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HEALTH RISKS FROM MIXTURES OF RADIONUCLIDES AND CHEMICALS IN DRINKING WATER (USED AS A REFERENCE IN OU1, OU2, OU4 AND OU5 RI REPORTS)

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OAK RIDGE
NATIONAL
LABORATORY

MARTIN MARIETTA

Health Risks from Mixtures of Radionuclides and Chemicals in Drinking Water

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Bruce A. Owen

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HEALTH RISKS FROM MIXTURES OF RADIONUCLIDES AND CHEMICALS IN DRINKING WATER*

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Date Published - March 1989

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SUMMARY

The National Interim Primary Drinking Water Regulations were codified in the Federal Register (EPA 1975), but historical accounts indicate that pollution of surface water and groundwater is not exclusively a modern problem.

> As namely of a river in Epirus, that puts out any lighted torch, and kindles any torch that was not lighted. Some waters being drank cause madness, some drunkeness, and some laughter to death. The river Selarus in a few hours turns a rod or wand to stone; and our Camden mentions the like in England, and the like in Lochmere in Ireland. There is also a river in Arabia of which all the sheep that drink thereof have their wool turned into a vermilion colour.
>
> Izaak Walton 1676.

These accounts must have been viewed with mixed emotion by Walton who was dedicated to an honest understanding of both science and nature.

Nevertheless, the three centuries between the fifth revision of "The Compleat Angler" by Walton and the establishment of National Interim Drinking Water Regulations saw tremendous changes in industry and population density but few restrictions on what could be put into water resources.

In the United States, the National Primary Drinking Water Regulations are authorized by the Safe Drinking Water Act, 42 U.S.C. 300f, et seq., as amended by the Safe Drinking Water Act Amendments of 1986 [Pub. L. 99-339, 100 Stat. 642 (1986)]. Section 1412(b)(1) requires the Environmental Protection Agency (EPA) to establish National Primary Drinking Water Regulations for 83 contaminants, including radionuclides, by June 1989 (EPA 1986). Similar regulations are anticipated for numerous other chemical pollutants on a somewhat longer time frame.

Currently, EPA proposed to regulate the combination of all man-made beta/gamma emitting radionuclides in drinking water to a cumulative dose equivalent of 4 mrem/year, individual chemical carcinogens to a per capita lifetime risk of 1/100,000, and chemicals not currently classified as carcinogens to concentrations below the "no observed adverse effect level" (NOAEL). There is a remarkable lack of consistency in the ways in which the three broad classes are evaluated and regulated. Also, there is great variation in individual assessments and regulations within each of the three classes. Of even greater concern is the emerging need to identify the realistic (in contrast to operational) meaning of such mandated action levels relative to considerations of potential health detriment deriving from the vast array of environmental pollutants. That need is becoming increasingly acute as fugitive emissions and waste storage areas create demands that easily outdistance the resources reasonably available to remediate all such calculated and/or extrapolated problems.

What do the mandated action levels mean? According to existing models of absolute risk, current levels of pollution would, in many instances, warrant serious concerns about catastrophic increases in human disease rates--especially cancer. However, from careful and accurate health monitoring studies, it is known that such effects do not commonly occur at any detectable level--certainly not at the rate predicted by

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conventional health assessment models. There may be a few locations where organ-specific diseases in the general population are increased in a statistical sense, but many preliminary claims are found later to be unsubstantiated by investigations based on sound scientific design. An additional complication is that locations where organ-specific diseases are increased are frequently found to be lower in overall mortality or in age-adjusted death rates from other causes (Doll and Peto 1981). Thus, most risk assessors experienced in biomedical areas have developed a complete distrust for the predictive validity of quantitative risk assessment (QRA) models, but most of the same individuals continue to agree that QRA models are adequately protective of human health--provided society can withstand the cost of potentially overprotecting man from each and every activity of importance. Much of the concern expressed here about overprotection or the need for balance is for risk-assessment activities that depend on complex mathematical extrapolation models to calculate risk probabilities of 10^{-5} or smaller. Such estimates are no better than educated guesses because it is impossible to derive that level of precision from either human or animal studies. In fact, the largest, most-complex mouse toxicological study conducted to date was designed to use more than 24,000 mice to explore the 1% level of tumorigenesis--without dependence on extrapolation models (Society of Toxicology 1983).

Obviously, for most exposure situations--particularly at minuscule concentrations--there is an inverse or opposing relationship between protection of human health and conservation of material and fiscal resources. Thus, it is obligatory to optimize between the two constraints. Lack of optimization is likely to be the main deficiency of current regulatory climate. This point is confused somewhat by the EPA's attempt to determine if a regulation is affordable, but the way that consideration is made does not address the concern expressed here.

In response to this concern, we have considered techniques of absolute decision making for current and future compliance considerations. However, to more realistically evaluate what, if any, are the health effects expected to result from environmental concentrations, we have proposed to supplement the conventional absolute decision-making process with a carefully calibrated (and validated within the limits of current knowledge and data) method for relative decision making. The method is used to compare toxicity levels deriving from technological activities with toxicity levels inherent to foods, cooking practices, drinking of utility processed but otherwise hypothetically pure water, and the natural radiation background (exclusive of radon exposure). Radon was excluded so that a baseline of risk that is more widely considered "acceptable" could be defined.

The Food and Drug Administration (FDA) has pioneered a "generally recognized as safe," or GRAS, concept. In this study, we propose to build on that infrastructure somewhat differently but in a way consistent with the general intent of the FDA. As three examples of potential GRAS-equivalent indexes, we explore: hypothetically pure utility drinking water containing fluoride (1 ppm) and chlorination residue products consumed at a personal ingestion rate of 2 L/d; consumption of one reference meal and 2 L/d and the 40-mrem annual natural terrestrial radiation background as described by the U.S. National of Academy of Sciences (NAS 1980).

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On the basis of conventional QRA models and the proposed relative method scaled to the described GRAS-equivalent indexes, we demonstrate techniques of relative comparisons to enhance absolute or QRA models and simultaneously to implement a "reality check." Additionally, this feature provides an alternative means of estimating the hazard posed by various agents. Thus, we have attempted to supply three methods of evaluating hazards from mixed-waste exposures. Those comparisons permit the decision maker to draw meaningful conclusions to better allocate resources. Next, we demonstrate this evaluation (but leave the deliberation process to policy makers) for two hypothetical wells in a waste storage area.

For purposes of illustration, two hypothetical water samples from a reference solid waste storage area (SWSA) were assumed. Concentrations were taken from representative measurements, but the example is hypothetical because only an abbreviated inventory of actual pollutants made up of chemicals and radionuclides was used.

From the two hypothetical wells, it is likely that compliance problems could exist within the reasonable near term for about half of the 25 index pollutants, based on the current EPA policy to regulate increasing numbers of chemicals according to existing extrapolation models. However, the GRAS-type comparisons, which we propose, project that only the presence of strontium-90 might appear to increase the composite relative hazard to a level above that corresponding to commonly accepted foods and utility processed but otherwise pure water. Also, these calculations suggest that the second water sample is about tenfold less toxic than the first sample. These projections are encouraging and indicate that the current environment is not extremely dangerous to the general population. We recommend that additional comparisons continue to be made to further calibrate or validate the findings reported here.

Finally, methods proposed within this study are intended to help standardize and apply the decision process intrinsic to current EPA regulations. A further goal is to calibrate calculations and actions to an operational definition of acceptable risk when the user has that option or when remedial and/or abatement concerns cause demands that seem excessive relative to the maximum potential gain.

Evaluation of a person's honesty seems to have been intrinsic to Walton's primary thought pattern and he used "honest" more than a score of times in "The Compleat Angler." The current study draws from many disciplines and numerous data bases. Thus, there is much opportunity to make serial choices that influence the many comparisons used. However, we are not aware of any need to support any particular position and, therefore, believe that we balance rather than bias our subjective assignments in what we hope Walton would have called an "honest" manner.

GLOSSARY

absolute: The traditional method of decision making used by the EPA, characterized by reliance on expert committees that utilize model-intensive, data-sparse exposure scenarios bolstered by large safety factors to evaluate.

absorption coefficient: an efficiency factor used to approximate the fraction of the exposure absorbed into the circulating fluids of the body. Absorption coefficients are used for ingestion, inhalation, and dermal exposures.

acceptable risk: Mathematical models are used to calculated the potential level of damage in a human population. Currently, if less than one person is expected to be injured pathologically from a population of 100,000 or more, this may be taken as an "acceptable" level of risk (i.e., 10^{-5} per person-lifetime).

animal slopes: The CAG uses a multistage model to fit experimental data from dose-response studies. Animal slopes refer to the linearity of the multistage model at low dose.

ATSDR: Agency for Toxic Substances and Disease Registry.

BED: Biologically effective dose. The dose of a compound necessary to produce an effect.

bioassay: an *in vitro* or *in vivo* test used to measure the effect of a chemical or physical agent.

CAG: Carcinogen Assessment Group of EPA.

CAG risk coefficient: a constant that, when multiplied by dose, describes a level of risk. The CAG publications usually call this value the "animal slope" or simply "slope." Units of the slope are typically given in $(mg/kg/d)^{-1}$.

carcinogenic chemicals: usually refers to chemicals listed as "known," "suspected," and "potential" carcinogens. The carcinogenic chemicals are typically those listed by the IARC.

carcinogenicity: the capacity to cause, enhance, or potentiate cancer.

carcinoma: a malignant tumor derived from epithelial tissue.

CERCLA: Comprehensive Environmental Response, Compensation, and Liability Act of 1980. It established the Superfund.

Cl of H_2O: Chlorination of water.

closure: the operational and legal shutdown of an activity.

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criteria: a legal limit that should not be exceeded. In the absence of regulatory criteria, an estimate derived by a nonofficial source for management and storage of hazardous waste.

data gaps: insufficiencies or inadequacies in toxicological data required to accurately assess health effects; usually compensated for by incorporation of large safety factors in risk calculations.

data intensive: a characteristic of an analysis designed to maximize the use of experimental data to evaluate an effect.

data sparse: the use of a small amount of data and a strong reliance on mathematical models to evaluate an effect.

decision point: a calculated or measured value that changes the course of action from what would be taken at a lower value.

delivered dose: The dose of a compound that actually reaches the target organ.

dosimetry: the measurement of dose or dose-related quantities.

DWPL: Drinking Water Priority List, as mandated by the SDWA; a list of priority contaminants found in public water systems that have documented or suspected adverse health impacts.

ED_{10}: the estimated dose associated with a lifetime excess cancer risk of 10%, the reciprocal of which is called the RQ potency factor and is used (with weight-of-evidence) in relative ranking of Superfund site chemicals.

EPA Water: this refers to EPA Water Quality Criteria activities.

expert committees: multidisciplinary groups of experts charged by an authoritative body such as EPA, NIOSH, etc., to evaluate a particular hazard or risk.

Group A: a human carcinogen based upon sufficient epidemiological evidence.

Group B1: a probable human carcinogen based upon limited epidemiological evidence.

Group B2: a probable human carcinogen based upon sufficient evidence of carcinogenicity in animals but inadequate evidence in humans.

Group C: a possible human carcinogen based upon limited evidence of carcinogenicity in animals.

Group D: not classified because of inadequate evidence of carcinogenicity in animals.

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Group E: no evidence of carcinogenicity in humans in at least two adequate animal tests or in both epidemiologic and animal studies.

hazard: a calculation or measurement of potential harm. Does not imply that the effect or harm will actually occur; typically an overestimate of actual outcome or risk.

Hazard Ranking System: a screening tool for assigning sites to the National Priorities List (NPL) wherein a numerical score is derived to reflect the potential for harm to humans or the environment from migration of hazardous substances by groundwater, surface water, or air routes.

hazardous chemicals: refers, in this report, to all chemicals. Harm can be induced by any chemical at some concentration. Even pure oxygen and distilled water are toxic at high concentrations. This usage is not consistent with EPA's use of the term.

HRS: see Hazard Ranking System.

human slopes: a term used by CAG to indicate a linear dose response fitted to human data. The multistage model was not used when CAG analyzed human data.

hyperplastic nodule: a precancerous response to tissue trauma characterized by cellular proliferation and increase in size and weight of the affected organ.

IARC: International Agency for Research on Cancer.

infant regulation: a guidance value derived early in the regulatory history of a particular chemical. Infant regulations are subject to sudden and potentially large changes.

initiate: to induce a precarcinogenic lesion or condition by administering a subeffective dose of a carcinogen.

interviewing chemical: a term used in a descriptive sense to denote a chemical being assayed for toxicology potency. That chemical may or may not be produced or used for industrial processes, depending upon its toxicity.

linearized multistage: see slopes.

LOAEL: lowest-observed-adverse-effect level.

mature regulation: a guidance value derived from a large amount of test data or actual human experience.

maximum tolerated dose (MTD): this is usually taken at two- or four-fold less than a dose that produces frank lesions of acute toxicity. The magnitude of the MTD is determined by experimental design and duration of treatment.

MCL: maximum contaminant levels; enforceable standards set by the EPA under amendments to the SDWA in 1986; should be set as close to the MCLG as practically feasible.

MCLG: maximum contaminant level goal; non-enforceable health goals set at a level of no known or anticipated adverse health effects with an adequate margin of safety.

model intensive: reliance upon mathematical models more so than upon experimental data to evaluate human health effects.

National Priorities List: a list of sites that qualify for Superfund-financed remedial action on the basis of their HRS score (above 28.5).

noncarcinogen: generally, a treatment not expected to cause or potentiate carcinogenesis. Thus, the intrinsic characteristics of the treatment, the characteristics of the test model, and the conditions of exposure determine whether a treatment is a carcinogen or a noncarcinogen.

NPL: see National Priorities List.

PCBs: polychlorinated biphenyls.

permissible: an exposure concentration of treatment not expected to cause an unacceptable level of hazard of risk.

potentiate: to enhance a pre-established carcinogenic activity.

promote: to establish carcinogenesis through chemical or physical means applied in conjunction with an initiator.

Q^*: Refers to the upper bound of the confidence interval used to estimate the human risk associated with low-dose exposure to a compound. This type of calculation is generally reserved for data obtained from long-term bioassays, analyzed using a multistage statistical model.

Q: Refers to the estimate of risk associated with low dose human exposure using a linear no-threshold model, generally reserved for data obtained from epidemiologic studies.

RAC: see reference air concentration.

radiochemical: a toxic chemical that contributes to toxicity predominantly through production of ionizing radiations.

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RASH rapid screening of hazard: A technique developed at Oak Ridge National Laboratory (ORNL) to assist in the quantitative evaluation of toxicologic data on potentially hazardous substances.

reference air concentration: for noncarcinogens, a threshold dose below which health is protected; derived from oral RfDs.

reference chemical: a well-studied chemical that serves as a standard for comparison with a chemical about which much less is known.

Reference Dose: a term used by EPA to designate the permissible concentration of a noncarcinogen.

reference standard: a term used to imply the most authoritative epidemiologically based standard. In this document it is proposed that the most authoritative standard may be a composite of risk-based experiences that may serve to dampen the effect of undesirable confounding factors.

relative: a newer supplemental method of decision making characterized by minimized reliance upon mathematical models and more data-intensive multipotency comparisons between various biological tests.

relative potency: the capacity of a chemical to produce a specified effect relative to the capacity of a standard chemical to produce the same effect. For equal response, relative potency = D_S/D_T, where D_S is the dose of the standard chemical and D_T is the dose the test chemical.

reportable quantity: an amount of a pollutant such that a spill in excess of that amount must be reported to EPA.

RfD: reference dose.

risk: actual harm to a population in contrast to an estimate of the potential hazard.

risk-equivalent: the use of a specific level of risk to compare the potency of different pollutants.

Risk-Specific Dose: a term used by EPA to designate the permissible concentration of carcinogen.

RMCL: recommended maximum contaminant level, renamed maximum contaminant level goal (MCLG) under amendments to the SDWA in 1986.

RP: relative potency.

RQ: see reportable quantity.

RSD: see risk specific dose.

safety factors: factors used to adjust the NOAEL, NOEL, or LOAEL reported for small experimental test populations to estimate the comparable NOAEL for chronic exposure to larger populations that may contain sensitive subgroups in calculations of ADI; generally used to provide a measure of protection in compensation for data gaps.

SAR: structure activity relation that is an evaluation of a chemical based on its chemical structure.

SARA: Superfund Amendments and Reauthorization Act of 1986, which sets schedules to be met in conduct of preliminary assessments and site inspections (for data collection) and also mandates improvements to be made in the HRS methodology.

Sax Index: a scheme of rating toxicity on a scale of 0 to 3 that is used in combination with a persistence score in evaluating waste characteristics in the HRS methodology; chronic toxicity is not addressed, which is a weakness in the index.

SDWA: Safe Drinking Water Act of 1974, which required the EPA to establish national interim primary drinking water regulations applying to public drinking water systems and specifying contaminants that may have any adverse health effects.

slopes: see animal slopes and human slopes.

test chemical: similar to an interviewing chemical except that the emphasis is on test results from bioassays instead of on the industrial usage of a chemical or chemical process.

uncertainty factors: factors that represent measurable estimates of experimental variability; sometimes incorrectly referred to as safety factors.

unit risk estimates: a term used by CAG to indicate a potential excess lifetime risk associated with breathing 1 $\mu g/m^3$ over a 70-year lifespan for a 70-kg person. The quantity is inaccurately named because the estimate is for hazard (not risk), and the unit designates concentration, not "unit risk."

weight of evidence: the overall strength of the data indicating the potential carcinogenicity of an agent, categorized into groups A through E.

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1. GOAL

The primary charge of this study was to develop a risk-based common scale for radionuclides, carcinogenic chemicals, and noncarcinogenic chemicals. The common scale is needed as a basis for management of waste products and control of environmental pollutants. Also, ranking of various remedial actions and decisions based on acceptable, unacceptable, voluntary, and involuntary exposures cannot be made on a sound technical basis unless different harmful agents can be compared with a high degree of relative accuracy on a common scale that either explicitly or implicitly reflects potential detriment to human health. The risk-based methodology proposed in this report depends on the fact that designation as a "noncarcinogen" is tentative, based on the subjective decision on how a particular expert committee evaluates the weight of evidence for a particular chemical. Obviously, the weight of evidence changes with time. Also, "carcinogenic" and "noncarcinogenic" are classifications that depend uniquely on the interaction of a hazardous agent with a biological test model under a particular unrealistic (and often novel) exposure protocol (Glass et al. 1988). Variations in the intrinsic characteristics of the hazardous test agent, the biological traits of the test model, or the parameters of exposure can shift the outcome of whether a chemical acts as a carcinogen or as a noncarcinogen--even for widely tested carcinogens. It is common for "carcinogens" to test negative in certain bioassays and/or experimental designs.

2. INTRODUCTION: HISTORICAL ASSESSMENTS FOR POLLUTANTS

Traditionally, radiological hazards have been and continue to be evaluated and regulated quite independently from contemporary methods used to assess chemical hazards. Furthermore, the subset of hazardous chemicals considered to be carcinogenic or potentially carcinogenic to humans has been perceived as grossly different from the class of chemicals commonly judged to represent hazards in the noncarcinogenic or classical pharmacological/toxicological sense. Because of analytical variations and the established custom of developing risk coefficients and/or acceptable daily intake values from one peer-reviewed biological experiment, the assessment and regulation procedures have been highly specific to individual hazardous chemicals. Chemicals evaluated to be carcinogenic to humans from epidemiological studies are analyzed by different mathematical models from those used for chemicals known to be carcinogenic to rodents and thought to be carcinogenic to humans. Additionally, different levels of acceptable risk or hazard have frequently been assigned depending on whether the evaluation was from epidemiological or animal dose-response data. That is, at the dose-response stage of the assessment, a more protective risk model is used for animal-based estimates, but that more-protective model has on occasion been used with a less conservative level of acceptable risk (EPA 1986b; Jones et al. 1988).

In summary, at least four distinct analytical methods having a similar number of different hazard control action levels are commonly used. It should also be noted that there is no rational, objective way currently available that can be used to express the composite hazard from

mixtures of chemicals and radionuclides into the single summary statistic needed to rank complex waste streams or waste storage areas according to priority. Instead, the decision maker must rely on relative and/or absolute decisions of expensive proportions (for a large number of pollutants) from arrays of information that reflect little, if any, commonality. The methods currently used will be summarized in the following sections.

We use those historical methods where possible, supplemented with additional data and methods to produce three easily usable common scales that will provide independent single-value summary estimates for each mixture of chemicals and radionuclides. This approach is shown schematically in Fig. 1. Figure 1 illustrates the major tasks required to develop a risk-based common scale for mixed pollutants. Each compartment of Fig. 1 comprises various subtasks, which can each be diagramed as shown. Figure 2 is an integration of the issues affecting the evaluation of potential human health hazard following exposure to toxic chemicals and radiation. Many tasks are required to standardize models of dose/hazard to maximum degree possible. Those tasks are described in the text but are not shown in the schematics. The two concepts used to delineate the three common scales for chemicals are shown in Fig. 2, where the box on "Rapid Screening of Hazard" feeds into boxes on "QRA Models" and generally recognized as safe (GRAS). One common scale quantitative risk assessment (QRA) in Fig. 2 is calibrated to a probability of per capita lifetime risk of 1/100,000 as used by the EPA, and the second and third common scales are calibrated to exposures which have been GRAS in the examples of the Food and Drug Administration (FDA).

3. BACKGROUND

3.1 RADRISK CODE FOR EVALUATING RADIOLOGICAL HAZARDS

RADRISK was developed to estimate dose rates and projected health effects to a hypothetical population from inhalation or ingestion of a radionuclide (Sullivan et al. 1981). Dosimetry calculations, based on ICRP Publication 30, were coupled with a life-table methodology. The cohort comprised 100,000 persons born simultaneously with competing risks based on the U.S. population. Lifetime exposure to a unit concentration of each radionuclide was assumed. Statistical weighting factors for the pathological patterns of cancer were from UNSCEAR (1972, 1977) and NAS (1972, 1980). Absolute and relative risk models were averaged to obtain a per capita risk coefficient of 200 x 10^{-6} fatal cancers per centiGray. The report by Sullivan et al. (1981) includes estimates of total deaths in the cohort population as a result of chronic ingestion of 1.0 pCi/year for each of 154 radionuclides. Because of the widespread acceptance of these radiological models, our goal was to match the various chemical models to the radiological models to the maximum degree possible within the resources of this study.

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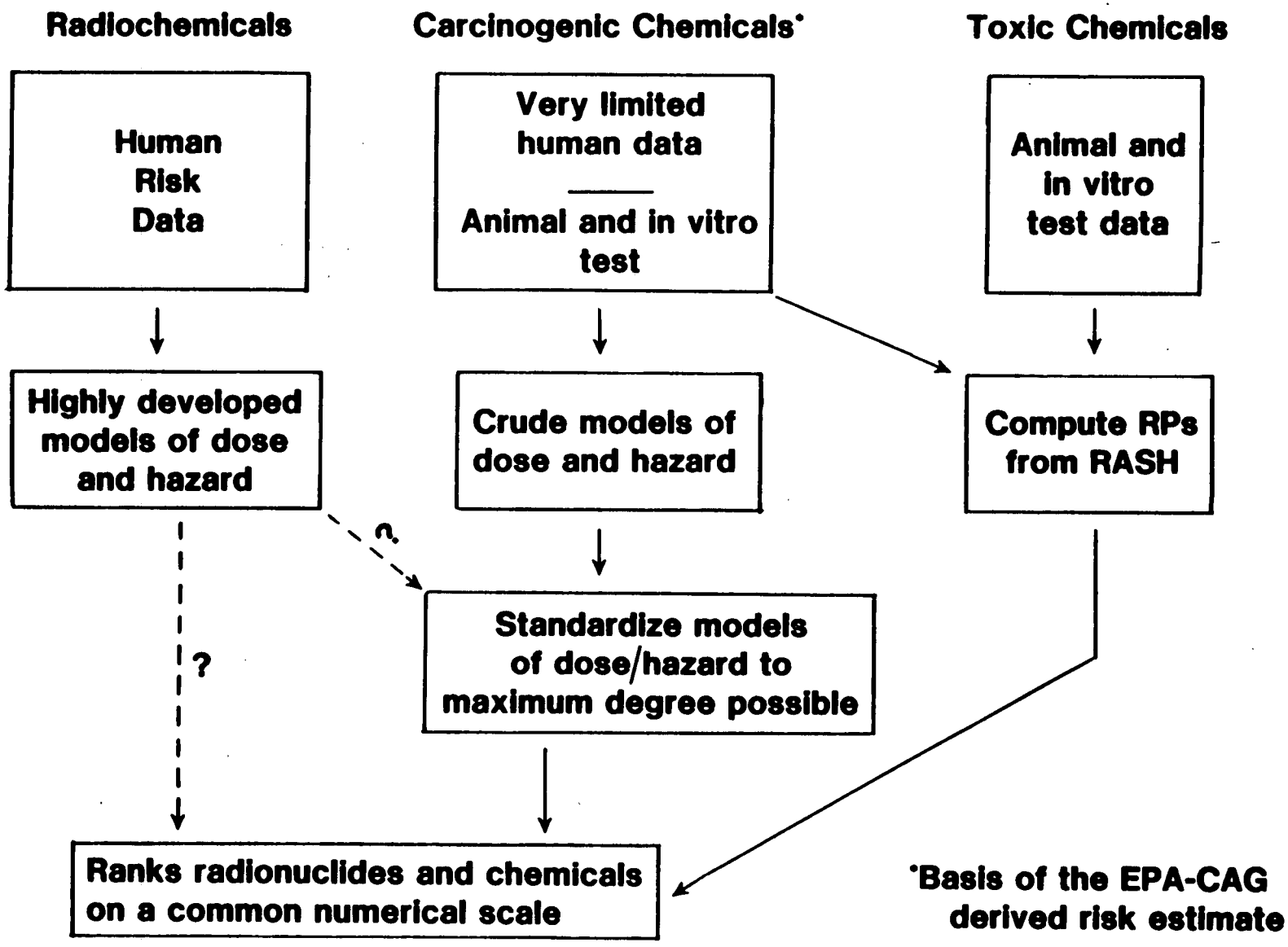

FIG. 1. SCHEMATIC OF THE MAJOR STEPS NEEDED TO ESTABLISH A COMMON-SCALE HAZARD EVALUATION FOR MIXTURES OF RADIONUCLIDES AND CHEMICALS.

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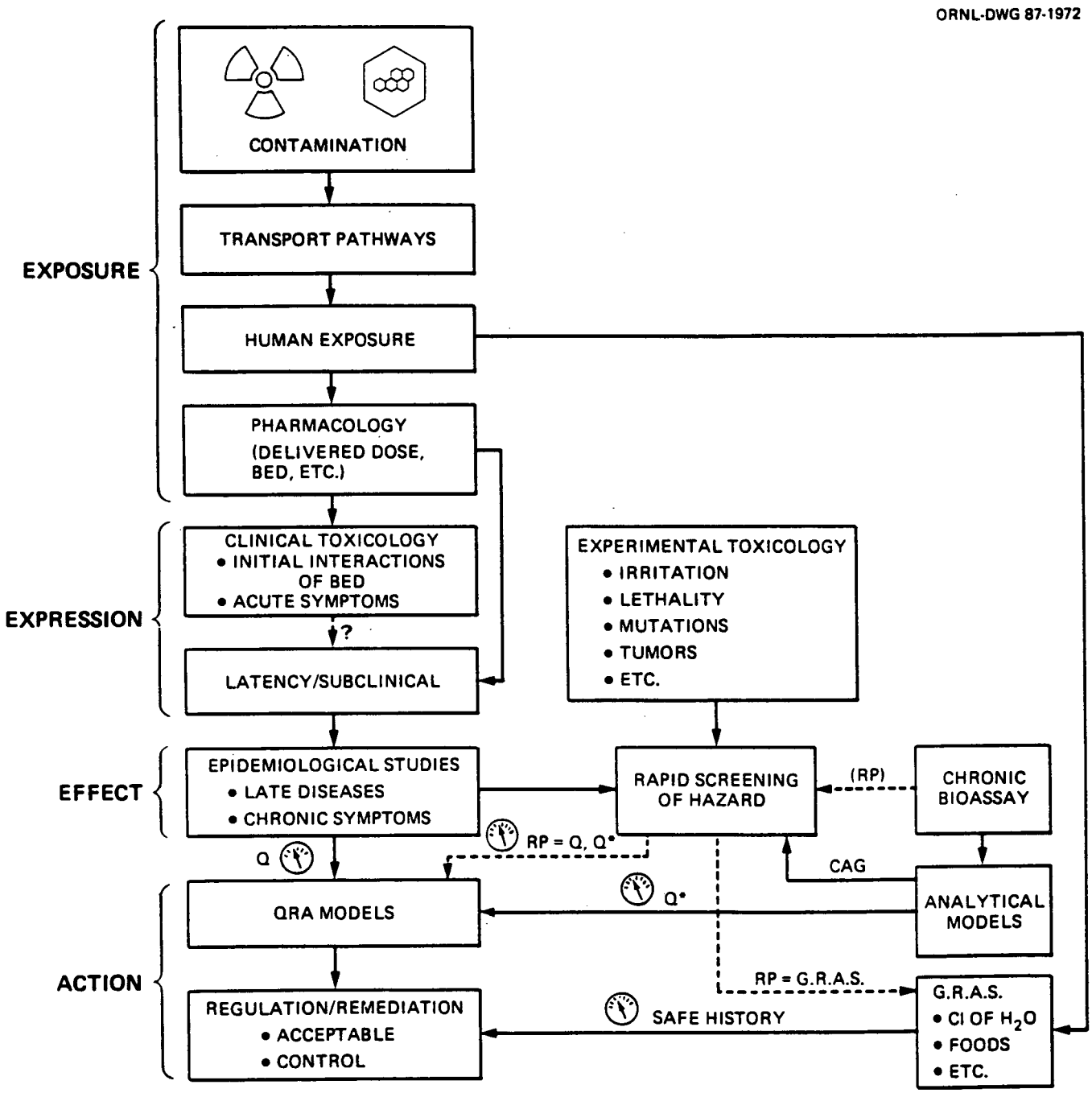

FIG. 2. INTEGRATION OF THE ISSUES AFFECTING THE EVALUATION OF POTENTIAL HUMAN HAZARD FOLLOWING EXPOSURE TO TOXIC CHEMICALS AND RADIATION.

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3.2 PERMISSIBLE EXPOSURES TO "NONCARCINOGENIC" CHEMICALS: HISTORICAL

Chemicals considered to be noncarcinogenic continue to be viewed by the EPA in the classical pharmacological/toxicological sense. That approach assumes that a theoretical no-harmful-exposure-level can be used. Exposures below this threshold value are assumed to represent no hazard, whereas exposures above the threshold may result in symptoms of acute toxicity and, perhaps, chronic toxicity for diseases other than cancer. The method commences with a peer review of the toxicological literature. From the study selected, a "no observed adverse effect level" (NOAEL) is determined. The NOAEL is then divided by a series of safety factors, which may include: 10 for potentially sensitive human subpopulations, 10 for transspecies considerations, 10 for the uncertainty caused by the duration of exposure, and 5 for uncertainty resulting from the route of exposure. Thus, for most chemicals, the NOAEL is decreased by 100- to 5000-fold, which may be further decreased by a modifying factor of between 1 and 10, assigned according to the quality of the study on which the NOAEL was based. Occasionally, NOAELs are not available, in which case "lowest observed adverse effect levels" (LOAELs) are used with an additional safety factor. When taken together such composite adjustments may result in a factor in the range of 10^5, which errs in the direction of safety but which may have expensive repercussions.

3.3 HAZARD EVALUATION FOR CARCINOGENIC CHEMICALS: HISTORICAL

Ten compounds are classed by the Environmental Protection Agency (EPA) as carcinogenic based on epidemiological data. Included are acrylonitrile, arsenic, benzene, benzidine, beryllium, cadmium, chromium VI, coke-oven emissions, nickel-refinery dust, and nickel subsulfide (EPA 1987). Risk coefficients for these compounds are derived in a manner similar to methods of the BEIR and UNSCEAR activities on radiogenic risk. Selected compounds are reviewed briefly in Appendix A.

The remaining 49 carcinogenic compounds as classified by the EPA CAG have been analyzed by methods that are designed to incorporate additional margins of safety to allow for possible differences between the design of the animal experiment and the potential risk to a human population exposed under different conditions. As a result, these assessments have very little in common with the risk coefficients derived from epidemiological studies (EPA 1987).

Typically, a "weight-of-the-evidence" analysis is used to determine whether a compound is carcinogenic or noncarcinogenic. Considerations are based on in vitro, in vivo, and perhaps fragmentary, statistically inconclusive human data. If the compound is judged to be carcinogenic, the next step is a peer review of available studies to select the best animal study to be used to evaluate the dose-response relationship. The selected study has a control or untreated group and as few as one dosed group--usually the treatment doses are near the acutely toxic (i.e., maximum tolerated) dose, which greatly weakens the credibility of any cancer study (Ames 1987; Glass et al. 1988). Next, a linearized multistage model is used to fit the dose-response data. Frequently, the experimental data include only one treated group and a control group. If multiple dose-response points are available, the high-dose points may be

rejected serially until the goodness of fit of the maximum likelihood estimate becomes acceptable (Anderson 1983). Rarely are more than three dose-response points available from experimental studies, and it is not uncommon for the fitting analysis to reject one or more high-dose points. Then, the upper 95% confidence limit of the maximum likelihood fit of the linearized multistage model is used, and extrapolation from rodent to human is scaled by the EPA on a body surface-area basis. Finally, the model is used to calculate the dose corresponding to some "permissible" level of human risk, frequently 1 event in 100,000 chances (Anderson 1983). The accuracy or validity for humans is totally unknown because the animal response data, from which the model was derived, are rarely valid below 10% incidence and the 95% upper limit applies only to the fitted model, not to the model scaled for humans. Thus, it is common for precision to be confused with accuracy; we suggest caution in this regard. This modeling procedure and attendant uncertainties are reviewed in Appendix B for polychlorinated biphenyls (PCBs).

3.4 SUMMARY OF HAZARD EVALUATION FOR CHEMICALS: HISTORICAL

The major advantages of the expert committee approach are (1) the results are widely accepted by the regulators and the general scientific community, (2) safety margins are incorporated to compensate for data gaps, and (3) a wealth of experience and knowledge are implicit in the evaluations. Even though subjective data selection and the use of an array of analytical models with attendant and varied safety factors would suggest that risk coefficients and associated action levels would vary wildly, a remarkable amount of consistency seems to exist for different carcinogenic agents, considering the variability in the quality of the epidemiological data and the evaluation processes (Owen and Jones 1988). The consistency probably results from the wide range of disciplines and professional experiences of the individuals that make up expert committees. Thus, operationally, expert committees seem to make consistent evaluations for most deliberations, so that the greatest weakness of the method is a lack of timeliness that results in an inability to meet the expectations of Congress and the general population. Nevertheless, each new evaluation from a particular expert activity is potentially subject to serious weaknesses: assessments are made independently chemical-by-chemical and cannot be predicted numerically by the regulated community in advance of the expert analysis (primarily because the evaluation process is dominated by data selection); decisions are slow and it is impossible to evaluate a significant fraction of compounds in a prudent time frame; considerations tend to be metabolic and descriptive (i.e., mechanistic) and thus may be misfocused, especially in cases in which data on single compounds are examined with the intent to control serial or simultaneous exposures to multiple pollutants; false-negative and false-positive conclusions are highly probable for poorly tested chemicals; processes are too cumbersome and the knowledge of chemical interactions too inadequate to consider complex mixtures in the usual analytical forum; and an inconsistent margin of safety (rather than a reliance on relative comparisons) has been used to compensate for variable data gaps, resulting in expensive overregulation of poorly tested chemicals.

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4. RASH ANALYSIS TO STANDARDIZE HAZARD EVALUATION FOR CHEMICALS

Figure 3 shows that unit doses of chemicals vary in toxicological potency by a factor in excess of 10^7 (Jones et al. 1988). Because of this large variation, and for the other reasons described in this document, a rapid screening of hazard (RASH) chemical scoring system has been developed. This approach, placed in perspective in Fig. 2, is well documented and will not be detailed further in this report (Jones et al. 1985 and 1988). The objective of RASH is to use well-defined risk coefficients and statutory concentrations from an array of chemicals coupled with relative potency comparisons to transfer experimental experience from one chemical to another and to draw conclusions in spite of major data gaps. In so doing, a relatively complete picture is built from a series of individually incomplete overlays. Thus, using a mosaic of all test data, relative comparisons, and human exposures, it is possible to bridge data gaps that block conventional risk assessments (Anderson 1983).

Advantages of a RASH-type analysis include a capacity to: be flexible to different users and applications; minimize the need to make mechanistic assumptions; evaluate the potentially increased rates of chronic diseases through the general toxicological profile of a chemical; use all types of biological test data; estimate a potency for each chemical; avoid mathematical modeling and extrapolations; use the accuracy of a fixed standard to obtain a consistent margin of safety determined by the available test data; accurately mimic the decisions of expert committees; be compatible with hazard index and harmonic mean assessments of blends; score, rank, or evaluate chemicals--including complex mixtures--in any consistent data base using one or more reference standards; compare pollution hazards directly to GRAS exposures (FDA 1985); derive permissible concentrations for currently unregulated chemicals; explore consistency of current regulations (Owen and Jones 1988); evaluate which existing regulations are subject to change and by what factor (Jones et al. 1988); use short-term in vitro and/or mutagenesis data to rank carcinogenic potency (Glass et al. 1988); define a common scale for chemical hazards; define a risk-based common scale for chemicals and radionuclides; and define a common scale for chemicals and radionuclides based on molecular toxicity and enzymatic repair. In addition, the RASH-type analysis is fast and easy to use.

5. ABSORPTION COEFFICIENTS FOR HAZARD EVALUATION

The RASH method provides the option to incorporate additional parameters to increase the rigor of the estimates. In this study, it was necessary to use absorption coefficients for inhalation to estimate the biologically effective dose and then use the absorption coefficients for ingestion to derive corresponding concentrations for currently unregulated chemicals in drinking water. The developments of inhalation and ingestion absorption coefficients for 39 compounds are given in Appendix C. In addition, absorption factors are needed to explore the consistency of existing regulations and the relative potency method. Finally, absorption coefficients can be used to safely increase exposure guidelines above the more cautious estimates based on the intrinsic

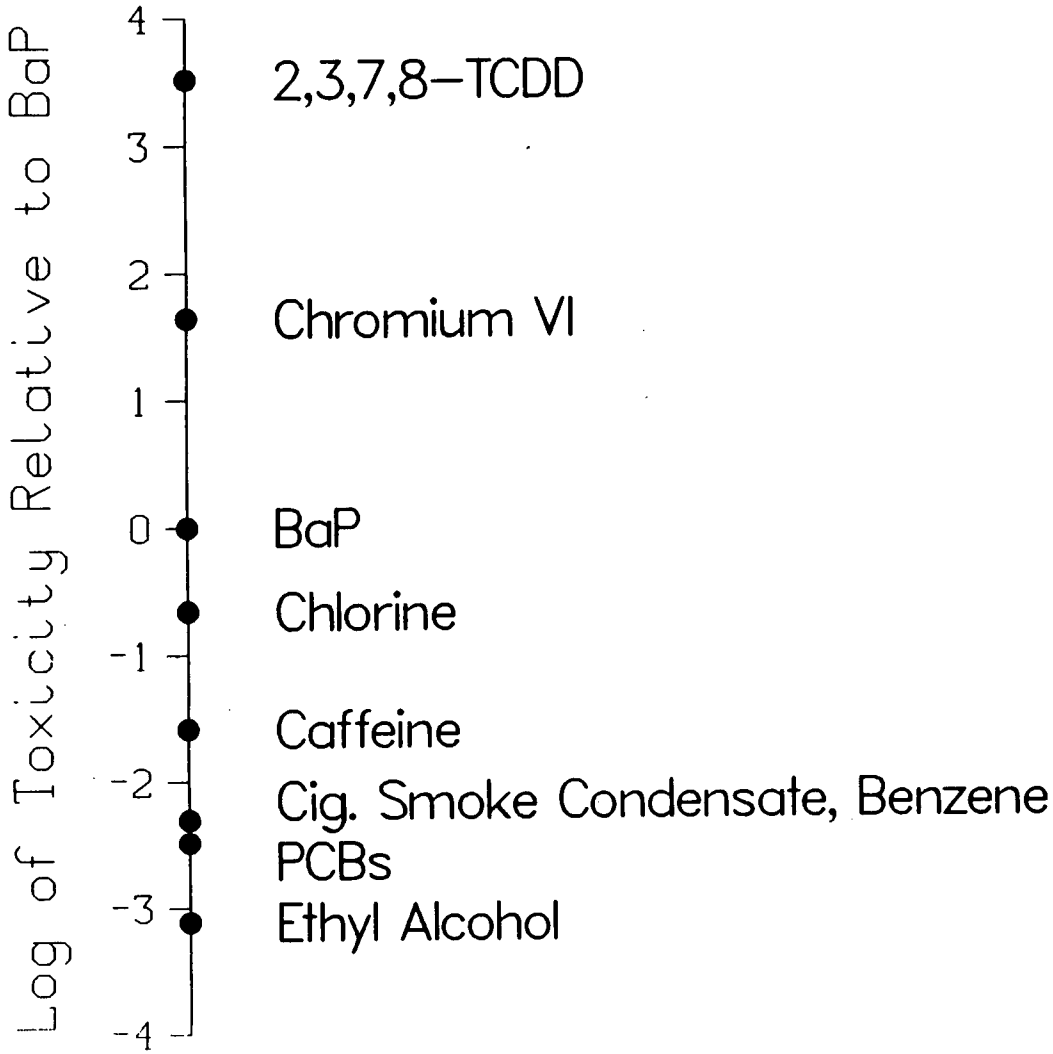

FIG. 3. HAZARD COMPARISON FOR SELECTED AGENTS BASED ON RELATIVE POTENCY COMPUTED BY THE RASH METHOD.

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toxicity of tissue concentrations for pharmacologically inert substances to achieve a more consistent regulatory or remedial action policy. Absorption coefficients for ingestion and inhalation of selected chemicals are given in Table 1.

6. INTERIM GUIDANCE FOR UNREGULATED CHEMICALS

Chemicals classed as noncarcinogenic are considered for regulatory purposes, to act individually without concomitant interactive effects with other noncarcinogenic or carcinogenic agents. More simply, if a chemical is lacking one intrinsic trait required to be classed as a complete and total carcinogen, it is not conceptually permitted to acquire that trait from simultaneous exposures with other chemical having that particular trait. Chemicals within this class can be used experimentally to potentiate or promote the carcinogenic potency of other agents. Perhaps carcinogens or other chemicals lacking at least one characteristic associated with being classified as a complete carcinogen in biological test models become classed as carcinogens from real-world human exposures. Several compounds listed as carcinogens seem to be from this class (e.g., DDT, benzene, arsenic, and TCDD), and we have proposed that the threshold-dose mode of hazard evaluation and control reflects "immature" regulation. A great number of those immature regulations are likely to change by about three orders of magnitude within a few decades (Jones et al. 1988). However, near-term future regulations for currently unregulated compounds from this class may be estimated crudely from Table 2 and the following formula, which derives from Table 2:

$$\text{acceptable concentration in drinking water (mg/L)} = (0.03\ \text{mg/L})/RP_i,$$

where the numerical coefficient is a composite value based on the median of normalized values, as given in Table 2. Values in Table 2 are relative to *benzo[a]pyrene (B[a]P)* and thus are on a common scale. These chemicals were chosen to represent the class of currently unregulated chemicals because barium, cresol, lead, mercury, pentachlorophenol, phenol, and toluene are regulated on the basis of extensive historical uses. The table illustrates how such experience can be used to identify a composite reference level, which is then used to predict initial permissible concentrations that may be proposed for currently unregulated chemicals.

Summary reviews of Health Assessment Documents for selected compounds of this class are given in Appendix D. The value of RP_i is the potency of the interviewing chemical relative to B[a]P. Values for 278 chemicals have been published previously (Jones et al. 1988). Many of those chemicals are unregulated, and thus the model can be used to derive tentative estimates of permissible concentrations or to anticipate forthcoming statutory values.

In a previous publication, we have reviewed studies that contribute to an understanding of the role of toxicity and/or homeostatically driven compensatory cell proliferation with respect to the initiation and potentiation of carcinogenesis (Jones et al., 1983). We proposed that, for human exposures to complex mixtures of pollutants, it is prudent for purposes of safety to evaluate chemicals according to their broad toxicity profiles in contrast to the widespread practice of classifying chemicals

Table 1. Absorption coefficients for 39 chemicals via oral and inhalation routes of exposure

Chemical	Oral (range)	Inhalation (range)	Classification
Acrylonitrile	0.95 (0.77-0.99)	0.98 (0.80-1.00)	reference carcinogen
Arsenic	0.98 (0.70-0.98)	0.35 (0.30-0.42)	RAP, reference carcinogen
Barium	0.10 (0.05-0.85)	0.75 (0.10-0.75)	RAP, reference carcinogen
Benzene	1.00 (0.40-1.00)	0.47 (0.28-0.60)	RAP, reference noncarcinogen
Benzidine	0.90	0.95 (0.95-1.00)	reference carcinogen
Benzo[a]pyrene	0.50 (0.43-0.58)	0.27	reference carcinogen
Beryllium	0.001 (0.00006-0.01)	0.50	RAP, reference carcinogen
Bis(chloromethyl)ether	1.00	0.50	reference carcinogen
1,3-Butadiene	1.00	0.65	reference carcinogen
Cadmium	0.06 (0.023-0.10)	0.40 (0.05-0.40)	RAP, reference carcinogen
Chlorine	1.00 (0.90-1.00)	1.00	reference noncarcinogen
Chloroform	1.00 (0.50-1.00)	0.63 (0.50-0.77)	RAP, reference carcinogen
Chromium (III)	0.01 (0.005-0.18)	0.10 (0.05-0.10)	RAP
Chromium (VI)	0.05 (0.02-1.00)	0.25 (0.10-0.75)	RAP, reference carcinogen
Coke oven emissions	0.50	0.27	reference carcinogen
Copper	0.50 (0.32-0.90)	0.50	RAP
Cresol	1.00	1.00	RAP, reference noncarcinogen
1,1-Dichloroethylene	0.93 (0.68-0.94)	0.98	RAP
Dimethylnitrosamine	0.98		reference carcinogen
Di-n-butylphthalate	0.85 (0.80-0.90)		RAP
Ethylbenzene	0.90 (0.72-0.92)	0.64 (0.44-0.64)	RAP
Ethylene oxide	1.00	1.00	reference carcinogen
Fluoride	1.00 (0.80-1.00)	1.00	reference noncarcinogen
Lead	0.10 (0.01-0.65)	0.50 (0.20-0.62)	RAP, reference noncarcinogen
Mercury-elemental	0.0001 (0.0001-0.45)	0.75 (0.50-1.00)	RAP, reference noncarcinogen
Mercury-inorganic	0.15 (0.02-0.15)	0.02 (0.00-0.85)	RAP, reference noncarcinogen
Mercury-organic	0.95 (0.40-1.00)	1.00	RAP, reference noncarcinogen
Methylene chloride	1.00	0.50 (0.50-0.75)	RAP
Naphthalene	1.00		RAP
Nickel	0.05 (0.01-0.10)	0.75 (0.70-0.75)	RAP
Nickel refinery dust	0.05 (0.01-0.10)	0.06	reference carcinogen
Nickel subsulfide	0.05 (0.01-0.10)	0.06	reference carcinogen
PCBs	0.95 (0.90-0.99)		RAP
Phosphorus	0.90 (0.80-1.00)	0.80	RAP
Selenium	0.60 (0.44-0.90)	0.27	RAP
Toluene	1.00 (0.74-1.00)	0.50 (0.37-0.70)	RAP, reference noncarcinogen
Vinyl chloride	0.90 (0.68-0.90)	0.64 (0.40-0.98)	RAP
Xylene	1.00	0.64 (0.54-0.68)	RAP
Zinc	0.50	0.50	RAP

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Table 2. "Immature" or interim guidance values projected from the relative potency of a chemical and the statutory values for other chemicals. The table illustrates how such experience can be used to identify a composite reference level, which is then used to predict initial permissible concentrations that may be proposed for currently unregulated chemicals. Expected accuracy is about an order of magnitude.

Chemical	EPA-RfD (mg/L)	Relative potency[a]	Column 2 x Column 3[b]
Mercury	0.0002	0.40	0.00008
Lead	0.05	0.092	0.0046
Barium	1.0	0.030	0.030
Cresol	2.0	0.015	0.030 - Median[c]
Toluene	10.0	0.0038	0.038
Phenol	4.0	0.027	0.11
Pentachlorophenol	1.0	0.11	0.11

[a]Potency relative to B[a]P as estimated from RASH.

[b]Based on this simple comparison, it appears that RfD values for mercury and lead are significantly more cautious than for other chemicals shown here.

[c]For any currently unregulated chemical in drinking water, projections of initial regulations can be made from $RfD_i = (0.030\ mg/L)RP_i$, where RP_i is from Table III of Jones et al. 1988.

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according to "weight of the evidence" and then pursuing one of the QRA options described previously. This underpinning led to the RASH method described by Jones et al (1988). On that basis, the relative potency values from the RASH analysis are coupled to a standard of chemical risk. For considerations of safety and long-term compliance, we recommend those estimates instead of the "interim" or near-term values for unregulated chemicals that can be estimated from the equation given in this section.

7. DEVELOPMENT OF A CHEMICAL-RISK STANDARD

Because we have proposed that noncarcinogenic pollutants may have the capacity to increase cancer and other chronic diseases in an environmental setting, we selected the EPA-CAG risk coefficients based on epidemiology to define the standard of chemical risk. Both carcinogens and noncarcinogens are then linked to that standard by relative potency comparisons (Jones et al. 1988, 1983). Human-based risk estimates are available for beryllium oxide, chromium (VI), acrylonitrile, nickel subsulfide, coke-oven emissions, nickel-refinery dust, arsenic, benzene, cadmium, and benzidine. The regulatory consistency, as evaluated from a relative potency comparison of those 10 chemicals and for the other 49 animal-based estimates, is described in Owen and Jones (1988) and is included as Appendix E. Appendix E is to be submitted for journal publication and is concerned with consistency of regulatory standards for chemical carcinogens and what those standards mean in terms of GRAS-like exposures. The main body of this report draws heavily on Appendix E to resolve the more general problems of the three classes of pollutants. Figure 4 illustrates the variability in risk for epidemiologically evaluated carcinogens. The level of risk as listed in the last column of Table 3 seems to vary by about 4 orders of magnitude between benzidine and beryllium. There is no evidence that the ten independent estimates derive from a normal or a log-normal distribution, and because it is not possible to select a "best" reference or standard chemical, the median is taken as the most useful measure of central tendency based on the method of RASH. From this analysis, the median is some hypothetical chemical with an intrinsic toxicity midway between coke-oven emissions and nickel-refinery dust--this is the reference standard to be used in Sect. 8. From Table 3, the median (or composite) risk coefficient is seen to be

$$4.7 \times RP_i \ (\mathrm{mg/kg/}D)^{-1},$$

and is to be used according to

$$\mathrm{risk} = 4.7 \times RP_i \ (\mathrm{mg/kg/}D)^{-1} \times D_i \ (\mathrm{mg/kg/}D),$$

for oral intake of dose D_i of any chemical considered to potentiate carcinogenesis as a result of chronic irritation and/or toxicity (Jones et al., 1983, 1988).

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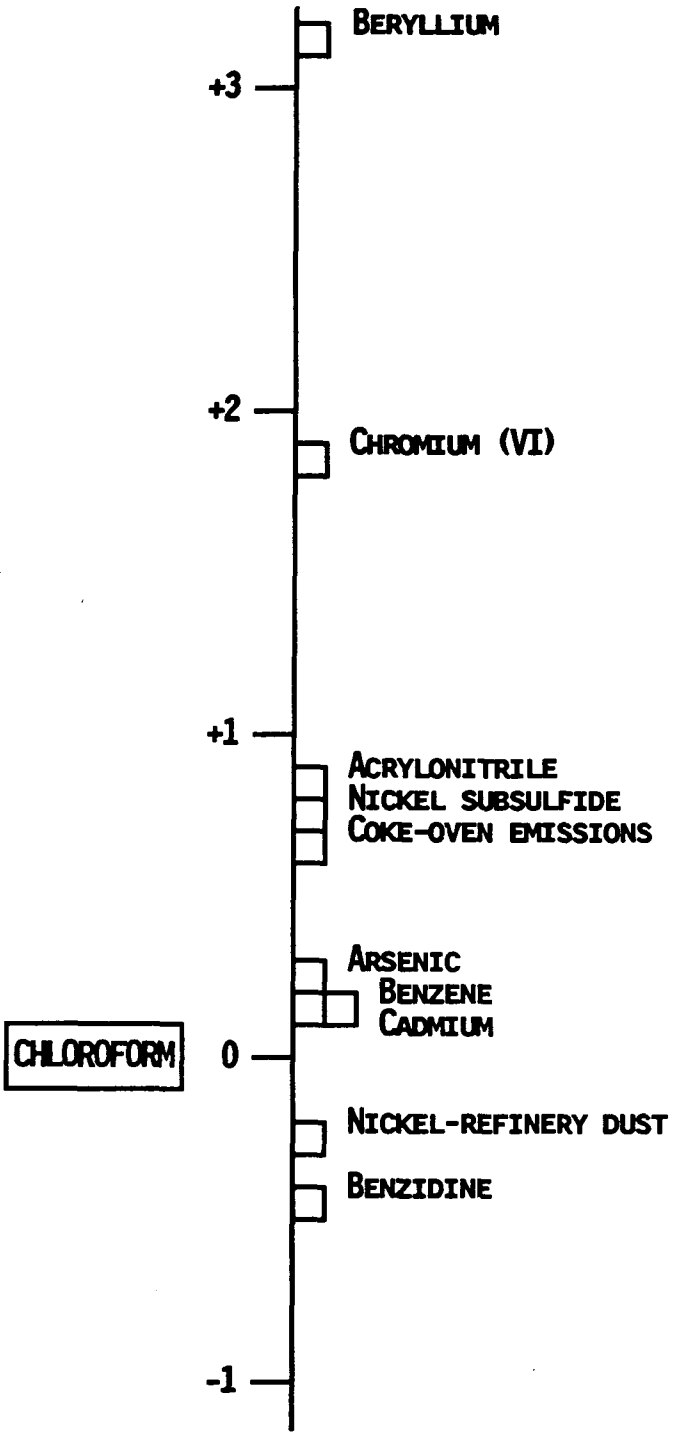

FIG. 4. CONSISTENCY OF EPA CAG RISK COEFFICIENTS ON A RELATIVE LOGARITHMIC SCALE (SEE APPENDIX E FOR A MORE COMPLETE COMPARISON).

Table 3. Median value of chemical hazard for chemicals having no statutory risk coefficients obtained from epidemiologically based risk coefficients modified by relative potency values.

Chemical	Risk coefficient[a] from CAG $(mg/kg/D)^{-1}$	Risk coefficient[b] adjusted for oral intake $mg/kg/D)^{-1}$	Potency[c] relative to B[a]P	(Col. 3/col. 4)
Beryllium oxide	7.0 (w)	0.014[e]	0.29E+01[e]	0.0048[d]
Chromium VI	41. (w)	8.2	0.44+02	0.19
Acrylonitrile	0.24 (w)	0.23	0.11E+01	0.21
Nickel subsulfide	1.7 (w)	1.4	0.50E+00	2.8
Coke oven emissions	2.16 (w)	4.0	1.0E+00	4.0
				<---- Median
Nickel refinery dust	0.84 (w)	0.70	0.13E+00	5.4
Arsenic	1.5 (h)	1.5	0.16E+00	9.4
Benzene	0.029 (w)	0.062	0.50E-02	12.
Cadmium	6.1 (w)	0.92	0.79E-01	12.
Benzidine	234 (w)	222	0.60E+01	37.

[a]From EPA/600/8-84/026F. w = human occupational exposures; h = human drinking water exposures.
[b]Column 2 x A_{oral}/A_{inhal}.
[c]Jones et al. (1988) and Owen and Jones (1988).
[d]Because the risk coefficient is directly proportional to the potency of a chemical, the risk coefficient divided by the relative potency should be constant if all data were equally valid and if regulatory guidelines were consistent (Owen and Jones 1988). Note: permissible concentrations for a constant level of risk are inversely proportional to potency values as shown in Table 4.
[e]The CAG value for beryllium oxide was adjusted according to the absorption coefficient and relative potency for beryllium.

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8. POTENCY VALUES, RISK COEFFICIENTS, AND CONCENTRATIONS

Table 4 lists the risk coefficients and permissible concentrations that can be used to assess chemicals as carcinogens or noncarcinogens. For reasons of contemporary statutory compliance and acceptability to the general scientific community, either the derived concentration based on the risk coefficient from CAG in column 4 of Table 4 or the EPA statutory concentration in column 9 is recommended, depending on the chemical of concern. However, both types of values are subject to major changes (Jones et al. 1988). For long-term assessments the values in columns 2 and 3 may be more robust because those values are based on the composite toxicity profile of each chemical. For the near-term analysis of currently unregulated chemicals, the estimates shown in column 8 should usually be within an order of magnitude of the value that the EPA may soon mandate. From Table 4, it is seen that RASH-derived values (column 6) and EPA-CAG derived values are in excellant agreement for 7 of 11 comparisons. Widest variations are seen for cadmium (100-fold), PCBs (200-fold), and vinyl chloride (700-fold). Also, elemental, inorganic, and organic mercury all seem to have similar levels of intrinsic toxicity (column 2), but a low absorption efficiency makes elemental mercury 1000-fold less hazardous as shown in column 6.

If an analysis needs to be both safe (according to current policy) and widely acceptable as scientifically valid, then the most reasonable choice would probably be to use the <u>rightmost</u> value listed for each chemical in Table 4.

9. DEVELOPMENT OF A GRAS STANDARD FOR CHEMICALS

To propose a safe standard, it is necessary to start with the basic definition of a poison. According to <u>Casarett and Doull's Toxicology</u>, a poison is defined "as any agent that is capable of producing injury or death when ingested or absorbed, then, as pointed out by Paracelsus over 400 years ago. . .

> 'All substances are poisons: there is none which is not a poison. The right dose differentiates a poison and a remedy.'

Since all chemicals can produce injury or death under some exposure conditions, it is evident that there is no such thing as a 'safe' chemical in the sense that it will be free of injurious effects under all conditions of exposure" (Klaassen et al. 1986).

Consistent with the wisdom of Paracelsus and the definition from Casarett and Doull, the FDA considered that <u>safe</u> or <u>safety</u> "means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered: (1) the probable consumption of the substance formed in or on food because of its use and (2) the cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically

Table 4. Risk coefficients and permissible concentrations that can be used to assess ORNL RAP chemicals as carcinogens or as noncarcinogens.

RAP Chemical	Relative potency[a] from RASH	Risk coefficient[b] based on RASH $(mg/kg/D)^{-1}$	Risk coefficient[c] from CAG $(mg/kg/D)^{-1}$	For control as a carcinogen: RASH[d] (ug/L)	For control as a carcinogen: RASH modified by absorption coefficient (ug/L)	For control as a carcinogen: EPA-CAG[c] (ug/L)	For control as a noncarcinogen: Projection of interim regs[e] from RASH (mg/L)	For control as a noncarcinogen: EPA water quality[f] (mg/L)
Arsenic	0.16E+00	0.75E+00	0.15E+01	0.19E+00	0.19E+00	0.23E+00		
Barium chloride	0.51E-01	0.24E+00		0.59E+00	0.59E+01		0.59E+00	1.0-
Barium (II) nitrate (1:2)	0.86E-02	0.40E-01		0.35E+01	0.35E+02		0.35E+01	Barium
Benzene	0.50E-02	0.24E-01	0.29E-01	0.60E+01	0.60E+01	0.12E+02		
Beryllium	0.29E+01	0.14E+02	0.70E+01	0.10E-01	0.10E+02	0.50E-01		
Cadmium	0.79E-01	0.37E+00	0.61E+01	0.38E+00	0.63E+01	0.57E-01		
Chloroform	0.50E-02	0.24E-01	0.81E-01	0.60E+01	0.60E+01	0.43E+01		
Chromium IV	0.44E+02	0.21E+03	0.41E+02	0.68E-03	0.14E-01	0.85E-02		
Copper	0.10E+00	0.47E+00		0.30E+00	0.60E+00		0.30E+00	
Cresol	0.15E-01	0.70E-01		0.20E+01	0.20E+01		0.20E+01	
1,1-dichloroethylene	0.14E-01	0.66E-01	0.12E+01	0.21E+01	0.23E+01	0.30E+00		
2,4-dimethylphenol	0.58E-02	0.27E-01		0.52E+01	ND		0.52E+01	
Di-n-butyl phthalate	0.23E-03	0.11E-02		0.13E+03	0.15E+03		0.13E+03	
Ethylbenzene	0.23E-02	0.11E-01		0.13E+02	0.14E+02		0.13E+02	0.34E+01
Lead	0.92E-01	0.43E+00		0.33E+00	0.33E+01		0.33E+00	0.50E-01
Mercury - elemental	0.40E+00	0.19E+01		0.75E-01	0.75E+03		0.75E-01	
- inorganic	0.48E+00	0.23E+01		0.63E-01	0.42E+00		0.62E-01	
- organic	0.23E+00	0.11E+01		0.13E+00	0.14E+00		0.13E+00	0.20E-02
Methylene chloride	0.22E-02	0.10E-01	0.14E-01	0.14E+02	0.14E+02	0.25E+02		
Naphthalene	0.48E-02	0.23E-01		0.63E+01	0.63E+01			
Nickel	0.13E+00	0.61E+00	0.84E+00	0.23E+00	0.46E+01	0.42E+00		
PCB's	0.33E-02	0.16E-01	0.77E+01	0.91E+01	0.96E+01	0.45E-01		
Phosphorus (phosphoric acid)	0.12E-01	0.56E-01		0.25E+01	0.28E+01		0.25E+01	
Selenium (selenious acid)	0.41E+00	0.19E+01		0.74E-01	0.12E+00		0.73E-01	0.10E-01
Toluene	0.38E-02	0.18E-01		0.79E+01	0.79E+01		0.79E+01	0.10E+01
Vinyl chloride	0.31E-03	0.15E-02	0.23E+01	0.97E+02	0.11E+03	0.15E+00		
Xylene	0.35E-02	0.16E-01		0.86E+01	0.86E+01		0.86E+01	0.22E+01
Zinc (zinc oxide)	0.56E-02	0.26E-01		0.54E+01	0.11E+02		0.54E+01	

[a]Jones et al. 1988 or from additional evaluations.
[b]From method shown in Table 3. Value given is not adjusted for oral intake--see column 6 for that adjustment.
[c]From the "Health Assessment Document for Beryllium." EPA/600/8-84/026F. Values are not adjusted for differential absorption (EPA and CAG do not usually incorporate absorption coefficients in estimates).
[d]Computed according to (0.03 ug/L) RP_i, where RP_i is the potency of the chemical relative to B[a]P. Page 116 of Jones et al. 1988.
[e]From Table 2.
[f]Values from 40CFR (EPA 1986b, EPA 1985, EPA 1975) and EPA Water Criteria Documents.

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Table 5. Derivation of GRAS baseline or index values for toxic chemicals from (1) daily consumption of utility processed but otherwise drinking water or (2) the composite value from utility water and one reference meal.

	T-bone steak	Bread	Lettuce	Tea	Water	Total
Consumption per day	10 oz (280 g)	2 slices (57 g)	1.5 oz. (43 g)	1 cup (250 mL)	2 liters	-- --
Chemical of concern	B[a]P	B[a]P	B[a]P	Fluoride	Fluoride and Chlorine residues	-- --
Concentration	50 ng/g	1 ng/g	1.6 ng/g	100 ppm	1 ppm and 28 ug/L	
Equivalent Toxic Dose of B[a]P[a]	14 ug	57 ng	69 ng	1200 ug[c]	92 ug[d]	1.3 mg
Dose of B[a]P (mg/kg/D)[b]	2.0E-04	8.1E-07	9.9E-07	1.7E-02	1.3E-03	1.9E-02
Risk coefficient from EPA-CAG $(mg/kg/D)^{-1}$	11.5	11.5	11.5	11.5	11.5	11.5
GRAS Index Value (Dose x Risk Coefficient)	2.3E-03	9.3E-06	1.1E-05	2.0E-01	1.5E-02	2.2E-1
GRAS Value for Hazard Index Equation					0.015	0.22

[a]The equivalent dose of B[a]P is computed from the product of the dose and the potency of that compound relative to B[a]P.

[b]Based on daily consumption and a 70 kg reference body weight.

[c]Fluoride contribution = $(250\ g)\ (10^{+6}\ ug/g)\ \frac{(10^{-6})}{ppm}\ (100\ ppm)\ (0.046) \simeq 1200\ ug.$

[d]Contribution from Cl residuals = (21 ug) (0.005) + (6 ug) (0.0065) + (1.2 ug) (0.021) = 0.17 ug/L, and

fluoride contribution = $\frac{(10^3 g)}{L}\left(\frac{10^{-6}}{ppm}\right)$ (1 ppm) (0.046) = 46 ug/L.

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related substance or substances in such diet. . . General recognition of safety may be based on the views of experts qualified by scientific training and experience to evaluate the safety of substances added to food. The basis of such views may be either (1) scientific procedures or (2) in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food. . ." (FDA 1985).

From these and other operational concepts of safety, we propose to use comparisons of relative toxicity to define GRAS-type concentrations or doses for various chemical pollutants that are consistent with procedures and/or foods considered by the FDA and listed as safe. We acknowledge that our proposal is grossly inconsistent with the EPA's policy for control of carcinogens and the Delaney Amendment (1958).

It is recognized widely that various foods and/or food preparation processes result in human intake of various xenobiotics--chemicals foreign to the human body (Ames et al. 1987; Finley and Schwass 1982; MacMahon and Sugimura 1983; FDA 1985). Examples of selected xenobiotics in food and drinking water are shown in Table 5. Table 5 provides two different baselines for comparison of concentrations of chemical pollutants in drinking water for a wide array of human exposures. One baseline or "GRAS index value" is obtained from postulating the consumption of a common reference meal plus 2 L of utility-processed but otherwise pure water assumed to be ingested daily. A second and lower "GRAS index value" is obtained from the daily consumption of 2 L of utility-pure water only. The product of the chemical dose and the risk coefficient is taken as the "GRAS index value" and is seen to be 0.22 and 0.015, respectively.

Obviously, some readers will question the acceptability of our standards derived from Table 5 because the fluoride ion is highly toxic. In fact, sodium fluoride has been used in rat poison and insecticides. Also, the Commissioner of Food and Drugs has concluded that it is in the interest of the public health to limit the addition of fluorine compounds to foods (1) to that resulting from fluoridation of public water, (2) to that resulting from the fluoridation of bottled water, and (3) to that authorized by 40 CFR Part 180 (FDA 1985). However, either directly or indirectly, most of society accepts fluoridation of public drinking water, even for potentially sensitive subpopulations. If one does not accept fluoridation as safe, then the GRAS-like values can be normalized to residual contaminants as a consequence of chlorination only. Chlorination results in a variety of chemical reactions as described in Appendix E and summarized in the next paragraph.

Based on the frequency of distribution of the halomethanes detected in the National Organics Reconnaissance Survey for halogenated organics (Symons et al. 1975), the utility-processed but otherwise pure water would contain about 21 μg/L of chloroform, 6 μg/L of bromodichloromethane, and 1.2 μg/L of chlorodibromomethane--all three compounds are probably carcinogenic. Other contaminants occur in lesser concentrations. Thus, one cannot live without constant exposure to chemical carcinogens (Ames et al. 1987).

On that argument, we use data in Table 5 and the cited references on xenobiotics in foods to compute two composite index values (shown in the bottom line of Table 5) to estimate GRAS-equivalent concentrations listed in Table 6.

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Table 6. Concentrations for RAP chemicals computed to be of toxicity equal to per capita consumption of 2 L of utility pure water daily or consumption of water and a reference meal consumed daily.

RAP Chemical	GRAS-equivalent[a,b] based on drinking water (mg/L)	GRAS equivalent[c] based on drinking water and a reference meal (mg/L)
Arsenic	0.71	10
Barium chloride	22	320
Barium (II) nitrate (1:2)	130	1900
Benzene	22	320
Beryllium	38	550
Cadmium	24	350
Chloroform	22	320
Chromium (IV)	0.05	0.73
Copper	2.2	33
Cresol	7.5	110
1,1-Dichloroethylene	8.6	120
2,4-Dimethylphenol	19	280
Di-n-butylphthalate	560	8200
Ethylbenzene	53	780
Lead	12	180
Mercury		
elemental	2800	41,000
inorganic	1.5	22
organic	0.50	7.4
Methylene chloride	53	770
Naphthalene	23	330
Nickel	17	250
PCBs	35	510
Phosphorus (phosphoric acid)	10	150
Selenium (selenious acid)	0.46	6.8
Toluene	29	430
Vinyl chloride	390	5700
Xylene	33	480
Zinc (zinc oxide)	40	590

[a]Computed from Dose = Risk/[(Risk coef.) x A_{oral})], 70 kg body weight, and 2 L/day.
[b]Risk is 0.015 based on Table 5. [c]Risk is 0.22 based on Table 5.

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10. RISK COEFFICIENTS AND CONCENTRATIONS FOR RADIONUCLIDES

Tabulated values of risk from ingestion of radionuclides (Sullivan et al. 1981), a risk estimate of 200 x 10^{-6} fatal cancers per centiGray; 40 mrem of natural background terrestrial radiation per year (NAS 1980), and a mean life span of 70 years were used to compute a lifetime risk of 5.6E-4 fatal cancers per person from natural background radiation. This baseline was used to compute GRAS-equivalent doses for individual radionuclides as shown in Table 7. The concentration for 10^{-5} risk as shown in column 4 of Table 7, and the GRAS-equivalent values in column 5 are intended to be used in the same manner as corresponding values in Tables 4 and 6.

11. COMPOSITE HAZARD OR GRAS-INDEX VALUE FOR MULTIPLE POLLUTANTS

The Composite Hazard Index Method for using measured or calculated concentrations of pollutants and criteria or performance standards has been used widely as a means to estimate the composite hazard represented by exposure to serial and/or simultaneous agents (EPA 1986c). The many values are condensed into a single summary statistic by the simple formula

$$HI = E_1/C_1 + E_2/C_2 + \ . \ . \ . + E_n/C_n \ ,$$

where E_i is the exposure concentration and C_i is the standard for the i-th pollutant. The method in this report combines noncarcinogenic chemicals, carcinogenic chemicals, and radionuclides into a single summary statistic in contrast to the cited EPA rule. The EPA maintains the distinction because, to date, it has not attempted to develop a uniform methodology to regulate pollutants.

We have attempted to supply three methods of evaluating hazards from mixed-waste exposures. Those comparisons permit the decision maker to draw realistic and relative conclusions in order to allocate resources. Next, we demonstrate this evaluation for two hypothetical wells from a solid waste storage area (SWSA).

12. EXAMPLE APPLICATION

For purposes of illustration, two hypothetical water samples for a reference SWSA were assumed as given in Table 8. Concentrations are from representative measurements, but the example is hypothetical because only an abbreviated inventory of actual pollutants was used to illustrate the process.

From the hypothetical well T-92, compliance problems may exist within the reasonable near term for about 13 of the 25 index pollutants listed in Table 8. From the second hypothetical well T-257, compliance problems could be reasonably expected for about 11 of the 25 index pollutants. But, the GRAS-type comparisons would seem to project that only the presence of strontium-90 in well T-92 would appear to increase the composite relative hazard to a level above that corresponding to commonly accepted foods and utility-processed but otherwise pure water. Also, these calculations suggest that the water sample from well T-257 is about

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Table 7. Development of risk-specific concentrations and GRAS-equivalent index values for radionuclides.

Nuclide	Deaths in 10^5 cohort[a] $(Bq/year)^{-1}$	Risk coefficient[b] $(Bq/L)^{-1}$	Concentration for 10^{-5} chance of death[c] (Bq/L)	GRAS-equivalent (natural background equivalent concentration)[d,e] (Bq/L)	51FR34859 (4 mrem/year) (Bq/L)
^{3}H	4.86E-6	3.55E-8	2.8E+2	1.6E+4	3E+3
^{60}Co	3.35E-4	2.45E-6	4.1	2.3E+2	7
^{90}Sr	5.86E-3	4.27E-5	2.3E-1	1.3E+1	2
	3.95E-4	2.89E-6	3.5	1.9E+2	3E+1
^{99}Tc	5.19E-5	3.78E-7	2.6E+1	1.5E+3	2E+2
^{106}Ru	8.89E-4	6.49E-6	1.5	8.6E+1	1E+1
^{137}Cs	2.49E-3	1.82E-5	5.5E-1	3.1E+1	4
^{154}Eu	1.88E-4	1.37E-6	7.3	4.1E+2	4E+1
^{232}Th	1.07E-2	7.78E-5	1.3E-1	7.2	
^{233}U	3.46E-4	2.52E-6	4.0	2.2E+2	
	1.39E-2	1.02E-4	9.8E-2	5.5	
^{235}U	3.57E-4	2.61E-6	3.8	2.1E+2	
	1.14E-2	8.30E-5	1.2E-1	6.7	
^{238}U	3.14E-4	2.29E-6	4.4	2.4E+2	
	1.16E-2	8.43E-5	1.2E-1	6.6	
^{239}Pu	7.84E-3	5.73E-5	1.7E-1	9.8	1E-1
	7.62E-2	5.57E-4	1.8E-2	1.0	
^{240}Pu	7.84E-3	5.73E-5	1.7E-1	9.8	
	7.62E-2	5.57E-4	1.8E-2	1.0	
^{241}Am	7.68E-2	5.59E-4	1.8E-2	1.0	1E-1
^{244}Cm	4.57E-2	3.32E-4	3.0E-2	1.7	

[a]Values converted from Table 7 of Sullivan et al. (1981). Second value for isotope is for least-soluble compounds.

[b]Example calculation for ^{3}H: Risk Coef. $(pCi/L)^{-1}$ = (4.86E-6 deaths)/[(10^5 persons) x (1 Bq/year) (1 year/365 d) (1 d/2 L)].

[c]Concentration (Bq/L) = Risk/Risk Coefficient

[d]200E-6 fatal cancers per person-cGy; 40 mrems/year; and lifespan of 70 years were used to compute a risk of 5.6E-4 fatal cancer/person.

[e]Risk of 5.6E-4 used with footnote "c".

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Table 8. Demonstration of the risk-based composite hazard index and the composite-GRAS index for hypothetical water samples from two wells near a solid waste storage area

Agent	Hypothetical well T-92[a]	Concentration[b] / GRAS	Concentration[c] / GRAS	Concentration[d] / P.C.	Hypothetical well T-257[a]	Concentration[b] / GRAS	Concentration[d] / GRAS
Benzene	<0.0044	2.0E-4	1.4E-5	3.7E-1	<0.0044	2.0E-4	3.7E-1
Ethylbenzene	<0.005	9.4E-5	6.4E-6	1.5E-3	<0.005	9.4E-5	1.5E-3
Toluene	<0.005	1.7E-4	1.2E-5	5.0E-3	0.035	1.2E-3	3.5E-2
Chloroform	<0.0016	7.3E-5	5.0E-6	3.7E-1	<0.005	2.3E-4	1.2E+0
1,1-dichloroethylene	<0.0028	3.3E-4	2.3E-5	9.3E+0	<0.005	5.8E-4	1.7E+1
Methylene Chloride	<0.0028	5.3E-5	3.6E-6	1.1E-1	<0.005	9.4E-5	12.0E-1
Xylenes	<0.005	1.5E-4	1.0E-5	2.3E-3	0.011	3.3E-4	5.0E-3
Vinyl chloride	<0.01	2.6E-5	1.8E-6	6.7E+1	<0.01	2.6E-5	7.1E-2
Naphthalene	0.051	2.2E-3	1.5E-4	3.6E-1	<0.01	4.3E-4	7.1E-2
Di-n-butyl phthalate	<0.01	1.8E-5	1.2E-6	7.7E-5	<0.01	2.0E-5	7.7E-5
Arsenic	<0.005	7.0E-3	5.0E-4	2.2E+1	<0.10	1.4E-1	4.3E+2
Cadmium	<0.005	2.1E-4	1.4E-5	8.8E+1	0.0012	5.0E-5	2.1E+1
Chromium[e]	<0.04	0.8E+0	5.5E-2	2.4E+2	0.0049	9.8E-2	2.9E+1
Copper	<0.02	9.1E-3	6.1E-4	6.7E-2	<0.002	9.1E-4	6.7E-3
Lead	<0.01	8.3E-4	5.6E-5	2.0E-1	<0.020	1.7E-3	4.0E+0
Mercury[f]	<0.0002	4.0E-4	2.7E-5	2.7E-3	<0.0002	4.0E-4	2.7E-3
Nickel	0.06	3.5E-3	2.4E-4	1.4E+2	0.014	8.2E-4	3.3E+1
Zinc	<0.02	5.0E-4	3.4E-5	3.7E+0	0.44	1.1E-2	8.1E+1
PCBs	NA[g]				NA[g]		
^{3}H	2.2E+3	1.4E-1	1.4E-1	7.9E+0	3.9E+3	2.4E-1	1.4E+1
^{60}Co	0.22	9.6E-4	9.6E-4	5.4E-2	1.4	6.1E-3	3.4E-1
^{90}Sr	86	6.6E+0	6.6E+0	3.7E+2	NA		
^{99}Tc	<100	6.7E-2	6.7E-2	3.8E+0	<100	6.7E-2	3.8E+0
^{137}Cs	2.6	8.4E-2	8.4E-2	4.7E+0	2.1	6.8E-2	3.8E+0
^{235}U	NAL[h]				NAL[h]		
Total		7.7	7.0	5,400		0.64	1,300
Total (w/o chromium and strontium)		0.32	0.30	350		0.54	680

[a]Chemical concentrations in mg/L and radionuclide concentrations in Bq/L.
[b]Concentration in water sample divided by the GRAS-equivalent based on drinking water. Values for chemicals are from Table 6 and values for radionuclides are taken from column 5 of Table 7.
[c]Concentration in water sample divided by the GRAS-equivalent based on drinking water and a reference meal.
[d]Concentration in water sample divided by the right-most value in the relevant row of Table 4 or column 4 of Table 7 (i.e., P.C. to indicate "permissible concentration").
[e]Treated all chromium as hexavalent.
[f]Treated all mercury as organic.
[g]NA = Analysis not performed.
[h]NAL = Analysis not performed because gross activity was low.

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tenfold less toxic than the sample from well T-92. This comparison is based on concentrations for the indicated sample dates and could change for additional samples.

13. CONCLUSIONS

Data in Table 5 and current EPA statutory levels for various chemicals (used in the manner of Table 5) were used to compare relative hazards as shown in Fig. 5. The data in Fig. 5 are all based on toxicity of the chemical components--not on epidemiologically derived estimates of risk. All values are normalized to the composite toxicity contained in a pack of cigarettes (Owen and Jones 1988). Each GRAS-like substance was evaluated for a daily consumption rate, and each water pollutant shown in the left portion was based on the statutory EPA concentration and a reference consumption of 2 L daily. As readily observed, the EPA statutory concentrations correspond closely to a wide variety of GRAS-type foods. It should be noted that the ordinate is in logarithmic hazard units. As illustrated, the standards for vinyl chloride and PCBs may be less hazardous than lettuce--by a factor of 100. These and other such relative comparisons have convinced us to develop alternative methods to currently used extrapolation models for quantitative decision making.

A bit of evidence is gained from these tentative comparisons that suggests possibly that some high-priority environmental problems may not necessarily be extremely dangerous to the general population, and great care should be taken before listing of a site on the National Priority List (NPL). The NPL commitment may compete with better uses for limited resources. Overall, we have much greater anxiety for the large number of chemicals currently unregulated in drinking water than we have for environmental concentrations found in reasonable excess (i.e., within one or two orders of magnitude) of statutory values for carefully regulated pollutants. However, at this time it is important that we qualify our position somewhat because an array of additional comparisons should be made to further calibrate or validate the current findings. Several comparisons in this report are based on the current EPA method of "acceptable" exposure to individual chemicals without an overriding limit to restrict the total exposure burden when vast numbers of pollutants are involved. Currently, only 26 chemicals are regulated in drinking water with an intent to regulate a total of 83 in 1989. Hence, the overriding limit for exposure to many chemicals has not been considered very important, but that situation can change greatly when hundreds or thousands of pollutants come under regulatory control. If this particular policy is changed by the EPA and if statutory concentrations continue to be derived from extremely cautious extrapolation models, then the composite hazard index of Sect. 11 may exceed unit values for most any assessment involving large numbers of pollutants, simply as a result of summing many ratios comprised of small exposures divided by extremely cautious criteria.

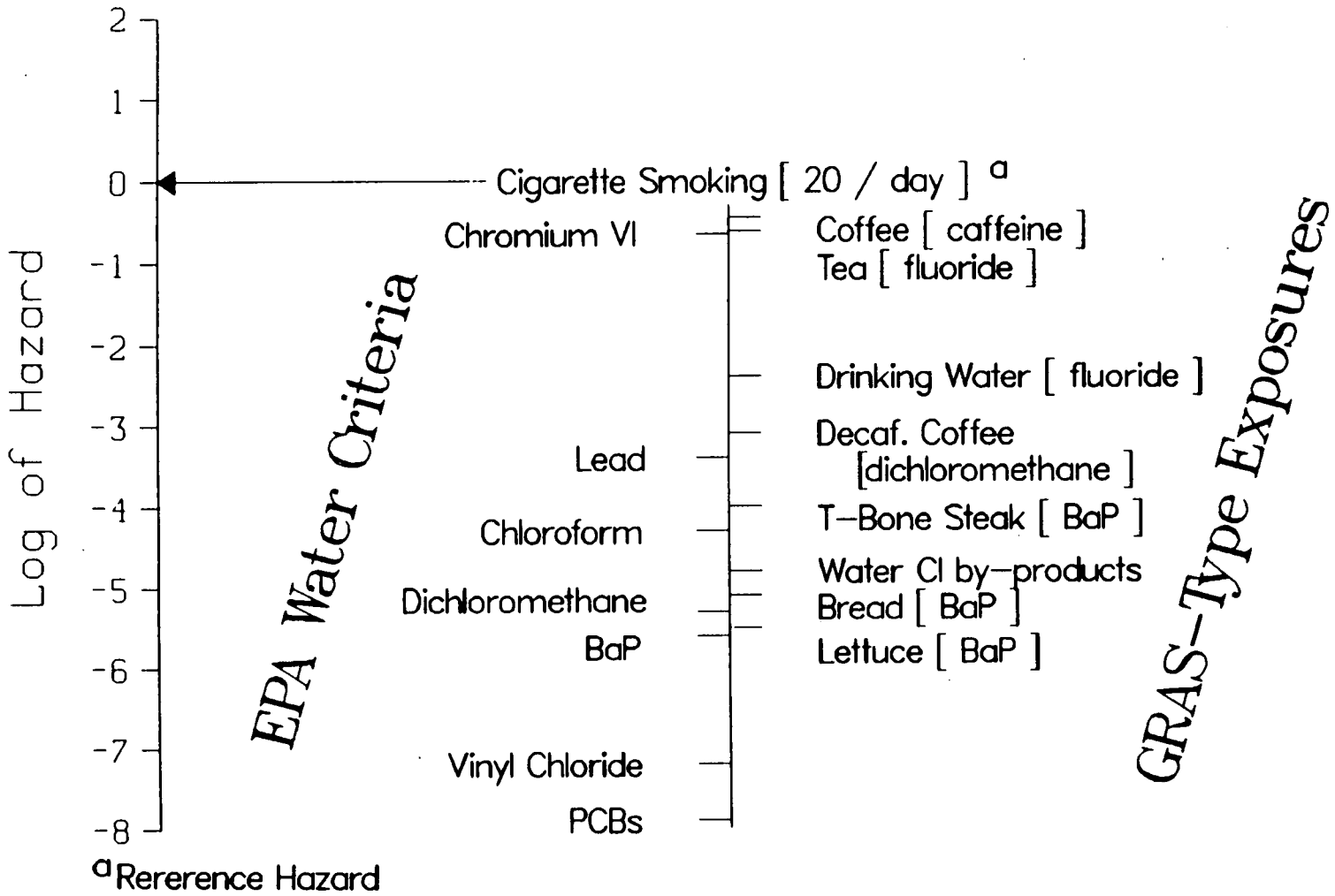

FIG. 5. HAZARDS FROM EPA DRINKING WATER CRITERIA COMPARED WITH CONSUMPTION OF GRAS-TYPE FOODS.

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Appendix A

REVIEW OF EPIDEMIOLOGICALLY BASED CARCINOGENS

ACRYLONITRILE

Evidence that acrylonitrile is a human carcinogen comes from both animal bioassays and epidemiologic studies. According to IARC criteria for evaluating the data, there is "sufficient" evidence for carcinogenicity based on animal data and somewhere between "sufficient" and "limited" evidence based on human data. Thus, acrylonitrile is classified as a Group 2A carcinogen, characterized as "probably carcinogenic in humans, where the evidence for human carcinogenicity is almost sufficient".

Acrylonitrile is not a direct-acting carcinogen and its effects are metabolism-dependent. The tumorigenic response to acrylonitrile in humans is lung cancer, whereas animals develop brain cancer.

Acrylonitrile is readily absorbed by both inhalation and ingestion and is subsequently metabolized to cyanide, which is then converted to urine-excretable metabolites. The toxicity of acrylonitrile is attributable to both the parent compound and its metabolites. Toxic effects include respiratory distress, cyanosis, nausea, and convulsions. Acrylonitrile has been shown to produce teratogenic events and mutations in bacterial test systems.

The CAG methodology for estimating carcinogenic risk from acrylonitrile based on human exposure data employs the linear relative model (Anderson 1983). Of the epidemiologic studies presented, the study by O'Berg (1980) presented the most significant evidence of acrylonitrile as a human lung carcinogen. This study of acrylonitrile workers at the DuPont May Plant in Camden, South Carolina, formed the basis of the CAG unit risk estimate for inhalation exposure to acrylonitrile. The unit risk estimate, representing the incremental risk associated with a lifetime exposure of 1 $\mu g/m^3$ in air, was calculated to be 6.8×10^{-5}

$(\mu g/m^3)^{-1}$. The relative potency estimate based on this value assumes a 20 m^3 air per day breathing rate by an average 70 kg human to convert the unit risk value into units of 0.24 $(mg/kg/d)^{-1}$. This value, multiplied by the molecular weight of acrylonitrile (53.1) yields a potency index of $1.3 \times 10^{+1}$ for relative comparison with other carcinogens.

The CAG risk coefficient (slope) for acrylonitrile as shown above is 0.24 $(mg/kg/d)^{-1}$. The daily inhalation dose of acrylonitrile representing a 10^{-5} level of risk is derived from the formula Risk (R) = Slope (S) x Dose (D), solving for D and assuming a 70 kg average weight for a human,

$$D = \frac{R}{S} = \frac{10^{-5}}{0.24} (70 \text{ kg}) = 2.9 \ \mu g/d \ .$$

Assuming 20 m^3/day is the breathing rate of reference man (ICRP 23), then

$$\frac{2.9 \mu g/d}{20 \ m^3/d} = 0.15 \ \mu g/m^3 \ ,$$

which is the concentration of acrylonitrile in air corresponding to a risk level of 10^{-5}. From the daily intake value modified by the literature-derived oral absorption efficiency of 0.95 and inhalation absorption efficiency of 0.98 (Appendix C) and assuming an average intake of 2 L of water per day, the permissible concentration in drinking water at the 10^{-5} level of risk is calculated as

$$\frac{(2.9 \ \mu g/d)(0.98/0.95)}{2 \ L/d} = 1.5 \ \mu g/L \ .$$

Summary - Acrylonitrile

Carcinogenic risk from acrylonitrile is based on the epidemiologic study of O'Berg (1980).

O'Berg 1980

Exposure period - 1950-1966

Follow-up period - through 1976

Number of subjects - 1345

Total number of deaths - 8

Level of exposure - High = 20 ppm
Medium = 10 ppm
Low = 5 ppm

Duration of exposure - unknown (estimated at 9 years)

Disease occurrence - lung cancer

Strengths and weaknesses - This study was weakened by the relatively poor documentation of exposure levels encountered by workers. Estimates were made 12 years after the exposure ended. Adjustments were made for latency of disease occurrence and the contributions of smoking, and still a significant excess of cancer mortality existed

CAG values: $1.3 \times 10^{+1}$ = carcinogenic potency
6.8×10^{-5} = unit risk

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INORGANIC ARSENIC

The IARC regards evidence to be sufficient for classifying arsenic as a human carcinogen through consideration of the "weight of evidence" for human carcinogenicity, placing arsenic in Group I, "carcinogenic to humans." Evaluations focused on epidemiologic evidence linking arsenic response to skin and lung cancer in humans. Animal studies are not definitive in demonstrating arsenic to be a carcinogen.

Data indicate that trivalent inorganic arsenic compounds are more toxic than pentavalent inorganic arsenicals, which are themselves more toxic than organic arsenic compounds. Acute effects of arsenic exposure range from hyperpigmentation and keratosis following oral intake to upper respiratory tract irritation (including nasal perforation following inhalation exposure. Results of chronic exposure to arsenic include both carcinogenic and noncarcinogenic effects ranging from respiratory tract and skin cancers to noncancerous skin lesions, peripheral neuropathological effects, and cardiovascular changes.

The CAG has estimated carcinogenic unit risk for both air and water exposures to arsenic using the linear, absolute risk model to provide a plausible estimate of the upper limit of risk; true risk could be slightly higher but, possibly, substantially lower than the estimate derived. The CAG also felt that low-level environmental exposure to arsenic was best represented by consideration of trivalent arsenic rather than the pentavalent form.

Unit risk estimates for air and water exposures were derived from six separate studies, and both linear and quadratic models in absolute and relative forms were fitted to the worker data. The CAG felt that the linear model in the absolute form gave a better fit than the quadratic, relative model. Unit risk estimates derived from the linear, absolute

model applied to exposure to only trivalent arsenic produced five values ranging from 1.25×10^{-3} to 7.6×10^{-3} $(\mu g/m^3)^{-1}$. A weighted average yielded a composite unit risk estimate for air exposure of 4.29×10^{-3} $(\mu g/m^3)^{-1}$.

A unit risk estimate for water exposure to arsenic was derived from an extensive drinking water study conducted in Taiwan, which established an association between arsenic in well water and skin cancer in the exposed population. Males were considered to be more susceptible than females; data from the male population yielded a unit risk estimate of 4.2×10^{-4} $(\mu g/m^3)^{-1}$.

To compare air and water unit risk estimates, the CAG converted each into units of mg/kg/d absorbed doses to produce slope estimates of 50.1 and 15.0 for air and water, respectively.

The potential of airborne arsenic to cause respiratory cancer was estimated using the method of maximum likelihood, assuming the observed number of respiratory cancer deaths followed a Poisson distribution. The calculation of expected respiratory cancer deaths in the control population accounted for the change in age-specific incidence rates with absolute time.

The CAG risk coefficient (slope) for arsenic is 15 $(mg/kg/d)^{-1}$ based on human drinking water exposure. The slope-based daily intake of arsenic at a 10^{-5} level of risk is thus calculated as

$$D = \frac{R}{S} = \frac{10^{-5}}{15} (70 \text{ kg}) = 0.047 \ \mu g/d,$$

assuming a 70 kg average weight for man. Therefore, based on a 2 L daily intake of drinking water, the concentration of arsenic in drinking water corresponding to a 10^{-5} risk level is calculated as

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$$\frac{0.047\ \mu g/d}{2\ L/d} = 0.023\ \mu g/L.$$

Absorption coefficients for arsenic are 0.35 for inhalation and 0.98 for oral exposure (Appendix C). Also, according to ICRP 23, reference man inhales 20 m^3 of air per day. Thus, the concentration of arsenic in air corresponding to a 10^{-5} risk level may be calculated as

$$\frac{(0.047\ \mu g/d)\ (0.98/0.35)}{20\ m^3/d} = 6.6\ ng/m^3\ .$$

Summary - Arsenic

Carcinogenic risk from arsenic in air is based on five data sets involving two distinct populations.

Lee-Feldstein 1983

Exposure period - pre-1957, 3 categories: 25+ years, 15-24 years, and <15 years

Follow-up period - 1938-1977

Number of subjects - 8047 white males in copper refinery (Anaconda, Montana)

Total number of deaths - 3550 with 302 from respiratory cancer

Level of exposure - Heavy = 11.27 mg/m^3
Medium = 0.58 mg/m^3
Light = 0.27 mg/m^3

Estimates are based on maximum exposure for 12 months or more. Intermittant use of respirators in the Heavy exposure area (reducing exposure levels by a rough factor of 10) probably resulted in average individual exposures much less than 11.27 mg/m^3

Duration of exposure - Cohort 1 (25+ years of exposure)-factored as 32 yrs.
Cohort 2 (15-24 years of exposure)-factored as 20 yrs.
Cohort 3 (<15 years of exposure)-factored as 5.3 yrs.

Disease occurrence - respiratory cancer

Strengths & weaknesses - Assignments to exposure categories were based on maximum exposures for at least a 12-month period instead of individual cumulative exposures. This tends to overestimate exposures and underestimate the derived carcinogenic potency of arsenic. Smoking data, which would have been helpful, was not included in this study. Only low- and medium-exposure groups were used in the risk estimate due to uncertainties with the high exposure groups in each of the three cohorts. Also, prospective studies such as this are subject to less bias than decedent studies

CAG values: 2.48×10^{-7} = carcinogenic potency (linear, absolute only)
2.80×10^{-3} = unit risk (linear, absolute)

Higgins et al. 1982

Exposure period - pre-1957 through 1978

Follow-up period - through 1978

Number of subjects - 1800 white males in copper refinery (Anaconda, Montana)

Total number of deaths - 80 (from respiratory cancer)

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Level of exposure - cumulative exposures measured in $\mu g/m^3$-years in 4 categories: 0-500, 500-2,000, 2,000-12,000, and $\geq$ 12,000

Duration of exposure - pre-1957 through 1978

Disease occurrence - respiratory cancer

Strengths and weaknesses - Smoking data were provided. The study indicated significant increases in respiratory cancer among workers exposed to high levels of arsenic, even among nonsmokers. It would have been more appropriate to relate exposure to each 5-year age interval than to the total observation period of an individual

CAG values: 2.36×10^{-7} = carcinogenic potency (linear, absolute model)
4.90×10^{-3} = unit risk (linear, absolute model)

Brown and Chu 1983

Exposure period - same as Lee-Feldstein

Follow-up period - same as Lee-Feldstein

Number of subjects - same as Lee-Feldstein

Total number of deaths - same as Lee-Feldstein except omitting deaths of workers who left the smelter before the age of 55.

Level of exposure - heavy, medium, and light

Duration of exposure - same as Lee-Feldstein

Disease occurrence - same as Lee-Feldstein

Strengths and weaknesses - This study uses the data from the Lee-Feldstein study to assess carcinogenic risk from airborne arsenic, assuming a multistage model of carcinogenesis in which only the penultimate stage is affected by exposure. The mathematical model factors in the age at initial exposure. Only the light exposure group was used to obtain a dose-response model, a choice supported by a chi-square goodness-of-fit analysis

CAG values: 9.45×10^{-16} = carcinogenic potency (linear, absolute)
1.25×10^{-3} = unit risk (linear, absolute)

Enterline and Marsh 1982b

Exposure period - one year or more during 1940-1964

Follow-up period - through 1976

Number of subjects - 2802 males in copper refinery (Tacoma, Washington)

Total number of deaths - 104

Level of exposure - Individual cumulative exposures in units of $\mu g/m^3$-years ranging from 91.8-4091 were estimated from urinary arsenic levels extrapolated to airborne concentrations. Exposure estimates are based on a ten year lag.

Duration of exposure - one year or more

Disease occurrence - respiratory cancer

Strengths and weaknesses - This study incorporated exposure estimates based on individual exposure histories, whereas Lee-Feldstein did not. The type of dose-response analysis in this study is considered more suitable for quantitative risk estimatation. Exposure estimates based on a ten-year lag are probably more realistic than no-lag dose responses. Uncertainty exists in applying urinary arsenic levels from years 1948-1952 to earlier years in that exposures prior to 1948 were probably underestimated (resulting in an overestimate of the carcinogenic potency subsequently derived). No smoking data were gathered for this study, but data from a 1975 survey of Tacoma workers indicate that a small fraction of excess respiratory cancer deaths could have been due to smoking

CAG values: (all based on absolute, linear models)
zero lag: 6.04×10^{-7} = carcinogenic potency
zero lag: 6.81×10^{-3} = unit risk
10-year lag: 8.85×10^{-7} = carcinogenic potency
10-year lag: 7.60×10^{-3} = unit risk

Ott et al. 1974

Exposure period - relatively short, in that only 25% of decedents had worked with arsenicals for more than one year.

Follow-up period - unknown

Number of subjects - 174 decedents exposed to arsenic in a pesticide production facility, compared with 1809 decedents not exposed

Total number of deaths - 28 from respiratory cancer

Level of exposure - cumulative, ranging from 41.8 - 29497 $\mu g/m^3$-years)

Duration of exposure - predominantly less than one year.

Disease occurrence - respiratory cancer

Strengths and weaknesses - This is a study comparing age-specific death patterns of arsenic-exposed decedents with exposed decedents. As a decedent study, it is subject to more bias than a prospective study such as that of Enterline and

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March (1982b). The cohort was ill-defined in this study. Also, the relatively short exposure periods are less appropriate for extrapolating risk from lifetime environmental exposure than are studies involving longer exposures. The number of respiratory cancer deaths (28) was quite small. Only a relative risk model could be applied to this study (data from highest exposure groups were omitted). Risk estimation was based on a life-table method of analysis and does not seem particularly appropriate for a decedent analysis. Exposure to pentavalent arsenic was considered in this study, whereas the other studies involved trivalent arsenic.

CAG values: 9.2×10^{-4} = carcinogenic potency (linear, relative model)
1.36×10^{-2} = unit risk (linear, relative)

Carcinogenic risk from arsenic in water is based on one study associating arsenic in well water in Taiwan with skin cancer.

Tseng et al. 1968

Exposure period - lifetime

Follow-up period - unknown

Number of subjects - males only from a group 40,421 Taiwanese who had consumed well water containing arsenic.

Total number of deaths - unknown (skin cancer is rarely fatal)

Level of exposure - from 0 to greater than 0.6 ppm

Duration of exposure - essentially lifelong

Disease occurrence - skin cancer

Strengths and weaknesses - A large, stable population known to have ingested arsenic in drinking water is suitable for use in predicting the lifetime probability of skin cancer caused by arsenic ingestion. However, racial, dietary, and nutritional differences contribute to uncertainty in extrapolating risk from this population to the generalized U.S. population. Furthermore, exposure to arsenic in the well water was confounded by concurrent exposure to ergotamine, which may have altered the results (although no evidence to support this view currently exists). A separate study tends to validate the Tseng data as the best currently available for predicting risk of skin cancer from arsenic ingestion

CAG values: 4.3×10^{-4} = unit risk

BENZENE

Benzene exposure has been associated with a broad range of acute and chronic health effects in both occupationally exposed humans and studies of laboratory exposures in animals. Acute exposures produce depression of bone marrow cellularity and neurotoxicity via oral and inhalation routes of exposure. Chronic exposures via both routes has produced carcinomas of the zymbal gland in rats. Oral dosages have not produced cancer in humans, but inhalation exposures in occupational settings have induced leukemia in exposed workers. Bone marrow toxicity is thought to be caused by benzene metabolites and not the parent compound.

The International Agency for Research on Cancer (IARC) considers there to be sufficient evidence to establish causality between benzene and human cancer and assigns benzene to Group 1 based on epidemiologic evidence.

Three separate epidemiologic studies (Rinsky et al. 1981, Wong et al. 1983, and Ott et al. 1978) were used by EPA's Carcinogen Assessment Group (CAG) to develop carcinogenic risk coefficients for benzene (EPA 1985). An earlier study by Askoy et al. (1974) was determined to contain sufficient uncertainties as to be unsuitable for use.

The CAG gave equal weight in the calculations to cumulative doses and weighted cumulative doses and to absolute and relative risk models. An average of various estimates produced a composite unit risk of 2.6×10^{-2} for inhalation of air containing 1 ppm of benzene, corresponding to a slope estimate of 0.028 $(mg/kg/d)^{-1}$.

Based on the CAG slope of 0.028 and the formula Risk (R) = Slope (S) x Dose (D) and assuming a 70 kg average weight of man, then

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$$D = \frac{R}{S} = \frac{10^{-5}}{0.028}(70\ \text{kg}) = 25\ \mu\text{g/d},$$

the intake level corresponding to a 10^{-5} level of risk. If man breathes an average of 20 m^3/d, then

$$(25\ \mu\text{g/d})/(20\ \text{m}^3/\text{d}) = 1.25\ \mu\text{g/m}^3,$$

which represents the air concentration producing a 10^{-5} level of risk for exposure to benzene.

From the inhalation (0.47) and oral (1.0) absorption coefficients for benzene (see Appendix C), computation of the drinking water concentration equivalent to a 10^{-5} level of risk (2 L daily intake assumed), is

$$\frac{(24.9\ \mu\text{g/d})/(0.47/1.00)}{2\ \text{L/d}} = 5.9\ \mu\text{g/L}.$$

Summary - Benzene

Carcinogenic risk from benzene is based on 3 separate epidemiologic studies: Rinsky et al. 1981, Ott et al. 1978, and Wong et al. 1983 (EPA 1985).

Rinsky et al. 1981

Exposure period -

Follow-up period - from 1940 - 1978

Number of subjects - 41,886 person-years

Total number of deaths - 385 for all causes, 8 from leukemia

Level of exposure - up to an average 1482.5 ppm-year in six categories

Duration of exposure -

Disease occurrence - leukemia (others noted)

Strengths and weaknesses -

Ott et al. 1978

Exposure period -

Follow-up period -

Number of subjects - 13,271 person-years

Total number of deaths - 102 from all causes, 2 from leukemia

Level of exposure - up to an average of 352.9 ppm-year in 5 categories

Duration of exposure -

Disease occurrence - leukemia (others noted)

Strengths & weaknesses - the few leukemia deaths noted impart a degree of uncertainty to this study

Wong et al. 1983

Exposure period -

Follow-up period -

Number of subjects -

Total number of deaths - 6 due to leukemia specifically

Level of exposure - cumulative in ppm-months (up to 720 + ppm-months)

Duration of exposure -

Disease occurrence - leukemia (others noted)

Strengths and weaknesses -

BENZIDINE

Benzidine is an aromatic amine used extensively in the manufacturing of industrial dyes. Human exposure occurs primarily in the industrial setting in operations involving synthesis of benzidine and its conversion to dyes. Workers in such industries are at greatest risk from skin absorption of the light, fluffy benzidine base, although poor industrial hygiene practices may result in exposures via inhalation or ingestion.

Benzidine is known to cause cancer in both humans and experimental animals. The site of tumor formation varies with the species tested, probably because of differential target organ specificity and routes of excretion. Both humans and dogs excrete benzidine and its metabolites through the urinary route. Exposure to benzidine in these species results in urinary bladder tumor formation, usually followimg a long latent period. The length of the latent period varies with the degree of exposure.

On the basis of sufficient evidence from short-term tests, animal experimentation and epidemiology, the IARC considers benzidine to be a Group I human carcinogen. Benzidine has been shown to be mutagenic, although definitive evidence of teratogenicity is lacking.

The epidemiologic study of Zavon et al. (1973) was selected for derivation of the carcinogenic risk coefficient by the EPA Carcinogen Assessment Group (CAG) (EPA 1980). In this study, workers at a benzidine manufacturing plant were observed for the development of urinary bladder tumors. Fifty-two percent of the study cohort developed bladder tumors after an average exposure duration of 13.61 years. Exposure levels were estimated from urinary excretion data.

This study forms the basis of the CAG slope estimate for benzidine of 234 $(mg/kg/d)^{-1}$. According to the formula Risk (R) = Slope (S) x Dose

(D), and assuming an average weight of 70 kg for man,

$$D = \frac{R}{S} = \frac{10^{-5}}{243} (70 \text{ kg}) = 2.9 \text{ ng/d},$$

which is the intake dose corresponding to a risk level of 10^{-5}, or one excess cancer mortality in a population of 100,000 persons exposed for a lifetime to 2.9 ng of benzidine daily.

Assuming a 20 m^3 intake of air daily,

$$\frac{2.9 \text{ ng}}{20 \text{ m}^3} = 0.15 \text{ ng/m}^3,$$

which is the air concentration resulting in a 10^{-5} risk level for inhalation of benzidine.

From the oral and inhalation absorption coefficients of 0.90 and 0.95, respectively, (Appendix C) and assuming a daily intake of 2 L of drinking water by the average man, then

$$\frac{2.9 \text{ ng/d } (0.95/0.90)}{2 \text{ L/d}} = 1.5 \text{ ng/L},$$

which is the concentration of benzidine in drinking water corresponding to a 10^{-5} level of risk.

Summary-Benzidine

Zavon et al. 1973

Exposure period - 13.61 years average

Follow-up period - 13 years

Number of subjects - 25

Total number of deaths - 13 (52% incidence)

Level of exposure - 130 mg/kg total accumulated dose, estimated from average primary levels of benzidine at the end of a work shift.

Duration of exposure - 11.46 years average

Disease occurrence - bladder cancer

Strengths and weaknesses - Uncertainty of exposure levels estimated from urinary excretion data, small cohort size, and possible confounding because of cigarette smoking were weaknesses of this study. The great incidence (52%) of the disease in the study cohort represents a strength of the study

CAG values: slope = 234 $(mg/kg/d)^{-1}$

BERYLLIUM

Beryllium is extracted from ore and is used extensively in industry. The metal and its alloys demonstrate both great resistance to corrosion and high thermal conductivity, permitting widespread application in the electronics, aerospace, and nuclear power industries.

Human exposure to beryllium derives from inhalation of airborne beryllium, primarily as the product of coal and fuel oil combustion, or from ingestion. Beryllium is poorly absorbed through the gastrointestinal tract (<1%) but may be absorbed to a much greater extent via inhalation, resulting in long-term retention in the lungs. Absorbed beryllium is deposited mainly in bone, which may explain its relatively long biological half-life.

Exposure to beryllium may result in acute respiratory disease or chronic respiratory disease ("beryllium disease"), which has occured in epidemic proportions in the past, primarily in occupational groups involved in the processing or otherwise handling of beryllium. Effects were mainly the result of inhalation of beryllium-contaminated dusts of workplace origin that had been brought to the household on contaminated clothing. Improved industrial hygiene practices have greatly reduced the current incidence of chronic beryllium disease. The disease is typically diagnosed only after a long latent period (up to 20 years).

Beryllium has been demonstrated to be mutagenic, resulting in chromosomal aberrations, gene mutations, and sister-chromatid exchange in cultured mammalian somatic cells. The potential for beryllium to produce adverse reproductive or teratogenic effects has not been definitely established by the scarce data currently available.

The IARC considers beryllium to be a Group 2A "probable human carcinogen" based on "sufficient" animal data and "limited" epidemiologic

evidence. The EPA has evaluated more recent unpublished data that corrects for errors in the data base considered by the IARC and has judged the epidemiologic evidence to be "inadequate". The EPA, thus, assigns beryllium to group B2 (EPA classification scheme), a probable human carcinogen, based on sufficient evidence from animal data. Beryllium has produced osteosarcomas and chondrosarcomas by injection in rabbits and lung tumors via inhalation (and intratracheal instillation) in rats and monkeys. Beryllium has not definitely produced tumors an any animals by ingestion, probably because of poor absorption by that route of intake.

In quantifying the carcinogenic risk from beryllium, the EPA has considered only inhalation data and has placed greater emphasis on studies involving beryllium oxide, the chemical form most likely to be encountered by humans (the oxide is the form emitted by combustion of coal and fuel oil). Becuase of insufficiencies in the animal studies, they are considered to provide only supporting evidence for the occupationally derived estimates.

The study of Wagoner et al. (1980) was selected as the best epidemiologic study for quantifying carcinogenic potency of beryllium. Analysis of the data employed the linear nonthreshold model to yield a total of eight upper-bound unit risk estimates on the basis of two exposure levels modified by two "effective dose" levels, again modified by two relative risk estimates. The geometric mean of these eight estimates was calculated to be 2.4×10^{-3} $(\mu g/m^3)^{-1}$, which was rounded to 2×10^{-3} $(\mu g/m^3)^{-1}$ because of uncertainty. This estimate agrees well with the geometric mean unit risk estimate based on animal data, 2.1×10^{-3} $(\mu g/m^3)^{-1}$.

Therefore, based on the human data (with supporting evidence from animal studies) a single unit risk estimate for exposure to beryllium

oxide of 2×10^{-3} $(\mu g/m^3)^{-1}$ was chosen. Based on a 70-kg man, breathing 20 m^3 of air per day, this number was converted to a slope (q_1^*) estimate of 7 $(mg/kg/d)^{-1}$. The corresponding slope estimate for exposure to beryllium salts was calculated to be 3×10^3 $(mg/kg/d)^{-1}$, based on animal data.

From the beryllium oxide slope estimate and the formula Risk (R) = Slope (S) x Dose (D) (assuming an average 70-kg weight for man), a daily intake level yielding a risk level of 10^{-5} is derived as follows:

$$D = \frac{R}{S} = \frac{10^{-5}}{7} (70 \text{ kg}) = 0.1 \ \mu g/d.$$

Assuming a man breathes 20 m^3 of air daily,

$$\frac{0.1 \ \mu g/d}{20 \ m^3/d} = 5 \ ng/m^3,$$

which is the permissible concentration of beryllium in air to yield a 10^{-5} risk level.

Based on an inhalation absorption efficiency of 0.50, an oral absorption efficiency of 0.001 (Appendix C), and a daily intake of 2 L of drinking water,

$$\frac{(0.1 \ \mu g/d)(0.50/0.001)}{2 \ L/d} = 25 \ \mu g/L,$$

which is the concentration in drinking water corresponding to a 10^{-5} level of risk.

Summary - Beryllium

Wagoner et al. 1980

Exposure period - sometime during the interval from 1942 to 1967

Follow-up period - through 1975 (various subcohorts were followed for 25 years or more from initial employment)

Number of subjects - 3055 white males

Total number of deaths - 46

Level of exposure - assumed to range from a median level of 100 to 1,000 $\mu g/m^3$

Duration of exposure - variable

Disease occurrence - lung cancer

Strengths and weaknesses - The Wagoner et al. (1980) study has been criticized extensively for various deficiencies. The lack of consideration for cigarette smoking could have confounded the study - recent analysis of company records suggest that 91% of the cases (lung cancer deaths) were smokers. The estimate of lung cancer deaths in the comparison population was underestimated by 11% because of data gaps in the NIOSH computer-based life-table program. One lung cancer victim was included in the study who did not ever actually report for work. A total of 295 individuals were lost from the study cohort. Finally, no consideration was given for exposure to other potential carcinogens either before or after employment in the beryllium facility.

In summary, the Wagoner et al. (1980) study tended to exaggerate the lung cancer risk in the worker population while not effectively addressing the shortcomings of the study. The result was an erroneous conclusion that a significant association existed between exposure to beryllium and the subsequent incidence of lung cancer in the worker cohort. When corrections were later made for the number of expected deaths in the comparison cohort and for the effects of cigarette smoking, the statistical significance of the lung cancer incidence was eliminated. Even though no excess cancer risk was demonstrated, the data may be validly used to calculate an upper limit of lung cancer risk

CAG values: unit risk = 2×10^{-3} $(\mu g/m^3)^{-1}$, the geometric mean of eight individual estimates.
slope = 7.0 $(mg/kg/d)^{-1}$

CADMIUM

Cadmium is classified as a Group 2A substance by the IARC, indicating it is a "probable" human carcinogen, based on "limited" evidence from human studies and "sufficient" evidence from animal studies. Significant dose-response relationships for lung cancer have been established for rats exposed to cadmium chloride aerosols via inhalation and for injection site sarcomas for rats and mice exposed to cadmium metal or cadmium salts. The epidemiologic study of Thun et al. (1985) demonstrated a significant dose-response relationship for lung cancer in humans exposed to cadmium oxide and fumes via inhalation. The carcinogenicity of cadmium via ingestion has not been established in either animal or human studies. Mutagenicity assays using a variety of endpoints and protocols have yielded both negative and positive results. These discrepancies have yet to be resolved.

Quantification of carcinogenic risk to man from cadmium exposure has relied on the application of the linear nonthreshold model to the data of Thun et al. (1985). The maximum likelihood estimate of the linear parameter obtained from Thun's data was used to provide a single estimate of unit risk 1.8×10^{-3} $(\mu g/m^3)^{-1}$. This value represents the incremental risk of cancer in a population of persons exposed continually from birth to a concentration of 1 $\mu g/m^3$ of cadmium in air. The unit risk estimate can be expressed as 6.1 $(mg/kg/d)^{-1}$ by assuming a 70 kg man breaths in 20 m^3 of air daily, from the equation

$$1.8 \times 10^{-3}\ (\mu g/m^3)^{-1} \times \frac{1\ d}{20\ m^3} \times \frac{1 \mu g}{10^{-3}\ mg} \times 70\ kg = 6.1\ (mg/kg/d)^{-1}.$$

Multiplying this value by the molecular weight of cadmium (112.4) yields a potency index of $6.9 \times 10^{+2}$.

The daily intake of cadmium representing a 10^{-5} level of risk (one excess cancer mortality in a population of 10^5 persons from lifetime exposure) can be estimated from the equation Risk (R) = Slope (S) x Dose (D) and solving for dose, assuming a 70-kg average weight for man. Thus,

$$D = \frac{10^{-5}}{6.1} (70 \text{ kg}) = 0.11 \ \mu g/d.$$

Assuming reference man (ICRP 23) breathes 20 m^3 of air per day, then

$$\frac{0.11 \ \mu g/d}{20 \ m^3/d} = 5.7 \ ng/m^3,$$

which is the concentration of cadmium in air associated with a 10^{-5} level of risk.

The concentration of cadmium in drinking water representing the same level of risk can be derived by modifying the daily intake value by the oral and inhalation absorption coefficients for cadmium, 0.06 and 0.40, respectively (Appendix C), and assuming an average daily intake of 2 L of water, as follows:

$$\frac{(0.11 \ \mu g/d) \ (0.40/0.06)}{2 \ L/d} = 0.37 \ \mu g/L.$$

Summary - Cadmium

Thun et al. 1985

Exposure period - for at least 2 years during the period Jan. 1, 1940 through December 31, 1969.

Follow up period - through December 31, 1978.

Number of subjects - 602 white males in a cadmium refinery

Total number of deaths - 16

Level of exposure - estimated to be an average of concentration of 125 $\mu g/m^3$ over a three-year period

Duration of exposure - variable

Disease occurrence - lung cancer

Strengths and weaknesses - The results of this study reveal a greater than two-fold increased risk of lung cancer resulting from airborne cadmium exposure. Both increased cigarette smoking and the presence of arsenic in the plant were evaluated as potential confounders and ruled out as contributors to the actual excess lung cancer risk observed

CAG values: 1.8×10^{-3} = unit risk
$6.9 \times 10^{+2}$ = carcinogenic potency

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CHROMIUM

Chromium (III) is considered to be an essential micronutrient at low concentrations because a deficiency results in a buildup of glucose in the blood. Animal studies have demonstrated that chromium-deficient rodents gain less weight and have shorter lifespans than animals maintained on a chromium-sufficient diet. In humans, symptoms of chromium deficiency consist of glucose intolerance, weight loss, and confusion. However, as with all other chemicals, high doses of chromium (III) are toxic.

Chromium (VI) compounds are more readily absorbed through skin, gut, lung, and biological membranes than are compounds of the trivalent form. Chromium (VI) is irritating and corrosive and is metabolically reduced to chromium (III).

The CAG accepted the study by Mancuso (1975) as providing limited but adequate information for estimating the carcinogenic potency of hexavalent chromium. In analysis of this study, the CAG assumed that the individual worker exposure schedules resulted in equivalent risk as that from a continuous exposure given at a time-weighted average or concentration rate over an equal time frame. The age-specific incidence was treated as a power function of time according to the model of Druckrey (1967), and lifetime cancer risk in terms of exposure and age took into account competing risks based on the probability of surviving to a specific age.

Numerical coefficients of the risk model were evaluated (based on the assumption that the number of lung cancer deaths at a specific age follows a Poisson distribution) by the method of maximum liklihood.

The CAG risk coefficient (slope) for exposure to chromium is 41 $(mg/kg/d)^{-1}$. For a risk level of 10^{-5}, the permissible dose would be

$(10^{-5}/41)$ (mg/kg/d) (70 kg) = 0.017 μg/d, based on inhalation. If reference man (ICRP 23) breathes 20 m^3 of air daily, then the permissible concentration in air would be 0.85 ng/m^3.

If the inhalation absorption coefficient of chromium is taken as 0.25 and the oral absorption coefficient is 0.05 (Appendix C), then the permissible concentration of chromium in drinking water would be (0.017 μg/d) (0.25/0.05)/(2 L/d) = 0.042 μg/L.

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Summary - Chromium

Mancuso 1975

Exposure period - from the period of 1931-1937 to 1974

Follow-up period - until 1974

Number of subjects - 332 white males in a chromate plant

Total number of deaths - 35

Level of exposure - <1 to 8 mg/m/year

Time Weighted Averages (TWAs) of exposure to insoluble, soluble, and total chromium per cubic meter were calculated for each occupation and for each worker in each department.

Duration of exposure - $\leq$43 years

Disease occurrence - lung cancer

Strengths and weaknesses - The CAG used only the dose-response data for total chromium to estimate the carcinogenic potency of hexavalent chromium. The CAG thought that this underestimation of the potency of chromium (VI) was compensated for by other factors that may have overestimated risk

CAG values: slope = 41 $(mg/kg/d)^{-1}$
potency index = 4×10^3

NICKEL AND NICKEL COMPOUNDS

Both animal and human studies provide evidence that at least some forms of nickel are carcinogenic via inhalation. In animal studies, injected nickel compounds produce injection-site tumors. Evidence of carcinogenicity of orally dosed nickel is inadequate. The IARC classifies nickel refinery dust and nickel subsulfide as Group 1 (carcinogenic to humans) and nickel carbonyl as Group 2B (probable human carcinogen based on sufficient animal evidence but inadequate human evidence).

Acute exposure to nickel carbonyl produces adverse respiratory effects of both immediate and delayed symptomology in man. Chronic exposures produce dermatitis in man and endocrine, cardiovascular, and reproductive effects in animals. Nickel has been shown to be genotoxic, but evidence of frank mutagenicity is weak. The existence of nickel-deficiency syndromes and the presence of nickel proteins in man and animals suggest that nickel may be an essential trace element.

Quantitative risk estimates derived from epidemiological studies employ models based on two assumptions:

1. that response is a function of cumulative dose or exposure and
2. that risk (excess risk or relative risk) is a linear function of that cumulative exposure.

Given these assumptions, a choice of two models is available for describing response to nickel exposure, the excess-additive-risk model and the multiplicative- (or relative-) risk model. The first of these assumes that the excess cause-age-specific rate resulting from nickel exposure is increased proportionally to the cumulative exposure up to that time. The relative-risk model assumes that the background cause-age-specific rate at

any time is increased proportionally to the cumulative dose up to that time.

Four data sets derived from epidemiological studies were analyzed from the perspective of adherence to each of the two models, additive risk and relative risk. One of the data sets (Copper Cliff, Ontario) could support only the relative-risk model because person-years experience was not available. It was seen that dose-response estimates from the four data sets could support either model. Therefore, each data set was analyzed by both models whenever possible.

Unit risk estimates were derived for nickel refinery dust associated with lung cancer. Nasal sinus cancer was not investigated because nasal cancer was thought to be only an occupational hazard associated with the pyrometallurgical process. A range of unit risk estimates was derived from both additive- and relative-risk models, whenever possible, applied to the four data sets. The range was from 1.1×10^{-5} to 4.6×10^{-4} $(\mu g/m^3)^{-1}$ and the midpoint of the range, 2.4×10^{-4}, was suggested specifically as a single point estimate. It was also suggested that twice this value would approximate unit risk for exposure to nickel subsulfide because refinery dust is composed of 50% nickel subsulfide.

Converting the unit risk estimate into units of $(mg/kg/d)^{-1}$ and multiplying by the molecular weight of nickel subsulfide (240.25) yields a potency index of $2.0 \times 10^{+2}$ for nickel refinery dust (or $4.0 \times 10^{+2}$ for nickel subsulfide specifically).

The risk coefficient, or slope, for nickel refinery dust is estimated by the EPA/CAG to be 0.84 $(mg/kg/d)^{-1}$. The daily intake of nickel refinery dust in air associated with a 10^{-5} level of risk may be calculated from the equation Risk (R) = Slope (S) x Dose (D). Solving for D as follows:

$$D = \frac{R}{S} = \frac{10^{-5}}{0.84} (70 \text{ kg}) = 0.83 \ \mu g/d.$$

If reference man (ICRP 23) breathes an average of 20 m^3 of air per day, the concentration in air reflecting a 10^{-5} risk level is calculated as

$$\frac{0.83 \ \mu g/d}{20 \ m^3/dy} = 42 \ ng/m^3.$$

Absorption coefficients for oral and inhalation absorption of both nickel refinery dust and nickel subsulfide are given as 0.05 and 0.06, respectively (Appendix C). The permissible concentration in drinking water at the 10^{-5} level of risk may be derived as

$$\frac{(0.83 \ \mu g/d) \ (0.06/0.05)}{2 \ L/d} = 0.5 \ \mu g/L \ .$$

The same type calculations shown above may also be applied to nickel subsulfide to determine 10^{-5} risk level concentrations in air and water by substituting the slope value of 1.7 $(mg/kg/d)^{-1}$.

$$D = \frac{R}{S} = \frac{10^{-5}}{1.7} (70 \text{ kg}) = \frac{0.41 \ \mu g \ d}{20 \ m^3/d} = 21 \ ng/m^3 \text{ in air,}$$

and

$$\frac{(0.41 \ \mu g/d) \ (0.06/0.05)}{2 \ L/d} = 0.25 \ mg/L \text{ in drinking water.}$$

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Summary - Nickel

Enterline and Marsh 1982a

Exposure period - $\geq$ 1 year

Follow-up period - average of 25.3 years

Number of subjects - 259 refinery workers exposed to nickel subsulfide

Total number of deaths - 8

Level of exposure - < 10 to $\geq$ 200 mg Ni/m^3 month

Duration of exposure - cumulative up to 20 years

Disease occurrence - respiratory cancer

Strengths and weaknesses - This is the best data set for risk extrapolation in that it is the least dusty refinery of those studied (exposures were lower), it is a U.S. refinery, data breakdown and analysis were conducive to risk extrapolation, data was adjusted to reflect a 20-year latent period from first exposure, and exposures were presented as mg Ni/m^3 months, incorporating both amount and duration

CAG value - unit risk = 2.8×10^{-4} additive-risk model (maximum liklihood estimate)
= 1.5×10^{-5} relative-risk model (maximum liklihood estimate)
= 3.1×10^{-5} average-relative-risk model
carcinogenic potency = $2.0 \times 10^{+2}$ from midpoint of unit risk range

Chovil et al. 1981

Exposure period - sometime between 1948-1962

Follow-up period - January 1963 to December 1978

Number of subjects - 495 who survived to 1963

Total number of deaths - 37 out of 54 cases

Level of exposure - "extremely dusty" (estimated to be 200 mg/m^3 before 1951 and 100 mg/m^3 after that date)

Duration of exposure - not specified

Disease occurrence - lung cancer

Strengths & weaknesses - Good dose response at a high-exposure facility but several weaknesses existed: (1) poor follow-up of only 75% of original cohort, (2) ill-defined cohort,(3) unspecified exposure level, and (4) lung cancer cases identified only through workmen's compensation records

CAG values: unit risk = 1.1×10^{-5} - relative-risk model only

Magnus et al. 1982, Thornhill 1986

Exposure period - for $\geq$ 3 years between 1910 and 1966

Follow-up period - to 1979, 26 years total

Number of subjects - 2247

Total number of deaths - 82

Level of exposure - 3 to 30 mg/m^3

Duration of exposure - estimated as "about one quarter of a lifetime"

Disease occurrence - lung cancer

Strengths and weaknesses - obscure exposure groups, loss of early-onset cases

CAG values: unit risk = 1.9×10^{-4} $(\mu g/m^3)^{-1}$ to 1.9×10^{-5} $(\mu g/m^3)^{-1}$

Doll et al. 1977

Exposure period - $\geq$ 5 years

Follow up period - 1934-1971 (37 years)

Number of subjects - 937

Total number of deaths - 145

Level of exposure - reduced significantly after 1925.

Strengths and weaknesses

CAG values: unit risk = 4.6×10^{-4} to 8.1×10^{-5} $(\mu g/m^3)^{-1}$ for low- and high-exposure groups (329 to 1644 $\mu g/m^3$).

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Appendix B

REVIEW OF PCBs

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POLYCHLORINATED BIPHENYLS

(adapted from *Drinking Water Criteria Document for Polychlorinated Biphenyls (PCBs)* (EPA 1985)

The study of Kimbrough et al. 1975 was selected by the CAG as the study most suitable for quantifying the carcinogenic potency of PCBs and served as the basis of the risk estimate until 1987. The more recent study by Norback and Weltman (Norback and Weltman 1985) was subsequently chosen to replace the Kimbrough study as the basis of the risk estimate, as reported in the *1987 Drinking Water Criteria Document for Polychlorinated Biphenyls (PCBs)* (EPA 1987).

Kimbrough et al. (1975) data:

SPECIES	rat
STRAIN	Sherman
BODY WEIGHT	0.4 kg (assumed)
LENGTH OF EXPOSURE	645 days
LENGTH OF EXPERIMENT	730 days
TUMOR SITE	liver
TUMOR TYPE	combined hepatocellular carcinomas and neoplastic nodules*
PCB ISOMER TESTED	Aroclor 1260

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DOSE (mg/kg/day)	INCIDENCE
0	1/173
4.42 (100 ppm)	170/184

*

hepatocellular carcinomas = 26/184 (14%) in treated group
1/173 (0.58%) in control group

neoplastic nodules = 144/184 (78%) in treated group
0/173 (0%) in control group

Application of the linearized multistage extrapolation model to the data yielded a slope value (also known as q_1*) of 4.3396 $(mg/kg/d)^{-1}$. The latest slope value, estimated from the Norback and Weltman (1985) data, is 7.7 $(mg/kg/d)^{-1}$.

From the Kimbrough study-based slope of 4.3396 $(mg/kg/d)^{-1}$ and the formula Risk (R) = Slope (S) x Dose (D) and solving for dose as the permissible concentration of PCBs in drinking water (assuming a 2 L daily intake by an average 70 kg man), then the permissible concentration (PC) yielding a 10^{-5} level of risk would be:

$$PC = \frac{R}{S} = \frac{10^{-5}}{4.3396\ (mg/kg/d)^{-1}} \times \frac{70\ kg}{2L/d} \times \frac{10^3\ \mu g}{1\ mg} = 0.08\ \mu g/L.$$

Using the revised slope estimate, 7.7 $(mg/kg/d)^{-1}$, the equation yields 0.045 $\mu g/L$.

These data indicate that the Kimbrough slope estimate was based on the response of a single dose group of a single strain of rats in one study, which measured response as the combined incidence of

hepatocellular carcinomas and neoplastic nodules (questionably valid), determined to be 92% in treated animals vs <1% in controls. For this reason, the Kimbrough study was considered to demonstrate the hepatocarcinogenicity of PCBs.

In a preliminary experiment of less than one year duration, the same investigator (Kimbrough et al. 1972) failed to detect either hepatocellular carcinomas or neoplastic nodules in this same strain of rat, testing both Aroclor 1254 and 1260 in 10 animals of both sexes at doses of 100, 500, and 1000 ppm. The 14% incidence in the 1975 experiment suggests that a nonpositive result in the 1972 experiment is not unexpected; a 14% incidence in a group of 24 rats is only 3 to 4 rats and the cancer would have appeared only after about a year.

Another experiment (Kimbrough and Lindner 1974) is of interest in this context. In this experiment, one group of 50 BALB/cJ male mice were fed a diet of Aroclor 1254 at 300 ppm for 6 months and plain rat chow for the next 5 months. A second similar group was fed the PCB at 300 ppm for 11 months, while a control group was fed only plain rat chow for 11 months. At the end of 11 months, 1 of the first group, and 9 out of 22 survivors of the second group developed hepatomas. No control animals developed hepatomas. The 41% incidence in the group of mice fed PCBs for 11 months (rats would not have demonstrated a positive response in a study of less than one year duration) reveals that 11 months is a significantly greater proportion of lifespan for a mouse than for a rat.

In the only other chronic bioassay performed (NCI 1978), 24 Fisher 344 rats of each sex were fed Aroclor 1254 at 0, 25, 50, or 100 ppm in the diet for 104 to 105 weeks. It was concluded that under the conditions of

the assay, there was no statistical difference in response between test animals and controls. Female rats receiving 100 ppm Aroclor 1254 revealed an incidence of 2/24 for hepatocarcinomas (8%). However, a study involving 24 rats per group would require an incidence of 35% (in excess of controls) to have a probability of 90% of being significant at the P = 0.05 level. For an 8% incidence difference (as in this study) to have a 90% chance of being statistically significant at P = 0.05, the size of both test and control groups would have to be about 120 animals. Nonetheless, this study is supportive of the Kimbrough (1975) study in that the 8% incidence of hepatocarcinomas in this study is not very much different from the 14% incidence in the Kimbrough (1975) study.

As discussed by Cordle (Cordle et al. 1982), the difference in carcinogenic outcome between the NCI study and the Kimbrough (1975) study may involve various explanations. The Kimbrough study used Sherman rats, whereas the NCI study used the Fisher strain. The Kimbrough study tested 184 rats at 100 ppm, where as the NCI study tested only 24. The Kimbrough study tested Aroclor 1260, but the NCI study tested Aroclor 1254. Finally, Cordle suggests that the difference may be purely statistical, in which the use of comparable protocols and similar numbers of animals could change the outcome in either direction.

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Appendix C

ABSORPTION COEFFICIENTS

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LITERATURE-DERIVED ABSORPTION COEFFICIENT ESTIMATES FOR 39 CHEMICALS VIA ORAL AND INHALATION ROUTES OF EXPOSURE[1]

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INTRODUCTION

The accurate assessment of human health effects of environmental and/or occupational exposure to potentially hazardous substances necessarily incorporates some quantitative estimate of dose. Typically, a dose level (e.g., no observable adverse effect level) is selected for modification by various conversion factors to accommodate such parameters as duration of exposure, degree of uncertainty in extrapolation, and the efficiency of absorption of the chemical or substance into the body.

For purposes of toxicological investigation, it is of practical concern that terms such as dose and absorption be defined precisely to engender consistency of use and facilitate comprehension of sometimes abstruse scientific concepts. The underlying concept of dose in this paper is the concentration of toxic chemical achieved in the target organ following exposure, not simply the amount of chemical administered. Absorption is defined as the fractional or percentage uptake of the chemical into the blood following exposure, which in concert with distribution, biotransformation, and excretion determines the actual dose delivered to the exposed individual (Klaassen et al. 1986). It is this dose that evokes subsequent toxicity.

Absorption of a chemical or substance is dependent upon the specific route of exposure, generally regarded as being either oral (through the gastrointestinal tract), inhalation (through the lungs), or dermal (through the skin). A chemical may demonstrate marked toxicity through one route of exposure but a remarkable lack of toxicity through a different route; the variable toxicity is largely the result of differential absorption efficiency through the different routes of intake. For example, elemental mercury is poorly absorbed via ingestion and generally is of low toxicity by this route. Elemental mercury vapors, however, are easily absorbed via inhalation and evoke serious toxicological consequences when inhaled. Toxicity is thus route-dependent for mercury exposure and for toxic chemicals, in general. Without absorption toxicity is lacking, except for caustic agents which act topically.

The absorption efficiency of a substance is characterized as its absorption coefficient, a number reflecting the fraction of the administered substance able to cross biological membranes and be taken up into the blood for subsequent distribution to organs and tissues. Absorption coefficients are currently used by various health effects researchers who are concerned with deriving quantitative estimates of risk. The drinking water criteria documents produced by the Environmental Protection Agency (EPA) uses absorption coefficients in calculations of acceptable daily intake (ADI) and health advisory indices. The International Commission on Radiological Protection (ICRP) Publication 30 *(Limits for Intakes of Radionuclides by Workers)* uses absorption coefficients in calculating risks of exposure to radionuclides. Apart from these sources, the general availability of absorption coefficients is poor. However, absorption coefficients are likely to be used increasingly in the context of more vigorous regulatory activity.

This report represents an attempt to improve access by health effects researchers to absorption coefficients for several hazardous substances via oral and inhalation routes of intake. Numerical estimates presented here are the product of extensive investigation of the toxicological, pharmacological, and biological literature. Three data bases - TOXLINE, the Hazardous Substance Data Base (HSDB), and the Chemical Information Service (CIS) - were consulted, as were various EPA, ICRP, and National Institute of Occupational Safety and Health (NIOSH) documents and nearly 200 articles from 30 scientific journals.

It is an intuitive concept, perhaps, that no single absorption coefficient can be universally applicable to a broadly diverse, heterogeneous class of human beings. It is widely known that absorption efficiency is directly influenced by age, species, metabolic status, diet, exposure duration, and other situation-specific considerations (Klaassen et al. 1986). The estimates presented here are intended to reflect absorption by the average healthy adult human. A preference for human-specific data was exercised whenever possible to circumvent the well-known uncertainties attendant animal to human extrapolation.

Table 1 contains oral and inhalation absorption coefficients estimated from a review of the literature for several potentially hazardous substances. The references specify the data sources forming the basis for each coefficient. Commentary follows on the rationale for selection of each coefficient.

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Table 1. Absorption coefficients for 39 chemicals via oral and inhalation routes of exposure

CHEMICAL	ORAL	INHALATION	REFERENCES
Acrylonitrile	0.95 (0.77-0.99)	0.98 (0.80-1.00)	69
Arsenic	0.98 (0.70-0.98)	0.35 (0.30-0.42)	17,24,70
Barium	0.10 (0.05-0.85)	0.75 (0.10-0.75)	1,2,3,4
Benzene	1.00 (0.40-1.00)	0.47 (0.28-0.60)	2,4,5,6,7,8, 17,52
Benzidine	0.90	0.95 (0.95-1.00)	71,72
Benzo*[a]*pyrene	0.50 (0.43-0.58)	0.27	9,10
Beryllium	0.001 (0.00006-0.01)	0.50	73,74,75,77
Bis(chloromethyl)ether	1.00	0.50	56
1,3-Butadiene	1.00	0.65	76
Cadmium	0.06 (0.023-0.10)	0.40 (0.05-0.40)	2,3,17,24,77,78,79,80,81,82
Chlorine	1.00 (0.90-1.00)	1.00	2,3
Chloroform	1.00 (0.50-1.00)	0.63 (0.50-0.77)	11,12,53
Chromium III	0.01 (0.005-0.18)	0.10 (0.05-0.10)	3,14,15,16,20,54,69
Chromium VI	0.05 (0.02-1.00)	0.25 (0.10-0.75)	15,17,18
Coke oven emissions	0.50	0.27	83
Copper	0.50 (0.32-0.90)	0.50	2,3
Cresol	1.00	1.00	13
1,1-Dichloroethylene	0.93 (0.68-0.94)	0.98	17,84,85,86,98,99
Dimethylnitrosamine	0.98	ND	46,47
Di-n-butylphthalate	0.85 (0.80-0.90)	ND	77
Ethylbenzene	0.90 (0.72-0.92)	0.64 (0.44-0.64)	17,19,55
Ethylene oxide	1.00	1.00	87,88
Fluoride	1.00 (0.80-1.00)	1.00	3,4,51
Lead	0.10 (0.01-0.65)	0.50 (0.20-0.62)	2,3,14,20,21,22,23,24,25,26,27,28
Mercury-elemental	0.0001 (0.0001-0.45)	0.85 (0.50-1.00)	3,24,28,29,30,31,62,64,67
Mercury-inorganic	0.15 (0.02-0.15)	0.85 (0.00-0.85)	2,3,24,32,33,34,62,64,67,68
Mercury-organic	0.95 (0.40-1.00)	1.00	3,24,28,34,35,36,37,62,64,67,68
Methylene chloride	1.00	0.50 (0.50-0.75)	17,38,56
Naphthalene	1.00	ND	9
Nickel	0.05 (0.01-0.10)	0.75 (0.70-0.75)	2,3,14,17,20,57,65
Nickel refinery dust	0.05 (0.01-0.10)	0.06	2,89
Nickel subsulfide	0.05 (0.01-0.10)	0.06	2,89,100
PCBs	0.95 (0.90-0.99)	ND	17,39,48,49,50,58,59
Phosphorus	0.90 (0.80-1.00)	0.80	2,3
Selenium	0.60 (0.44-0.90)	0.27	2,10,90,91,92
Toluene	1.00 (0.74-1.00)	0.50 (0.37-0.70)	8,17,19,40,42,43,44,60,63,66
Vinyl chloride	0.90 (0.68-0.90)	0.64 (0.40-0.98)	85,93,94,95,96,97
Xylene	1.00	0.64 (0.54-0.68)	17,41,42,45,61
Zinc	0.50	0.50	2,3

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COMMENTS ON THE RATIONALE FOR CHOOSING THE ESTIMATES

Acrylonitrile

Oral: The oral absorption value is based on a metabolic study in rats conducted by Young (Young *et al.* 1977) as reported in the *Health Assessment Document for Acrylonitrile* (EPA 1983).

Inhalation: The inhalation absorption value is also based on the rat study by Young et al. (1977). The number is derived from recovery of a radiolabelled dose given by inhalation for 6 h.

Arsenic

Oral: The value given here is based on human data cited in the references given. The literature sources are in general agreement that soluble salts of inorganic arsenic are almost completely absorbed via the oral route of intake.

Inhalation: The inhalation value is also based on human data. The value stated is the average of the inhalation absorption estimates described in the literature cited.

Barium

Oral: Although oral absorption of barium varies widely according to age, dietary factors, etc. (EPA 1985e), the value chosen reflects the *EPA Drinking Water Criteria Document* value for adult absorption (0.7-2.0), modified by the values in ICRP publications 23 (ICRP 1975) and 30 (ICRP 1980) (0.1-0.15 and 1.0, respectively). No definitive study of barium absorption in humans has been done (EPA 1985e).

Inhalation: The value chosen for inhalation absorption is supported by animal experimental data (Cuddihy and Griffith 1974) and agrees with the majority of values discovered in the scientific literature.

Benzene

Oral: The oral absorption value chosen is derived from valid animal experimental data (oral intubation of rabbits with radiolabeled benzene) (Parke and Williams 1953). All of the dose was either metabolized or exhaled unchanged, implying virtually complete absorption by this route.

Inhalation: The inhalation value is derived from several human studies of uptake and excretion (Nomiyama and Nomiyama 1974; Hunter 1966; Srbova et al. 1950) and is supported by general agreement of literature values.

Benzidine

Oral: The value given here is based on human and animal data indicating <10% excretion of an oral dose.

Inhalation: The inhalation absorption estimate given here is based on unpublished observations cited in the references. A more specific estimate could not be located in the available literature.

Benzo[a]pyrene (B[a]P)

Oral: Quantitative absorption data for orally administered B[a]P are scarce, but inference from fecal recovery data (Chang 1943) suggests ~50% oral absorption.

Inhalation: Data specific to inhalation of B[a]P were not located in the literature. The value presented here is based on particle size, adsorption, and respiratory deposition models (Natusch and Wallace 1974), which address exposure to B[a]P as a product of high-temperature combustion.

Beryllium

Oral: The estimate for oral absorption of beryllium is based on animal data (no appropriate human data were located) and is representative of the values obtained from the literature.

Inhalation: The inhalation absorption value is based on animal data cited in the *Health Assessment Document for Beryllium* (EPA 1987). No data on absorption in humans via inhalation exposure were located in the available literature.

Bis(chloromethyl)ether

Both the oral and inhalation absorption estimates are based on the only reference located.

1,3-Butadiene

Oral: No appropriate oral absorption data were located.

Inhalation: The stated value is estimated from the in vivo blood:air distribution coefficient determined from rabbits breathing 25% butadiene in air. Sources of absorption data other than the article cited were not located in the literature.

Cadmium

Oral: The oral absorption value for cadmium is representative of the estimates discovered in the literature cited.

Inhalation: The inhalation absorption estimate is based on retention of inhaled cadmium in dogs and is supported by estimates based on modeling of lung deposition and clearance of inhaled particles.

Chlorine

Oral: The oral absorption value is based on ICRP Publications 23 (ICRP 1975) and 30 (ICRP 1980) to a human study of excretion of orally administered chlorine (Burrill et al. 1945). Other data derived from appropriate studies were not located in the literature.

Inhalation: The inhalation value is also derived from ICRP Publications 30 (ICRP 1980). Other suitable data were not located.

Chloroform

Oral: The oral absorption value is based on human experimental data from a study of orally administered radiolabelled chloroform (Fry et al. 1972). Virtually all of the dose was recovered in expired air as either the CO_2 metabolite or as unchanged chloroform.

Inhalation: The inhalation absorption value was derived from appropriate human experimental data (Lehmann and Hasegawa 1910).

Chromium III

Oral: An exact value for oral absorption of chromium cannot be given (NAS 1974). The value chosen is representative of the range of values specified in the majority of literature quotations. The low value reflects the relative insolubility of trivalent chromium and its inability to cross biological membranes.

Inhalation: The inhalation value is chosen on the basis of experimental data referred to in ICRP Publication 30. Absorption of inhaled trivalent chromium is a function of particle size and solubility of retained chromium (EPA 1984).

Chromium VI

Oral: The oral absorption estimate is representative of the range of values discovered in the literature. That this value is somewhat higher than the corresponding chromium III value is a consequence of the increased solubility of chromium VI and its ability to cross biological membranes (EPA 1985a). The value chosen is supported by human experimental data (Donaldson and Barreras 1966).

Inhalation: The value chosen is based on inference from valid animal experimental data (Baetjer et al. 1959), specifying at least 25% distribution of dose to blood and tissue following intratracheal administration.

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Coke oven emissions

Absorption estimates for both oral and inhalation exposure to coke oven emissions are based on the B[a]P content of coal tar pitch volatiles as discussed in the references cited. The oral absorption estimate is based on fecal recovery data (Chang 1943). The inhalation absorption value is estimated from respiratory deposition modeling of inhaled particulates (Natusch and Wallace 1974).

Copper

Oral: Dietary absorption of copper by humans as cited in the references forms the basis of the oral absorption estimate given here.

Inhalation: The inhalation absorption estimate is based on recommendations by the Task Group on Lung Dynamics reported in ICRP Publication 30 (ICRP 1980).

Cresol

Specific quantitative data on oral and inhalation absorption of cresol in humans were not found in the literature. The values chosen reflect the similarity of cresol to phenol, as noted in the NIOSH 78-133 Criteria Document (DHEW 1978).

1,1-Dichloroethylene

Oral: The value for oral absorption is derived from studies of absorption of radiolabeled 1,1-dichloroethylene in animals, as discussed in the literature references.

Inhalation: The inhalation absorption estimate is derived from metabolic excretion data from an inhalation study of radiolabeled dichloroethylene in the rat (McKenna et al 1977)

Dimethylnitrosamine (DMNA)

Oral: This value was derived from animal experimental data from excretion studies of radiolabeled dimethylnitrosamine in rats (Gomez et al. 1977) and unlabeled DMNA in mice (Magee 1956).

Inhalation: Appropriate inhalation data were not discovered in the scientific literature.

Di-n-butylphthalate

Oral: The basis of the oral absorption estimate is the urinary excretion of dietary di-*n*-butylphthalate in rats. No appropriate human data were located.

Inhalation: No appropriate inhalation data were located.

Ethylbenzene

Oral: The oral absorption value is based on excretion studies of orally administered ethylbenzene in rats (El Masry et al. 1956). No suitable human data were discovered in the literature.

Inhalation: The inhalation value derives from human experimental data referenced in the EPA health advisory and drinking water criteria document (Bardodej and Bardodejova 1970). Other human inhalation absorption data were not located in the literature.

Ethylene oxide

Both oral and inhalation absorption estimates are based on evidence of total absorption in the mouse in the literature cited. The extensive solubility of the compound in the blood suggests complete absorption by humans.

Fluoride

The oral and inhalation values were chosen based on the general agreement of literature values and are derived from human experimental data (WHO 1970).

Lead

The oral and inhalation values given are representative of the ranges of values discribed in the literature and are based on appropriate human data (Rabinowitz and Kopple 1974; Rabinowitz et al. 1978; Kehoe 1960).

Mercury - elemental

Oral: The value given here reflects the general agreement of low values quoted in the scientific literature.

Inhalation: The inhalation value is based upon valid human experimental data (Kudsk 1965) and agrees with most estimates of inhalation absorption of mercury vapor located in the literature.

Mercury - inorganic salts

Oral: The value chosen derives from valid human and animal experimental data (Rahola et al. 1971; Miettinen 1973) and is supported by general agreement of literature values.

Inhalation: Few values for inhalation absorption of inorganic mercury salts were located in the literature. The estimate given here reflects the available data.

Mercury - organic

The great preponderance of animal and human data suggests the virtually complete absorption of organic mercury by both oral and inhalation route of exposure (Junghans 1983; Clarkson 1972; ICRP 1980).

Methylene chloride

Oral: The oral absorption value is based on the only appropriate estimate found in the literature (McKenna and Zembel 1981).

Inhalation: This value was chosen based on the general agreement of the values found in the literature (Astrand 1975; IARC 1982; NRC 1978).

Naphthalene

Oral: The oral value is an estimate based on fecal recovery data suggesting the nearly complete oral absorption of naphthalene (Chang 1943). Other appropriate studies were not located in the literature.

Inhalation: No suitable references to inhalation absorption of naphthalene were located in the literature.

Nickel

Oral: The oral absorption value was chosen based on the general agreement of literature values and is supported by human and animal experimental data (EPA 1985b; EPA 1986; ICRP 1975).

Inhalation: The few estimates of inhalation absorption of nickel (IARC 1982; NAS 1975) were in general agreement and form the basis of the value presented here.

Nickel refinery dust

Oral: The oral absorption estimate is based on general agreement of the values in the literature cited.

Inhalation: The inhalation absorption estimate is derived from modeling of inhaled particulate-bound nickel (fly ash) using the ICRP inhalation model for dust deposition (ICRP 1980), as explained in section 4.1.1 of the *Health Assessment Document for Nickel and Nickel Compounds* (EPA 1986).

Nickel subsulfide

Both oral and inhalation absorption estimates are based on nickel refinery dust, which is composed of 50% nickel subsulfide.

Polychlorinated biphenyls (PCBs)

Oral: The oral absorption value derives from valid animal experimental data (Allen et al. 1974; Albro and Fishbein 1972) and agrees with the majority of values in the literature.

Inhalation: No specific references to inhalation absorption of PCBs were found in the literature.

Phosphorous

Oral: The estimate for oral absorption of phosphorous is the average of the values in the literature cited.

Inhalation: The inhalation value is based on ICRP Publication 30 (ICRP 1980). No other estimates for inhalation absorption of phosphorous were found in the literature.

Selenium

Oral: The oral absorption estimate is based on human data from a study of ingestion of radiolabeled selenite (Burk 1976).

Inhalation: The inhalation absorption value is based on the ICRP aerosol deposition model as discussed in the references cited.

Toluene

Oral: Rabbit studies (Smith et al. 1954; El Masry et al. 1956) indicate that up to 80% of an oral dose of toluene can be accounted for as eliminated metabolites; the remainder of the dose is exhaled unchanged. As discussed in the EPA criteria document (EPA 1985c), these data imply >99% absorption from the gastrointestinal tract.

Inhalation: The inhalation absorption value given here is representative of the ranges and values discovered in the literature and is based on appropriate human and animal experimental data (EPA 1985c; Nomiyama and Nomiyama 1978).

Vinyl chloride

Oral: The oral absorption estimate is based on general agreement of the values discovered in the literature cited.

Inhalation: The inhalation absorption estimate is the most frequently appearing value in the literature cited.

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Xylene - *meta*, *ortho*, and *para* isomers

Oral: The oral absorption value is derived by inference from limited excretion data (Bray et al. 1949) specifying 85-90% recovery of an oral dose as urinary metabolites, pulmonary excretion accounting for the remainder of the dose.

Inhalation: The inhalation value is based on the majority of human and experimental data suggesting 64% absorption of inhaled xylene (EPA 1985d; Sedivec and Flek 1976).

Zinc

Both oral and inhalation estimates are based on general agreement of the values discovered in the literature cited.

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Appendix D

REVIEW OF SELECTED NONCARCINOGENS

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BARIUM

Barium is a naturally occurring, highly reactive substance that is widespread in the environment. It is used commercially as a paint pigment, as an oil additive, and in a variety of photographic and manufacturing applications.

Compounds of barium are absorbed primarily through oral and inhalation routes of exposure, with variable toxic effects deriving from profound stimulation of cardiac, striated, and smooth muscles and inhibition of neurotransmission. Neuromuscular symptoms may lead to increased blood pressure, tachycardia, and paralysis preceding death at high doses. Barium is an antagonist to potassium, and most signs of acute toxicity are alleviated by potassium infusion. Toxicity increases with increasing solubility of the compound administered.

The Maximum Contaminant Level (MCL) for barium is 1.0 mg/liter of drinking water. The basis for this level is the threshold limit value (TLV) of 0.5 mg/m^3, set by the American Conference of Governmental Industrial Hygienists (ACGIH). The Stokinger and Woodward (1958) technique was used to adjust the TLV by incorporating an inhalation absorption efficiency of 75% applied to the calculated daily intake, based on an 8-h daily exposure and assuming $10m^3$ of air breathed during that 8-h exposure, thus

$$10\ m^3 \times 0.5\ mg/m^3 \times 0.75 = 3.75\ mg\ ,$$

representing the respiratory dose to the blood. Based on a gastrointestinal absorption efficiency of 90% (later reevaulations indicate closer to 10% absorption) and a daily intake of 2 L of drinking water,

$$3.75\ mg/d \times \frac{1}{0.9} \times \frac{1}{2\ L/d} = 2.085\ mg/L.$$

Incorporating a safety factor of 2 to account for sensitive subpopulations yields an MCL of 1.0 mg/L for barium.

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LEAD

Lead is a metallic element that is widespread in the environment and occupational setting. It has an abundance of industrial and manufacturing uses as a paint pigment, fuel additive, solder alloy, and component of storage batteries. It is poorly absorbed through the gastrointestinal route; fumes are more easily absorbed. Blood-lead levels correlate well with atmospheric lead concentrations.

Lead toxicity is characterized by vomiting, abdominal pain, hemolysis, and liver and kidney damage. Chronic exposures produce neurological impairment, especially in children. Effects seen in children with blood-lead levels above 20 μg/dL include sensorimotor deficits, short attention span, and various behavioral disorders.

Calculations of Acceptable Daily Intake (ADI) for children and adults began with selection of 15 μg/dL (of lead in blood) as the empirical NOAEL based on many human studies; this level provides protection for sensitive subpopulations (infants and pregnant women). Assuming blood lead in children is proportional to 0.16 x daily dietary lead intake, with an uncertainty factor of 5,

$$\frac{15\ \mu g/dL}{[(1\ \mu g/dL)/(0.16\ \mu g/d)](5)} = 19\ \mu g/d.$$

A 1 L daily intake of drinking water is assumed for children. Therefore, the Adjusted Acceptable Daily Intake (AADI) for children is 19 μg/L. For adults, 0.062 substitutes for 0.16 μg/d to yield 48 μg/d as an equlivalent value.

The above calculations assume that 100% of lead exposure derives from drinking water. Available data indicate that lead ingested in drinking water comprises about 15% of the total daily intake in children (other sources are food, air, and dust) and about 31% of total adult intake. In that 15% of lead intake is generally ascribed for drinking water consumption in children,

$$\frac{(0.15)(19\ \mu g/d)}{1\ L/d} = 3\ \mu g/L,$$

the final AADI for children. Calculated values for adults would be higher, so this number is chosen as the overall AADI in order to be protective of both populations.

The MCL for lead currently is 50 μg/L, recognizing that water is not a major route of lead exposure. A revised MCL of 5.0 μg/L has been proposed.

PHENOL

Phenol is a monocyclic aromatic alcohol that is extensively absorbed via inhalation and ingestion, resulting in excretion of free and conjugated phenol in the urine of exposed humans.

Subchronic exposures in animals has resulted in paralysis, weight loss, pathological changes, and death. Ingestion of phenol by rats has been reported to result in reproductive changes. There is slight evidence of phenol mutagenicity, but data regarding carcinogenicity in either man or animals have not been located in the available literature.

An experimental LOAEL of 50 mg/kg/d was established based on a Dow Chemical Co. (1976) subchronic rat study. Applying a safety factor of 500, the EPA calculated an interim ADI for phenol of 0.1 mg/kg/d. Based on a taste threshold of 0.3 mg/L for phenol in drinking water, that value was selected as the criterion for phenol in water.

A TLV of 19 mg/m^3 for phenol was established on the basis of data from subchronic animal studies.

TOLUENE

Toluene is a volatile organic solvent that is predisposed to exist as a vapor in the environment. Thus, human exposures are more likely to occur via inhalation than ingestion.

Absorption of inhaled toluene is about 50% efficient followed by rapid metabolism by the liver, excretion being generally complete within 18 to 24 h, depending on the dose. Gastrointestinal absorption is apparently complete; dermal absorption is quite efficient but unlikely to occur because of toluene's high volatility.

Acute effects in humans exposed to toluene have been reported as narcosis, central nervous system dysfunction, nausea, lassitude, and fatigue. Chronic exposures (and long-term abuse) has resulted in nervous system and neuromuscular dysfunction.

Although some reproductive effects have been noted in animal studies, toluene has not been demonstrated to be mutagenic or carcinogenic based on the currently available data.

Groups considered to be at the greatest risk from exposure to toluene are toluene-exposed workers, pregnant women, smokers, and toluene abusers.

An ADI of 20.2 mg/d was calculated on the basis of a 2-year inhalation study in rats (CIIT 1980), where 300 ppm (28.8 mg/kg/d absorbed dose) was seen to be a NOAEL, as

$$\text{ADI} = \frac{28.8\ \text{mg/kg/d} \times 70\ \text{kg}}{100} = 20.2\ \text{mg/d},$$

assuming a 70 kg average human body weight and an uncertainty factor of 100.

Assuming a 2 L daily intake of drinking water, then

$$\text{AADI} = \frac{20.2\ \text{mg/d}}{2\ \text{L/d}} = 10.1\ \text{mg/L},$$

the adjusted acceptable daily intake for toluene. This value was chosen as the most conservative AADI calculated from animal inhalation data and is supported by a corroborative value of 15 mg/L derived from a gavage study in rats.

MERCURY

Mercury is a unique element that exists as a liquid at room temperature. Metallic (elemental) mercury and mercury compounds are used extensively in a variety of industrial and manufacturing applications and as a fumigant and grain preservative.

The toxic consequences of human exposure to mercury depend on the form of mercury encountered and the route of exposure. Elemental mercury is poorly absorbed through the gastrointestinal tract and is generally nontoxic by this route of intake. However, elemental mercury vapors are easily absorbed via inhalation and are highly toxic. Inorganic mercury (both mercuric and mercurous forms) are absorbed more extensively via ingestion than inhalation. Organic mercurials are easily absorbed by either route of exposure.

Distribution of absorbed mercury is also dependent on the form of mercury encountered. Inorganic mercury compounds tend to preferentially accumulate in the renal cortex of the kidneys. Long-chain organic mercurials are rapidly broken down in vivo and show a similar deposition pattern and prior to their conversion to inorganic mercury, are primarily accumulated in the liver. Organic mercury, especially methyl mercury, easily crosses biological membranes and tends to cause extensive damage to the central nervous system. The ability of methyl mercury to traverse the placental barrier evokes serious neurological consequences in the developing fetus. Inhaled mercury vapors also elicit CNS damage, although intake by this route does not contribute significantly to the body burden.

The mutagenicity of mercury has not been extensively studied. It is considered to be a noncarcinogen in humans, although renal tumor formation has been reported in rats (Druckrey et al. 1957).

The form of mercury most likely encountered in drinking water is the inorganic mercury salt. Therefore, the rat study of Druet et al. 1978 involving this form of mercury was selected for development of an AADI of mercury in drinking water for humans. The strain used was genetically susceptible to the endpoints of concern (antibody formation and proteinuria) and are considered to be an advantage in establishing intake levels that also protect sensitive subpopulations of industrial workers.

From this study, a NOAEL of 50 μg/kg was selected based on proteinuria. A safety factor of 1000 was considered appropriate to extrapolate from a subchronic to a chronic exposure, for animal to human extrapolation, and for protection of sensitive subpopulations. An additional factor of 0.739 was included to account for the percentage of mercury by weight in the mercuric chloride actually tested. A does of 1800 μg/kg was injected over an 84-d period; 100% absorption by this route was assumed. Based on a daily 2 L intake of drinking water by an average 70-kg human, then

$$\text{AADI} = \frac{100 \times 1800\ \mu g/kg \times 0.739 \times 70\ kg}{10 \times 84\ d \times 1000 \times 2\ L/d} = 5.5\ \mu g/L.$$

The total daily intake from drinking water would then be close to the ambient water criterion of 10 μg/L for total mercury. This criterion was based on a LOEL of 200 μg/d for a 70-kg man, divided by an uncertainty factor of 10.

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Appendix E

CONSISTENCY OF REGULATIONS

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HAZARD EVALUATION FOR COMPLEX MIXTURES: RELATIVE COMPARISONS TO IMPROVE REGULATORY CONSISTENCY

B. A. Owen

T. D. Jones

ABSTRACT

The traditional "absolute decision-making" process used by federal regulatory agencies to derive permissible exposure concentrations for hazardous substances is initiated by an evaluation of the "weight of evidence" that a substance has potential for human carcinogenicity. Subsequent conservative procedures applied variably to noncarcinogens and carcinogens yield exposure limits for individual substances based on "data-sparse, model-intensive" techniques that may lack consistency and may not readily address the hazards from complex mixtures directly. This paper describes how a "relative decision-making" technique capable of assessing the toxicity of complex mixtures can supplement the "absolute" approach currently widely used. The technique makes a large number of data comparisons (short-term tests and chronic bioassays) between the chemical of concern and one or a number of "reference" chemicals having more completely characterized toxicological profiles than the chemical of concern. Estimates obtained through this "data-intensive, model-sparse" technique may be evaluated by comparisons to estimates representing a range of hazards "generally regarded as safe" derived through analyses of chlorinated drinking water, cigarette smoke condensate, and other common human exposures. Comparisons are also used to evaluate the relative degree of consistency in risk estimates between 58 suspect human carcinogens analyzed by the U.S. Environmental Protection Agency (EPA) Carcinogen Assessment Group (CAG) and by the authors.

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BACKGROUND

The traditional approach of federal regulatory agencies charged with the protection of human health from the adverse consequences of exposures to hazardous substances has relied on an initial determination that the substance of interest has human carcinogenic potential. This determination is made through an evaluation of the "weight of evidence" for carcinogenicity provided by the available epidemiological, toxicological, biological, and chemical data for the substance.

This approach to regulation of toxic chemicals is guided conceptually by assumptions that suggest "noncarcinogenic" toxicants exert effects through mechanisms that demonstrate thresholds (Anderson et al. 1983). Subthreshold doses of toxicants are considered to be pharmacologically ineffective and stimulate no adverse response; doses above the threshold concentration may elicit an adverse response. Thus, regulation of toxicants attempts to limit exposures to levels that are of low enough concentration to be considered "safe," as characterized by such indices as acceptable daily intake (ADI) for the general population and threshold limit value (TLV) for occupational groups.

In the absence of human data (often the case) the U.S. Environmental Protection Agency (EPA) derives ADIs for noncarcinogenic toxicants from "no observed adverse effect levels" (NOAELs) from animal experiments. The NOAELs are adjusted by incorporation of large, chemical-specific safety factors to predict essentially "safe" levels of exposure in the human population (Anderson et al. 1983). These factors are numerical modifiers used to compensate for such uncertainties as extrapolations from subchronic to chronic exposure and alternative routes of exposure, inter- and intraspecies variability, and use of a lowest observed adverse effect level (LOAEL) when a NOAEL is unavailable (Dourson and Stara 1983). Safety factors commonly ranging from 100 to more than 5000 are used to compensate for deficiencies in toxicological data with the intent of ensuring that calculated values will indeed be protective of public health. However, the choice of specific safety factors to ensure an adequate margin of safety may be subjective and their application may be variable.

The current approach to carcinogen regulation is guided by the assumption that carcinogens act through nonthresholded mechanisms. Accordingly, any degree of exposure to a carcinogen is assumed to impart an increment of risk, a concept born of the well-known 1958 Delaney Amendment to the Food and Drug Act (Public Law 85-929) that mandates the Food and Drug Administration (FDA) to prohibit any amount of a carcinogen in additives to processed foods. From this perspective, the EPA has restricted derivation of ADIs to noncarcinogens.

Human risk estimates for carcinogens are most credibly derived from epidemiologic data in which well-documented exposures elicit a statistically significant increase in cancer incidence as a function of increasing dose. However, few risk coefficients for carcinogens are based on epidemiologic data. Inadequate exposure documentation, unavailability of adequately matched control cohorts, confounding from multifactorial

workplace exposures, and statistically limited power of detection frequently render epidemiologic studies unsuitable for risk assessment (NAS 1983).

In the absence of satisfactory human data, the EPA Carcinogen Assessment Group (CAG) typically derives risk coefficients by (1) selecting the best or most appropriate animal experiment, (2) fitting a linearized, multistage model to the data, (3) deriving the upper-95% confidence interval of the maximum likelihood value, and (4) extrapolating from the test animal to 70-kg man (Anderson et al. 1983). However, valid extrapolation from test animal data to humans is undermined by a lack of understanding of the basic mechanisms of carcinogenesis, the relationship of cancer to aging and life-span, species differences in metabolism and pharmacokinetics, and human heterogenicity (Ames et al. 1987). Extrapolation/conversion factors commonly employed are without definitive scientific validation (Gillette 1985).

An example of how a carcinogen is regulated using absolute decision-making techniques is seen in the case of polychlorinated biphenyls (PCBs) (EPA 1985). Prior to 1987, the study of Kimbrough et al. (1975) had been selected by the CAG as the most appropriate animal experiment on which to derive a quantitative estimate of carcinogenic potency for PCBs [the study of Norback and Weltman (1985) has since replaced the Kimbrough study for quantitative carcinogenic risk assessment]. In the Kimbrough study, female Sherman rats were fed Aroclor 1260 at a rate of 4.42 mg/kg/d for 645 d. After 730 d from initial feeding, 26 of 184 rats had hepatocellular carcinomas and 144 of 184 had neoplastic liver nodules. A control group of 173 rats had no nodules and one carcinoma. In the risk analysis, 170/184 was taken as the incidence rate (for pathologically abnormal livers) and a linearized, multistage mathematical model was fit to these data. The maximum likelihood estimate (Q^*) and the upper-95% bound (Q_1^*) were evaluated. Finally, an acceptable level of lifetime risk was selected and a permissible concentration of 0.08 μg/L of PCBs in drinking water was calculated. The risk coefficient was ultimately based on the total incidence of pathologically abnormal livers of one dose group of rats from a single study.

We may evaluate the degree of protection afforded by regulatory-based permissible exposure limits in the context of exposure levels most likely to enter the human experience. Benzo[a]pyrene (B[a]P) is a polynuclear-aromatic hydrocarbon (PAH) commonly found in a wide variety of foods (Strobel 1984). Its presence in grains and breads results from uptake from contaminated soil by the growing plant, with perhaps some contribution from endogenous biosynthesis of the compound as demonstrated with rye, wheat, and lentils (Graff and Diehl 1966). B[a]P is also common in meats, where its concentration is commonly increased through pyrolysis at the high temperatures used in cooking. The EPA has determined the acceptable level of PAHs in drinking water to be 0.03 μg/L. If B[a]P intake from foods were regulated to the same body burden as all PAHs, including B[a]P, then one would be permitted only 10 oz of charbroiled T-bone steak every eight months or either two slices of bread or 1.5 oz of lettuce daily. The criterion for B[a]P permitted in drinking

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water is doubtlessly exceeded daily by most persons in routine food consumption.

This comparison serves to illustrate how permissible exposure levels derived from absolute decision-making protocols may not accurately reflect real-world variables and exposure scenarios or the actual level of risk commonly accepted by most individuals. The absolute approach is thus undermined by a lack of much-needed, well-documented epidemiologic data and subsequent forced reliance on mathematical extrapolations from high-dose animal exposure data to predict chronic human health effects from low-dose environmental exposures.

Further, current assessment techniques evaluate each chemical individually and do not directly address the effects of multiple simultaneous exposures. Environmental and/or occupational exposures to complex mixtures of pollutants obviously predominate over exposures to a single substance. The potential interactions of chemicals in complex mixtures (i.e., additive, synergistic, and antagonistic) are not effectively addressed within the context of current risk assessment approaches.

INTRODUCTION

Direct comparisons of toxicological potential between different substances can be made with a high degree of relative accuracy, but subsequent extrapolations to assess the resultant impact on human health may be highly uncertain (Ames et al. 1987). Hazard evaluation techniques that minimize the uncertainties inherent in absolute decision-making extrapolations, that are applicable to complex mixtures, and can concurrently put hazards from typical exposures in normal daily life on the same scale would seem to be very useful as an adjunct to the more traditional approaches currently employed. Such a technique exists in the Rapid Screening of Hazard (RASH) concept (Jones et al. 1985, 1988).

As opposed to the data-sparse, model-intensive techniques of absolute decision making, which are integral to the expert committee philosophy, the RASH technique is data intensive and model sparse. The technique makes maximal use of toxicological data to derive an array of relative potency values that characterize the potential toxicity of a substance relative to one or a number of well-studied reference compounds. The median value of the array is selected as the single relative potency value, which lends a high degree of stability to the value when volumes of data are considered. The technique has been used to estimate relative potencies (RPs) for nearly 300 diverse substances thus far (Jones et al. 1988). Specific details and rules for matching toxicological endpoints have been published previously (Jones et al. 1988) and are not reproduced here. However, the method is rapid, inexpensive, has been shown to be relatively accurate (Jones et al. 1988), and uses no theoretical models or safety factors. Also, subjectivity of evaluations is minimized and estimates of uncertainty integral to the process are provided. All chemicals can be evaluated on a unitless common scale that is not

restricted to estimating permissible exposure concentrations in environmental media.

Alternatively, the common scale can be normalized to one or more regulatory concentrations, enabling all chemicals to be evaluated on a consistent basis. All chemicals can be evaluated for potential to induce chronic toxicity regardless of their classification as carcinogen or noncarcinogen. The common scale can be used to rank chemicals or to standardize an inventory of chemical pollutants to an effective dose of a reference chemical. This is possible because RASH evaluates the level of damage from a dose instead of the biological mechanism by which the biological damage is produced (Jones et al. 1983).

Based on a relative-potency framework, this report will attempt to evaluate the degree of regulatory consistency in the evaluation of 58 suspected human carcinogens of concern to the CAG. Suggestions for use of the RASH technique as an adjunct to the current regulatory approach will also be offerred.

METHODS

Relative Potency

The relative potency (RP) approach is most useful when biological data are too sparse to support complex or nonlinear mathematical models. In such cases, linearity of the dose-response function is assumed. For example the increased response $R_{B[a]P}$ from an arbitrary test dose of B[a]P $D_{B[a]P}$ is given by

$$R_{B[a]P} = S_{B[a]P} \times D_{B[a]P} ,$$

where $S_{B(a)P}$ is the slope. For a chemical of concern (or "interviewing" chemical, i) the same functional form is assumed:

$$R_i = S_{B[a]P} \times RP_{i/B[a]P} \times D_i ,$$

where $RP_{i/B[a]P}$ is the strength of chemical i relative to the strength of B[a]P, and D_i is the dose of the interviewing chemical required to produce the same level of response caused by the dose of the B[a]P standard.

For equal levels of response, $R_{B(a)P} = R_i$

so that $$S_{B[a]P} \times D_{B[a]P} = S_{B[a]P} \times RP_{i/B[a]P} \times D_i ,$$

or $$RP_{(i/B[a]P)} = \frac{D_{B[a]P}}{D_i} ,$$ from Jones . (1988).

Similarly, it is easily shown that when data reflect equal treatment doses ($D_i = D_{B[a]P}$) instead of equal effects ($R_i = RB_{[a]P}$), the relative potency is given by

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$$RP_{(i/B[a]P)} = \frac{R_i}{R_{B[a]P}} .$$

Other chemicals can be used as a standard in place of B[a]P. The potency of chemical i relative to the potency of chloroform, for example, is derived from

$$RP_{(i/\text{chloroform})} = \left(\frac{D_{B[a]P}}{D_i}\right) \left(\frac{D_{B[a]P}}{D_{\text{chloroform}}}\right)^{-1} ,$$

where each factor is taken from previously tabulated calculations (Jones et al. 1988).

The RP method can be used to convert a concentration of an interviewing chemical, C_i, to a hypothetical equivalent toxic concentration, x, of chloroform as a standard according to

$$x = C_i \bullet RP_{(i/\text{chloroform})} .$$

If x is set as the "permissible concentration" of chloroform, then the equation can be solved for C_i such that

$$\frac{x}{RP_{(i/\text{chloroform})}} ,$$

would be an estimate of the permissible concentration for any chemical i if the implicit level of hazard for exposure to chemical x is also acceptable for exposure to chemical i.

Use of Relative Comparisons to Evaluate the Consistency of Risk Estimation of CAG-Suspect Human Carcinogens

These normalizations will now be compared with the CAG risk coefficients (or "slopes") as presented in tables of relative carcinogenic potencies for suspect human carcinogens found in most EPA Health Assessment Documents (see EPA 1987, for example). The CAG slopes are "unit risk" estimates from the linearized multistage model of experimental animal data or point estimates from the linear, nonthreshold model of human exposure data. CAG slopes (S) may be used to estimate risk according to the formula:

$$\text{Risk } (R) = \text{Slope } (S) \times \text{Dose } (D),$$

where S has inverse units of D [i.e., $(mg/kg/d)^{-1}$]. Substituting permissible concentration (PC) for D and solving for PC and assuming an intake of 2 L of water daily by an average 70-kg man, then at a risk level of 10^{-5} per person-lifetime

$$PC_i = \frac{10^{-5}}{S_i (mg/kg/d)^{-1}} \quad (70\ kg) \quad \left(\frac{1\ d}{2\ L}\right) \left(\frac{10^3 \mu g}{1\ mg}\right) ,$$

$$PC_i = \frac{0.35}{S_i} \mu g/L \quad .$$

Table E-1 presents the CAG slope estimates and the permissible concentration of each chemical relative to chloroform. The slope-based PCs are first corrected for absorption (if based on inhalation data) to reflect oral intake and then modified by the potency of each chemical relative to the potency of chloroform. The result is the PC of each chemical in terms of the hypothetical equivalent concentration of chloroform, based on an oral intake of dose.

If equal hazard control was intended for each chemical, the slopes were all estimated from epidemiologic or animal data of equal quality, and the dose-response extrapolation models all had the same levels of calculational precision, then the values in the last column of Table E-1 (log variation) should be constant, assuming the RP estimates accurately reflect the potencies of the 58 chemicals. As stated previously, direct comparisons of toxicological potential between different substances can be made with a high degree of relative accuracy (Ames et al. 1987). However, a considerable spread with values varying almost plus or minus three to four orders of magnitude is apparent (illustrated in Fig. E-1). Nearly a third of the chemicals vary by more than one order of magnitude from the hazard level represented by chloroform. Because the RP factors reflect a high degree of stability when much data are considered, one implication of this analysis is that currently employed methods introduce a wide and variable margin of safety for chemicals.

Fig. E-1 reveals that most risk coefficients based on human data fall within an order of magnitude of the level of control afforded chloroform. This reflects well on consistency between the use of the linear nonthreshold model applied to epidemiologic data and the RASH method, which uses laboratory-derived data. However, it may be inferred that current techniques of data selection/interpretation and application of the 95% upper confidence limit of the linearized multistage model can lead to overregulation of certain chemicals [e.g., PCBs, vinyl chloride, and bis(chloromethyl)ether (BCME)], while resulting in underregulation of others (e.g., beryllium and allyl chloride).

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Table E-1. Variation in hazard control

Chemical	Slope	Source[a]	A_{ihl}[b]	A_{oral}[b]	PC'[c]	RP'[d]	Variation[e]	Log variation[f]
1. Acetaldehyde	0.77E-2	AO			0.45E2	0.28E1	0.13E3	1.50
2. Acrylonitrile	0.24E0	HW	0.98	0.95	0.15E1	0.22E2	0.33E2	0.89
3. Aldrin	0.16E2	AO			0.22E-1	0.50E2	0.11E1	-0.59
4. Allyl chloride	0.47E-3	AO			0.74E3	0.46E1	0.34E4	2.90
5. Arsenic	0.15E2	HH			0.23E0	0.32E2	0.74E1	0.23
6. Benzo[a]pyrene	0.12E2	AO			0.30E-1	0.20E3	0.60E1	0.15
7. Benzene	0.29E-1	HW	0.47	1.0	0.56E1	0.10E1	0.56E1	0.11
8. Benzidine	0.23E3	HW	0.95	0.90	0.14E-2	0.12E4	0.17E1	-0.40
9. Beryllium	0.84E1	HW	0.50	0.001	0.21E2	0.58E3	0.12E5	3.45
10. 1,3-Butadiene	0.18E1	AI	0.65	1.0	0.12E0	0.30E0	0.37E-1	-2.06
11. Cadmium	0.61E1	HW	0.40	0.06	0.38E0	0.16E2	0.61E1	0.15
12. Carbon tetrachloride	0.13E0	AO			0.27E1	0.44E0	0.12E1	-0.55
13. Chlordane	0.13E1	AO			0.27E0	0.26E2	0.70E1	0.20
14. 1,2-Dichloroethane	0.91E-1	AO			0.38E1	0.14E1	0.53E1	0.079
15. Hexachloroethane	0.14E-1	AO			0.25E2	0.72E0	0.18E2	0.62
16. 1,1,2,2-Tetrachloroethane	0.20E0	AO			0.18E1	0.88E0	0.16E1	-0.43
17. 1,1,2-Trichloroethane	0.57E-1	AO			0.61E1	0.10E1	0.61E1	0.15
18. Chloroform	0.81E-1	AO			0.43E1	0.10E1	0.43E1	0
19. Chromium (VI)	0.41E2	HW	0.25	0.05	0.40E-1	0.88E4	0.35E3	1.90
20. Coke oven emissions	0.22E1	HW	0.27	0.50	0.94E-1	0.20E3	0.19E2	0.64
21. DDT	0.34E0	AO			0.10E1	0.66E1	0.66E1	0.18
22. 3,3-Dichlorobenzidine	0.17E1	AO			0.21E0	0.14E2	0.29E1	-0.17
23. 1,1-Dichloroethylene	0.12E1	AI	0.98	0.93	0.33E0	0.28E1	0.92E0	-0.68
24. Dichloromethane	0.14E-1	AI	0.50	1.0	0.13E2	0.44E0	0.57E1	0.11
25. Dieldrin	0.20E2	AO			0.18E-1	0.60E3	0.11E2	-0.41
26. 2,4-Dinitrotoluene	0.31E0	AO			0.11E1	0.42E2	0.46E2	1.00
27. Diphenylhydrazine	0.77E0	AO			0.45E0	0.36E1	0.16E1	-0.43
28. Epichlorohydrin	0.99E-2	AO			0.35E2	0.12E2	0.42E3	2.00
29. Bis(2-chloroethyl)ether	0.11E1	AO			0.31E0	0.16E2	0.50E1	0.079
30. Bis(chloromethyl)ether	0.93E4	AI	0.50	1.0	0.19E-4	0.18E2	0.34E-3	-4.09
31. Ethylene dibromide	0.41E2	AO			0.85E-2	0.11E3	0.94E0	-0.66
32. Ethylene oxide	0.35E0	AI	1.0	1.0	0.10E1	0.44E1	0.44E1	0.009
33. Heptachlor	0.45E1	AO			0.78E-1	0.34E2	0.27E1	-0.20
34. Heptachlor epoxide	0.91E1	AO			0.38E-1	0.32E2	0.12E1	-0.55
35. Hexachlorobenzene	0.17E1	AO			0.21E0	0.19E2	0.40E1	-0.032

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Table 1 (continued)

Chemical	Slope	Source[a]	A_{ihl}[b]	A_{oral}[b]	PC'[c]	RP'[d]	Variation[e]	Log variation[f]
36. Hexachlorobutadiene	0.75E-2	AO			0.45E1	0.80E1	0.36E2	0.92
Hexachlorocyclohexane (37-40)								
37. Technical grade	0.20E1	AO			0.18E0	0.19E1	0.34E0	-1.10
38. Alpha isomer	0.27E1	AO			0.13E0	0.24E2	0.31E1	-0.14
39. Beta isomer	0.15E1	AO			0.23E0	0.78E0	0.18E0	-1.40
40. Gamma isomer	0.11E1	AO			0.32E0	0.20E2	0.15E1	0.18
41. Hexachlorodibenzodioxin	0.62E4	AO			0.56E-4	0.18E5	0.23E0	-0.64
42. Nickel refinery dust	0.84E0	HW	0.06	0.05	0.50E0	0.52E1	0.26E1	-0.218
43. Nickel subsulfide	0.17E1	HW	0.06	0.05	0.25E0	0.10E3	0.25E2	0.76
Nitrosamines (44-46)								
44. Dimethylnitrosamine	0.26E2	AO			0.14E-1	0.48E2	0.67E0	-0.80
45. Diethylnitrosamine	0.44E2	AO			0.80E-2	0.34E2	0.27E0	-1.20
46. Dibutylnitrosamine	0.54E1	AO			0.64E-1	0.34E1	0.22E0	-1.30
47. N-nitrosopyrrolidine	0.21E1	AO			0.16E0	0.50E1	0.80E0	-0.72
48. N-nitroso-N-ethylurea	0.33E2	AO			0.11E-1	0.34E2	0.37E0	-1.10
49. N-nitroso-N-methylurea	0.30E3	AO			0.12E-2	0.46E2	0.60E-1	-1.90
50. N-nitrosodiphenylamine	0.49E-2	AO			0.71E2	0.11E2	0.78E3	2.30
51. PCBs	0.77E1	AO			0.45E-1	0.66E0	0.30E-1	-2.20
52. TCDD	0.16E6	AO			0.35E-4	0.66E6	0.23E2	0.72
53. Tetrachloroethylene	0.51E-1	AO			0.69E1	0.24E0	0.17E1	-0.40
54. Toxaphene	0.11E1	AO			0.31E0	0.20E2	0.62E1	0.15
55. Trichloroethylene	0.11E-1	AO			0.32E2	0.16E0	0.51E1	0.079
56. 2,4,6-Trichlorophenol	0.20E-1	AO			0.18E2	0.38E1	0.68E2	1.20
57. Unleaded gasoline vapor	0.35E-2	AO			0.10E3	0.76E0	0.76E2	-1.25
58. Vinyl chloride	0.23E1	AO			0.15E0	0.62E-1	0.90E-2	-2.70

[a]AO = animal oral; HW = human occupational; HH = human drinking water; AI = animal inhalation.

[b]Literature-derived absorption estimates.

[c]$PC' = PC \frac{A_{ihl}}{A_{oral}}$, where PC is estimated from Risk = Slope x Dose and based on 10^{-5} risk (per person-lifetime) (letting Dose = PC). PC' = oral-based intake dose based on slope.

[d]$RP' = \frac{RP}{RP_{chloroform}}$ (i.e., 0.005)

[e]Variation = (PC')(RP').

[f]Log of $\frac{(PC')(RP')_{chemical}}{(PC')(RP')_{chloroform}}$

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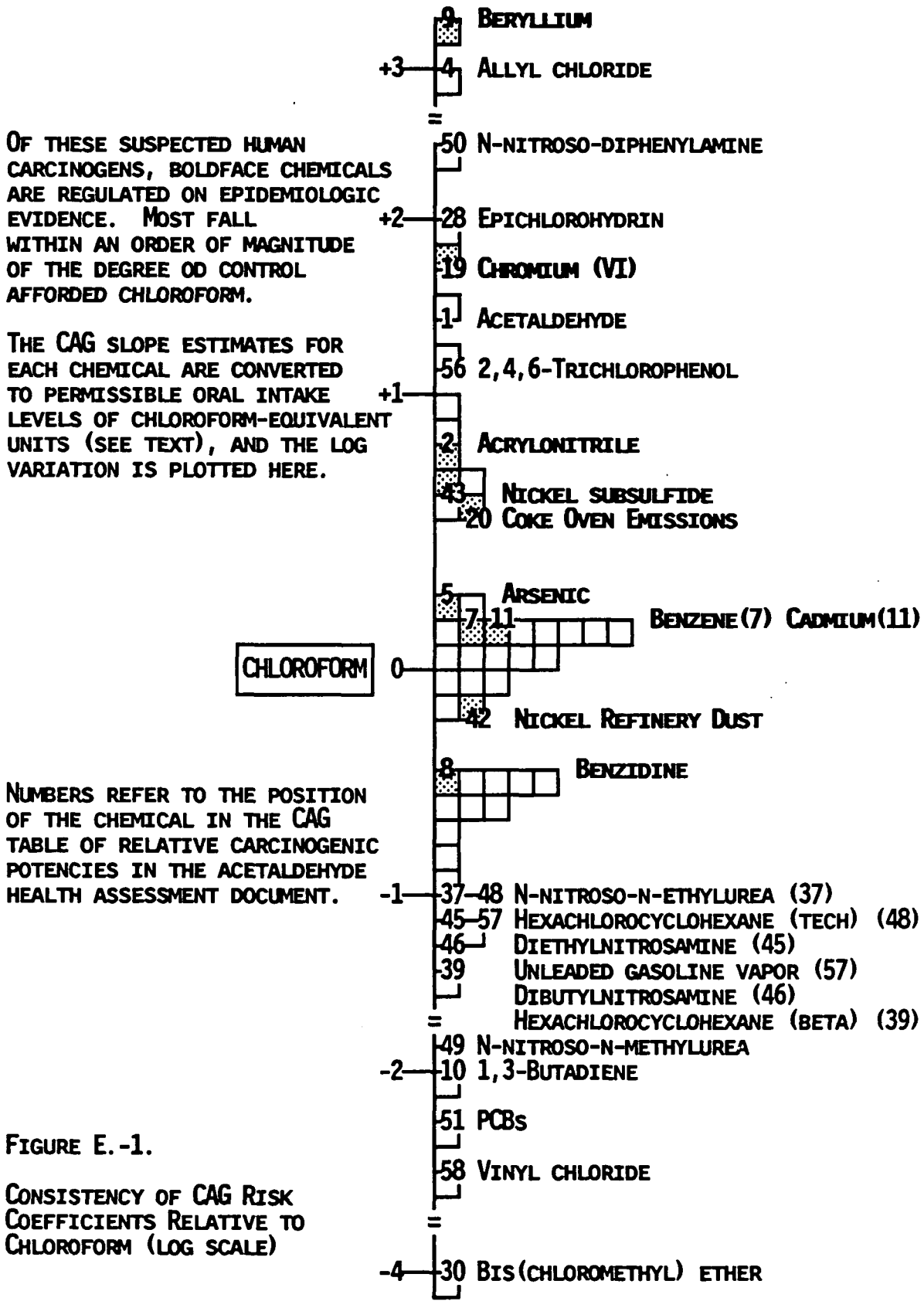

OF THESE SUSPECTED HUMAN CARCINOGENS, BOLDFACE CHEMICALS ARE REGULATED ON EPIDEMIOLOGIC EVIDENCE. MOST FALL WITHIN AN ORDER OF MAGNITUDE OF THE DEGREE OD CONTROL AFFORDED CHLOROFORM.

THE CAG SLOPE ESTIMATES FOR EACH CHEMICAL ARE CONVERTED TO PERMISSIBLE ORAL INTAKE LEVELS OF CHLOROFORM-EQUIVALENT UNITS (SEE TEXT), AND THE LOG VARIATION IS PLOTTED HERE.

NUMBERS REFER TO THE POSITION OF THE CHEMICAL IN THE CAG TABLE OF RELATIVE CARCINOGENIC POTENCIES IN THE ACETALDEHYDE HEALTH ASSESSMENT DOCUMENT.

FIGURE E.-1.

CONSISTENCY OF CAG RISK COEFFICIENTS RELATIVE TO CHLOROFORM (LOG SCALE)

Obviously, carcinogens as a group must, by policy, be regulated much more strictly than noncarcinogens. It is also acknowledged that the generally nonfatal nature of arsenic-induced skin cancer and the possibility that arsenic is an essential dietary component for hemopoesis and phosphorylation (Gori 1980) may permit a more relaxed regulatory posture for arsenic than is given most other carcinogens. A certain degree of variation in hazard control is understandable. However, it would not be unreasonable to think that apparently unexplained inconsistencies in regulation within the group of carcinogens (or within any similar group) might possibly undermine confidence in the regulatory process.

The RASH technique is generally used to characterize individual chemicals or substances through potency evaluations relative to a standard or reference chemical. Realistic occupational or environmental exposures, however, are often likely to involve complex mixtures of unknown chemicals in largely unknown proportions. Cigarette smoke, for example, is a complex mixture of thousands of chemicals (DHEW 1979).

The inherent flexibility of the RASH concept enables one to apply it to complex mixtures in two ways. If the mixture has been subjected to toxicological evaluation as a single substance, the Registry of Toxic Effects of Chemical Substances (RTECS) (Lewis and Sweet 1985) will have the data necessary to estimate the mixture's RP using a RASH analysis. Such is the case with cigarette smoke condensate, root and leaf extracts, commercial cleaning products, and other complex mixtures currently listed in the RTECS. Alternatively, if one can quantify the proportional contribution of the individual components (or even only the major toxic components) and RTECS data exist for the components individually, then RASH analysis can derive an estimate of the relative potency of the mixture from the RPs inherent in the mixture components. This is accomplished by incorporating the harmonic mean formula of Finney (1952) into the RASH analysis.

Finney's harmonic mean formula (1952) for estimating additive joint toxicity was originally restricted to evaluations of mixtures composed of substances demonstrating parallel dose response regression lines that also show similar modes of action on the test animal. However, as stated by Smyth et al. (1969), "Prediction of the safety or hazard of various exposures to mixtures of chemicals must often be made in the absence of knowledge of the mode of their joint toxic action." Inspired by an earlier study (Pozzani et al. 1959), Smyth and colleagues investigated the performance of the harmonic mean formula in predicting LD_{50} values (lethal dose for half the tested population) of mixtures from the LD_{50} values of the mixture components. This inquiry produced two classic studies that applied the harmonic mean formula to analyses of both equivolume (Smyth et al. 1969) and equitoxic (Smyth et al. 1970) mixtures of commercial organic chemicals. The Pozzani study (1959) earlier had used Finney's formula to predict LC_{50} values (lethal concentration for half the exposed test population) of mixtures of vapors as derived from the paired component vapors. In each study, it was established that Finney's harmonic mean formula for estimating additive joint toxicity was

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satisfactory in predicting the LD_{50} of the mixture from the LD_{50} value of the components (i.e., the single dose toxicity of a mixture could be estimated from the single dose toxicities of the mixture components) (Smyth et al. 1969).

An important finding emerged from statistical analysis of the data [viz., that the joint toxic action of randomly selected pairs in a mixture is most often of an additive nature (as opposed to synergistic, antagonistic, independent, or partially associated)] (Smyth et al. 1969). Implicit in this is finding the assertion that the joint toxic action of components of commonly encountered environmental mixtures is more or less of an additive nature such that harmonic mean analysis would provide a reasonable estimate of the mixture toxicity from the components' toxicities. Based on this rationale, the harmonic mean formula is of value when incorporated into RASH analysis of a complex mixture.

Harmonic Mean Analysis of Cigarette Smoke Toxicity

In consideration of the importance of the harmonic mean formula in the forthcoming calculations, it seems appropriate to demonstrate its performance first with a representative complex mixture. The availability of quantitative data on the components of cigarette smoke (DHEW 1979) and of data for cigarette smoke condensate (CSC) in the RTECS makes cigarette smoke a satisfactory choice for use as a representative complex mixture. The extreme degree of complexity of cigarette smoke as a mixture containing large number of compounds reflecting diverse biological mechanisms suggests that cigarette smoke might almost be a "worst case" complex mixture.

Table E-2 lists the major constituents of cigarette smoke specific to the gas and particulate phase components based on data provided by the U.S. Department of Health, Education, and Welfare (DHEW). The relative potency of each chemical was derived by RASH analysis of RTECS data (Jones et al. 1988). Cigarette smoke condensate, as a single chemical, was similarly scored for relative potency to yield a target value for comparison with the value derived through harmonic mean-based RASH analysis.

In this application, Finney's harmonic mean formula for estimating additive joint toxicity applied to cigarette smoke reduces to

$$RP_{cs} = \sum_i f_i \bullet RP_i ,$$

where f_i is the fractional abundance (by weight) of the mixture components and RP_i is their individual RP derived by RASH analysis (Jones et 1988).

Table E-2. Constituents of cigarette smoke

Chemical	μg/cigarette	Relative potency	Product[a]
Gas phase			
Carbon monoxide	13,400	0.019	254.6
Carbon dioxide	50,600	0.002	101.2
Ammonia	80	0.035	2.8
Hydrogen cyanide	240	0.47	112.8
Isoprene	582	0.0012	0.70
Acetaldehyde	770	0.014	10.78
Acrolein	84	0.61	51.24
Toluene	108	0.0038	0.41
N-nitrosodimethylamine	0.08	0.24	0.02
N-nitrosomethylethylamine	0.03	0.068	0.002
Hydrazine	0.03	1.0	0.03
Nitromethane	0.5	0.0095	0.0048
Nitroethane	1.1	0.019	0.021
Nitrobenzene	25	0.0061	0.153
Acetone	578	0.0014	0.81
Benzene	67	0.005	0.34
Total	66,535.74		535.91
Particulate phase			
Nicotine	1800	0.38	684
Phenol	86.4	0.016	1.38
o-cresol	20.4	0.038	0.78
m,p-cresol	49.5	0.015	0.74
2,4-Dimethylphenol	9.0	0.0081	0.07
β-naphthylamine	0.028	0.81	0.023
N-nitrosonornicotine	0.14	0.168	0.024
Carbazole	1.0	0.027	0.027
Indole	14	0.013	0.18
Hydrogen cyanide	74	0.47	34.78
Benz[*a*]anthracene	0.044	1.0	0.044
Benzo[*a*]pyrene	0.025	1.0	0.025
Fluorene	0.42	0.0041	0.0017
Fluoranthene	0.26	0.0061	0.016
Chrysene	0.04	0.22	0.0088
DDD	1.75	0.031	0.054
DDT	0.77	0.033	0.025
p-ethylphenol	18.2		
n-methylcarbazole	0.23		
n-methylindole	0.42		
4,4′-Dichlorostilbene	1.73		
Total	31,500 [b]		722.18

[a]Values in this column can be thought of in terms of a dose of B[*a*]P equal in toxicity to the dose per cigarette given in column 2.
[b]Total particulate matter + H_2O + nicotine = 31,500 μg/cigarette.

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Incorporating the available data yields

$$RP = \frac{\sum_i f \cdot RP_i}{98035.74} = \frac{535.91 + 722.18}{98035.74} = 0.0128 ,$$

where 98035.74 = the total weight (in micrograms) of both phases, 535.91 = the sum of *RP* x μg of gas phase components, and 722.18 = the sum of RP x μg of particulate phase components.

The RP of cigarette smoke condensate estimated from RASH analysis of the RTECS toxicity data for that substance is found to be 0.0049, or about the same as benzene (Jones . 1988). Thus, the value derived through RASH/harmonic mean analysis of the mixture components differs from this target value derived for the mixture (CSC) by a factor of about 3.

The uncertainties in this particular analysis derive from (1) data gaps for a few chemicals that ultimately contributed to the total weight but not to the total RP, (2) use of relatively few components to predict the combined toxicity of the thousands of chemicals produced by a burning cigarette, and (3) the degree to which CSC actually represents the combined constituents of the gas and particulate phases. In consideration of these uncertainties and neglecting interaction factors, the difference by a factor of 3 seems small. Thus, the harmonic mean formula is considered to be appropriate when applied to the RASH analysis of this complex mixture.

As stated previously, concentration levels corresponding to risk levels of 10^{-5} per person-lifetime are derived from mathematical analogies with implicitly wide and chemical-specific margins of safety. As an adjunct to absolute decision-making approaches, the remainder of this report will apply the RASH methodology in comparative evaluations that may provide insight into relative hazard-relationships.

We propose to use the aforementiond examples of complex mixture exposure and hazard control to compare hazards from all toxic chemicals, including those for which we have CAG risk coefficients and those for which we have test data but no risk coefficients (Jones et al. 1988), to other common human exposures. Such exposures may derive from ingestion of B[a]P resulting from cooking and/or growing foods or from drinking chlorinated and/or fluoridated water. In this manner, no explicit level of risk is assumed. Instead, the evaluation of hazard is implicit [i.e., the expression of exposures relative to exposures that as a society we commonly accept (chlorination by-products in drinking water) or other exposures that as a society we clearly reject]. Some of the latter hazards (e.g., smoking cigarettes) may be acceptable to certain individuals.

Defining a Zone "Generally Recognized as Safe"

Chlorination of drinking water was introduced in the United States in 1908 and has been called the single most important advance in water treatment (NAS 1977). The principle goal of chlorination is disinfection to reduce the pathogen content of drinking water to safe levels. Ample epidemiologic evidence supports the major role chlorination has played in dramatically reducing the incidence of water-borne infectious diseases such as cholera and typhoid fever (NAS 1977).

Addition of chlorine to drinking water results in the formation of the hydrolysis product HOCl, or hypochlorous acid, according to the following reaction:

$$Cl_2 + H_2O = HOCl + H^+ + Cl^-$$

(NAS 1980). Hypochlorous acid then dissociates to release OCl^-, the hypochlorite ion, by the reaction

$$HOCl = H^+ + OCl^-.$$

HOCl and OCl^- are referred to as "free residual chlorine" and exist in equimolar concentrations at pH 7.5 and 25°C. At a higher pH, OCl^- predominates; HOCl predominates at lower pH values.

Other by-products of chlorination result when chlorine interacts with organic material naturally occurring in water, such as humic and fulvic acids (Morris 1975). These substances can be further oxidized and chlorinated to yield trihalomethanes (THMs) and other substances of as yet unknown identity or potential health risk. One such THM is chloroform, a known animal carcinogen (IARC 1982).

Other products resulting from water chlorination are many and varied. Ammonia, which may be present, can undergo substitution and oxidation to yield chloramines such as NH_2Cl (monochloramine), $NHCl_2$ (dichloramine), and NCl_3 (nitrogen trichloride). If bromine is present, the oxidation product HOBr (hypobromous acid) may produce bromamines through interaction with ammonia. Phenols undergoing chlorination produce chlorinated phenols such as 2-chlorophenol, which is suspected of enhancing the mutagenicity of ethylnitrosourea (Exon and Koller 1985). Other by-products of chlorination include halogenated ketones and aldehydes, haloacetonitriles, and chlorobenzenes. Adverse health effects associated with exposure to these substances range from hepatic and renal toxicity to mutagenic and carcinogenic activity.

Thus, one can see that a low incidence of potentially negative health effects may theoretically result from lifetime exposure to halogenated organics produced as a result of chlorination. Nonetheless, these effects are generally deemed insignificant relative to the adversities of epidemic water-borne disease. From such a perspective, risks from chlorination are surely regarded as acceptable to a majority of the U.S. population.

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In estimating risk from chlorination by-products, the RASH methodology has focused to date on the THM content alone. Certainly all halogenated organics produced by chlorination contribute to actual risk, but the present lack of quantitative data does not permit their incorporation into an RP calculation.

Based on the frequency of distribution of the halomethanes detected in the National Organic Reconnaissance Survey for Halogenated Organics (Symons et al. 1975), the theoretical finished water with the median concentration of each compound would contain about 21 μg/L of chloroform, 6 μg/L of bromodichloromethane ($CHBrCl_2$), 1.2 μg/L of chlorodibromomethane ($CHBr_2Cl$), and bromoform ($CHBr_3$) below the limit of detection by the analytical method used.Application of Finney's harmonic mean formula to RASH analysis of the relative potency of drinking water as a mixture yields the equation

$$RP_{dw} = \sum_i f_i \cdot RP_i$$

where i = the three quantifiable halomethanes listed previously.Assuming 10^9 μg in 1 L of water, it is seen that

$$RP_{dw} = \frac{21\ \mu g}{10^9 \mu g} CHCl_3\ (0.005) + \frac{6\ \mu g}{10^9 \mu g} CHBrCl_2\ (0.0065) + \frac{1.2\ \mu g}{10^9 \mu g} CHBr\ Cl\ (0.021)$$

$$= \frac{0.105 + 0.039 + 0.025}{10^9} = 1.7 \times 10^{-10}.$$

The relative potency of each compound is standardized to pure B[a]P as the primary standard, and the small calculated value suggests a very weak composite toxicity relative to the standard.Additionally, the value is an underestimate of the relative potency of chlorinated drinking waterbecause data for only three chemicals were incorporated into the calculation.As a result, subsequent comparisons of other risk estimates with this value as the standard should err on the side of safety.

Whereas chlorination of public drinking water is considered necessary for protection of human health, fluoridation is considered a supplemental measure to enhance the dental health of children (up to 12 years of age). Target levels of fluoride in public drinking water are generally on the order of 1 mg/L.At this level, no adverse health effects associated with fluoride intake from drinking water have been detected in the world's temperate zones.At levels of 2 mg/L and above, objectionable mottling of teeth (dental fluorosis) may occur in children; at higher levels, crippling skeletal fluorosis may result following prolonged ingestion (WHO 1970).

Based on fluoride content alone, and given that there are 10^6 mg/L of water, the relative potency of drinking water may be derived from the formula

$$RP_{dw} = RP_f \times \text{Concentration/L}$$

$$= 0.046 \times \frac{1\ \text{mg}}{10\text{mg}6}$$

$$= \frac{0.046}{10^6} = 4.6 \times 10^{-8}.$$

The calculated RP value is an estimate of the potency of 1 L of drinking water (based on its fluoride content) relative to the potency of B[a]P.An *RP* value of 1 would suggest a potency equal to that of B[a]P.

In many communities, both chlorination and fluoridation of the public drinking water are practiced.The relative potency of such drinking water would be calculated from Finney's harmonic mean formula applied previously to RASH analysis of chlorinated water incorporating fluoride data to yield

$$RP_{dw} = \frac{(0.005)}{10^9\ \mu g} + \frac{(0.065)}{10^9\ \mu g} + \frac{(0.021)}{10^9\ \mu g} + \frac{(0.046)}{10^9\ \mu g}$$

$$= \frac{0.105 + 0.312 + 0.025 + 46.0}{10^9} = \frac{46.442}{10^9}$$

$$\cong 4.64 \times 10^{-8}$$

Thus, the RP of drinking water based on its content of chlorination by-products and fluoride is essentially the same as if based on fluoride content alone.This calculation suggests that use of chlorine dioxide, for example, as a less toxic purification method, would beimpractical in water supplies fluoridated at 1 mg/L.In consideration of the greater relative potency of fluoride and its greater concentration per liter than is seen with chlorination by-products, this finding is not unexpected.It should be noted that the calculated value is quite small, suggesting a very weak potency relative to B[a]P.

To compare the risk of exposure to hazardous chemicals with the risk from ingestion of chlorinated drinking water, the following equation can be used:

$$\frac{\text{Risk}_{test}}{\text{Risk}_{dw}} = \frac{(\text{Conc. } \mu\text{g/L})\ (1\text{L}/10^3\text{g})\ (RP_c)}{RP_{dw}}$$

where $RP_{dw} = 1.7 \times 10^{-10}$ (previously derived).Thus, if one knows the RASH-derived relative potency of the hazardous chemical under consideration and the concentration per liter (perhaps derived from a chemical analysis), an approximation of its toxicity relative to the toxicity deriving from chlorination of drinking water can be made.Calculated values less than unity would suggest a level of risk less than risk from ingestion of chlorinated drinking water.Such relative analogies would seem to provide a more realistic perception of actual risk than can be extracted from model-based estimates that index theoretical calculated risk levels of 10^{-5} per person-lifetime.

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Ideally, the best standard for comparative hazard evaluation would be a substance for which the true hazard from very low dose exposure was known with certainty.However, we have argued that true hazard cannot be determined from estimates based on safety factors (in evaluation of toxic chemicals) or mathematical models based on untestable assumptions (in evaluation of carcinogens).In this context, a composite standard based on various commonly acceptable hazards may possibly serve as a more meaningful reference standard than any single substance with attendant risk estimates of unknown accuracy.

We have shown how the hazard represented by chlorinated drinking water can provide a reference by which to evaluate exposures to other environmental hazards.This approach has been extended to consider additional substances to which exposure is commonly routine and considered to impart a level of risk acceptable to most persons.The resulting composite of hazards represented by these commonly encountered substances can then define a zone of hazard conceptually equivalent to the U. S. Food and Drug Administration (FDA) list of generally recognized as safe (GRAS) food additives (42FR14640, March 15, 1977).Hazards represented by environmental agents may be evaluated relative to the GRAS zone of commonly acceptable hazards.This process provides insight into the actual hazard represented by a particular agent and also reveals relative hazard relationships among substances.

Table E-3 provides data used to develop this concept and establish a composite GRAS zone of commonly acceptable hazards, graphically represented by Fig. E-2.The reference activity providing the GRAS baseline is loosely derived from the consumption of a charbroiled steak dinner, complete with beverage, bread and salad, an ordinary meal to many in our society.Attendant risks derive from exposure to the increased B[a]P content of charbroiled meats, the B[a]P content of breads and lettuce (grown near industry), fluoride in tea, caffeine in coffee, residues of dichloromethane (DCM) in decaffeinated coffee, and chlorination by-products and fluoride in the water used to prepare the coffee or tea.The toxicity estimate from exposure to these substances is normalized to the toxicity estimate from smoking cigarettes (commonly unacceptable to many persons) to establish relative hazard relationships.

In this investigation, toxicity is based on a lifetime dose reflecting a 70-year exposure (except 50 years for coffee and cigarettes) and daily consumption levels of 2 L of drinking water, 1 L of tea or coffee, and one pack of cigarettes.The concentration of drinking water contaminants are based on maximum contaminant level (MCL) values except for B[a]P, PCBs and dichloromethane, which are projections derived from CAG slope estimates.

In Fig. E-2, the hazards determined for the GRAS reference substances are plotted to the right of the log axis and hazards from exposure to established regulatory levels of drinking water contamination are plotted to the left of the log axis.A survey of general relationships revealed in this graph indicates that the GRAS zone of acceptable hazards falls roughly two to six orders of magnitude below the hazard associated with smoking a pack of cigarettes daily.Hazards from exposure to most

Table E-3. Comparative Hazards Relative to Cigarette Smoking

Substance	Concentration	Lifetime dose(D)[a] (μg)	RP_i[b]	(D)(RP_i)	Ratio[c]	Log ratio
Cigarette smoke (1 pack/d)	300 mg CSC[d] per cig.	0.11E12	0.49E-2	0.54E9	1	0
Benzene (8 h time-weighted average)	1 ppm	0.38E9	0.50E-2	0.19E7	0.35E-2	-2.5
Drinking water contaminants (2 L/day intake)						
Chromium (VI)	50 μg/L[e]	0.26E7	0.44E2	0.11E9	0.21	-0.67
PCBs	0.045 μg/L	0.23E4	0.33E-2	7.6	0.14E-7	-7.9
B[a]P	0.03 μg/L	0.15E4	1	0.15E4	0.28E-5	-5.6
DCM	25 μg/L	0.13E7	0.22E-2	0.29E4	0.53E-5	-5.3
Lead	50 μg/L	0.26E7	0.92E-1	0.24E6	0.44E-3	-3.4
Vinyl chloride	2 μg/L	0.10E6	0.31E-3	0.31E2	0.57E-7	-7.2
Chloroform	100 μg/L	0.51E7	0.50E-2	0.26E5	0.47E-4	-4.3
B[a]P in foods						
Sirloin (10 oz/week)	11.1 ng/g[f]	0.11E5	1	0.11E5	0.20E-4	-4.7
T-Bone (10 oz/week)	50.4 ng/g	0.51E5	1	0.51E5	0.95E-4	-4.0
Bread (6 slices/d)	1 ng/g	0.43E4	1	0.43E4	0.80E-5	-5.1
Lettuce (1.5 oz/d)	1.6 ng/g	0.17E4	1	0.17E4	0.32E-5	-5.5
DCM/Coffee (1 L/d)	10 ppm[f]	0.18E9	0.22E-2	0.40E6	0.73E-3	-3.1
Caffeine/Coffee (1 L/d)	100 mg/cup[f,g]	0.74E10	0.26E-1	0.19E9	0.36	-0.45
Fluoride/Tea (1 L/d)	100 ppm[h]	0.26E10	0.46E-1	0.12E9	0.22	-0.65
Treated drinking water						
THMs	28.2 μg/L	0.14E7	0.60E-2	0.84E4	0.16E-4	-4.8
Fluoride	1 ppm	0.51E8	0.46E-1	0.23E7	0.44E-2	-2.4

[a]Based on 70-year exposure, except 50-year for coffee and tea.

[b]From RASH analysis (Jones et al. 1988).

[c] $$\frac{(D_{test})\ (RP_{test})}{(D_{cig.smoke})\ (RP_{cig.smoke})}$$

[d]From DHEW 1979.

[e]Based on MCL values except for PCBs, B[a]P, and DCM (dichloromethane), which are slope-based estimates (see text).

[f]From Banbury Report 17 (Strobel 1984).

[g]Author's estimate of 1 cup = 250ml.

[h]From WHO 1970.

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HAZARDS FROM EXPOSURES TO PERMISSIBLE LEVELS OF REGULATED CHEMICALS AND FROM COMMON LIFESTYLE EXPOSURES "GENERALLY REGARDED AS SAFE" ARE NORMALIZED TO THE ESTIMATED HAZARD OF SMOKING A PACK OF CIGARETTES DAILY. A GRAS-ZONE OF HAZARD FALLS ROUGHLY 2 TO 6 ORDERS OF MAGNITUDE BELOW THE ESTIMATED HAZARD OF SMOKING CIGARETTES.

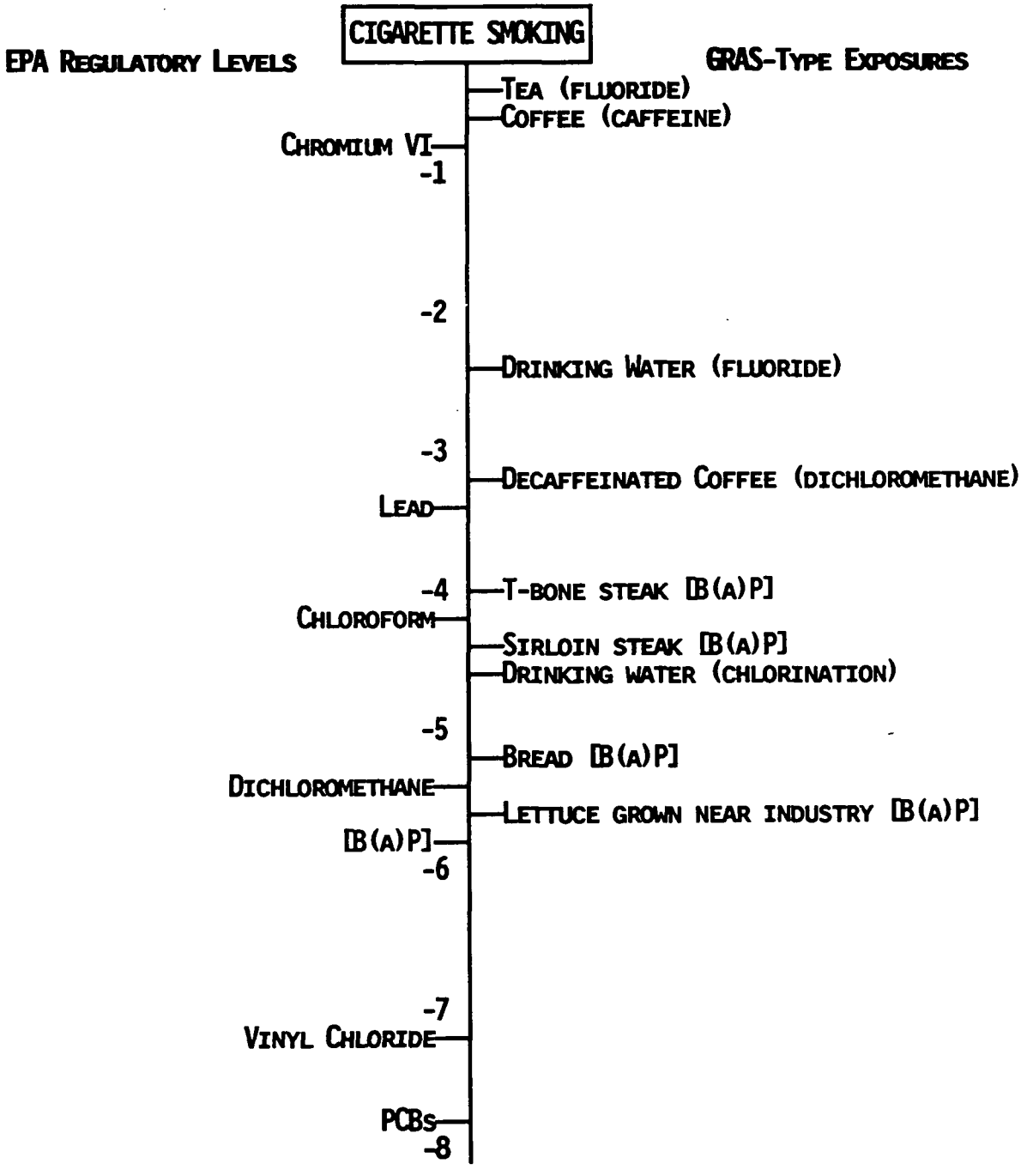

FIG. E-2. COMPARATIVE HAZARDS RELATIVE TO CIGARETTE SMOKING EXPRESSED ON A LOGARITHMIC SCALE

contaminants in drinking water considered here fall generally within the GRAS zone.However, hazards from exposure to vinyl chloride and PCBs are determined to fall two to three orders of magnitude below the GRAS zone, whereas the hazard from exposure to chromium (VI) is nearly two orders of magnitude above the GRAS zone, roughly equivalent to the hazard deriving from an intake of a 1 L/d of coffee or tea.

Because the hazards from drinking water contaminants depicted in this graph are based on regulatory levels of exposure, one may consider that vinyl chloride and PCBs may be overregulated, and chromium (VI) may be underregulated relative to other commonly acceptable hazards.Indeed, the preceeding analysis of regulatory consistency of EPA-CAG risk coefficients fully supports this contention (see Appendix E, METHODS).Thus, established action levels of regulated substances in various environmental media may be evaluated from the perspective of relative hazard relationships such that more consistent estimates of comparable risk may be infused into a framework of regulation.

CONCLUSIONS

In this manuscript, we have examined some aspects of regulation of hazardous substances by government agencies currently charged with the task.Current approaches characterized as data-sparse andmodel-intensive attempt to determine acceptable concentrations in various environmental media for individual substances (not complex mixtures) based on prior designation as carcinogen or noncarcinogen, as adjudged by expert committee evaluation of the weight of evidence for carcinogenicity. Manipulations of the available data incorporate often large and potentially variable safety factors in estimating risk from noncarcinogenic toxic chemicals as well as unvalidated, untested assumptions in mathematically modeling risk from carcinogens. Risk coefficients and action levels for various substances derived from absolute decision-making approaches were seen to vary with respect to a relative potency-derived standard.

We have shown how RASH analysis incorporated into an RP framework could be used to estimate hazard from exposures to individual substances as well as complex mixtures through a rapid and inexpensive data-intensive, model-sparse approach to relative decision making.The process generally makes extensive use of existing published toxicity data, incorporates no theoretical models, and evaluates all chemicals regardless of their prior determination as carcinogen or noncarcinogen.

When applied to comparative hazard evaluations, the RASH technique was shown to be effective in providing a basis for evaluating the degree of consistency emanating from current regulatory approaches.Through hazard evaluation relative to a GRAS zone of commonly acceptable hazards, it was seen that a RASH-based relative potency approach could offer a different perspective for regulation of hazardous substances such that a consistent level of regulation may be achieved.RASH analysis could thus serve as a screening tool to rank the many chemicals currently requiring evaluation. The approaches and analyses presented in this manuscript are

offered as a possible supplement to the regulatory machinery already in place. They are presented in recognition of the need to reduce uncertainty, improve consistency, and bolster public confidence in the regulatory process.

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