life of

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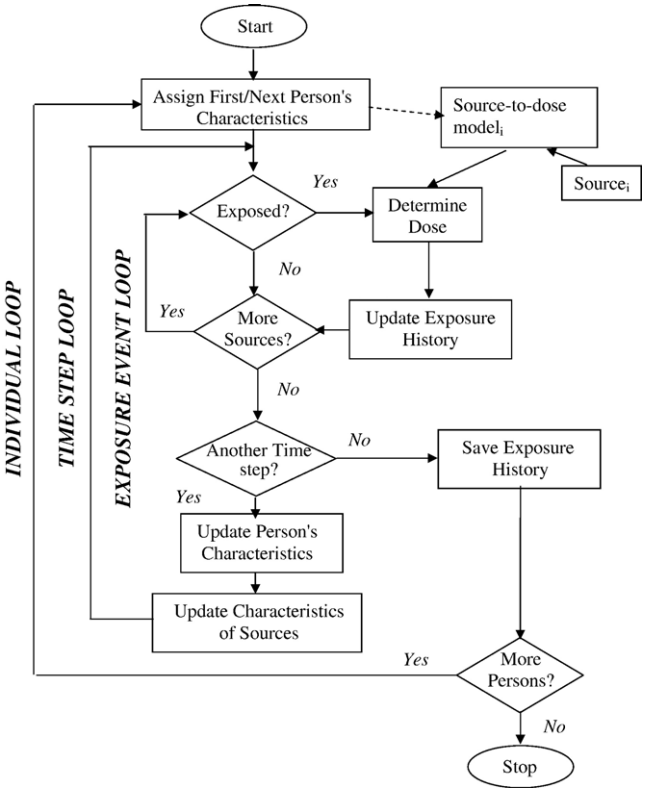

Fig. 2. Flow chart for the complete framework consisting of three loops: individual, time step, and exposure event.

a simulated individual (birth to 85 years) and can model up to 100,000 individuals. In these models the exposure-related characteristics for each individual include:

- The individual's age, gender, height, weight, skin surface area, resting breathing rate;
- Daily activities, diet and water consumption rates;
- Socioeconomic status;
- Housing characteristics such as location in the US, type of home (free standing or apartment), number and size of rooms, presence and size of backyard and other characteristics.

These characteristics are assigned to the simulated individuals based on publicly available data from the National Center for Health Statistics (NCHS), the Third National Health and Nutrition Examination Survey (NHANES III), Current Population Statistics, US Census, and the National Human Activity Pattern Survey (NHAPS).

The POM approach is not unique to the LifeLine models but has to a greater or lesser extent been adopted by a number of modeling projects. These exposure models include APEX (air pollutants), CARES (pesticides), and SHEDS (pesticides and air pollutants) (Price et al., 2003a).

Linking exposure and PBPK/PBPD models

The focus on the individual in POM designs provides several advantages in modeling the effects of exposures to mixtures. The estimates of dose can be used as inputs (exposure histories) to physiologically based pharmacokinetic models (PBPK) and the definition of the individual in the exposure modeling can be used as a basis for defining the physiology of the individual in PBPK modeling. The POM models can be used to define route-specific exposures over time (Price and Chaisson, 2005; Zartarian et al., 2000). These time-varying doses are expressed as discrete values for time steps of durations as short as a few minutes or a few seconds. These data form an exposure history for a simulated individual that PBPK models can convert into prediction of the time-course of organs and tissue specific concentrations of the various substances in a mixture. These concentrations can in turn, support physiologically based pharmacodynamic (PBPD) models of injury and recovery.

The strength of the POM approach is that the same definition of the exposed individual used in the exposure modeling is used to define the physiological characteristics of the individual. Thus if the exposure model assumed that a child aged three years was exposed and received a certain dose the values of blood flow and compartment volumes selected for the PBPK modeling were made to be consistent with this definition. An example of how the POM approach can be used to define detailed physiological data used by PBPK models is given in the software Physiological Parameters for PBPK Models (P^3M) available at the LifeLine webpage (Price et al., 2003b).

Tables 1 and 2 are taken from a recent white paper on linking exposure and PBPK models (LifeLine, 2004). In this effort a methodology is proposed for modeling the demographic and physiological characteristics of the simulated individual. In this case they are expressed as the volumes of the different compartments of the individual and the fraction of cardiac output for each compartment.

Table 1
Time-independent data

Demographic information			Compartment-specific volumes (l)			
Age	Gender	Race/ethnicity	Well perfused	Poorly perfused	Liver	Blood
7	M	White	3.1	7.7	0.56	1.7

Summary

Experts in the field of exposure assessment are actively working to address the need for characterizing exposures to chemical mixtures that occur from multiple sources.

Table 2
Time-dependent data

Time step		Cardiac output (l/m)	Alveolar ventricular rate (l/m)	Fraction of cardiac output for each compartment			
Begin time	End time			Well perfused	Liver	Poorly perfused	Fat
6:10	6:20	3.4	7.0	0.59	0.20	0.16	0.05
6:20	6:30	4.4	9.0	0.65	0.15	0.15	0.05

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Person-oriented modeling provides a useful framework for modeling concurrent exposures to multiple substances. First, it allows the modeling of route specific doses from multiple concurrent exposures. Second, it allows the modeling of doses from time varying exposures across individuals. Third, defining the person in the exposure assessment portion provides a basis for modeling the person-related characteristics in subsequent steps (PBPK and PBPD modeling) in the process of assessing risks from mixtures.

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