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UCRL-JRNL-209245-REV-1

Risk Analysis for Environmental Health Triage

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January 18, 2006

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January 30, 2005

Revised: March 31, 2005

Accepted May 9, 2005, for publication in:
Risk Analysis

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[1]Dr. Bogen served on the National Research Council committees that drafted the reports, *Science and Judgment in Risk Assessment* (1994) and *Review of the Army's Technical Guides on Assessing and Managing Chemical Hazards to Deployed Personnel* (2004), referred to herein. Opinions expressed here do not necessarily reflect those of fellow NRC committee members or of LLNL.

Abbreviations: AEGLs = Acute Exposure Guideline Levels, CCEGs = Chemical Casualty Estimating Guidelines, COA = coarse of action, DHS = U.S. Department of Homeland Security, DOD = U.S. Department of Defense, GIS = geographic information system, LC = lethal concentration, MEGs = military exposure guidelines, NAC = National Advisory Committee on Acute Exposure Guidelines Levels for Hazardous Substances, NRC = National Research Council.

Abstract

The Homeland Security Act mandates development of a national, risk-based system to support planning for, response to and recovery from emergency situations involving large-scale toxic exposures. To prepare for and manage consequences effectively, planners and responders need not only to identify zones of potentially elevated individual risk, but also to predict expected casualties. Emergency response support systems now define "consequences" by mapping areas in which toxic chemical concentrations do or may exceed Acute Exposure Guideline Levels (AEGLs) or similar guidelines. However, because AEGLs do not estimate expected risks, current unqualified claims that such maps support consequence management are misleading. Intentionally protective, AEGLs incorporate various safety/uncertainty factors depending on scope and quality of chemical-specific toxicity data. Some of these factors are irrelevant, and others need to be modified, whenever resource constraints or exposure-scenario complexities require responders to make critical trade-off (triage) decisions in order to minimize expected casualties. AEGL-exceedance zones cannot consistently be aggregated, compared, or used to calculate expected casualties, and so may seriously misguide emergency response triage decisions. Methods and tools well established and readily available to support environmental health protection are not yet developed for chemically related environmental health triage. Effective triage decisions involving chemical risks require a new assessment approach that focuses on best estimates of likely casualties, rather than on upper plausible bounds of individual risk. If risk-based consequence management is to become a reality, federal agencies tasked with supporting emergency response must actively coordinate to foster new methods that can support effective environmental health triage.

Key words: Chemical toxicity, decision making, Homeland security, risk management

Prevention and protection against environmental, occupational and food-related chemical hazards has been the primary goal of quantitative methods increasingly applied over the past thirty years to assess human health risks posed by environmental chemical contaminants.[1-5] Protective regulatory and industrial hygiene measures do not ordinarily require unbiased prediction of chemical risks or resulting casualties. Extensive human pharmacokinetic, epidemiological and/or clinical-trial data—that have allowed reasonably accurate risk assessment for agents such as ionizing radiation and medical pharmaceuticals—simply do not exist for most toxic industrial chemicals and other chemical threat agents. Consequently, assessments of environmental chemical risk generally entail substantial toxicity dose-response uncertainties, due to unavoidable reliance in many cases on quite limited laboratory animal data. To address such uncertainties, health-protective assessment methods traditionally have involved routine application of "uncertainty" factors designed to guarantee acceptable levels of minimal risk.[6] However, a number of less biased approaches are preferable.

Best estimates of toxic chemical risks and casualties require unbiased characterization, rather than precautionary adjustments for, any and all underlying uncertainties. An unbiased approach to chemical toxicity assessment is appropriate in a number of decision making contexts. In judicial settings, for example, a fair and timely verdict must be reached in each case. In the U.S., reasonably fair assessments of environmental chemical harm, albeit approached through a deliberately adversarial process, are thus regularly attempted in civil "toxic tort" litigation, and at times also in criminal prosecutions. In judicial settings, quantitative risk methods are increasingly employed by expert witnesses to help meet civil "more likely than not" or criminal "beyond a reasonable doubt" legal standards of evidence, constrained by the requirement to be persuasive to a lay jury. Timely and unbiased assessment of chemical threats

and casualties can also be important for effective insurance and disaster planning. In general, such unbiased assessment is needed whenever circumstances require choosing among, trading off or prioritizing options associated with different chemical risks or different combinations of chemical and other risks.[7] This is perhaps most dramatically the case in urgent military or emergency response circumstances.

This paper focuses on the present need for more effective methods of timely and unbiased chemical risk assessment specifically to support domestic emergency response management. The need for assessment methods to support trade-off decisions, in addition to currently supported traditional protection-oriented decisions, is discussed in Section 1. Section 2 discusses why current approaches fail to provide effective and timely support of trade-off decisions involving chemical risks. The importance of bridging historically divergent professional perspectives to successful development and implementation of new methods to support environmental health triage when needed for domestic emergency response is discussed in Section 3. Section 4 summarizes recent National Research Council (NRC) recommendations directed at the analogous problem of how best to support military coarse-of-action decisions that involve chemical risks. A default approach to modeling integrated risk posed by dynamic respiratory exposure to one or more chemicals is outlined in Section 5. Section 6 offers suggested steps toward an additional, unbiased framework for toxic chemical risk assessment to support more effective risk-based homeland security planning and consequence management.

1. Risk-Based Emergency Response Should Support Both Protection and Triage

The Homeland Security Act of 2002 mandates the U.S. Department of Homeland Security (DHS) to support research and development of technology and systems for "detecting, preventing, protecting against, and responding to terrorist attacks;" to help "ensure the

effectiveness of emergency response providers to terrorist attacks;" and to "reduce the loss of life ... by leading and supporting a risk-based emergency management program ... of increased efficiencies, by coordinating efforts relating to mitigation, planning, response, and recovery."[8] In the rush to foster prevention, planning and emergency response systems for homeland defense, it is important to consider carefully how current methods used to assess impacts involving large-scale chemical dispersion are not risk-based, and how they may actually hinder risk-based strategies to minimize casualties.

Many systems in place or in development today link real-time plume modeling and mapping capabilities with a variety of toxic exposure guidelines. Such systems can effectively support emergency planning and response for many large-scale toxic exposure scenarios, as well as facilitate training and design of prevention strategies. However, such systems generally provide no systematically consistent way to compare risks that involve chemical exposures. If planners and responders cannot reliably compare chemical risks, or compare chemical vs. non-chemical risks, then they cannot prevent or minimize associated casualties in a risk-based fashion. Reliable comparison of consequences associated with response alternatives will be critical whenever resource constraints or exposure-related complexities force a choice among possible options. Under such conditions, current approaches do not permit risk-based choices, and so will inevitably produce *ad hoc* decisions that tend to allow preventable casualties.

A risk-based approach to trade-offs is possible only if responders use unbiased information on chemical toxicity to predict residual casualties associated with alternative response strategies.[7] Current protective guidelines for acute and chronic chemical exposures[8-13] cannot serve this purpose because (as discussed in Section 2 below), they incorporate a number of "uncertainty" factors and conservative assumptions that may vary quite substantially in combined magnitude

from chemical to chemical, depending on scope and quality of available toxicity data. Planning and response strategies that effectively prevent exceedance of such conservative guidelines will clearly achieve risk-based consequence management. However, domestic terrorism events may involve either of two factors that complicate response and recovery decisions in ways that can make conservative chemical exposure guidelines irrelevant to effective consequence management. First, widespread dispersal of hazardous materials may create exposure scenarios that are potentially *complex*, by involving multiple exposed populations, agents (chemical, perhaps also biological and/or radiological), contaminated media, exposure routes, exposure durations, and/or types of casualty (acute, chronic, quasi-threshold, stochastic, short-term, and/or long-term). Second, logistic constraints, clustering of multiple events in time, and the sheer magnitude of damage incurred may limit response-and-recovery resources, either in the short term or for extended or indefinite periods.

Resource constraints and exposure-scenario complexities will, at times, make it impossible for planners and responders to operate within a traditional *environmental health protection* paradigm, which focuses on preventing the realization of conservatively estimated risks. Instead, decision makers will be forced to operate within an *environmental health triage* paradigm, which focuses on making trade-off (triage) decisions that mitigate the greatest amount of expected casualty. Because DHS is mandated to foster and use risk-based response methods[8], these methods will thus need to address reasonably foreseeable triage goals. While traditional protection decisions aim to avoid potential risks by preventing the exceedance of exposure guidelines, triage decisions aim to minimize the anticipated number of unavoidable casualties. Consequently, while effective protection decisions may err on the side of safety by factors that need not be consistent, effective triage decisions require unbiased casualty predictions.

2. Current Chemical Exposure Guidelines Cannot Support Triage Decisions

To facilitate risk-based decisions, planners and responders will ideally have real-time access to good data on a host of critical factors, such as estimated source terms, media-specific concentration gradients, geography, demography, climatology, hydrogeology, multiroute exposures, agent- and dose-specific toxicity, response/recovery costs and consequences. Risk-based environmental health triage decisions, in particular, require that planners and responders evaluate relevant data in a framework that allows them to compare the relative casualty-reduction merit of alternative options, accounting also for any option-induced casualties. Relative merit will be assessed most conveniently using a unified measure, or set of severity-level-specific measures, such as net cases averted, net cases averted per available dollar spent, net quality-adjusted years of life gained per dollar spent, etc. The numerator of such a metric may, if desired, be raised to a power >1 in order to reflect risk aversion.

Defining a casualty metric, or set of metrics, useful for environmental health triage is not a trivial problem, and adopting any such definition is a risk-policy decision that should fairly reflect broad societal preferences and input. Clearly, acute and severe casualties (such as deaths, or person-years lost) that are fairly straightforward to aggregate will tend to be a dominant concern. But, for purposes that require comparisons, estimates for these endpoints may need to be aggregated with associated subacute and/or less severe injuries. It may be difficult to agree on the relative importance of averting different types of injury, ranging from sub-lethal to lethal. Additional complicating factors—such as temperature dependence of severity for some types of injury, injurious or lethal secondary effects of certain casualty types or circumstances, and the relative value of averting acute vs. delayed injury or death, to name but a few—increase the difficulties likely to be involved in reaching consensus on rules and definitions to be used for

unavoidable environmental health triage. However, the price of failing to adopt such rules and definitions will be to prevent risk-based emergency response, and so increase the likelihood of missed opportunities to prevent many unnecessary casualties. The required rules and definitions need not have Talmudic complexity, when a simple approach may suffice as a reasonable basis to prevent gross errors in triage strategy.

Systems that integrate emergency response data with tools for analysis, visualization, GIS-linked mapping and decision support have an increasingly pivotal role in consequence management and related planning. Although some systems now in place or in development address a broad range of potential chemical exposures, these systems typically characterize "consequences" not by predicting casualties, but rather simply by predicting whether or not modeled concentrations happen to exceed Acute Exposure Guideline Levels (AEGLs)[9], or sets of similar acute and/or corresponding chronic chemical exposure guidelines.[10-13] AEGLs have been and continue to be developed by the National Advisory Committee (NAC) on Acute Exposure Guidelines Levels for Hazardous Substance, which has members from the U.S. EPA, the U.S. Department of Homeland Security, U.S. Department of Defense (DOD), the U.S. Department of Energy, the U.S. Department of Transportation, the National Institute of Occupational Safety and Health, and other federal and state agencies, industry, and academia. Current support systems for emergency response routinely use chemical exposure guidelines, particularly AEGLs, in order to classify and display "risk envelopes" defined as chemical concentration contours that exceed or fall below specified exposure levels.[9] In its operating procedures for AEGL development, the NAC makes clear that it specifically intended this type of AEGL application:

> "It is anticipated that the AEGL values will be used for regulatory and nonregulatory purposes by U.S. federal and state agencies and possibly the international community in conjunction with chemical emergency response,

> planning and prevention programs. More specifically, the AEGL values will be used for conducting various risk assessments to aid in the development of emergency preparedness and prevention plans, as well as real-time emergency response actions, for accidental chemical releases at fixed facilities and from transport carriers. The AEGL values, which represent defined toxic endpoints, are used in conjunction with various chemical release and dispersion models to determine geographical areas, or "vulnerable zones," associated with accidental or terrorist releases of chemical substances. By determining these geographical areas and the presence of human populations and facilities within those zones, the potential risks associated with accidental chemical releases can be estimated. ... By comparing the projected airborne chemical concentrations of the chemical substance in question with the exposed populations, human health risks associated with a chemical release can be estimated. Using these risk estimates, emergency response personnel can make effective risk management and risk communication decisions to minimize the adverse impact of the release on human health." [11 (pp.31-32)]

Atmospheric dispersion modelers have widely adopted this NAC philosophy concerning utility of AEGLs for consequence management involving large-scale chemical exposures. For example, modelers currently claim that AEGL-exceedance-zone maps can "be interpreted quickly by emergency managers in terms of expected toxic consequences"[14] and "aid in determining health risks, recommending emergency actions (such as sheltering, evacuation, relocation, reentry), and deploying emergency personnel."[15]

Clearly, such claims are valid *only if* exposure scenarios addressed are simple enough, and *only if* resources available for response and recovery are large enough, to obviate any need to make trade-offs or priorities. As pointed out in the NRC report, *Science and Judgment in Risk Assessment*, when risk managers must make trade-offs and priorities, they ought to "take into account information on uncertainty in quantities being ranked so as to ensure that such trades do

not increase expected risk and such priorities are directed at minimizing expected risk." [7] In contrast, AEGLs and similar chemical exposure guidelines for the general public "are not true effect levels," insofar as they incorporate multiple "uncertainty" factors that are "designed to protect the general public, including susceptible subpopulations, from short-term exposures to acutely toxic chemicals."[11 (pp. 36, 63)]

One such factor applied routinely to develop AEGLs and similar guidelines for chemical non-cancer risks, is the so-called "intraspecies uncertainty" factor sometimes denoted UF_H (10 by default, unless data justify using 3 or 1).[6,11,16] This factor is applied to account for the range of interindividual variability (i.e, heterogeneity or differences) in sensitivity or susceptibility to toxic response that is expected in a general human population.'[11 (p. 80)] It reflects a default assumption concerning the typical ratio of chemical concentration eliciting a specified toxic endpoint in relatively susceptible individuals or subpopulations (e.g., due to age, health status, genetics, etc.), to that eliciting the same endpoint in average healthy humans.[16] Susceptibility-related variation addressed by UF_H, concerning a chemical toxicity risk R relative to its population-average value $\overline{R}$, is completely irrelevant to estimating the expected value E(N) of the number N of casualties (i.e., "population risk") for any exposed population, because by definition $E(N) = N\,\overline{R}$; moreover, exact knowledge of a UF_H-variability distribution is typically of little or no value because, if considered to be of interest, the corresponding N-uncertainty distribution is typically very well approximated as a Poisson-binomial function of $\overline{R}$ alone.[17-19]

In addition to safety/"uncertainty" factors, AEGLs for non-cancer endpoints incorporate two systematically "conservative" (health-protective) assumptions. First, a conservative toxicity endpoint is used to estimate toxic response. For example, subclinical endpoints are among those used to derive AEGL-2 guidelines, which are intended to prevent "irreversible or other serious

long-lasting health effects or an impaired ability to escape"[11 (p. 35)]; and lower-bound response endpoints—such as a lethal concentration (LC) to 1% or 5%, or an arbitrary fraction of the LC to 50%, of exposed animals—are used to derive AEGL-3 guidelines (the most protective category of AEGL guidelines), which are intended to prevent "life-threatening health effects or death" in a general population including sensitive individuals.[11 (p. 35)] Second, by default when data are unavailable or inadequate, a conservative value is assumed for the exponent n used to extrapolate response vs. exposure duration from the generalized Haber's law relation, $C^n t = k$ (e.g., $n = 3$ is assumed to extrapolate from an observed longer to an estimated shorter exposure duration).[11 (pp. 103-110)] For carcinogens, AEGLs[11 (pp. 116-121)] "attempt to limit potential cancer risk to 10^{-4} or less" considering the "maximum risk to an infant" calculated by default using a linearized multistage risk-extrapolation model, which model is generally considered to reflect mechanistically health-protective (conservative) assumptions concerning low-dose dose-response relations for many, if not most chemical carcinogens.[20]

For the specific purpose of protecting health by preventing any substantial occurrence of injuries or casualties, such conservative factors and assumptions used to derive AEGLs are explicit, intentional and entirely appropriate. However, this conservatism will interfere if the goal is instead to compare or minimize casualties expected to arise from alternative chemical or mixed chemical/non-chemical exposure scenarios, unless both (1) expected chemical-specific casualties are in each case an approximately linear function of environmental concentration; and (2) there is near homogeneity among known, chemical-specific levels of aggregate "relative bias" (for each chemical defined as the product of relative biases due to each protective factor or assumption used). Neither of these two exceptions would appear to apply for most chemicals and toxicity endpoints relevant to emergency response, because quite nonlinear dose-response

models (e.g., no-effect levels or log-probit models) tend to be used in this context[10], and the magnitude of aggregate dose-response conservatism evidently varies quite substantially, and quite non-intuitively, from chemical to from chemical.

For each of ten toxic chemicals among 18 addressed in AEGL volumes 2-4[9] (volume 1 does not include 10-min AEGLs), Table 1 summarizes the aggregate relative bias created by uncertainty factors and conservative assumptions used to develop 10-min AEGL-3 guidelines, relative to an estimated concentration (LC_{50}*) lethal to 50% of a population having typical susceptibility. Methods used to calculate an approximate relative bias in 50% lethality (RBL = LC_{50}*/[10-min AEGL-3]) are described in notes to this table. Because AEGL-3 guidelines are intended to prevent acute lethal or life-threatening injury to nearly all members of a general population exposed for 10-min[11], RBL values certainly reflect no intentional bias. Rather, they represent only hypothetical bias that would be created only if 10-min AEGL-3 guidelines listed were misinterpreted as information that could be used to estimate either absolute or relative magnitudes of casualties to be expected from a 10-min exposure to the corresponding chemicals.

[*Note to editor: Insert Table 1 about here.*]

Table 1 makes two important points. First, RBL values listed in Table 1 span a 200-fold range. Second, the degree to which RBL values listed in Table 1 are all (as expected) substantially >1 depends entirely on specific attributes or deficiencies in animal toxicity data that happen to be available for each chemical. Consequently, it would in general be impossible to estimate a specific LC_{50}* value, let alone a corresponding number of casualties expected if specific populations are exposed dynamically to specific air concentrations over time, using information currently summarized by AEGLs or similar exposure guidelines. The ability to obtain such estimates, particularly for use in emergency circumstances, requires that credible

methodology first be developed and applied in advance to re-analyze underlying toxicity data specifically for this purpose.

Due to systematic incorporation of protective bias, AEGLs are widely recognized to "provide no way to estimate expected health risks or the fraction of any exposed population that will actually experience symptoms."[14] The conservative bias in AEGLs and most other chemical exposure guidelines contrasts with the intended predictive nature of analogous guidelines concerning exposures to ionizing radiation. Chemical exposure guidelines typically incorporate multiple safety factors, while radiation protection guidelines tend to reflect "best" (unbiased) estimates of risk that are based primarily on models of human epidemiological data and so considered to have relatively little uncertainty.[21-23] Unbiased estimates are also available and/or currently used to evaluate predictable risks of injury or death from non-exposure-related aspects of emergency response and recovery, such as evacuation, or economic dislocations caused by long-term mitigation costs.[24-27]

AEGL-derivation methods for chemical carcinogens recognize that because "public health and safety risks associated with evacuation and other response measures might pose greater risks of injury or perhaps death [and thus] AEGL values based on uncertain theoretical cancer risk estimates might lead to response measures that increase actual or total risk for the exposed population," some "measure of population based risk" should be considered.[11 (p. 116)] However, this caveat does not clearly explain how different (protective vs. triage) decision-making contexts in general ought to affect the application of cancer-specific AEGLs. Nor do the methods specifically address how these different contexts should affect the nature of toxicity information and type of toxicity estimates used to make decisions. As noted above, non-uniformly protective bias in AEGLs makes them inappropriate to use for predicting casualties

(i.e., population risks) that can be compared meaningfully among different chemical and/or other sources of risk. Thus, only in the case of chemical carcinogens does AEGL methodology discuss the problem of what measures of chemical risk are appropriate to use for trade-off decisions, and even this restricted discussion is flawed. These problems are, of course, not unique to chemical carcinogens, but pertain to all toxic agents and toxicity endpoints.

3. Integrating Two Paradigms Requires Bridging Two Professional Perspectives

Scientific and regulatory bodies have not clearly and consistently communicated the fact that effective environmental health protection requires toxicity characterizations different from those required for effective environmental health triage. This is unfortunate, but understandable. Emergency and military medical personnel routinely grapple with the need to make tragic choices in the form of triage decisions, which attempt to minimize losses by efficiently allocating limited resources after assessing competing risks and benefits as accurately as feasible. In contrast, those engaged in assessing and controlling chemical risks have been professionals primarily in the fields of occupational and public health, industrial hygiene, sanitary engineering, environmental and regulatory toxicology, and regulatory risk analysis. These specialists typically have operated within an environmental health protection paradigm, involving dedication to promoting human health by limiting potentially harmful environmental exposures to toxic chemicals. The historic emphasis of these fields has appropriately been on protection and prevention through exposure limitation, rather than on accurate prediction of adverse consequences. Environmental health practitioners typically help generate or ensure compliance with protective exposure guidelines, and do not routinely make life-and-death triage decisions. Life-and-death triage decisions have played little or no role in the recent history of U.S. environmental health policy. The recently recognized potential for homeland security situations

involving widespread dispersion of toxic agents has created a new need for effective environmental health triage. Consequently, methods and resources—analogous to those well established and readily available to support occupational and environmental health protection—do not yet exist specifically to support environmental health triage decisions that will need to be made in complex scenarios involving large-scale chemical exposures.

The Homeland Security Act now mandates a national capability to operate effectively in a new "environmental health triage paradigm" for consequence management. The new paradigm will not replace the traditional protection paradigm, which remains appropriate whenever trade-off or prioritization decisions can be avoided. When such decisions cannot be avoided, the triage paradigm clearly requires a new general approach to chemical risk assessment. To be effective, the appropriate approach for the new paradigm must facilitate timely casualty estimates that can be compared meaningfully, rather than on upper plausible bounds of individual risks that are the main focus of the traditional protection paradigm. Those who can best contribute to developing the new approach happen to be those engaged in areas of environmental health protection. They are the ones most knowledgeable about the variety of safety factors and conservative assumptions currently integrated into most chemical risk assessments and exposure guidelines. However, current legislative and policy frameworks in certain agencies may impede the important contribution these professionals can make in developing new chemical risk assessment methods and guidelines needed to support effective environmental health triage decisions. National leadership could help to bridge different agencies and professional perspectives that must work together to realize an effective system of risk-based consequence management. The fact that triage and protection paradigms neither conflict with nor detract from one another, but rather clearly have the same objective to prevent unnecessary harm, will help build this bridge.

4. Chemical Risks to Deployed Military Personnel: An Analogous Problem

Congressional concern about Gulf War troops' toxic exposures led to a series of National Research Council (NRC) reports, advising DOD on how to develop effective procedures and policies for monitoring and managing health risks of acute or subchronic chemical exposures faced by military personnel during overseas deployment. One NRC recommendation to DOD was that it adopt a risk assessment framework including separate decision making paradigms for environmental health triage vs. environmental health protection:[28] (pp. 66-67; italics added)

> "… the establishment of 'conservative' estimates of dose-response relations, that is, those deigned to err on the side of safety when faced with uncertainty about how to project expected human responses from available data, might not be appropriate for certain military uses. *When risks cannot be avoided and decisions are made to accept some risks rather than others*, or to bear some risk in furtherance of a more fundamental military objective, *it is important to make these trade-off decisions with unbiased estimates of the impacts of various courses of action*. In other applications, such as the setting of health-protective exposure standards for application in less severe circumstances, conservative estimates might be much more acceptable. … [Analyses should be] conducted and … results presented, so that different uses appropriate for different risk-management settings can be made."

DOD developed and implemented not the recommended dual-paradigm framework, but a single set of "military exposure guidelines" (MEGs) to serve as a comprehensive approach to managing chemical risks to deployed military personnel.[12] MEGs are modified versions of preexisting, protectively biased chemical exposure guidelines, with greatest weight given to AEGLs in the case of chemicals for which AEGLs are available.[12] The modifications used do not include any (even context-dependent) reference to "best" estimates of likely casualties, only military-specific adjustments concerning exposure (e.g., water intake) and susceptibility (e.g., among relatively

healthy, but also some potentially pregnant, adults).[12] The MEGs, and a system of corresponding qualitative risk-ranking procedures, together were developed explicitly to serve as a unified system with which DOD pursues two different requirements: (1) force health protection, and (2) coarse-of-action (COA) decisions in support of specific (including non-combat) military missions.[12]

After careful review of DOD's single-paradigm, MEG-based framework to manage chemical risks to deployed troops, the NRC recently recommended that DOD scrap this system in favor of a dual-paradigm framework.[29] The newly proposed framework involves one set of methods and guidelines for making force health protection decisions, and a different set for making COA decisions.[29] Noting that the MEG-based framework for chemical risks continues to be used in the field, the NRC specifically warned DOD that "Because [MEGs] are protective in nature, it is exceptionally difficult (if not impossible in some instances) to use them for direct comparisons with other operational threats."[29 (p. 83)] Although the NRC endorsed the application of MEGs specifically for force health protection (and recommended ways to improve MEGs for this purpose)[29], it recommended that DOD develop entirely new Chemical Casualty Estimating Guidelines (CCEGs) specifically to support COA decisions, explaining that:

> "The goal of CCEGs is to provide risk estimates of impacts on troop strength, including consideration of individuals affected to different extents by ... exposure. CCEG values must be unbiased estimates of risk. They should be predictive estimates of casualties and they should not incorporate margins of safety or adjustments for missing information except under unusual circumstances. ... As predictive values, the CCEGs should not include protection for civilian population sensitivities (e.g., pre-existing disease), which is typically achieved by applying an intraspecies UF [uncertainty factor]. When chemicals of interest have known susceptible populations, it might be necessary to formulate more reliable

> estimates of the mean responses of the entire deployed population at risk if those susceptible groups were not represented appropriately in the key studies [used to derive guidelines for such chemicals]. ... CCEGs ... will be predicting casualties, not suggesting safe levels buffered for error ..." [29 (pp. 80-82)]

Being predictive rather than protective in design, the proposed CCEGs would be appropriate for helping to make trade-offs or set priorities concerning chemical risks, in relation to each other as well as additional operational threats.

The joint objectives of force health protection and effective COA decisions, which DOD seeks to address through a framework for the assessment and management of chemical risks to deployed personnel, are directly analogous to requirements for environmental health protection and for environmental health triage, respectively, in a domestic homeland-security context. Consequently, the key point of the recent NRC recommendation summarized above—that a fundamentally new, predictive methods and guidelines are needed to support triage decisions involving chemical risks—applies directly to the problem of how to implement effective, risk-based planning and consequence management for homeland security situations that may involve widespread and/or complex chemical exposure scenarios.

5. Assessing Risks from Exposure to Time-Varying Chemical Concentrations

For the purpose of implementing CCEGs, the approach NRC recommended is similar to that taken to develop AEGLs, except that each CCEG would incorporate adjustment ("uncertainty") factors only insofar as they make casualty predictions more accurate. CCEGs would thus summarize information needed to predict total casualties, rather than concentrations likely to prevent nearly all casualties. For quantitative chemical risk assessment, the NRC recommended the log-probit dose-response model as a default approach to analyze available data on each toxicity endpoint of interest.[29 (pp. 86-87)] By this model, the probability P of individual response,

conditional on exposure to concentration C for a specified duration T_o, may be expressed conveniently as

$$P = \Phi\left[z_{1-f}\frac{\log(C/C_o)}{\log(C_o/C_f)}\right] = \Phi\left(b\log(C/C_o)\right) , \quad (1)$$

where C_o and C_f denote values of C at which 50% and 100f% responses, respectively, are estimated from the best available data (with $0<f<1$), where b is defined implicitly, and where $z_{1-f} = \Phi^{-1}(1-f)$ in which Φ is the cumulative standard normal distribution function and Φ^{-1} its inverse. Additional methods were described allowing quantitative aggregation of individual risk from multiple toxic agents acting by similar, or by independent, mechanisms of action.[29 (Appendix E)]

For practical application to decision making problems involving dynamic exposure to a chemical concentration $C(t)$ as a function of time t (in either a military COA or a domestic triage context), Eq. (1) can be generalized to account for observed dependency of chemical potency on exposure duration T, assuming a log-probit-plane dose-response model[11,30-32] of the form

$$P = \Phi\left(a + b\log C + d\log T\right) . \quad (2)$$

Eq. (2) is equivalent to a generalized Haber's law ($C^n T$ = constant) relation in which the "toxic load exponent" of concentration C is defined as $n = (b/d) = [\log(T_o/T_f)]/[\log(C_o/C_f)]$, where T_f denotes the duration of exposure at concentration C_o estimated to yield a 100f% response. All three fitted parameters of Eq. (2) are readily available only for a few endpoints and chemicals, such as lethality for chlorine gas and a number of other respiratory toxicants.[31,33-34] More often, related estimates may be reported in the form C_o, C_f and T_f, conditional on T_o. In either case, the corresponding probability of response at time t may be expressed conveniently as

$$P(t) = \left[1 - f \frac{\log\left(T_o^{-1} \int_0^t [C(s)/C_o]^n ds\right)}{\log(T_o/T_f)} \right] = \left(d \log\left(T_o^{-1} \int_0^t [C(s)/C_o]^n ds\right)\right) , \quad (3)$$

where n was defined above, d is defined implicitly, and $a = -\log(C_o^b T_o^d)$ (see Eq. 2). Risks from multiple sources of dynamic chemical exposure can be aggregated by combining Eq. (3) with methods like those discussed in the NRC report on chemical risks to deployed military personnel.[29 (Appendix E)] Corresponding casualties and associated uncertainty can then be estimated using methods previously described.[17-19]

6. Road to Risk-Based Planning and Consequence Management for Homeland Security

Protective chemical exposure guidelines appropriately incorporate substantial and widely varying degrees of conservatism, which depend on the nature of available dose-response data. Trade-off and priority-setting decisions require unbiased estimates of expected casualties. Such best estimates are not readily available, in easily accessible form, for most of the wide array of chemicals of concern. Consequently, no readily accessible, reliable basis for risk-based planning or consequence management is available for incidents that require comparing casualties from different chemical agents, or from mixtures of chemicals and other sources of risk (e.g., radiation, biological agents, or evacuation measures). What is missing is a comprehensive database of unbiased estimates of chemical toxicity and associated uncertainty characterizations. Current systems intended to assist consequence management for chemical exposure scenarios generally are limited to mapping areas in which AEGLs or similar guidelines are exceeded. This approach is flawed because the mapped "consequences" incorporate widely varying degrees of conservatism, including factors that are partly or totally irrelevant to predicting actual casualties. Moreover, current systems fail to account for likely chemical casualties in a way that integrates

over all potentially relevant media, exposure pathways, time horizons and toxic endpoints, to provide casualty measures useful for making trade-off decisions.

To address chemical emergency situations that require trade-off and prioritization decisions, a fundamentally new, general approach to assessing and managing chemical risks is needed. The new approach must focus on expected casualties rather than "upper-bound" individual risks. The NRC's CCEG-based approach, and related quantitative methods discussed above, can serve as a starting point. Additional quantitative methods to characterize chemical toxicity and related uncertainty may also be of help.[e.g., 35-41] As recommended by the NRC[29 (p. 81)], such a new approach should be developed through a process that involves scientific peer review. Active and coordinated involvement by federal agencies tasked with supporting emergency response would also clearly contribute to progress toward new data structures and methods to support effective environmental health triage.

Acknowledgements—The author is grateful for insightful comments by anonymous reviewers. This work was performed under auspices of the U.S. Department of Energy by University of California, Lawrence Livermore National Laboratory (LLNL) under Contract W-7405-Eng-48, with support from the LLNL Risk and Response Management Program.

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Table 1. Bias of 10-min AEGL-3 relative to "best" estimates of lethal exposure to ten toxic chemicals.[a]

Compound	AEGL vol.	10-min AEGL-3 (ppm)	Toxicity study		UF_A	UF_H	MF	*n*	Relative AEGL bias in estimated 50% lethality, RBL[b]
			Endpoint	Duration					
Chlorine gas	4	50	Rat NLC	1 h	3	3	1	2	3 □ 1 □ 1.5 □ 5 [10]
Diborane	3	7.3	Mouse LC_{01}	4 h	3	3	1	[1]	3 □ 3.3 □ 3.3 □ 30
Hydrogen cyanide	2	27	Rat LC_{01}	15 min	2[c]	3	1	2.6	6 □ 1 □ 1.4 □ 8
Hydrogen fluoride	4	170	Rat LC_{05}	10 min	3	3	1	[2]	3 □ 1 □ 2.2 □ 6
Methyl isothiocyanate	3	1.2	Mouse pup NLC	6 h[d]	3	10	1	1	10 □ 1 □ 100 □1000
Phosgene	2	3.6	Rodent NLC	10 min	3	3	1	[1]	3 □ 1 □ 2.2 □ 6
Propylene glycol dinitrate	2	16	Monkey NLC	6 h	3	3	1	[3]	10 □ 4.8 □ 1.3[e] □ 60
Sulfur mustard	3	0.59	Mouse NLC	1 h	3	3	1	3	3 □ 1.8 □ 2 □10 [20]
Toluene 2,4- and 2,6-diisocyanate	4	0.65	$\frac{1}{3}$Mouse LC_{50}	4 h	3	3	1	[3]	3 □ 4.2 □ 3 □ 40
VX (nerve agent)	3	0.0027	Rat LC_{01}	10 min	3	10	3	[2]	30 □ 1 □ 1.6 □ 50

[a] 10-min AEGL-3 (life-threatening or lethal) concentrations in air for 10 of 18 compounds covered in the indicated AEGL volume[9] among AEGL volumes 2-4. LC_P = concentration lethal to P% of exposed test animals; NLC = non-lethal concentration; UF_T = "uncertainty" factor of type T, for T = A (interspecies extrapolation of toxicity from animals to humans) and T = H (human

interindividual variability in susceptibility); MF = modifying factor (e.g., for inadequate data); n = generalized Haber's law extrapolation exponent, assuming $C^n\ t = k$ at concentration C for duration t and a constant toxic load k. By convention, UF_T values listed as "3" actually denote $\sqrt{3}$. The value of n is listed in brackets if it was not used to extrapolate a 10-min AEGL-3 value, either because the endpoint used involved a 10-min exposure duration, or because AEGL methods[11] do not allow endpoint data at exposures ≥4 h to be scaled to extrapolate 10-min effects (unless justified by empirical data, as was considered the case for methyl isothiocyanate), and instead define the 10-min AEGL-3 value more conservatively to be the same as that scaled to 30 min.

[b] RBL = LC_{50}*/(10-min AEGL-3) = approximate bias in estimated 50%-lethal concentration (LC_{50}*, in ppm) relative to 10-min AEGL-3 (in ppm), rounded to one significant digit. RBL values listed were each approximated as the indicated product, $F \cdot N \cdot E$, where: $F = UF_A \cdot UF_H \cdot MF$ conditional on $UF_A = 1$ if a primate endpoint was used (also in the case of hydrogen cyanide—see note *c*); $N = (t_0/[10\ \text{min}])(1/n^* - 1/n)$ where t_0 = endpoint study duration in min, and $n^* = 3/2$ = the approximate geometric mean of the range of n values (0.8 to 3.5) for respiratory toxicants reported by ten Berge *et al.*[31]; and E = endpoint-extrapolation ratio = (LC_{50} estimate cited in the corresponding AEGL documentation for the species/study used for the listed endpoint)/(endpoint-specific concentration cited in that documentation). The value of E =1.6 implied for nerve agent VX is the 10-min LC_{50}:LC_{01} ratio for nerve agent GB.[9 (vol. 3, p. 250)] Bracketed RBL values shown for chlorine and sulfur mustard are each defined as the ratio (LC_{50} estimate cited in corresponding AEGL documentation derived specifically for humans based on review of available data)/(10-min AEGL-3 value).

[c] Humans considered to be *no more and likely less* sensitive than rodents for this endpoint.[9 (vol. 2, p. 253)]

[d] Repeated on four consecutive days.

[e] The plausible lower bound of D = 1.3 for propylene glycol dinitrate used in this table reflects the unavailability of acute lethality studies for this compound at AEGL-related exposure durations.[9 (vol. 2, p. 84)]