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PERMISSIBLE CONCENTRATIONS OF CHEMICALS IN AIR AND WATER DERIVED FROM RTECS ENTRIES: A "RASH" CHEMICAL SCORING SYSTEM

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Many chemicals are of concern to human health, but only a few have epidemiologically derived risk estimates. About 45,000 chemicals are listed in RTECS, most of which have had some testing in subhuman models. RTECS entries range from cellular effects through organoleptic damage to lethality, with many pathological endpoints listed, including mutagenic changes, irritation, teratogenesis, cancer, mortality, etc. However, it is difficult to extend any biological test results to human risk assessments. If the results are extended, the degree of validity is highly uncertain.

This paper describes a logical basis for using the entire complex spectrum of test results to evaluate the overall toxicological potency of a chemical to be assayed (i.e., an interviewing chemical) and describes how to derive tentative, permissible concentrations in air and water for any particular chemical for which no regulatory guidance exists. This approach has been tested for 16 reference chemicals discussed in NIOSH Criteria Documents, EPA-CAG reports, etc. The evaluations are uncomplicated, but occasionally it is difficult to match RTECS entries for two different chemicals. Difficult comparisons may require some familiarity with experimental design and the toxicological literature.

One important product of this novel approach is that a distribution or array of potency values is obtained for any chemical evaluated. This distribution reflects many uncertainties stemming from low sta-

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2. Key words: air, chemical scoring, permissible concentrations, relative potency, uncertainty analysis, water.

3. Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; ADI, acceptable daily intake; AMTL, ambient monitoring trigger levels; B(a)P, benzo(a)pyrene; CAG, Carcinogen Assessment Group; DMTL, discharge monitoring trigger levels; EPA, U.S. Environmental Protection Agency; LDLo, low acute mortality; LD50, lethal dose to 50% of test organisms; MATE, minimum acute toxicity effluents; MEG, multimedia environmental goals; MTL, monitoring trigger levels; NCI, National Cancer Institute; DMNA, nitrosodimethylamine; NIOSH, National Institute of Occupational Safety and Health; NRC, National Research Council; PNA, polynuclear aromatics; OECD, Organization for Economic Cooperation and Development; RASH, rapid screening hazard; RTECS, Registry of Toxic Effects of Chemical Substances; TLV, threshold limit values.

tistical power, experimental design, pharmacological processes, interspecies variability, dose rate, biological effect monitored, route of treatment, etc. The array of relative values for a particular chemical reflects many different biological and physical conditions. The distribution of the array helps to index a composite toxicological profile for many different biological effects resulting from numerous treatment protocols.

To minimize the effect of extreme sensitivity of certain (perhaps novel) biological test models, possible errors in the RTECS database, and possible human pharmacological insensitivity to a particular chemical and/or a particular route of administration, we consider the interquartile range (i.e., the central 50%) of the array of relative potency values between two chemicals being compared as a practical measure of uncertainty. Thus, the range in response derived from variability in relative potency should be useful in addressing the range of response in man as estimated from extrapolations of test data.

INTRODUCTION AND OBJECTIVE

Analyses that estimate permissible concentrations of pollutants in water and air (based on potential health effects) are used to obtain, quickly and cheaply, an approximate idea of the relative hazard of an untested chemical (or technology) or a well-studied chemical under untested conditions. This relative potency or hazard assessment approach is being developed explicitly for setting priorities and research needs related to synfuels-derived contaminants. Because the mutagenic and carcinogenic potencies of different chemicals have been demonstrated to vary by about seven orders of magnitude, this paper will discuss a method for hazard assessment that is designed (1) for ease of evaluation, (2) for accuracy in the range of twofold to tenfold and (3) to estimate the range of uncertainty associated with the best estimate, which should serve to indicate how relevant to human response the best estimate may be. The best estimate and its range can be used to dispense with many pollution-related health-effects considerations. However, apparent problems may be treated in more detail before they can be considered insignificant or judged to require pollution abatement technology. The goal of this paper is to provide an objective, quantitative basis for temporary human exposure guidance. The guidance is to be used in the absence of Federal and state standards or to preview how standards may change as more analytical studies are completed. For example, the Environmental Monitoring Plan for the Synthetic Fuels Corporation (1983) states that the corporation should have the burden of justifying the need to monitor specific unrelated substances and of providing threshold values above which these substances must be monitored.

To provide a comprehensive study for each chemical or mix of interest would be impossible. For example, the cost for testing one chemical or mixture in a simple animal study is $0.5 million—and possibly more unless the initial tests are unambiguous. Testing may then be followed by intensive analytical studies and extrapolation of test results to man. NIOSH Criteria Documents and reports by the EPA-CAG provide quantitative estimates of risk. Other studies, such as the IARC monograph series (1979-1983), provide comprehensive reviews of a given chemical from which one can make some qualitative judgment of the risk level. Thus, a good shortcut is needed to supplement these effort-intensive, but limited-in-scope, activities and to address environmental problems stemming from many different fugitive pollutants around a chemical dump or an industrial plant.

A heuristic approach to health-effects analysis, based on currently available, and constantly increasing, biological test data is shown in Table 1. The method to be proposed in this paper will use data from classes I through V to demonstrate a new chemical scoring process that can be used to guide supplemental monitoring activities (Synthetic Fuels Corp., 1983), to rank different chemical dumps for remedial action or to estimate permissible concentrations of chemical pollutants in air and water.

A relative potency approach will be used. The relative potency approach to assessing chemical toxicity is at the core of most efforts to extrapolate from what is known to some hypothesized exposure situation for which no data are available for quantifying risk in a reasonably direct manner (McMillin et al., 1980; Albert et al., 1983; Jones et al., 1983; Dudney et al., 1983).

Several recent activities have resulted in philosophical guidelines and principles as related to toxicological risks. Some of the concepts are presented in a carcinogenesis framework, but many of the ideas are generally suitable to assessments involving mutagenesis, teratogenesis, acute effects, cardiovascular disease, etc. (i.e., general toxicology). Representative efforts include: the NRC Steering Committee on Identification of Toxic and Potentially Toxic Chemicals for Consideration by the National Toxicology Program (NRC, 1984); Office of Science and Technology Policy (1984); Interdisciplinary Panel on Carcinogenicity (1984); OECD Chemical Group and Step Systems Group Working on Exposure Analysis (1980); Quantitative Approaches of the Carcinogen Assessment Group (Anderson and EPA-CAG, 1983), etc.

Most such activities do not bridge the wide gap between theoretical principles and the needed product—quantitative guidance at a pollution site. The NIOSH, CAG and similar groups have studied a few industries and/or chemicals, but fossil-fuel-based plants must have a reasonably good estimate of pollution levels and toxicities of hundreds or thousands of chemical compounds and mixtures. The Oak Ridge National Laboratory has worked extensively in both theory of risk analysis and technology-specific applications (Walsh et al., 1982; Dudney et al., 1983; Jones et al., 1983; Jones, 1984; Jones et al., 1984).

Many different chemical scoring systems are available, and we have reviewed the important features of more than 40 such systems. Most of the systems are designed for a

TABLE 1
A Heuristic Approach to Human Health Analysis Based on Short-term Biological Tests and Any Available Epidemiological Data

Class	Type of Data	Toxic Agent	Issues to be Resolved
I	Epidemiological	Specific agent of interest	- Study Design - Confounding factors (e.g., age, sex, smoking, exposure to other agents) - Dose–response modeling
II	Epidemiological	Agent similar to Class I	- Class I issues - Pharmacological differences - Toxicological differences
III	Animal	Specific agent of interest	- Collection or simulation of toxic agent - Experimental design - Physical scaling of dose to man - Biological scaling of response to man (e.g., comparison on basis of genetics, morphology, immunology, enzymology)
IV	Animal	Agent similar to Class III	- All Class III issues - Pharmacological differences - Toxicological differences
V	Data of mechanistic value	Potentially all	- Mechanistic understanding of disease processes - Relative behavior of different substances - Appropriate surrogate or indicator agents - Unified model of biological organization (i.e., molecules to man) - Individual variability in biological organization

specific purpose, but some are more general. It may seem foolish to propose still another different chemical scoring system, so in the remainder of this section we will briefly describe six of the best and/or most prominent. From this minireview, it will be clear why we propose a new RASH assessment for chemicals.

Permissible concentrations of 65 chemicals in water are estimated in the NIOSH Criteria Documents, and the EPA-CAG activity has estimated carcinogenic risk for 43 chemicals in water and 21 chemicals in air. These efforts usually involve very limited data selection, selection of one particular dose-response model or selection of some arbitrary level of risk (e.g., 10^{-5}) (Anderson and EPA-CAG, 1983). Permissible concen-

trations given by the Criteria Documents and by CAG reports may have a significant degree of uncertainty but are intended to avoid underestimating risk. For example, the estimates of risk given for bischloromethylether seem to be extremely high. These estimates are high probably because the data analysts chose the most sensitive biological tests and the one-hit model (in the Criteria Document [Sittig, 1980]), a linear model or a linearized multistage model (by the CAG [Albert et al., 1977; Anderson and EPA-CAG, 1983]).

CAG and Criteria Document concentrations were generally derived for extreme safety, or for a risk level of 10^{-5}, although the composite biological potency of bischloromethylether may be substantially lower, based on all the available test data (Lewis and Tatken, 1980). Nevertheless, the Criteria Document and CAG values should be taken as primary standards or "benchmarks" because of the large investment of effort and scientific experience. However, uncertainty in animal models cannot be eliminated and should be used to our advantage in extrapolating to humans. CAG estimates are somewhat different from values in the Criteria Documents. A single number (for relative potency) may help to classify a kinetic system (i.e., a specified biological model under fixed conditions), but cannot be considered adequate to profile the kinetic system under different operating conditions. Thus, there may be no best estimate except for a fixed biological test model subjected to constant biological and physical conditions.

A third benchmark value (in addition to CAG and Criteria Document values) may be derived by relative comparisons between TLVs as defined by the ACGIH (1980b). TLVs are provided for about 500 chemicals.

For most of the chemicals studied, relative potency estimates derived from the three benchmark values are in close agreement; however, for certain chemicals, there may be significant spread. Any scoring method that can serve as a good shortcut to ranking technological priorities or to assessing risk for many unregulated chemicals should be expected to differ somewhat from individual benchmark values. But to be useful, there must be reasonable agreement between estimates of a candidate system and the benchmark values for most regulated chemicals; i.e., no consistent bias.

Most chemical scoring systems are special-purpose systems not well suited to ranking chemical dumps or guiding industrial plants. The systems are generally characterized by (1) dependence on expert judgment, which leads to much controversy between experts when comparing different chemicals, different exposures or establishing remedial priorities, (2) arbitrary safety factors that change from chemical to chemical, (3) very limited selection of test data—even limited selection of data from one dose-response experiment (i.e., not all data from a given study are used [Anderson, and EPA-CAG 1983]), (4) being subject to false positive and false negative conclusions (false conclusions are greatly reduced by using all or much test data and by considering the complex progression of toxicological responses, in contrast with assessment activities that select one or two biological tests and on this basis consider potential risks to humans), (5) arbitrary combination of numerical subscores, (6) inaccuracy when

compared with the benchmarks (which are subject to errors, but because of the extensive analytical effort of a great many experts, the benchmark values are assumed to be accurate in this analysis) and (7) lacking a reasonable estimate of possible uncertainty. For general problems, two of the more prominent scoring systems are the EPA-MATE/MEG approach (Kingsbury et al., 1979) and the method of McMillin et al. (1980), commonly referred to as the Monsanto system.

The MATE/MEG approach is based mostly on the rat oral LD_{50} for some chemicals and the NIOSH ordering number for other chemicals. The ordering number is a four-digit number that simply reveals the history of toxicity testing on a specific chemical—nothing more. For example, the first digit corresponds to the "highest priority species" that has been tested and found to have a positive response. Species assignments include: human = 7; monkey = 6; domestic animal = 5; rat = 4; mouse = 3; and hamster = 2. This first digit dominates the resulting hierarchy.

The EPA is currently reviewing a report on MTLs for process characterization studies (Kingsbury and Chessin, 1985). The MTLs are offered to guide data acquisition but are not intended for risk assessments or to identify concerns. Values are given for ambient conditions (AMTL) for a 24-hr exposure and for discharge conditions (DMTL) for a 15-min exposure in air, water and soil. It is assumed that DMTL = 100 x AMTL (based on 24 hr/15 min = 96) with some exceptions for irritants, toxicants known to produce late somatic effects and chemicals that persist in air or water.

Separate values are also given for potential health effects, zero threshold considerations and potential environmental effects. Uncertainty or safety factors of 10, 100 and 1000 are assigned depending on available data. The AMTL value for what is called a "nonthreshold" pollutant is defined as corresponding to an estimated human cancer risk of 10^{-5} in 70 years. Based on the CAG values, the DMTL values correspond to a cancer risk of 10^{-3} in 70 years.

For MTLs, cancer is taken to be independent of route of intake. A potency index, which equals (Incidence of Tumors in Animals)$(\text{dose})^{-1/3}(100)$, serves to determine trigger levels for many nonthreshold chemicals. The values may be modified according to absorption factors for inhalation or ingestion.

For the Monsanto Corporation, McMillin et al. (1980) used production volumes, emission factors, atmospheric half-lives and potency relative to B(a)P to rank atmospheric pollutants. They

> decided that the potency of the possible and probable carcinogens would be determined, where possible, by the average of the mutagenic potency relative to benzo(a)pyrene using two different mutagenic tests and the carcinogenic potency relative to benzo(a)pyrene using two species or routes of administration.

McMillan and co-workers also reviewed 125 chemicals and found that required data were unavailable for many compounds. Thus, they developed a more relaxed system to compare relative potencies. Features of this system included the following: (1) potency

was an average of one value for mutagenesis and one value for carcinogenesis; (2) missing data were treated using an average from other compounds within a chemical group; (3) B(a)P was used as the standard because of the availability of data from a large number of tests; (4) relative carcinogenic potencies were based only on data from the same species and route; (5) when several potencies were computed, the log average was used; (6) average mutagenic potencies were assigned to test compounds—even if those compounds were found to be negative by the test concerned; and (7) for test systems without (B(a)P data, secondary standards were used.

Although the Monsanto system seems to be one of the better general-purpose scoring systems, several improvements are needed for many practical applications. Desirable modifications include: (1) quicker and simpler access to the toxicological literature—McMillin reviewed 2300 publications to rank 125 chemicals; (2) potency factors should be based on the entire toxicological profile of an interviewing chemical or technology; (3) only real data should be used in preference to extrapolated values, i.e., average values from chemical homologues should be assigned for missing data on the chemical of interest only as a last resort (if all available test data on the chemical of interest are used, then it should not usually be necessary to extrapolate from chemical homologues); (4) the computation of relative potencies should be carefully prescribed when much relevant data are available, but the algorithm should be subject to several less rigorous modes of comparison when very limited toxicological testing has been performed; and (5) a meaningful measure of uncertainty should be provided to illustrate the consistency of the test data and the mode of comparison described in point 4.

Thus, in this paper we propose to use all existing toxicity test data that can be evaluated by many different analytical techniques. The scatter of all the numerical evaluations attempted probably serves as a useful measure of total error in the system, i.e., random or statistical sampling error plus the much larger error descriptive of deviations between different experimental designs and the true scenario of interest.

Because we plan to rely on readily available information—as exemplified by the NIOSH single-source document for basic toxicity information and for other data (i.e., RTECS)—many backup considerations are desirable to help flag concerns that may result from chemicals that test either as false negatives or false positives, as well as to help index overall uncertainty.

The backup logic is especially attractive because

> the metabolism of a toxicant may differ between test species and humans in ways that produce false-negative or false-positive results with regard to possible human hazards. The appropriate test battery may be incompletely performed, but there may be other data, such as extensive information on the mechanisms of action in several species, to obviate a need for additional tests (NRC, 1984).

Also, "it should be emphasized that calculating quantitative estimates of cancer risk does not require that an agent be a human carcinogen" (EPA, 1984).

We have developed (but not published) a very complex, idealized and tiered logic tree (which selectively chooses from toxicity data) that would probably be our preferred approach if large amounts of biological test data were available. However, in practice, test data are usually very scarce. It is usually necessary to consider all existing test data for both acute and chronic effects that encompass both *in vitro* and *in vivo* test models, but this simple act helps greatly to obviate the false negatives and false positives. Even considering all levels of toxicity data, many chemicals will be untested or tested in only one or a very few biological models that may be very poor analogues of man.

METHODS

Mechanisms of action: Usefulness of RTECS comparisons. Although the relative potency approach is used extensively in most chemical assessments, it is frequently and harshly criticized by some, who sometimes accept the general concept in a slightly different format—e.g., structure-activity comparisons.

According to Saffiotti, potency is measured by an effect that is produced by an interaction of the agent with a host. Thus, effects are dependent on the conditions under which the interaction occurs.

> Therefore, we are measuring something that is a variable by itself. At the present time we find such a marked variation in the response, both at the inter-individual level, particularly as it applies to people, and at the species-to-species or biological system to biological system level, that we cannot really extrapolate the magnitude of an effect as measured in one case to the prediction of an effect in another (Saffiotti, 1980).

The etiological molecular processes of late somatic effects such as cancers or cardiovascular diseases are much studied but incompletely understood. Correspondence between molecular interactions and human diseases have not been established; however, there is generally good correlation between DNA damage and initiation of primordial carcinogenic lesions (Ashurst et al., 1983; Rajewsky, 1972; Farber, 1973; Brooks and Lawley, 1964; Amlocher et al., 1977). Furthermore, there is strong and rapidly increasing evidence that compensatory cellular proliferation in response to toxic injury is a direct quantitative measure of induced carcinogenic promotion (Jones et al., 1983; Jones, 1984; Jones et al., 1984; Greenfield et al., 1984; Cohen et al., 1982; Argyris and Saga, 1981; Evans et al., 1978; Shami et al., 1982; Ying et al., 1981).

Significant doses of most chemicals can cause irritation, focal necrosis, compensatory cellular proliferation and a general progression of toxic response symptoms ranging from acute transitory effects to late (or chronic) somatic effects. Because of these factors and because of the general correspondences outlined above, the relative potency of a chemical should maintain some degree of consistency when measured in various biological models, spanning molecular interactions to organoleptic processes, when pharmacological toxification/detoxification processes have been taken into account

(Carver et al., 1979; Meselson and Russel, 1977; Bridges, 1980; Heddle and Athanasiou, 1975; Ames, 1979; Bender, 1980). Of course, some variability must occur depending on the pathological effect observed, dose level, dose rate, species, strain, age, nutrition, environmental conditions, pharmacological rate constants, enzyme inventory, membrane permeability, route of chemical intake, chemical carrier or aerosol used and pathological protocol of diagnosis, among others. These and many others processes can induce variability in the potency of one particular chemical relative to a reference chemical. In many cases the range may be small, but in some cases the range may encompass orders of magnitude. Usually, in any particular biological study, the level of response is highly sensitive to only one or a few of the listed variables. Thus, one observes a fairly stable relative potency value instead of a potency value that has great variability. However, experimental and physical parameters can be adjusted to illustrate the extreme effect. We consider the range of uncertainty to be one of the *extremely useful parameters of human risk* associated with a given chemical, in contrast to Dr. Saffiotti, who considered the variability as an impediment to risk studies. The range in response derived from variability in relative potency should be useful in addressing the range of response in man as estimated from extrapolations of test data and also the range of individual sensitivity of animals within a given biological test model. The other scoring methods which we have reviewed have no comparable measure of uncertainty.

The relative potency approach provides a framework for the use of multiple models and data bases to estimate the potential impacts of chemicals about which we know little. For example, if sufficient human exposure-response data exist, it is possible to make direct estimates of health risk in the exposed population. If sufficient human data are not available, the relative potency method can be used to consider all relevant biological test data as long as the chemical of concern and the reference chemical have both been tested in the same biological model (preferably under the same experimental conditions). In this framework, we can also choose different models of dose response and judge the predictability of various subhuman systems as indicators for human health effects.

Sources of data. There are many well-known ways to collect test data on a chemical of interest. Examples include: Chemical Abstracts, Carcinogenesis Abstracts, Medline, Toxline, Cancerline, Index Medicus, Documentation of the Threshold Limit Values (ACGIH, 1980a), Patty's Industrial Hygiene and Toxicology (Clayton and Clayton, 1981), Criteria Documents, Survey of Compounds which Have Been Tested for Carcinogenic Activity (NCI, 1961-1973), National Toxicology Program: Second Annual Report on Carcinogens (U.S. Department of Health and Human Services, 1981), etc.

Data selection requires painstaking consideration in the Criteria Documents, CAG reports and the McMillin/Monsanto method. It appears that the data selection effort offers the greatest opportunity to shorten the evaluation or scoring process. Because it is both difficult and controversial to select the most relevant test data given the condition that maximum resources are available (Anderson and EPA-CAG, 1983), we

decided to use the entire toxicological testing profile as listed in an updated and supported single-source document.

The RTECS is published annually, and the 1980 publication (in 1982) contained 45,156 substances.

> By presenting data on the lowest reported doses that produce effects by several routes of entry in various species, the Registry furnishes valuable information to those responsible for preparing safety data sheets for chemical substances.
>
> It is not the purpose of the Registry to quantitate a hazard through the use of toxic concentration or dose data that are presented with each substance. UNDER NO CIRCUMSTANCE CAN THE TOXIC DOSE VALUES PRESENTED WITH THESE CHEMICAL SUBSTANCES BE CONSIDERED DEFINITIVE VALUES FOR DESCRIBING SAFE VERSUS TOXIC DOSES FOR HUMAN EXPOSURE (Lewis and Tatken, 1980.)

However, in our opinion, tentative, permissible exposures for many different chemicals must be derived. Also, the authors of the RTECS most likely did not anticipate our particular use of the RTECS database. Risk assessments and chemical scoring *must* be performed. For this particular application we have chosen RTECS to be the most practical and convenient single-source reference, but our RASH method could use other sources of data.

Rules for RTECS comparisons. According to the RTECS listings, one may find that x (mg/kg) of a chemical has produced a particular effect such as LDLo in a particular species (i.e., low acute mortality) and y (mg/kg) of B(a)P or some other reference chemical tested by some other investigator was required to induce LDLo in the same species. The potency of the first chemical relative to the standard or reference chemical would be y/x. Thus, if the reference chemical was considered by NIOSH Criteria Documents, CAG, or some other regulatory agency to be safe at a concentration in water of 1 μg/L, then the unregulated chemical could be limited to (1 μg/L)/(y/x).

Another type of comparison of RTECS entries is that x (mg/kg) of a chemical produced an effect such as unscheduled DNA synthesis in 24 hr, but x (mg/kg) of B(a)P caused unscheduled DNA synthesis in 3 hr. The relative potency of the interviewing chemical could then be taken as 3/24 that of B(a)P. Some comparisons will require both techniques. In this paper, we are simply using different biological test results; we are not suggesting that unscheduled DNA synthesis, delayed DNA synthesis, etc., are direct measures of carcinogenesis and mutagenesis. However, the array of different potency values stemming from all the different tests help to index the toxicity profile of any chemical of interest. When computing the array of relative potency values, one should use a consistent system of units for all comparisons, i.e., either mg or μmol. Units should not be mixed when going from test to test.

For chemicals that have 20 or more RTECS entries, it may be straightforward to match several RTECS entries (i.e., "exact" matches) between B(a)P and the interviewing chemical. Sometimes it is necessary to use secondary standards to supplement B(a)P.

The chemicals chosen as secondary standards should have several RTECS entries that match the interviewing chemical *and* several RTECS entries that match the primary standard, i.e., B(a)P in our case. In this paper, benzene, cadmium and DMNA (N-nitrosodimethylamine) were sometimes used as secondary standards. Their median potency values relative to B(a)P were 0.079, 0.0050 and 0.23, respectively.

For some chemicals that have a small number of RTECS entries, it may be difficult to match the primary and secondary standards in an "exact" match. Often, however, "near" matches are possible. For example, lethality endpoints of LD_{50} or LDLo may be matched across species. Also, certain routes of intake in the same species may be compared; e.g., intraperitoneal injections may be matched with subcutaneous injections, intramuscular injections, certain implants, etc., but may not compare well with intravenous or intracerebral injections. Many other examples of "near" matches can be given.

The third and more difficult mode of comparison of RTECS entries requires a significant degree of experience with the toxicological literature and with dose-response modeling. This third mode is referred to as "reasonable" comparisons. These comparisons are needed for chemicals that have had limited testing or have been tested by a few novel assays that do not match tests of the primary and secondary standards. This mode of comparison is more subjective and can be as good or as bad as the experience of the person making the comparison. We feel that "reasonable" comparisons can produce good estimates if the logic is well based (e.g., see Jones and Walsh, 1985; Jones et al., 1984; Jones et al., 1983). Limited space prohibits a complete description of "reasonable" matches, but the data in Table 2 illustrate the mechanics of the relative comparisons. Basic relative potency comparisons were described in the first two paragraphs of this section. If secondary standards are used, the comparison is only slightly more complex. For example, in Table 2, LDLo for subcutaneous (scu) injections in rabbits (rbt) is 300 mg/kg for arsenic and 6 mg/kg for cadmium. The relative potency is 6/300. Because the potency of cadmium relative to B(a)P is 0.079, the potency of arsenic relative to B(a)P is $(6/300)(0.079) = 1.6 \times 10^{-3}$.

Although many "reasonable" comparisons are difficult and subjective, the interquartile range is a measure of the success of the comparison, and there can be much stability through the "exact," "near" and "reasonable" modes of comparison—provided the modeler is careful.

From the array of potencies for a particular chemical, we select the median potency as most characteristic of the interviewing chemical relative to the standard and the interquartile range as the most practical estimate of uncertainty. The range will probably span as many processes as are reflected in the tests used to make the comparisons, e.g., random statistical uncertainty, variables of experimental design and variables of individual response (e.g., enzyme levels). Thus, the characteristic toxicological profile derived from many comparisons may in some cases be more representative of an interviewing chemical than data obtained from a carefully planned and analyzed

TABLE 2
Comparison of the Toxicity of Arsenic with the Toxicity of B(a)P Aided by the Use of Cadmium, Benzene and N-nitrosodimethylamine as Secondary Standards (symbols are the same as those in NIOSH-RTECS)

Chemical	Biological Test[a]	Type of Estimate	Dose	Toxic Effect	RTECS Reference	Ref. #	Potency Relative to B(a)P
("Exact Comparisons")							
Arsenic	scu-rbt	LDLo	300 mg/kg	--	ASBIAL	24, 442, 38	
Cadmium			6 mg/kg	--	PROTA	--, --, 55	1.6×10^{-3}
Arsenic	ipr-mus	TDLo	40 mg/kg/(preg.)	TER	TJADAB	15, 31A, 77	
B(a)P			240 mg/kg/(11-15D preg.)	TER	ADTUAS	7, 3, 70	6.0
Cadmium			2248 µg/kg/(8D preg.)	TER	TJADAB	13, 33A, 76	4.4×10^{-3}
Arsenic	ipr-gpg	LDLo	10 mg/kg	--	CRSBAW	81, 164, 18	
Benzene			527 mg/kg	--	HBTXAC	1, 42, 56	0.26
("Near Comparisons")							
Arsenic	ipr-mus	TDLo	40 mg/kg/(preg.)	TER	TJADAB	15, 31A, 77	
Benzene	scu-mus	TDLo	2700 mg/kg/(13D preg.)	TER	AMBMAS	17, 285, 70	0.34
B(a)P	scu-mus	TDLo	240 mg/kg/(11-15D preg.)	TER	PSEBAA	135, 84, 70	6.0
Arsenic	img-rat	LDLo	20 mg/kg	--	NCIUS	43-64-886, SEPT. 70	
Benzene	ipr-rat	LDLo	1150 mg/kg	--	TXAPA9	1, 156, 59	5.8×10^{-2}
Arsenic	scu-gpg	LDLo	300 mg/kg	--	ASBIAL	24, 442, 38	
Benzene	ipr-gpg	LDLo	527 mg/kg	--	HBTXAC	1, 42, 56	8.8×10^{-3}
("Other Reasonable Comparisons")							
Arsenic	scu-rbt	LDLo	300 mg/kg	--	ASBIAL	24, 442, 38	
Benzene	ivn-rbt	LDLo	88 mg/kg	--	JTEHD6	(Suppl. 2), 45, 77	1.5×10^{-3}
DMNA	ivn-rbt	LDLo	40 mg/kg	--	BJIMAG	11, 167, 54	3.2×10^{-2}
DMNA	ipr-mus	LDLo	9 mg/kg	--	TXAPA9	23, 288, 72	7.2×10^{-3}
B(a)P	ipr-mus	LDLo	500 mg/kg	--	TXAPA9	23, 288, 72	1.7
Benzene	ipr-rat	LDLo	1150 mg/kg	--	TXAPA9	1, 156, 59	1.9×10^{-2}
Benzene	irp-gpg	LDLo	527 mg/kg	--	HBTXAC	1, 42, 56	8.8×10^{-3}
Cadmium	ims-ham	LDLo	25 mg/kg	--	NCIUS	PB-43-64-886	6.6×10^{-3}
Arsenic	ipr-mus	TDLo	40 mg/kg/(preg.)	TER	TJADAB	15, 31A, 77	
Cadmium	ivn-rat	TDLo	1250 µg/kg/(9D preg.)	TER	EVHPAZ	28, 245, 79	2.5×10^{-3}
Cadmium	ivn-ham	TDLo	2 mg/kg/(8D preg.)	TER	EXPRAM	25, 56, 69	4.0×10^{-3}

TABLE 2 continued

Chemical	Biological Test[a]	Type of Estimate	Dose	Toxic Effect	RTECS Reference	Ref. #	Potency Relative to B(a)P
Arsenic	orl-mus	TDLo	120 mg/kg/(preg.)	TER	TJADAB	15, 31A, 77	
B(a)P	orl-rat	TDLo	1000 mg/kg/(preg.)	TER	EXPHAN	20, 224, 64	8.3
Arsenic	ipr-gpg	LDLo	10 mg/kg	—	CRSBAN	81, 164, 18	
B(a)P	ipr-mus	LDLo	500 mg/kg	—	TXAPA9	23, 288, 77	50
Benzene	ipr-rat	LDLo	1150 mg/kg	—	TXAPA9	1, 156, 59	0.58
Benzene	ivn-rbt	LDLo	88 mg/kg	—	JTEHD6	(Suppl. 2) 45, 77	4.4×10^{-2}
Cadmium	scu-rbt	LDLo	6 mg/kg	—	PROTA	--, --, 45	4.7×10^{-2}
Cadmium	ims-ham	LDLo	25 mg/kg	—	NCIUS	pH-43-64-886	0.20
DMNA	ivn-rat	LDLo	40 mg/kg	—	BJIMAG	11, 167, 54	0.96
DMNA	ipr-mus	LDLo	9 mg/kg	—	TXAPA9	23, 288, 72	0.22
Arsenic	scu-gpg	LDLo	380 mg/kg	—	ASBIAL	24, 442, 38	
Cadmium	scu-rbt	LDLo	6 mg/kg	—	PROTA	--, --, 55	1.6×10^{-3}
Cadmium	ims-ham	LDLo	25 mg/kg	—	NCIUS	pH-43-64-886	6.4×10^{-3}
Benzene	ivn-rbt	LDLo	88 mg/kg	—	JTEHD6	(Suppl. 2), 45, 77	1.5×10^{-3}
B(a)P	ipr-mus	LDLo	500 mg/kg	—	TXAPA9	23, 288, 72	1.7
DMNA	ivn-rat	LDLo	40 mg/kg	—	BJIMAG	11, 167, 54	3.2×10^{-2}
DMNA	ipr-mus	LDLo	9 mg/kg	—	TXAPA9	23, 288, 72	7.2×10^{-3}
Arsenic	imp-rbt	TDLo	74 µg/kg	ETA	ZEKBAI	52, 425, 42	
B(a)P	ipr-rat	TDLo	16 mg/kg	ETA	BJCAAI	12, 65, 58	0.21
B(a)P	ims-rat	TDLo	5 mg/kg	ETA	VPITAR	30, 31, 71	6.7×10^{-2}
B(a)P	scu-mus	TDLo	1000 µg/kg	ETA	TRMAAY	29, 109, 71	1.3×10^{-2}
B(a)P	ivn-mus	TDLo	10 mg/kg	ETA	JNCIAM	1, 225, 40	0.13
B(a)P	ipr-mus	TDLo	200 mg/kg	CAR	BJCAII	39, 761, 79	2.7
B(a)P	scu-mky	TDLo	40 mg/kg	ETA	PSEBAA	127, 594, 68	0.53
B(a)P	scu-ham	TDLo	400 mg/kg	ETA	CNREAS	32, 360, 72	5.3×10^{-2}
DMNA	ipr-rat	TDLo	20 mg/kg	NEO	BJCAAI	41, 385, 80	6.4×10^{-2}
DMNA	ims-rat	TDLo	18 mg/kg	ETA	INURAQ	4, 39, 66	5.8×10^{-2}
DMNA	ivn-rat	TDLo	18 mg/kg	ETA	INURAQ	4, 39, 66	5.8×10^{-2}
DMNA	ipr-mus	TDLo	7 mg/kg	NEO	CBINA8	1, 395, 70	2.2×10^{-2}
DMNA	scu-mus	TDLo	70 mg/kg/1W-C	NEO	BJCAAI	20, 871, 66	0.22
DMNA	ipr-rat	TD	30 mg/kg/100-C	ETA	GISAAA	45(4), 17, 80	9.6×10^{-2}
DMNA	ipr-mus	TD	14 mg/kg	ETA	CNREAS	30, 11, 70	4.5×10^{-2}
DMNA	ipr-mus	TD	10 mg/kg	ETA	JNCIAM	62, 1199, 79	3.2×10^{-2}
DMNA	ipr-rat	TD	30 mg/kg	NEO	BJCAAI	29, 50, 74	9.6×10^{-2}

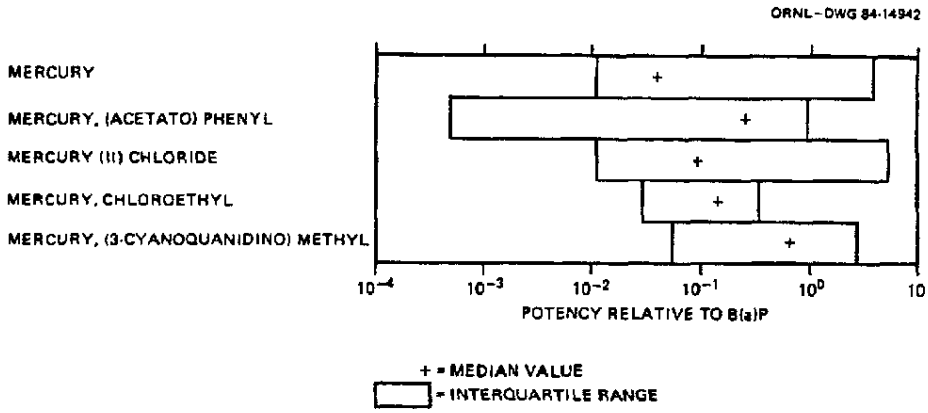

FIGURE 1. A comparison of the toxicity of metallic mercury to the toxicity of four important organic and inorganic mercury compounds.

study of laboratory animals. Because we are using upper 95% estimates or concentrations corresponding to a risk level of 10^{-5} from the Criteria Documents and CAG for our chosen standards (e.g., B[a]P) and are also using a relative potency scheme, the estimates of permissible concentrations derived by our RTECS comparisons should also be considered as very approximate upper estimates of risk for most of the chemicals being assayed. A larger safety margin could be attained if the upper limit of the interquartile range were used instead of the median value. However, for many practical concerns, this degree of added safety is unnecessary and expensive.

RESULTS

The Criteria Documents and other comparable activities often include chemical derivatives with the precursor chemical when permissible concentrations are derived. Sometimes the daughter chemicals have similar pharmacological, absorption, transport, conjugation and elimination rates, and sometimes the rates are very different. The critical organ may be different, and the daughter may be more or less toxic than the parent. Figure 1 illustrates the toxicological profiles of elemental mercury and representative mercury derivatives. Of course, the overall toxicological potency will include pharmacological processes that can be greatly different for organic and inorganic compounds of mercury. The persistent problems in risk analysis activities are also common to the RTECS database. Frequent problems include: (1) in some cases very few biological tests are available for a particular chemical; (2) the entries (tests conducted) for an interviewing chemical do not correspond to entries for the reference or comparison chemicals; (3) the biological test data for some chemicals, such as arsenic

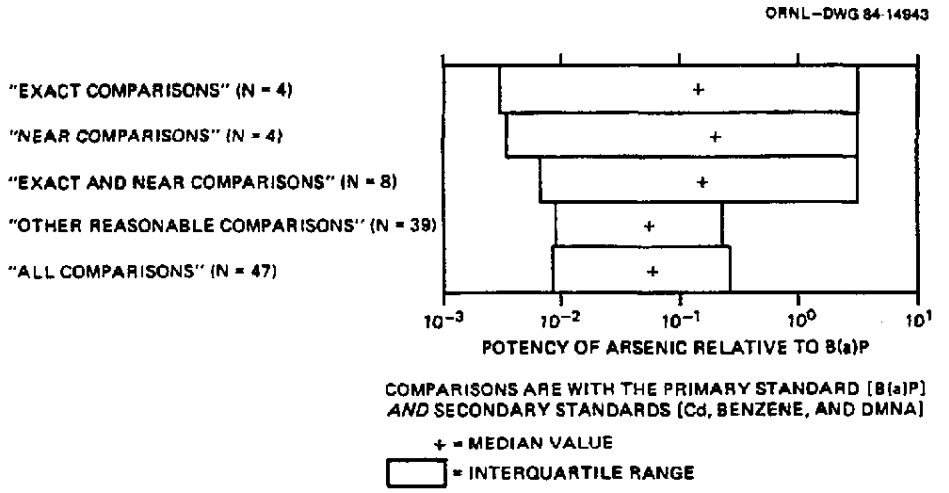

FIGURE 2. Variations in the estimated potency of arsenic as different comparisons were made from RTECS entries.

and bischloromethylether (and previously with benzene), may be quite ambiguous, or erroneous tests may have been conducted. Table 2 and Figure 2 illustrate the effect, on the median potency and the interquartile range, of different modes of relative comparisons of the RTECS listings. Arsenic is a difficult chemical to evaluate because, according to some (e.g., see Gori, 1980), it is a chemical needed for the biological processes of hemopoiesis and phosphorylation. However, according to others, it has yet to be demonstrated that arsenic is essential or needed in physiological processes in man. Arsenic is toxic at higher doses and induces tumors in man. Many other chemicals are essential at low concentrations, but can be toxic or carcinogenic at higher doses. For example, a toxic dose of selenium is only about twice the desired nutritional intake. Thus, dose-response curves that are of a nonsymmetric U-shape are typically envisioned for a large number of chemicals, and any chemical (even oxygen or water) can be used to stimulate a complex spectrum of toxicological effects that could include mutagenesis and enhanced tumor potentiation (Jones et al., 1983). However, carcinogenesis testing in animals under strict "one chemical treatment" protocols is negative. Figure 2 illustrates the high degree of stability in the somewhat subjective process of deriving relative potency values from RTECS entries. Orders of magnitude range in relative potency and/or in different biological responses should come as no shock to persons of diverse biological experience. However, to certain specialists, large ranges are often confusing. Large ranges are often forgotten at the end of assessments or standard setting activities. But uncertainty is ubiquitous to permissible concentrations, ADIs, and risk assessments.

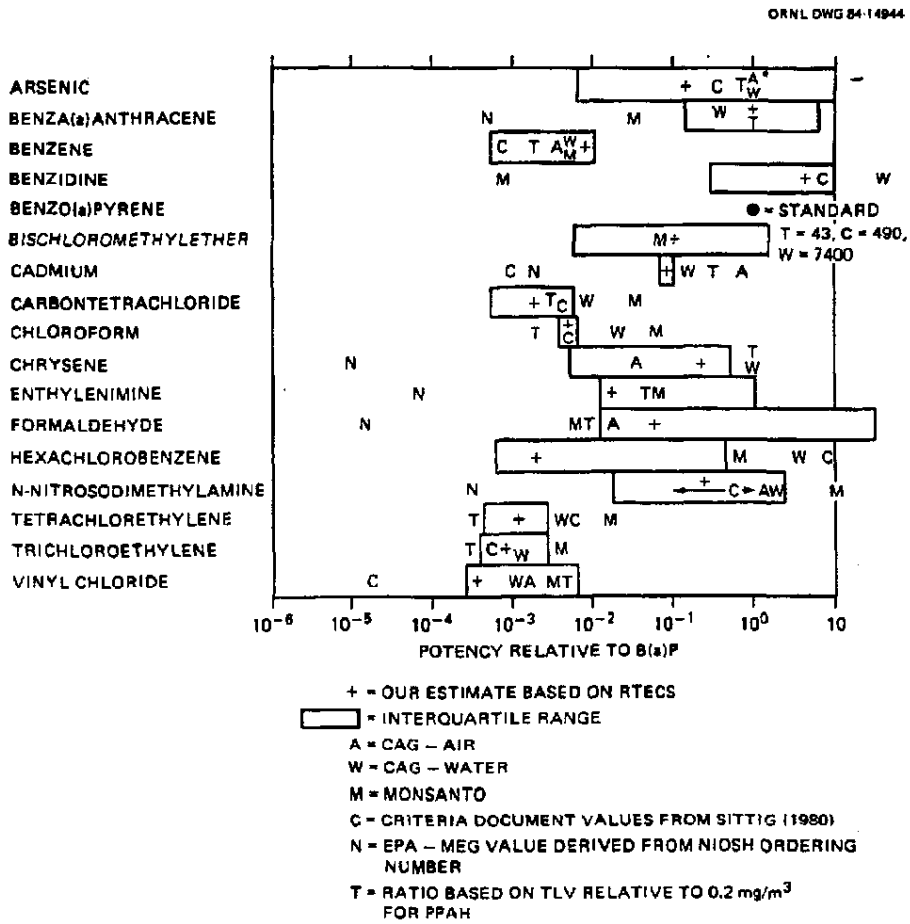

FIGURE 3. Relative toxicities of 16 well-documented chemicals as estimated by EPA-CAG, Monsanto, Sittig (1980), EPA-MEG, ACHIG-TLVs, and our "New Health Effects Scoring Model."

There are two basic approaches for dealing with uncertainty. The first approach is to apply large safety factors to account for uncertainties in data and analytical models and, from this process, to recommend a precise estimate of an "acceptable" concentration. The second is to use currently available analytical models and data and to estimate an "acceptable" concentration and the range of possible uncertainty. The first method

TABLE 3
Permissible Concentrations in Water and Air Based on (a) CAG Values for PNAs in Water, (b) a Permissible Risk of 10^{-5} and the CAG Risk Estimator for Nitrosodimethylamine in Air (i.e., $2.9 \times 10^{-3}/[g/m^3]$) and (c) Relative Potency Factors Derived from RTECS Entries

	Water							Air	
Chemical	c^b (µg/L)	w^c (µg/L)	t^d (µg/L)[e]	Interquartile Range of t (µg/L)[e]	Number of Entries in RTECS 1980	Number of RTECS Comparisons	Toxic Effect in RTECS[f]	Values Derived from RTECS Comparisons ($\mu g/m^3$)[g]	Interquartile Range ($\mu g/m^3$)[g]
Anthracene	9.7×10^{-3}	0.028	0.28	0.05 to 1.1	7	5	I,M,N	8.3	1.5 to 33
Arsenic	0.02	0.022	0.18	8.8×10^{-3} to 4.2	9	47	E,(M),T	5.2	0.26 to 120
Benz(a)anthracene	9.7×10^{-3}	0.028	0.028	4.5×10^{-3} to 0.22	20	9	M,N,T	0.83	0.13 to 6.4
Benzene	15	6.6	5.6	2.5 to 51	31	5	E,I,M,N,T	170	75 to 1,500
Benzidine	1.67×10^{-3}	1.2×10^{-3}	6.7×10^{-3} (0.028)	2.8×10^{-3} to 0.093 Standard	22	7	M,M,T	0.20 (0.83)	0.083 to 2.8 Standard
Benzo(a)pyrene	9.7×10^{-3}	0.028			85	Standard	E,I,M,N,T		
Benzo(e)pyrene	--	--	0.23	0.045 to 0.85	12	9	M,N	6.9	1.3 to 25
Biphenyl	--	--	22	12 to 25	2	3	I,T	640	360 to 750
4-Biphenylamine	--	--	0.088	4.7×10^{-3} to 0.37	18	13	M,M,T	2.6	0.14 to 11
Bischloromethylether	2.8×10^{-5}	3.8×10^{-6}	0.31	0.018 to 4.7	14	13	M,T	9.2	0.52 to 140
Bis(2-ethylhexyl)-phthalate	5,000+	--	100	36 to 850	14	15	E,I,T	3000	1000 to 25,000
Butyl-benzylphthalate	5,000+	--	120	8.1 to 370	1	7	T	3600	240 to 11,000
Cadmium	10	0.26	0.35	0.25 to 8.39	18	5	E,M,T	18	7.5 to 12
Caffeine	--	--	1.1	0.035 to 4.5	54	13	E,I,M,T	32	1.0 to 130
Carbon tetrachloride	2.6	4.0	13	4.8 to 53	38	7	I,M,T	380	140 to 1600
Chloroform	2.1	1.9	5.6	4.1 to 7.8	29	4	E,I,M,T	170	130 to 230
Chromium	6.0×10^{-3}	--	7.8×10^{-3}	2.2×10^{-3} to 0.014	3	18	(M)	0.23	0.06 to 0.42
Chrysene	9.7×10^{-3}	0.028	0.13	0.055 to 5.6	8	6	M,N	3.8	1.7 to 170
Dibenz(a,h)anthracene	9.7×10^{-3}	0.028	0.028	9.3×10^{-3} to 0.20	35	16	M,N,T	0.63	0.28 to 5.9
Di-n-butylphthalate	5,000+	--	28	1.8 to 250	6	10	E,T	830	52 to 7500
Diethylphthalate	5,000+	--	25	6.7 to 390	8	13	E,I,T	750	200 to 12,000
7-12,Dimethylbenz(a)-anthracene	9.7×10^{-3}	0.028	0.023	2.5×10^{-3} to 0.044	77	27	E,I,M,N,T	0.69	0.08 to 1.3
2-4,Dimethylphenol	Minimize Contact ND	--	4.8	0.97 to 14	4	6	M,T	140	29 to 428
Di-n-octylphthalate	5,000+	--	280	33 to 2500	4	16	E,I,T	5900	988 to 75,000
Dodecane	--	--	1.6	1.3 to 22	1	3	(M)	49	38 to 640
Ethyl alcohol	--	--	36	16 to 175	40	22	E,I,M, (M),T	1100	460 to 5200
Ethylene oxide	--	--	1.3	0.082 to 2.8	19	9	E,I,M,N,T	38	2.4 to 59
Ethyleneimine	--	--	2.2	0.028 to 2.3	23	4	I,M,N,T	64	0.83 to 69
Fluoranthene	200	--	0.46	0.18 to 4.5	5	17	M,(M),T	14	5.2 to 130
Formaldehyde	--	--	0.85	9.0×10^{-4} to 2.3	34	5	I,M,N,T	25	0.027 to 69
Hexachlorobenzene	1.0×10^{-3}	7.2 to 10^{-3}	169	0.67 to 45	6	4	E,M,T	4609	20 to 1380

TABLE 3 continued

Chemical	Water							Air	
	c[b] (μg/L)	w[c] (μg/L)	t[d] (μg/L)[e]	Inter-quartile Range of t (μg/L)[e]	Number of Entries in RTECS 1980	Number of RTECS Comparisons	Toxic Effect in RTECS[f]	Values Derived from RTECS Comparisons (μg/m³)[g]	Inter-quartile Range (μg/m³)[g]
Mercury	0.2	--	0.70	8.2×10^{-3} to 2.5	4	9	(N),T	21	0.24 to 75
Mercury, (acetato)phenyl	0.2	--	0.12	0.032 to 50	12	12	E,I,M,T	3.6	0.94 to 1500
Mercury, (II)chloride	0.2	--	0.22	0.088 to 1.0	9	8	I,M,T	6.4	2.6 to 30
Mercury, chloroethyl	0.2	--	0.28	5.7×10^{-3} to 2.5	26	22	M,T	8.3	0.17 to 16
Mercury, (3-cyanoguanidino)methyl	0.2	--	0.41	0.011 to 0.51	6	16	E,T	12	0.33 to 15
3-Methylcholanthrene	9.7×10^{-3}	0.028	0.019	5.6×10^{-3} to 0.033	72	32	E,M,M,T	0.55	0.17 to 0.98
Methylene chloride	--	--	13	2.3 to 85	23	17	I,M,(M),T	380	69 to 2500
1-Naphthylamine	9.7×10^{-3}	0.028	1.4	0.67 to 13	9	12	M,(M),T	42	20 to 300
2-Naphthylamine	9.7×10^{-3}	0.028	0.014	0.035 to 0.074	28	8	M,M,T	0.42	1.0 to 2.2
Nicotine	--	--	0.074	2.9×10^{-3} to 1.8	34	15	E,T	2.2	0.086 to 52
N-Nitrosodimethylamine	--	0.014	0.12	0.013 to 1.6	80	22	M,M,T	(3.4)	0.38 to 46
Phenanthrene	9.7×10^{-3}	0.028	0.051	0.8×10^{-3} to 0.82	7	6	M,M,T	1.5	0.26 to 24
Pentachlorophenol	140	--	0.25	0.076 to 3.7	16	16	E,I,(M),T	7.5	2.2 to 110
Pyrene	9.7×10^{-3}	0.028	2.8	0.055 to 30	5	4	I,M,(M)	83	1.6 to 900
Pyridine	--	--	3.7	1.3 to 9.3	12	15	I,M,T	110	40 to 280
Quinoline	--	--	0.61	0.023 to 2.2	12	12	I,M,M,T	18	0.69 to 64
Resorcinol	--	--	2.0	0.48 to 44	13	10	I,(M),T	59	14 to 1300
Tetrachloroethylene	2	8	23	11 to 67	18	14	I,M,T	690	330 to 2000
Thiophene	--	--	1.1	0.33 to 3.9	2	10	T	32	9.7 to 120
Toluene	12.4	--	7.4	3.9 to 22	13	11	I,T	220	115 to 640
1,1,1-Trichloroethane	--	--	22	14 to 82	21	8	I,T	640	440 to 2400
Trichloroethylene	21	27	36	11 to 74	32	12	I,M,M,T	1100	330 to 2200
Vinyl chloride	517	20	90	4.7 to 120	30	8	M,M,T	2700	140 to 3600
Xanthene	--	--	4.0	1.3 to 70	1	8	T	120	40 to 2100
Xylene	--	--	8.0	5.7 to 28	13	12	I,T	240	170 to 590
m-xylene	--	--	7.8	2.5 to 23	4	7	I,T	230	75 to 690
o-xylene	--	--	18	1.2 to 29	3	6	T	520	35 to 860
p-xylene	--	--	7.4	2.0 to 23	3	7	T	220	59 to 690

[a] For RTECS comparisons, B(a)P was the primary standard and benzene, nitrosodimethylamine, and cadmium were secondary standards. Values given are extra safe in that they are not corrected for potentially different absorption factors in lung, skin or gut. Also, atmospheric and water reactions are not considered. For example, bischloromethylether decomposes in water and many other compounds are insoluble, or only slightly soluble in pure water.

[b] c = Criteria Document values from Sittig (1980).

[c] W = CAG values for cancer.

[d] t = values derived from RTECS comparisons.

[e] Values in this column are normalized to a permissible exposure of 0.028 μg/L of PNAs. For a different concentration x, given values should be multiplied by (x/0.028).

[f] E = Teratogenesis, I = Irritation; M = Mutagenesis; N = Neoplasia; (N) = Possible Neoplasia, T = Toxicity.

[g] Values in this column are normalized to a permissible exposure of 3.4 ng/m³ of nitrosodimethylamine. For a different concentration y, given values should be multiplied by (y/3.4).

[h] Difficult to match RTECS entries - estimate is very uncertain.

yields precise-appearing numbers that do not overlap, unless one considers the uncertainty factors (often as large as 5000) that have been used in the calculations. The second approach helps us to remember the sizes of the different uncertainties and also to define the likely range of variability in humans.

Relative potencies estimated from NIOSH Criteria Documents, EPA-CAG assessments, Monsanto, MATE/MEG, TLVs, ACGIH-TLVs and RTECS comparisons are shown in Figure 3. Estimated permissible concentrations in air and water are given for these and other chemicals in Table 3. As seen, the values derived from the RTECS comparisons agree quite well with the NIOSH and CAG values; however, we recommend that our values of permissible concentrations could be improved in a theoretical sense if corrected for differential absorption; e.g., GI (or inhalation) absorption of B(a)P divided by the GI (or inhalation) absorption of chemical of concern. The GI and lung absorptions of B(a)P are certainly much less than unity, and if the absorption factors are ignored (i.e., both taken as unity), then the concentrations in Table 3 would seem to be "extra" safe. In the event that projected human exposures exceed the values presented in Table 3, then somewhat relaxed, but still safe, permissible exposures could be calculated by taking differential absorption into account. The important point of Figure 3 is that (taken over the 16 comparison chemicals) the proposed method seems as accurate as any of the other six activities and requires orders of magnitude less analytical effort.

DISCUSSION

Ideal decision making from permissible concentrations. For a single chemical and one transport medium (i.e., air or water in this paper), a projected exposure would be considered safe if it is less than the corresponding value in Table 2 (i.e., $Q_E/Q_L < 1$ where Q_E is the projected exposure and Q_L is the derived permissible concentration). For exposures to complex mixtures, the composite biological response may be equal to, greater than or less than the sum of the individual component responses, depending on such factors as the chemical blend, the exposure protocol or the test receptor. Because the problem of estimating the toxicity of complex mixtures remains unsolved, the composite response is typically taken to be the sum of the component responses. Thus, for a mixture, the ideal assessment would consider

$$\sum_i (Q_E/Q_L)_{i\ \text{air}} + \sum_i (Q_E/Q_L)_{i\ \text{water}}$$

where i = all chemicals.

The higher the sum, the greater the potential for health impairment. This approach seems objective and ideal for establishing priorities when one is faced with several sites that compete for remedial actions. If the

$$\sum_i (Q_E/Q_L)_{i\ \text{air}} + \sum_i (Q_E/Q_L)_{i\ \text{water}} < 1,$$

then less concern or remedial action would be warranted based on current data and available models, unless Q_Es or Q_Ls were subject to significant changes in the future.

Decision making without projected exposures. If projected exposures cannot be expressed in the same units as permissible limits, or if perhaps the exposure estimates are not available at the desired exposure site, then a relative comparison can still be made. In that case, the derived permissible concentrations can be ordered on some arbitrary numerical scale in the fashion of the Sax method (1979). For example, the estimated permissible concentrations in water given in Table 3 range from 10^{-6} for bischloromethylether to about 10^{4} for zinc. This finding would suggest the use of some subjective scale such as $y = 4 - \log_{10}(x)$, where x is the permissible exposure from Table 2 and y is a toxicity index. Using this algorithm and permissible concentrations in water from the Criteria Documents, bischloromethylether would score about 8.7; B(a)P would score about 6.0; beryllium would score about 5.1; benzene, about 2.8; dichlorobenzenes, about 1.6; zinc, about 0.3; etc. Of course, other such arbitrary scales can be evaluated from Table 3 depending on the nature of the problem to be ranked.

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