RISK ASSESSMENT AND OCCUPATIONAL HEALTH:

Overview and Recommendations

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THE MODERN WORKING ENVIRONMENT imposes a variety of risks on worker health and safety. Many of these risks involve toxic chemicals, which may have serious acute, or chronic impacts on the health of workers and their families. (1, 2, 3) Occupational exposures to such chemicals are widespread and are often at levels considerably greater than those attributable to environmental pollution. (4) Significant numbers of workers are exposed to toxic chemicals on the job each year and thousands of these individuals suffer significant adverse effects as a result. (1)

Toxic chemicals can lead to both reversible and irreversible health effects, some of which may not be clinically detectable for years following exposure. (3, 5) Respiratory diseases (6), neurological effects (7, 8), reproductive impairment and birth defects (9, 10, 11, 12), cardiovascular effects (13, 14), as well as a variety of cancers (15, 16, 17, 18) have all been associated with occupational exposures to toxics. Depending on the chemical(s), the dose, and the susceptibility of those involved, the risk of experiencing adverse outcomes following such exposures may range from minimal to severe. Fortunately, once identified, most of these risks are controllable. (1) Yet exposures to many toxic agents in the workplace are allowed under current regulations, often at levels which may pose highly significant risks to worker health and safety. Risk assessment methods, when used appropriately, can provide useful tools to help identify, evaluate, and justify appropriate regulation of such occupational risks and are being increasingly relied upon by regulatory agencies. (19, 20, 21)

The following paper discusses the use of risk assessment in the occupational health arena, providing a general overview of this developing field and concluding with a number of recommendations which we believe will improve the use of risk assessment in occupational health. We have attempted to highlight the rationale for, and strengths and weakness associated with, the increasing use of risk assessment to guide the regulatory agenda concerning occupational chemicals. Some of the key areas of current controversy in risk assessment methods and their application to controlling occupational risks are discussed, drawing on the authors' perspectives as public health scientists engaged in occupational health and toxicological research.

RISK ASSESSMENT AND RISK MANAGEMENT

From the standpoint of regulatory decision-making, a distinction is usually made between the activities and responsibilities of risk assessors and risk managers. (21, 22) The term risk refers to the possibility of an adverse outcome and often involves some estimate of the magnitude of the outcome, its nature, and the probability that such an event will occur. The field of risk assessment has developed to help both identify and quantify risks, including those posed by exposures to toxic chemicals in the workplace. (22) Alternative approaches to the evaluation and regulation of occupational chemical hazards exist which do not explicitly consider risk levels (for example, relying on hazard identification schemes to identify potential dangers or structuring regulations to minimize significant chemical exposures regardless of risk). Most of these alternative approaches do, however, implicitly consider the magnitudes of the risks involved especially when applied to actual regulatory decisions. Thus, the distinctions between these non-risk-based approaches and more formal risk assessments are often less than clear-cut.

Risk management, within the context of this paper, refers to the process whereby decisions are made about what is to be done (or not done) to reduce a given health risk. In the occupational arena, such risk management

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efforts most obviously include the promulgation and enforcement of occupational standards by the Occupational Safety and Health Administration (OSHA). Important decisions that significantly impact the management of occupational health risks are, however, also made at a variety of other levels including the courts (2), the Office of Management and Budget (OMB) (23, 24), and other elements of the executive branch to name but a few. In a broader sense, significant risk management decisions in the workplace also may be made by a variety of other groups including occupational health professionals (for example, industrial hygienists and occupational physicians), and representatives of management and labor. Such risk management decisions are often, but not always, guided by an explicit evaluation of the risks in question. Other criteria and information, however, are also usually taken into account by risk managers. These may involve considerations of technological feasibility, economic impacts, ethics, and politics. Clearly, these latter factors often play a more significant role in risk management decisions than the nature and magnitudes of the risks themselves.

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In contrast to risk management, risk assessment is a somewhat more scientific undertaking. Scientists and others involved in risk assessment strive to use the available scientific data to gain insight into the nature and degrees of risk posed by various activities and chemicals. The goal of risk assessment is to provide the various risk managers with objective information upon which to base their decisions. (22) Ideally, risk assessment should be based on solid science. In reality, the endeavor is by no means a fully objective scientific undertaking, devoid of policy choices. Due to the inherent uncertainties in the process, scientific judgements and assumptions regarding the quality of various data, analyses, and models are always required (the science involved is rarely definitive and is often open to differing interpretations). Considerable debate has occurred in recent years over the appropriateness of many of the assumptions commonly made in risk assessment and over approaches for making these assumptions. Several groups are currently reviewing risk assessment methodologies, including the National Academy of Science's Committees on Risk Assessment, the Office of Science and Technology Policy's Federal Coordinating Council on Science, Engineering, and Technology, and the Committee on Risk Assessment for Hazardous Air Pollutants, among others. These groups are considering a wide range of methodological issues pertaining to issues such as high-dose to low-dose extrapolation models, pharmacokinetics, mechanistic models of disease causation, methods for assessing and reporting uncertainty, and markers of susceptibility, among others. Attempts to coordinate and, perhaps, standardize risk assessment methods between various federal agencies also are being made. The Office of Management and Budget (OMB) also has begun to play a more active role in this process, expressing concern that chemical risk assessment as practiced by many government agencies (notably the Environmental Protection Agency (EPA), National Institute for Occupational Health and Safety (NIOSH), and Occupational Safety and Health Administration (OSHA)) has become too "conservative" (health-protective) in its assumptions. (24) OMB has argued that this may lead to a misdirection of regulatory attention towards areas of little real significance to public health and at great governmental and private expense. These ongoing debates, particularly those surrounding the potential conservativeness of the current risk assessment process, may lead to significant changes in federal risk assessment efforts in the future.

Risk assessment relies on a variety of different methods and may consider many types of scientific information including data from short-term tests (for example, the Ames test (25)), mechanistic studies (for example, pharmacokinetics and pharmacodynamics (27)), animal bioassays (26), and human epidemiological studies. (15) Assessing the risks posed by toxic chemicals requires that several factors be considered. Paramount among these are: 1.) the inherent toxicity of the chemical, including the nature of its effects and potency; 2.) the expected range of exposures likely to be experienced by the target population; and, 3.) the susceptibility of those

exposed. It should be noted that these factors can be considered both **quantitatively** and **qualitatively** and both of these approaches have been used to guide occupational and environmental health efforts. In all of these cases, the purpose of the risk evaluation process is fundamentally the same — to evaluate the possible adverse health effects that a given activity or chemical exposure may exert upon a population, an individual, or the environment. Because of this commonality of goals and for the sake of simplicity, these various risk evaluation approaches will all be referred to as risk assessments in this paper. It should be noted, however, that the field of risk assessment has, unfortunately, come to be associated to a large degree with quantitative assessment approaches, particularly the quantitative extrapolation methods which are used to generate numerical estimates of human cancer risk from animal bioassay data. (28, 29) Although these quantitative methods have been extensively used and are often appropriate, other approaches also are available (see below) that may often be preferable given the inherent uncertainties in the underlying science. As has been noted many times in the risk assessment literature, quantitative risk assessments require numerous assumptions (both in potency and exposure estimations), yielding numerical estimates of risk that are highly uncertain. (31, 32, 33) In the face of these fundamental limitations, we believe that risk managers should view computationally and structurally complex models that have not been adequately validated with skepticism and suggest that qualitative methods receive renewed attention by the risk assessment and risk management communities.

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Some of the less quantitative approaches to risk assessment include 1.) qualitative characterizations of risks, where potential health risks are identified but not quantified (for example, hazard evaluations (22), carcinogen classification schemes (34, 35), and so forth); 2.) qualitative risk estimation approaches, where chemicals are ranked or classified by broad categories of risk (for example, potency classification schemes (36, 37)); 3.) semi-quantitative approaches, where effect levels (for example, no observable adverse effect levels, benchmark doses (38) and so forth) are used in combination with uncertainty factors to establish "safe" exposure levels. Each of these approaches can and has been used to assess occupational health risks and, in a broad sense, each constitutes a form of risk assessment. Thus, the field of risk assessment should be viewed as encompassing both quantitative and qualitative methods. For many chemicals, it can be argued that the qualitative approaches provide a more realistic picture of the ability of scientists and risk assessors to estimate human risks.

RISK ASSESSMENT AND OCCUPATIONAL HEALTH

Efforts to regulate occupational exposures to toxic agents are at their best when adequate pre-existing epidemiologic data is available from which to directly estimate the human toxicity of a chemical. Such epidemiological studies provide a very valuable source of information for risk assessment and, furthermore, offer perhaps the best chance to validate extrapolative risk assessment models. Waiting for this data to emerge, however, is not an ideal approach to public health since disease, often irreversible, will have occurred in at least some segment of the population. For a variety of reasons, epidemiological data are often not available, or are of limited usefulness, to occupational health specialists and regulators. (3) For new chemicals, human exposures may not yet have occurred. For others, exposures may have been so low or restricted to such a small population that effects of the chemical are nearly impossible to detect. Classical epidemiological studies also have well-known design and analytical limitations. (3) Many health effects of concern, including diverse outcomes such as respiratory impairment, neurological effects, and cancers, may not arise or be detectable until years after the causative exposures have ceased or may be the result of progressive accumulation of sub-clinical damage that is not immediately identifiable. (1, 2, 3) Such delayed effects often are not easy to associate with specific occupational exposures and may be difficult to detect epidemiologically. Other limitations of epidemiology, including issues of statistical power, exposure measurement uncertainty, the healthy worker effect, and

misclassification also may make it difficult to detect potentially significant health risks. (3)

Due to these limitations, much effort in risk assessment has gone into the development of methodologies to address less well-documented risks, using models of disease and injury that attempt to predict human health outcomes. Predictive models like these are advantageous to public health protection since they allow potentially significant threats to public health to be considered before disease or injury occurs or is detectable. Unfortunately, all of these predictive approaches are fraught with many uncertainties and limitations which make precise estimates of risk levels impossible. For example, occupational exposures to toxins often involve multiple agents. (1, 3) In this situation, complex dose-response relationships and potential interactions between toxic compounds make it difficult to predict the human health impacts of even well-characterized toxins. For chemicals where human data is lacking or limited, the use of information from animal or other model systems may be required. (22, 26, 39) In these cases, risk assessment must rely on high-dose to low-dose and interspecies extrapolations that introduce considerable uncertainty in potency calculations. Uncertainties with respect to intraspecies variability in response and in exposure estimates further limit the accuracy of many risk assessments.

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In spite of all these uncertainties, the application of scientific principles to assess risks is widely, although by no means universally, accepted. What is the rationale for this? The simplest case for risk assessment is that, without some procedure to identify toxic chemicals and consider their potencies, regulators must either assume the default positions that all chemicals are deadly and should be equally and stringently controlled or that all chemicals are safe and we need not worry about any of them. Clearly, these extreme options do not make much sense. Yet, without some approach to assessing risks, regulatory agencies face just this dilemma.

Indeed, without some evidence of harm or the potential for significant harm, regulatory agencies and society as a whole often choose not to regulate environmental or occupational exposures to chemicals. This situation continues today where many chemicals with weak epidemiological data, and most toxicologically untested chemicals are, by default, essentially regulated as though they are safe. (23, 40) Risk assessment can play an important role in identifying such potential risks and mobilizing regulatory action.

Most efforts at chemical risk assessment have been driven by three factors. One is the diverse nature of the toxic responses and disease endpoints involved; some toxic endpoints are clearly worse than others. The second is the wide range of potencies that toxic agents exhibit; some toxins are clearly 'stronger' than others. The third is that toxicity depends on dose which varies considerably between exposure situations. Toxicologists have demonstrated that, at a given level of exposure, the toxicity of different chemicals can vary by up to several million fold. These differences in potency have been observed in animal model systems, and for a smaller number of chemicals in humans as well, for both acute and delayed effects like cancer. Human exposures to chemical agents also can vary considerably. These variations in potency and exposure levels imply that the human risks posed by different chemicals will vary by many orders of magnitude. From a public health standpoint, occupational health regulatory efforts should be directed towards the worst chemicals (a function of the probability of harm and the potential severity of the outcomes). Ideally, the potent toxins that cause severe, irreversible effects should be more stringently regulated compared to those of lower potency. Greater efforts should be made to minimize occupational exposures to these agents, perhaps by reducing their use in the workplace and they also should be the focus of strict enforcement and monitoring efforts to ensure compliance with regulatory standards. Risk assessment techniques have largely been developed to help regulators take these

wide variations in risk into account in their risk management efforts.

OCCUPATIONAL RISK ASSESSMENT AND RISK MANAGEMENT STRATEGIES

Occupational health decision-making and standard-setting have always been guided to some degree, either explictly or implicitly, by evaluations of risks to worker health and safety. Both quantitative and qualitative approaches have been used in such assessments. In the occupational setting, chemical risk reduction efforts usually include one or more of the strategies outlined in Table 1.

Risk assessments, including both qualitative and quantitative approaches, can play a role in directing such efforts, providing guidance to risk management decisions which might otherwise be driven solely by one-sided analyses of control costs, technological feasibility or by wholly subjective political considerations. Table 2 briefly summarizes some of the potential uses of risk assessment in the occupational setting. In addition to these specific uses, the procedural aspects of risk assessment are themselves important, as they provide a framework that can ensure that occupational health risks are at least considered. These methods can provide information useful in setting exposure limits and in establishing other components of occupational health standards such as hazard communication requirements, engineering controls, and medical removal provisions, among others. Careful assessments of risks also can help regulatory agencies to better target their limited resources towards the most significant risks. Provided **appropriately conservative** assumptions are used, quantitative approaches also can identify **de minimus** risks, ones too small to warrant regulatory attention (although, as will be discussed below, determining appropriate analytical approaches and acceptable risk levels is problematic).

Targeting and choosing appropriate engineering controls also can be facilitated by judicious use of risk assessment, which can identify potentially significant

Table 1: Summary of Occupational Risk Reduction Strategies

1.) Regulation of exposures, through

a) engineering controls (for example, ventilation, closed-loop production technologies, and so forth);

b) process changes, including toxic use reduction and chemical substitution (that is, eliminating or reducing the use of toxins or substituting toxins with non or less toxic agents);

c) worker training;

d) monitoring of exposure levels via area or personal sampling;

e) use of personal protection devices (for example, gloves, respirators, and so forth).

2.) Minimization or treatment of effects

a) Screening for toxic effects with medical removal and/or treatment;

b) Monitoring of dose (for example, blood lead levels) with removal and/or treatment.

Table 2: Potential Uses of Risk Assessment in Occupational Health

1.) identification of risks;
2.) targeting of regulatory attention;
3.) targeting of enforcement and compliance efforts;
4.) evaluation of risk tradeoffs;
5.) identification of **de minimus** risks;
6.) investigation of risk/benefit distributions (even if hypothetical);
7.) identification of data gaps;
8.) guidance in the design of worker training programs and risk communication materials;
9.) guidance in the design of medical monitoring and surveillance efforts;
10.) establishing need for technology-forcing standards.

health risks that should be investigated further or regulated. They also may help in choosing between competing process, design, or control alternatives. For example, some engineering controls, such as ventilation, may shift risks from the workplace to the more general environment. If this results in significant risks to other populations, then alternative management strategies such as toxic use reduction (TUR) should be considered. Risk assessment provides a mechanism that allows these and related questions of risk distribution to be addressed.

With respect to TUR, which may involve substitution of potently toxic chemicals with ones less dangerous, risk assessment allows for the initial identification of the toxic substances to be reduced, replaced, or eliminated. Although one can argue that all chemical use in the workplace should be reduced, given the demands of a modern society, such reduction efforts are likely to occur only if a reasonable case can be made that the chemicals in question pose some significant risk. Qualitative and quantitative risk assessment provide tools that occupational health decision makers can use to more effectively make such a case and can provide a framework within which comparisons of risks between potential chemical or process substitutes can be made. Simplistic evaluations of such chemical risks can, and have in the past, led to the substitution in the workplace of one set of chemical hazards for another.

Risk assessment also may be useful in considering other risk tradeoffs as well, including the potential creation of new workplace risks in the process of dealing with the old. The targeting and design of worker training programs, workplace monitoring efforts, medical surveillance, and epidemiological studies can all benefit from both quantitative and qualitative risk assessment, which can focus attention on the key risk endpoints. In some situations risk assessments also may be useful in establishing probabilities of causality in occupational and environmental compensation disputes.

Finally, quantitative or semi-quantitative risk assessments also may play a role in establishing and justifying technology-forcing standards or goals. Depending on factors such as control costs and technological feasibility, currently available control methods may not be able to eliminate a given chemical exposure. Thus, substantial and in some cases unacceptably high, residual risks may remain. Risk assessment provides a tool to determine whether the feasible control strategies are sufficiently protective of worker health. In some situations, additional reductions in exposure, which will require the development of new technologies, may be required. In other situations, an outright ban on the use of the chemical may be justified.

Although of great importance, risk assessments do not, however, provide a panacea for managing occupational health risks. Some of these assessments may be so uncertain as to provide little practical guidance to the decision makers and their ability to quantitatively estimate human health risks should not be oversold lest excessive reliance on such assessments lead regulators to ignore other important elements in setting occupational standards. These limitations should not, however, cause us to abandon their wise use.

ROLES OF OSHA AND NIOSH

At the federal level, risk management efforts in the occupational arena, including the promulgation and enforcement of occupational standards, are largely the responsibility of OSHA. OSHA is required to consider recommendations from other agencies including the National Institute for Occupational Safety and Health (NIOSH). (2) NIOSH plays an important role in developing and recommending occupational safety and health standards and, among other duties, provides OSHA with scientifically based assessments of worker health and safety issues. Quantitative risk assessment methods are being increasingly relied upon by NIOSH in these evaluations. (5, 19, 20) OSHA is not, however, required to base its decisions on these NIOSH assessments and often relies on the recommendations of other groups including the American Conference of Governmental and Industrial Hygienists (ACGIH). (41) Although NIOSH, ACGIH and other groups often evaluate similar risks, an overall lack of coordination and consistency in the application of risk assessment methodologies between these various groups exists.

The OSH Act established both OSHA and NIOSH and provides the statutory basis for their activities. (2) Among other requirements, the OSH Act states that OSHA must establish standards **"dealing with toxic materials *(which) most adequately assures, to the extent feasible, on the basis of the best available evidence, that no employee will suffer material impairment of health or functional capacity even if such employee has regular exposure to the hazard. In addition to the attainment of the highest degree of health and safety protection for the employee, other considerations shall be the latest scientific data in the field, (and) the feasibility of the standards ...*"** (OSH Act Sec. 6(b)5)

The direct reference to toxic materials in this section

implicitly requires OSHA to make an initial determination as to the toxic potential of a chemical. Such a determination requires, at the very least, a qualitative assessment of the potential hazard or risk posed by the agent in question. Furthermore, the language embodied in the act which reads **"no employee will suffer material impairment of health," "to the extent feasible,"** suggests that the agency must consider the nature, the likelihood of occurrence, and the feasibility of reducing risks to even one employee. Subsequent case law has further delineated OSHA's responsibilities in this regard. Largely as the result of two Supreme Court cases (on the agency's proposed benzene and cotton dust standards), OSHA has been required to demonstrate that its proposed standards reduce **"significant risks to worker health"** (42 a, b). **"Significant"** was suggested to be an increase in lifetime risk of developing cancer of greater than one in 1,000 and that it was more likely than not that harm would occur without regulation. In essence, these rulings have required OSHA to support its standards with some type of risk assessment demonstrating that 'significant risks' to worker health are being addressed. Although the court did not explicitly require the use of quantitative risk assessments, these approaches do provide one of the few tools able to generate reasonable inferences or assumptions about the magnitudes of the risks involved. In practice, OSHA and NIOSH are now using quantitative techniques whenever possible (19, 20) to determine whether proposed regulations pass the threshold test of 'significant risk' using both epidemiology and animal bioassay data.

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The significant risk threshold effectively established by the Supreme Court can be criticized on several grounds. Although the court did not require that OSHA risk estimates be scientifically precise, the requirement that harm be more likely than not to occur if no regulations were to be enacted suggests a higher burden of proof than is actually achievable in most risk assessments. Furthermore, given the uncertainties inherent in the process, risks higher than those calculated using current risk assessment procedures may actually be experienced by susceptible sub-groups of the population (see below for additional comments). A very significant limitation of this requirement is that a numerical significant risk threshold cannot be met for a large number of chemicals because insufficient toxicological data exist to allow for any quantitative estimate of risk to be made. Thus, chemicals which exhibit potent toxicity based on qualitative data (for example, structure activity relationships, short-term tests indicative of genotoxicity, and so forth) may not be regulated. Lastly, aggregate risks resulting from multiple chemical exposures are not explicitly considered. Thus, exposures that result in worker risks considerably above the risk threshold may completely escape regulatory attention.

BRIEF DISCUSSIONS OF SEVERAL IMPORTANT ISSUES

Acceptable Risk: In general, higher risks have been deemed to be acceptable in the management of occupational risks compared to those experienced in environmental settings. (61) For example, excess lifetime cancer risks of less than one in 1,000 have usually been deemed acceptable for workers (see discussion above) while risks as low as one in a million have often been deemed unacceptable in the regulation of environmental carcinogens. The differences in acceptable risk levels may in fact be greater than this because of differing assumptions used to determine the risk estimates — more conservative assumptions are often used in estimating risks due to environmental exposures to carcinogens (for example, NIOSH used a body weight species scaling factor to extrapolate butadiene cancer risks from rodents to humans (19) vs. the more conservative surface area scaling factor currently used by EPA (26)).

The notion of what constitutes an acceptable level of risk in regulatory standard-setting is controversial and is clearly an issue of ethics and policy rather than one of science. (62) Extensive discussion of this issue is beyond the scope of this paper but there are several points worth mentioning. Regulatory decisions regarding acceptable risk levels generally consider two aspects of the risk matrix: 1.) the public health implications of risk level; that is, the total number of expected disease cases or deaths that may be attributable to the exposure in question; and,

2.) issues of ethics and equity pertaining to the imposition of risks on limited numbers of people where the population burden of disease would be expected to be small. (43, 44) Clearly the imposition of small risks on large populations may result in a highly significant exposure-induced disease burden and should be prevented. Just as clearly, the issue goes beyond statistical deaths or cases of disease; a one in 100 excess risk of death applied to a population of five would be expected to yield no actual deaths but would be considered by most to be an unacceptably high risk level. Furthermore, an extensive body of work (as well as a good dose of common sense) indicates that all risks of equal magnitude are not of equal concern to most people. (63, 64) Society cares about other issues as well as the risk level. These issues include whether the risk is voluntary, the individual's perceived and actual control over the risk, the benefits (if any) associated with the risk, and so forth.

Several additional points should also be kept in mind when comparing a risk estimate with an acceptable risk level. First of all, risk estimates in themselves are only that — estimates. Although conservative assumptions are generally used in estimating these risks, our ability to judge the degree of conservativeness for any individual chemical is usually limited (see below). A comprehensive reporting of the uncertainties involved in most numerical estimates of risk would reveal wide probability distributions,which are also likely to be of unknown shape. Actual risks for any given chemical may be higher as well as lower than the estimates calculated using standard quantitative risk estimation procedures, and assignment of a meaningful percentile (for example, fraction of the probability distribution of risk that falls below any given risk level) to these risk estimates is clearly difficult. Secondly, some risk estimates are better than others and the weight given a risk estimate in the risk management process should be related in some explicit way to our confidence in it. Current risk assessments, which usually do not adequately acknowledge their inherent uncertainties, make such evaluations impossible. Thirdly, risk estimates often fail to consider issues such as susceptible individuals and aggregate risks which may well distort regulatory efforts towards less health protective avenues.

Aggregate Risks and Sensitive Populations: Aggregate risks are rarely considered in either occupational or environmental risk management decisions. Workers are often exposed to multiple agents on the job, may be exposed to the same agents via multiple pathways (including exposures that occur outside the job), and may experience additional, non-chemical, job-related risks as well. Many regulations, however, are targeted towards single compounds or single exposure pathways. If, in theory, one accepts a "one in 1,000 excess cancer risk" as "significant" and as a threshold risk level for regulatory action (as implied in the US Supreme Court cases discussed previously (41, 42), then we believe that aggregate risks must be considered when determining whether an occupational regulation is warranted.

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In addition to aggregate risks, the possibility that some members of the population may be particularly susceptible to toxic insults must also be considered. Progress in detecting and identifying genetic traits associated with increased probabilities of contracting disease and increased susceptibility to toxins suggests that wide variations in susceptibility to these agents may occur. (45, 46, 47, 48) Failure to consider such sensitive subgroups may lead to underestimates of both individual and overall population risks. For regulations which are supposed to protect all workers this is a critical issue and provides a strong argument for retaining "conservative assumptions" in occupational health risk assessment (since at this time we have no way of knowing whether sensitive individuals in the human population are more or less sensitive than the animal bioassay systems from which we often extrapolate human risks).

Poorly Characterized Chemicals: Untested or poorly characterized chemicals present another major problem to risk assessment. Of the more than 70,000 chemicals synthesized by humans, less than 10 percent have been toxicologically characterized to any appreciable degree. (26) To date, most untested chemicals have been, by default, assigned toxic potencies of zero in both the occupational and environmental regulatory arenas. (23,

40) Of course establishing an experimentally based quantitative risk estimate for these agents is clearly not feasible (statistical approaches to assigning default potencies to untested chemicals are being considered but to our knowledge have not been used in a regulatory setting). Thus, a blind reliance on threshold risk determinations, such as the one-in-1,000 excess cancer risk discussed earlier, would preclude regulating many chemicals of unknown toxicity. Clearly alternative approaches need to be considered in these situations including the application of technology-based standards where risk levels cannot be estimated.

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Conservativeness: There is currently considerable debate over conservativeness in risk assessment. (23, 40, 49, 50, 51, 52, 53) Although most risk assessors and toxicologists try their best to use the most defensible scientific evidence and methods available to guide their decisions, such judgements may, nonetheless, vary considerably from scientist to scientist. These differences can lead to divergent risk estimates and usually arise from honest scientific disagreements. In the face of these uncertainties, regulators, in consultation with scientists, have attempted to choose "reasonably" (consistent with scientific theory or data) "conservative" (ones judged **unlikely** to lead to an underestimate of true risk) assumptions when faced with scientific uncertainty.

Some argue that the procedures currently in use, notably those associated with extrapolations of human cancer risks from animal bioassays, are too conservative; that is to say that they consistently exaggerate actual risks. If true, such a situation could lead to an inefficient allocation of public health resources towards controlling exposures that actually present minimal risks. (49) Others argue that several of the assumptions in risk assessment are either clearly not conservative or are of questionable conservativeness. A full discussion of this issue is again beyond the scope of this paper and the reader is urged to refer to the additional references as noted above for a fuller discussion. A few points, however, warrant discussion. First, the empirical evidence pertaining to the issue of conservativeness in carcinogen risk assessment appears to us to be weak and inconclusive. This is largely because of limitations in the human epidemiology available; potency estimates based upon epidemiology are available for fewer than 30 agents and these estimates are themselves highly uncertain. (4, 15, 54) Although the accuracy of cancer potency factors derived from animal bioassays is open to question, significant evidence suggests that they do not consistently exaggerate human risk levels. For example, cancer potency factors based on animal bioassays were not inconsistent with human epidemiological data for 18 out of 20 chemicals investigated. (4) For two chemicals, the animal bioassay results appeared to overestimate human risk. (Note that the term **not inconsistent** is used because the results do not really allow for comparisons of the low-dose potencies of the chemicals in question). Furthermore, a recent epidemiological study by NIOSH suggests that the "conservative" EPA cancer potency factor for dioxin cannot be ruled out by the human cancer experience of the best studied cohort of workers occupationally exposed to this agent. (55, 56) Although this study cannot address the possibility that the human low **dose** potency of TCDD is less than that predicted by the extrapolative approach currently used by the EPA, these results clearly do not support this contention. Also note that the epidemiological studies considered above did not, in general, explicitly consider potentially susceptible sub-groups of the population. Such sub-groups are likely to exist and would be expected to experience risks greater than those of the cohorts studied.

In any case, many of the specific issues involved in this debate are not resolvable over the short term and others, such as dose extrapolation models, may never be. Overall, the best **judgement** of many scientists is that the current approach to estimating human cancer risk based on animal bioassays is likely to be "conservative" for most chemicals. The degree of conservativeness, however, is unknown and for some individual chemicals the methods now used may actually underestimate risks. (40) A brief discussion of some of these issues follows.

The MTD Debate. Animal carcinogenicity bioassays are usually performed at the maximum tolerated dose (MTD) and/or some large fraction thereof. (26, 57, 58)

MTD dosing is used to enhance the power of these bioassays to detect a carcinogenic effect (power is an issue because technical and economic considerations limit the number of animals that can be tested to relatively small groups). MTD dosing has been criticized for several reasons. Most significantly, critics argue that these high doses (which are usually much higher than expected human doses) may lead to organ toxicity, inflammation (which may lead to the production of endogenously generated mutagens) and an increase in cell proliferation in target organs of the test species (for example, regenerative proliferation in the liver). (36, 57) Many scientists and a substantial body of research suggests that cell proliferation may enhance carcinogenesis by increasing the rate at which mutations occur in the target organ and/or allowing altered cells to clonally expand their populations. (59, 60) Although this hypothesis is plausible, we should keep in mind that organ toxicity can, in theory, act in the opposite direction. For example, most cancer chemotherapeutic agents in use today are cytotoxins (many of them DNA-damaging agents that are thought to themselves be carcinogenic) that preferentially kill rapidly dividing cells including many that are cancerous and pre-cancerous. MTD-related cytotoxicity may in theory act in a similar fashion, preferentially killing such cells, thus leading to a potential decrease in the ultimate number of tumors observed. This may be a particular problem with animal strains that exhibit high background rates of cancers. For most carcinogens, insufficient data is currently available on the relationships between MTD dosing and the kinetics of cytotoxicity and cell proliferation in target organs to evaluate the significance of these arguments. A more complete understanding of these issues may well allow for better low-dose estimates of risk in the future. Finally, the significance of the MTD issue with respect to many occupational exposures must also be questioned because of the high exposure levels that often occur in the workplace. In the occupational setting, exposures to carcinogens often occur at a significant fraction of the animal MTDs. (59) These higher doses suggest that occupational cancer risks for many chemicals may more nearly mimic those observed in high-dose animal experiments (that is, the uncertainty attributable to the high-dose to low-dose extrapolation should be less).

Susceptibility. The extrapolated carcinogenic potencies of chemicals are usually based on the most sensitive species tested. Some of the species (strains) commonly tested have high background rates of cancer. Taken together these two observations have been used to argue that many of the cancer potencies used by regulatory agencies over-estimate human risks. However, one must keep in mind that: 1.) only two species are usually tested (mice and rats), which does not provide a very broad-based look at interspecies differences in potency; 2.) the human population exhibits a relatively high rate of cancer (although the organ distribution is quite different from that observed in the animal bioassays); 3.) the animal strains tested are highy inbred and will not exhibit the genetic variability associated with disease susceptibility in the human population. Sensitive individuals (for example, those bearing mutations in the tumor suppressor gene p53 (48)) may be at even greater risk than the animals tested. In conclusion, we can not tell where the species tested fall compared to either the average human or susceptible sub-groups in the population. Continued reliance on the most sensitive species appears to constitute a reasonable default assumption unless compelling evidence to the contrary is available.

CONCLUSIONS AND RECOMMENDATIONS

In conclusion, we believe that risk assessment, in some form, has always been and should continue to be used to guide occupational health decision-making. If used appropriately, these approaches can provide useful tools, but are clearly not a panacea, for directing occupational health efforts. Risk assessment methods can provide important procedural guidance to the evaluation of risks and provide a framework that allows risks to be considered before actual impacts to human health have occurred. It is, however, crucial that risk assessment be performed and applied in a fashion that realistically reflects its strengths and weaknesses. Furthermore, the use of risk assessment in the occupational arena must be consistent with occupational health principles. Table 3 lists some of the important issues which we believe need to be considered when using risk assessment to evaluate and to guide efforts to reduce risks to worker health. We believe the recommendations summarized in this Table will improve the use of risk assessment in the occupational health arena and urge that the occupational health community consider them carefully. ▲

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Table 3: Recommendations to Improve the Use Of Risk Assessment in Occupational Health

1.) Occupational health risk assessment methods should be standardized to the extent feasible, while allowing flexibility to consider the best science available.

2.) Additional attention should be paid to the use of risk assessment data by risk managers and regulators. For example, risk managers and regulators should be required to justify decisions which appear to discount risk assessment data.

3.) Risk assessment should rely on careful use of the best science available. To maintain integrity and public trust, the uncertainties inherent in the process, including those that may lead to underestimates as well as overestimates of risk, must be better identified. A fair, balanced approach must be used to evaluate the available scientific information.

4.) The present attempt to be reasonably conservative in the choice of assumptions in risk assessment should remain. Conservative assumptions are the appropriate starting point for more detailed analysis. They do, however, need to better consider the available science, including mechanisms of toxicity. Mechanistic models also should be considered conservatively.

5.) New scientific evidence regarding the toxicity of chemicals should be validated before it is used to supplant conservative assumptions. Guidelines need to be developed for determining what constitutes appropriate validation.

6.) Aggregate risks, untested chemicals and sensitive populations are issues which need critical attention and are not treated conservatively in current approaches to risk assessment. The significance of these issues to worker health risks should receive increased attention.

7.) Risk managers should keep in mind that complex analyses and models are not necessarily better; they often just obfuscate the process making it more difficult for diverse participation in the regulatory process itself. Applying the principle of Occam's razor, we urge that computationally and structurally complicated models that have not been demonstrated to do a better job of predicting risks be viewed with skepticism.

8.) Qualitative representations of risk should receive additional attention since numerical estimates often imply more precision than our current scientific understanding warrants.

9.) **De minimus** or threshold risk findings, because of their inherent uncertainty and the inability to even generate such estimates for many chemicals, should not themselves close the door on regulatory action.

10.) Risk assessment should not be the sole tool used to determine occupational risk management decisions. Other values that should be explicitly considered include: the distribution of hypothetical risks and benefits in the population, the essentiality or need of the process or product, the longevity of the chemical(s) in the environment or in people, feasible alternatives that reduce exposures regardless of risk.

11.) Precautionary principles should receive more attention in regulating occupational risks, especially when dealing with poorly characterized chemicals or complex exposure scenarios. For chemicals that have a poor database, technology-based regulations should be required.

12.) Since risk assessment cannot provide precise, reliable estimates of risk, the best approach for regulating many chemical exposures will require a combination of technology- and risk-based methods.

13.) Risk assessment and risk management decisions should be clearly elaborated and explained via an open process with opportunity for scientific, labor, community, and management participation. Because of the unequal distribution of expertise in this field, we urge that a fund be established to enable worker groups to hire their own experts on toxicological and risk assessment matters.

14.) Worker exposure information should be made more accessible to independent researchers. This will facilitate epidemiological investigations in the work environment, leading to better protection of worker health and ultimately allowing for more robust validations of our risk assessment methodologies against actual human data.

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