



# The Report Of The Human Health Subcommittee

## Relative Risk Reduction Project



## Reducing Risk Appendix B

## NOTICE

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## ABSTRACT

The Human Health Subcommittee of the Relative Risk Reduction Strategies Committee (RRRSC) of the U.S. Environmental Protection Agency's Science Advisory Board (SAB) reviewed the Agency's 1987 report entitled "Unfinished Business: A Comparative Analysis of Environmental Problems." (UB.) The Subcommittee's goal was to evaluate the report's methodology for ranking environmental health problems, determine the extent to which the risk rankings for different environmental problems should be revised or updated, combine if possible, rankings for carcinogenic and non-carcinogenic effects into a single aggregate ranking, and recommend approaches for the improve methodologies for assessing and ranking environmental risks to human health. The Subcommittee was critical of the original EPA ranking of problem areas which included a mixture of specific environmental pollutants, sources of pollutants, exposure media, and exposure situations--and which appeared not to have been selected on the basis of their relevance to environmental and health hazard assessment, or on the basis of overall public health significance. Most of the 31 categories are so broad, and include so many toxic and non-toxic agents, that ranking of these categories could not be performed with any rigor or confidence.

Problems areas in the UB report representing proximal human exposure situations were assigned the highest relative risk rankings for cancer and/or other adverse health effects. Of the "high" relative risk rankings assigned in the UB report, those for criteria air pollutants, hazardous air pollutants, indoor radon, other indoor air pollution, drinking water pollutants, the application of pesticides, and occupational exposure to chemicals were considered to be supported more firmly by the available data than were the rankings for the others:

Future efforts should focus on broad environmental problems, without regard to internal organizational strictures or to ultimate regulatory responsibility. The Subcommittee recommends a new approach to the risk ranking process, using a matrix-based on sources, exposure situations, agents, and health outcomes. This approach will identify specific agents and mixtures (and the principal sources and exposure situations in which they are found) that should receive priorities for applying risk reduction efforts. The Subcommittee further recommends that the Agency assign a specific management focal point for this effort to assure accountability, establish a risk assessment framework for other toxicants consistent with that used for carcinogens, establish a formal mechanism for risk anticipation, expand long-range research on the assessment of human exposure, and improve the relevant toxicological science base.

Key Words: environmental health risk assessment; exposure assessment; risk ranking; toxicological assessment

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## 1.0 Executive Summary

### 1.1 Introduction

This is the report of the Human Health Subcommittee of the Relative Risk Reduction Strategies Committee (RRRSC), convened by the U. S. Environmental Protection Agency's Science Advisory Board (SAB). The report was written as part of an overall effort by the SAB to assist in developing strategic risk reduction options that would be helpful to the Agency in assessing its research and regulatory activities.

In conjunction with other studies undertaken by the RRRSC, the Subcommittee was charged with reviewing EPA's report entitled "Unfinished Business" (EPA, 1987) to: (1) evaluate its methodology for ranking environmental problems in terms of their relative risks to human health, (2) determine the extent to which the relative risk rankings it had assigned to different environmental problems should be revised or updated on the basis of methodological limitations or newer data, (3) combine if possible into a single aggregate ranking the risk rankings for carcinogenic effects and the risk rankings for other adverse effects on human health, and (4) recommend approaches for the further development of a long-term strategy to improve the methodology for assessing and ranking environmental risks to human health. Given the breadth of the charge, the Subcommittee focused its attention on methodological and research issues, with the intent of providing recommendations to a future expert group convened specifically for the purpose of ranking relative environmental health risks.

### 1.2 Evaluation of Methodology

Toxicants that may be encountered in air, water, food, consumer products, the home, the workplace, and other environments, can pose risks to human health. In some instances, the risks from such toxicants have already been adequately controlled by limiting human exposure to the agents in question, but in other instances environmental toxicant-related risks to health continue to exist, as reported in "Unfinished Business." The Subcommittee agrees that it is important therefore, that all such risks be assessed in order that appropriate measures for controlling them may be developed.

In the "Unfinished Business report (UB), 31 environmental problem areas were identified and ranked according to the relative magnitude of the risk of cancer or other adverse health effects associated with each. No attempt was made to combine the rankings for cancer with those for other adverse health effects.

On reviewing the "Unfinished Business" report, the Subcommittee recognized the Agency's need to compare the relative risks of different environmental problems in order to set appropriate priorities for the allocation of its resources. The Subcommittee also recognized that the 31 specific environmental problems considered in "Unfinished Business"--which included a mixture of specific environmental pollutants, sources of pollutants, exposure media, and exposure situations--had been selected largely on the basis of their relevance to the Agency's legislative history and programmatic organization rather than on the basis of their relevance to environmental and health hazard assessment, or on the basis of overall public health significance. Consequently, most of the 31 categories in the UB taxonomy are so broad, and include so many toxic and non-toxic agents, that ranking of these categories cannot be performed with any rigor or confidence.

Future EPA efforts should focus more on broad environmental problems, without regard to internal organizational strictures or to ultimate regulatory responsibility. To conceptualize risks better, the Subcommittee recommends a new approach to the risk ranking process, using a matrix based on sources, exposure situations, agents, and health outcomes. This approach will identify specific agents and mixtures (and the principal sources and exposure situations in which they are found) that should receive priorities for applying risk reduction efforts.

Among the most serious of the limitations in the risk assessments in UB was the inadequacy of the exposure information on which they had been based. Without more adequate characterization of the human exposure relevant to the environmental agents or situations in question, the corresponding risk assessments will remain tenuous. Consequently, the UB report was based, per force, on a foreshortened hazard identification process. Even today, the relevant exposure information is fragmentary or lacking, for the most part. Measures for improving the assessment of exposure should be pursued vigorously.

Human or animal data that can be extrapolated to the low dose domain in order to support risk assessment is available for only a relative few environmental agents. In these cases, moreover, the extrapolations are often based on incomplete or inconsistent data and therefore involve uncertain assumptions about the shapes of the dose response curves, the influence of age and other factors on the susceptibility of the exposed persons, and the extent to which the effects of the agent or situation may be modified by other environmental variables.

Other limitations noted in the UB methodology include:

- a) The report was based on a fundamental and largely undefined hazard identification process, which relied heavily on preexisting listings of candidate problems, instead of a systematic and exhaustive effort to identify all relevant hazards according to clearly stated criteria.
- b) Lack of comparability in the risk estimates for different exposure and source categories or "problem areas" (as defined in the UB report), because the estimates were frequently based on different models and/or assumptions.
- c) The frequent use of only a few agents or exposures to estimate risk for a problem area in which many agents or exposures were involved
- d) The exclusion of significant factors from the selection of risk areas, e.g., economic or technical controllability of the risk
- e) As acknowledged in the UB report, the failure to state the scope that specific problems would pose without the continuation of in-place control and regulatory activities. Consequently, some problem areas appeared to pose relatively low risks precisely because of existing high levels of effort devoted to their control.
- f) The failure to incorporate the assessment of preclinical and subclinical effects of environmental agents into the relative risk rankings, which undercut the ultimate goal of risk prevention.

- g) The failure to consider the relative magnitude of additional benefits to be gained from completing partial programs to reduce risks of specific toxicants, particularly when the major expense of changing production or use patterns had already been incurred and the marginal costs of further risk reduction were considerably reduced (e.g., removing the last lead from gasoline; banning PBBs as well as PCBs).

### 1.3 Comments on the Risk Rankings

Although the UB report was an important initial effort to systematize a comparison of environmental problems, the risk rankings presented must, because of the limitations noted above, be regarded as provisional.

For want of sufficient time, the Subcommittee did not attempt to update or reassess the rankings. Rather, the Subcommittee focused on methodological issues inherent in a risk comparison exercise of this type, as well as on the need for updated and expanded databases to improve relevant human exposure and toxicity information. As shown in Table 6.1.1 and discussed below, the Subcommittee recommends a restructuring of the environmental problem areas in the UB report in a way that can more accurately reflect the different risk factors represented in each area and the interrelationships among them.

Given the limitations in the taxonomy of the environmental problems areas in the UB report and in the toxicity and exposure data on which their respective risk assessments were based, it is not illogical that those problem areas representing proximal human exposure situations were assigned the highest relative risk rankings for cancer and/or other adverse health effects in the UB report. Such problem areas included the following: criteria air pollutants, hazardous air pollutants, the application of pesticides, indoor air pollution (excluding radon), indoor radon exposure, drinking water, pesticide residues on food, consumer product exposure, and occupational exposure to chemicals.

Of the "high" relative risk rankings assigned in the UB report to the above nine problem areas, those for the following seven areas were considered to be supported more firmly by the available data than were the rankings for the others:

- ⊙ criteria air pollutants
- ⊙ hazardous air pollutants
- ⊙ indoor radon
- ⊙ indoor air pollution (excluding radon)
- ⊙ drinking water pollutants
- ⊙ application of pesticides
- ⊙ occupational exposure to chemicals

The data for the other two problem areas--pesticides residues on food, and consumer product exposure--were less robust, but the "high" relative risk rankings for these problems also might prove to be justified on the basis of further study.

Depletion of stratospheric ozone (problem No. 7) was ranked high for cancer effects and medium for other adverse effects in the UB Report. The Subcommittee considers the supporting data for the categorization of this particular problem to be less robust than for those noted just above, but still sufficient to support the classifications given. It should be emphasized, however, that if the methodology for assessing relative risk that is proposed in this report were applied to all other problem areas (or their component toxicants) identified in the UB Report, certain other areas might also be classified as "high." Conversely, the classification of some areas noted above as "high" in the UB report might possibly be changed to "medium" or "low."

In addition to the relative magnitudes of the risks to health posed by different environmental problem areas, the controllability of the risks is another factor that must be considered in evaluating alternative risk-reduction strategies. Hence it must not be forgotten that the adverse health effects of certain environmental toxicants--such as carcinogens--may not appear until decades after exposure, with the result that termination of exposure to the toxicants does not abolish the risk for those who have been previously exposed. Also, certain environmental toxicants--such as heavy metals, PCBs, and long-lived radionuclides--tend to persist indefinitely in the environment, and may actually become concentrated in certain components of the human food chain. Such toxicants may, therefore, pose a continuing threat to human health, primarily through the ingestion pathway, long after their release into the environment has been reduced.

#### 1.4 Developing An Aggregate Risk Ranking

The development of a single aggregate risk ranking that would combine the relative risks for cancer with the relative risks for other types of adverse health effects was addressed by the Subcommittee, which evaluated the data and methodology required for the purpose. Such an aggregate ranking would provide additional guidance to the Agency in setting priorities. Although possible in principle, the development cannot be accomplished without comparing the impacts of different types of health effects on the total population as well as on the individuals directly affected. The Subcommittee recognized that the development of any aggregate risk ranking that attempts a single scaling requires resolution of many implicit value judgments and ethical issues beyond the scope or authority of this Subcommittee or the EPA. That is, to attempt a relative ranking in terms of severity (or significance) of such disparate health outcomes as birth defects in infants compared to paralysis in older persons requires consideration on many dimensions of the values we place on various members of society, families, and the utility of specific physical and mental functions for individuals and society. Such a comparison requires that the impact of each effect be scored for severity, a process necessitating selection of suitable measures and scales of severity, as well as appropriate weighting factors. In addition, the current disparity in risk assessment approaches for carcinogens and systemic toxicants makes it exceedingly difficult to construct a universally acceptable aggregate ranking. Although the data and time needed for such a complex task were not available, the Subcommittee described ways by which such an aggregated ranking might be undertaken in the future, assuming that the important value-laden issues can be equitably resolved.

#### 1.5 Recommended Approaches

In considering how risk areas might be better defined and relevant information organized for ranking/assessment purposes, the Subcommittee proposes as a possible approach the development of a matrix, the principal dimensions of which include sources, exposure situations, agents, and health endpoints. For example, a two-dimensional array, with rows representing ultimate sources (such as agriculture) and columns representing direct or proximate sources impacting human health (such as drinking water), would help to identify those intersections at which risk reduction initiatives

would produce the greatest benefits (see Table 6.1.1). Expanding the dimensions of such an array, by including specific agents (as in Figure 6.1.2) and health endpoints, would allow an even more detailed identification of where the Agency could act most effectively.

Developing the matrix in usable form and entering information into it would be no small task. In the final analysis, the task will never be quite complete; whatever initial system is adopted will undergo continual change, expansion, and development (as distinct from maintenance) as it is used and as experience is gained from cataloguing new information in it.

The Subcommittee recommends that the Agency undertake the development of such a prototype matrix, beginning with a limited pilot effort using a few, widely spread agents, and designed to explore its feasibility. Existing relational data base software would support such an effort, and the resulting four-dimensional information system would itself be usable, and would also provide information for the development of an "ultimate" system. This approach would reveal complexities and practical difficulties at an early stage. A later stage of development would expand by adding a larger number of agents selected for potency and ubiquity. They could be selected from preexisting lists (such as those developed under Title 3 of the SARA "Community Right to Know Provisions"). As the system is developed, it should be linked to existing databases, such as the EPA's Integrated Risk Information System (IRIS).

Once the system were to become even partially functional, its value would be great. Applying the concept of the interconnected four-dimensional system as an aid to the thought process when human health risk issues are addressed should improve the risk assessment process at once; documentation of such applications would be a source of information for insertion into the system itself.

The Subcommittee further recommends that the Agency assign a specific management focal point for this effort to assure accountability.

With the ultimate aim of improving the assessment and ranking of environmental risks to human health, the Subcommittee recommends the following additional actions:

- a) Establishment of a risk assessment framework for other toxicants consistent with that used for carcinogens. The recommendations in b), c), d), e), and f) below, while useful in and of themselves, will also contribute directly to achieving this goal.
- b) Establishment of a formal mechanism for risk anticipation (i.e., identification of emerging problems), as recommended in the Future Risk report (EPA, 1988), including an expert in-house committee, peer oversight, and a means of supporting long-term research on emerging problem areas.
- c) Expansion of long-range research on the assessment of human exposure. Topics should include developing data and models on the variation of exposure with time and place, and obtaining detailed and comprehensive exposure measurements (including data on: (1) ambient exposure levels; (2) tissue burdens; (3) uptake, distribution, metabolism, and excretion of the toxicants of interest, and the extent to which these parameters may vary with age, sex, diet, physiological state, and other variables; and (4) relevant biological and molecular markers of exposure.
- d) Improvement of the relevant toxicological science base, including more systematic data on the toxicity of environmental agents for humans of different ages, more comprehensive assessment of their toxicity in surrogate toxicological test systems, and better understanding of the appropriate dose-response and trans-species scaling functions to be used in assessing their risks to human health.
- e) Development of the extensive exposure and toxicity databases needed, through closer cooperation with other federal (e.g., NCHS, NIH, NIOSH, FDA, and DOE), state and local agencies, as well as with institutions in the private sector.
- f) Establishment of a long-term program to improve the capability for assessing and ranking environmental risks to human health. The program should involve extramural peer

review and should be organized in such a way as to deal most effectively with the relevant research issues.

- g) Further development of scientific capability in the requisite disciplines; i.e., since assessment of the health risks of environmental agents requires the coordinated efforts of biologists, chemists, epidemiologists, mathematicians, physicians, toxicologists, geneticists, and scientists of other disciplines, and since few institutions have the multidisciplinary teams required for such research, there is a need to develop programs for fostering such collaboration on a broader scale, for focusing it on the key problems that deserve to be pursued, and for the further training of scientists with the necessary expertise, through long-term support of graduate and postgraduate training in toxicology, epidemiology, exposure assessment, and the other relevant disciplines.

Future risk rankings should be based on risk assessments for specific single toxic agents or definable mixtures, and on the cumulative human exposure to such agents. In actually conducting future risk ranking exercises, the following factors, discussed in the Subcommittee's report, should be considered:

- a) The effects of uncertainty in exposure estimates should be stated explicitly and factored into any risk characterizations, and possible interactions for exposures involving complex mixtures should be addressed.
- b) Consistent criteria should be developed for the assessment of toxicity and the identification of hazards. To accomplish this, the Agency should develop and apply consistent criteria for hazard identification, include sub-clinical and pre-clinical effects of pollutants as endpoints of concern, and expand its assessments of substances/agents within selected "problem areas" (however defined) to encompass truly representative samples.
- c) The distribution as well as the mean, should be evaluated when considering the severity of health effects. In the case of lead, an average decrease of five percent in IQ scores for individuals would translate into a greater than

fifty percent decrease in the number of individuals scoring in the upper intelligence ranges, and a quadrupling of the number of persons with IQ scores less than 80.

- d) Assessments should consider risks to individuals, as well as risks to the general population and to susceptible subgroups.
- e) The Agency should be cautious in using merged ranking schemes for cancer and non-cancer endpoints. Difficulties arise from the lack of a clear biological rationale, divergent histories, and the absence of an acknowledged scoring system for severity of effect. Approaches to a merged ranking system are described in the Subcommittee report (section 6.3) as well as an illustration of the steps and problems involved in the complex process of merging rankings of different types of risks to human health.
- f) Consideration should be given to the time period over which different risk reduction strategies may be effective when evaluating the risk posed by a given toxicant, as well as to the persistence of risks if uncontrolled.
- g) It should be recognized that the assessment of relative risk is a value-laden process (particularly with respect to relative severity and equity), which should involve toxicologists, epidemiologists, exposure assessors, medical experts, sociologists, ethicists, and informed representatives of the general public.
- h) Risk rankings should explicitly address the extent to which existing control strategies effect risk reduction, and conversely, the estimated risk in the event that existing programs were not to be continued at the current levels.

## 2.0 Introduction

### 2.1 Background

Broader use of the concept of risk reduction in EPA's planning of research and regulatory strategies was recommended to the Agency by its Science Advisory Board in 1988, in the "Future Risk" report noted above. The recommendation was followed in 1989 by a request from the EPA Administrator, William K. Reilly, for SAB's technical assistance in developing strategic risk reduction options to aid the Agency in assessing its activities. In response, the SAB undertook to provide the requested assistance, forming the Relative Risk Reduction Strategies Committee (RRRSC) to expedite the process.

The SAB recognized at the outset that one of the first steps to be taken was a review of the 1987 report entitled "Unfinished Business: A Comparative Assessment of Environmental Problems" (UB) which summarized EPA's evaluation of the relative risks of the major environmental problems of concern to the Agency at the time. That evaluation had assessed the comparative risks of some 31 environmental problems (Table 2.1), judged in terms of:

- a) their risks of contributing to the occurrence of human cancer
- b) their risks of causing other adverse effects on human health
- c) their risks of causing damage to the ecosystem, and
- d) their risks of causing adverse effects to societal welfare

In light of these earlier assessments by the Agency, the SAB charged the RRRSC to:

- a) provide a critical review of the "Unfinished Business" report, taking into account any significant new information bearing on the evaluation of the risks associated with specific environmental problems
- b) provide, to the extent possible, merged evaluations of cancer and non-cancer risks (i.e., health risks) and of ecological and welfare risks (i.e., environmental risks)

- 1 - Criteria air pollutants
- 2 - Hazardous/toxic air pollutants
- 3 - Other air pollutants, e.g., flourides, total reduced sulfur
- 4 - Radon (indoor pollution only)
- 5 - Indoor air pollution (other than radon)
- 6 - Radiation (other than radon)
- 7 - Substances suspected of depleting stratospheric ozone layer
- 8 - Carbon dioxide and global warming
- 9 - Direct point-source discharges to surface waters (e.g., industry)
- 10 - Indirect point source discharges, e.g., POTWs
- 11 - Non-point source discharges to surface water plus in-place toxics in sediments
- 12 - Contaminated sludge (includes municipal and scrubber sludges)
- 13 - Discharges to estuaries, oceans, ect (all sources)
- 14 - Discharges to wetlands (all sources)
- 15 - Drinking water at the tap (includes chemicals, lead from pipe, biological contaminants, radiation, etc)
- 16 - Active hazardous waste sites (includes hazardous waste tanks, inputs to groundwater and other media)
- 17 - Inactive hazardous waste sites (includes Superfund, inputs to groundwater and other media)
- 18 - Municipal non-hazardous waste sites (inputs to groundwater & other media)
- 19 - Industrial non-hazardous waste sites
- 20 - Mining wastes, e.g., oil and gas extraction wastes
- 21 - Accidental releases of toxics (all media)
- 22 - Accidental oil spills
- 23 - Releases from storage tanks (includes product & petroleum tanks)
- 24 - Other groundwater contamination (septic tanks, road salt, injection wells)
- 25 - Pesticide residues on food eaten by humans or wildlife
- 26 - Application of pesticides (includes risk to pesticide workers and consumers who apply pesticides)
- 27 - Other pesticides risks
- 28 - New toxic chemicals
- 29 - Biotechnology
- 30 - Consumer product exposure
- 31 - Worker exposure to chemicals

**Table 2.1 Original EPA list of Environmental Problems considered in the 1987 "Unfinished Business" report (pages 10-11)**

- c) provide optional strategies for reducing major risks
- d) develop a long-term strategy for improving the methodology for assessing and ranking risks to human health and the

environment and for assessing the alternative strategies to reduce the risks.

In order to facilitate the accomplishment of these tasks, the SAB formed three Subcommittees of the RRRSC: the Ecology and Welfare Subcommittee, the Human Health Subcommittee, and the Strategic Options Subcommittee. The report of Human Health Subcommittee follows.

## **2.2 Charge to the Human Health Subcommittee**

The Human Health Subcommittee was charged with the following tasks: a) to provide a critical review of the "Unfinished Business" report in light of new information bearing on the evaluation of the risks to human health attributable to specific environmental problems; b) to provide, insofar as possible, updated and merged evaluations of the relative risks of cancer and the relative risks of other adverse effects on human health attributable to specific environmental problems; and c) to recommend approaches for the development of a long-term strategy to improve the methodology for assessing environmental risks to human health.

## **2.3 Format of this Report**

Section Three of this report reviews the kinds of information and analyses that must go into any assessment of environmental risks to human health. These include evaluation of the toxicity of the environmental agent(s) in question, as well as the degree(s) of human exposure to the agent(s). The next section appraises the extent to which the data and methodology in "Unfinished Business" were adequate for accomplishing the intended assessments. The following section considers approaches for developing a long-term strategy to improve the evaluation and ranking of environmental risks to human health, including the merging of cancer and non-cancer risk rankings. The final section, presenting the Subcommittee's conclusions and recommendations, is followed by appendices containing case studies to illustrate the difficulties inherent in environmental risk assessments as well as detailed discussions of suggested methods for ranking different risks.

### 3.0 Essential Elements in Assessment of Environmental Risks to Health

#### 3.1 Overview

The development of any risk assessment and risk ranking process requires specification of the criteria for ranking. The UB participants, especially when dealing with non-cancer health effects, struggled to impose order on a heterogeneous universe of exposure scenarios, agents, and endpoints. They adopted the tactic of focusing on a limited number of agents within each problem area, selecting those for which a reasonable amount of data were available. On the basis of estimates of the severity of health endpoints, the sizes of the exposed populations, and the potencies of the different agents (actually defined as a margin of safety), they assigned rankings to each of the 31 problem areas.

As a preliminary strategy, the effort was commendable because it clarified the difficulties posed by the absence of definitive information. In fact, much of the exercise had to proceed in the absence of sufficient information. Naturally, the first item in any strategy for improving risk predictions is the acquisition of adequate data.

#### 3.2 Assessment of Exposure

The "Unfinished Business" (UB) report addressed the fact that there was significant uncertainty in estimates of exposure, and hence risk. However, the discussion of potential exposure was limited.

In Appendix I, the report of the Cancer Work Group, it was noted (p. 16) that "Ranking environmental problems was complicated by a lack of information, uncertainties in estimating exposures, the diversity of methods used to assess different problems and to project national cancer incidence from smaller-scale studies, and differences in the degree of coverage of potential carcinogens." It also noted that "the quality of the human exposure for the 31 environmental problem areas varies greatly, making comparisons difficult." It was pointed out (p. 14) that "various methods of assessing exposure may also have biased comparisons of different problem areas. Not all analyses made exposure assumptions with the same degree of conservatism." These statements are persuasive in

suggesting caution in using their quantitative risk assessments, as well the relative ranking of categories as a basis for decision-making in environmental regulation, particularly since the potential limitations were emphasized in this fashion by the group performing the assessments.

### **3.2.1 Data Gaps and Uncertainties**

In assessing exposure the UB report was faced with the kinds of data gaps relative to exposure assessment that are not unique to its undertaking and which are frequently encountered in assessing risks to environmental contaminants. These include:

#### **3.2.1.1 Specific Chemicals**

For some categories there is insufficient information about the presence of specific chemicals due to the fact that the data base was either limited, established for other purposes or may not be recent. Thus, for example on p. 13 of Appendix I (Report of the Cancer Work Group) it was noted that for pesticide residues on food the Group "extrapolated from a few suspected carcinogens to the universe of potential carcinogens..." Another example is the omission of arsenic among the list of carcinogens in Problem Area 15, Drinking Water. It appears to have been omitted because it was not a member of the three categories of water constituents that were addressed. In the case of Problem Area 17, Hazardous Waste Sites-Inactive, it was noted that the data for the 12 chemicals for which the risks were estimated were based on 35 sample sites which were chosen to represent thousands of such sites. It is indeed understandable that in an undertaking of this magnitude omissions and limitations must necessarily occur. The question arises as to their impact on the estimated population risks and the relative ranking of categories.

#### **3.2.1.2 Concentrations**

For the UB report various methodologies were used to establish concentrations of chemicals. These included measurements from surveys, both large scale and small, as well as modeling, such as dispersion modeling applied in Problem Area 2, Hazardous/Toxic Air Pollutants. The calculated risks were in many cases based on skimpy concentration data. The sludge section (#12), for example, lists contaminants in sludge in Table A-1 and page B-70. However,

no information is given about the levels. Also, in Problem Area 17, Hazardous Waste Sites-Inactive, the number of best-guess cancer cases was extrapolated to an estimated potentially exposed population of 6.8 million, based on concentrations of 6 chemicals at 35 sites with an estimated exposure population of about 50,000. Aside from the uncertainties of extrapolating to such a large number of other sites, the question necessarily arises as to the validity of the concentrations reported as a basis for these exposure estimates. Often at hazardous waste sites the modeling of risk is based on a wide range of assumptions and often very limited data. Thus, it may not follow that the calculated exposures based on such limited data and the application of groundwater modeling are accurate even within orders of magnitude as expressions of the concentrations to which people are exposed in their water supplies.

The document itself points out (pages B-44) that the data on the occurrence of synthetic organic chemicals (SOCs) in drinking water are severely limited. However, since the document was developed, additional monitoring or survey data have become available and should be examined. These data include Superfund SARA Title III reports, the health assessments for inactive hazardous waste sites prepared by the Agency for Toxic Substances and Disease Registry (ATSDR), and monitoring data required for newly regulated constituents in public water supplies. The risk assessments should be updated to determine whether it would be consistent with the expanded database that is now available.

Frequently the calculations of lifetime risks are based only on the current concentrations and do not consider how these might change over decades of time. Estimates at a specific site are subject to great uncertainty. If extrapolations are to be made to estimate national risks, the uncertainties are necessarily much greater yet. Finally, it must be emphasized that exposure concentrations based on very few measurements or modeling are not likely to reflect accurately those to which a complete population is exposed. For example, at water supply treatment plants the concentrations may be substantially different than at various points in the distribution system. Or, in the case of lead, corrosion in the system can add substantially to its concentration. In the case of volatile organics (VOCs), their very volatile nature will affect exposures by both ingestion and inhalation. These factors that affect the concentration at the point of actual exposure are important in accurately determining risk.

### 3.2.1.3 Nature of Exposures

The contaminated media to which people are exposed are frequently assessed on the basis of only one mode of contact, e.g., ingestion for water, inhalation for air, skin contact for soil. The UB report does recognize that there may be multiple routes of exposure, as well as intermedia transport. However, it is not clear that these are sufficiently considered. For example, in the case of Problem Area #15, Drinking Water at the Tap, the report states (in Appendix I, p. B-44) that "if the chemical has been shown to be carcinogenic through inhalation and not ingestion, it will not be considered a potential carcinogen via drinking water."

This does not seem to recognize the inhalation exposures to volatile chemicals that regularly occur from indoor uses of water. At the same time, it does not appear that skin contact with such carcinogens from bathing with contaminated water were considered as well.

Recent exposure estimates suggest that the ingestion pathway may be of much greater importance than that for inhalation for persistent chemicals, such as lead and the polychlorinated dibenzodioxins and furans. These chemicals can be taken up or deposited on plant or forage crops which in turn can be eaten by people or food-producing animals. These same chemicals are deposited in rivers and lakes, or are transported to water bodies by surface water run-off; they can accumulate in fish consumed by people. A recent EPA report estimates that these ingestion exposures are likely to be greater than those via inhalation of emissions from municipal solid waste incinerators. Thus these integrated postdeposition routes of exposure may be important in assessing exposure and risk from originating sources that release substances into the air, but impact upon land and surface waters.

### 3.2.1.4 Ranges and Variabilities of Exposure

The UB document doesn't provide sufficient perspective of the range of exposures that can occur within a given problem area, or how the exposure may vary over time. On page 17 of the overview the document states that descriptions of aggregate populations and individual risk were of interest. The differences that were considered appear to be limited to differences in exposure between groups, such as pesticide applicators and their exposures, in

comparison to pesticide exposures of the general population from food or in their homes.

Some of the smaller public water supplies or private wells may be highly contaminated from waste sites and other sources, especially those that are usually not tested for unusual or esoteric contaminants. Some private water supplies have been found to be contaminated with organic chemical concentrations greater than 10 ppm, and some public supplies greater than 1 ppm. Whether or how such unusually high exposures were considered is not clear.

There are a number of individual behavioral factors that can affect exposure. They include the frequency and use of materials containing contaminants, the behavior that causes release of contaminants, and the time-location patterns of individuals. For the most part these do not appear to have been addressed in the UB report. There is a brief discussion (p. 14, Appendix I) that refers to mitigating behavior. This is described as the extent to which people reduce their exposure when they know that they are at risk. As an example, it is mentioned that "people may stop drinking water that tastes bad or is known to be polluted." Such mitigating behavior was not, however, specifically evaluated with respect to its effect on exposure. However, this is indeed a difficult area to assess. More importantly, the frequency and locations where people spend their time will necessarily have a substantial impact on assessing inhalation exposures to air pollutants. National and regional studies in this regard are now being undertaken and will provide a valuable data-base on the range and distribution of individual behavior patterns of peoples' uses of time indoors and outdoors, with specific reference to the impact on exposure to air pollutants. Data on the variability of the ingestion of water have been developed that indicate that standard reference intakes of 2-liters per day for a 70 Kg adult needs to be reassessed when estimating the exposures to waterborne pollutants. The ingestion pattern is quite variable. Average consumption of tapwater by children is estimated to be higher than for adults on a body-weight basis (1 liter per 10 Kg--NAS, 1986). In addition, while for many adults the average consumption of tapwater may be less than 2 liters per day, the results of a recent survey showed that 5% of adults 20-64 years old have an average daily water consumption of tapwater of 2.71 liters per day, and an average total water intake of 3.79 liters per day (Ershow and Cantor, 1986). There is a large variability around the mean. Whether this

is important in relation to the probably considerably greater uncertainty in dose-response relationships, however, is a separate question. Finally the uses of water, other than for ingestion, which lead to human exposures are also highly variable. Bathing and showering lead to inhalation and dermal exposures, and other indoor-water uses release volatile chemicals, causing inhalation exposures to all the inhabitants of the building. Thus the interaction of the behavior causing the releases, and the time spent within the various rooms of the building all influence the final determination of indoor-inhalation exposure.

#### **3.2.1.5 Exposure to Complex Mixtures**

Many of the problem areas involve exposure to complex mixtures, or the selection of an indicator chemical as a surrogate for a mixture. In many situations the specific mixture of chemicals to which people are exposed is characterized to only a limited extent. In these situations very few data may be available to assess adequately assess the risks. However, new exposure surveys could be used to identify additional chemicals of concern.

#### **3.2.2 Summary and Recommendations**

It is clear that there are a variety of factors that have not been, and probably could not readily be, determined in establishing exposure for the purpose of assessing risk in the framework of the UB report. The question arises as to the extent to which these deficiencies bias or invalidate the quantitative impacts that were calculated and, hence, the relative rankings of risk for the various problem areas. Although it may be difficult to improve the precision of the calculations of quantitative risk for each of these areas by considering in detail the deficiencies in the various exposure factors cited above, it would be useful to attempt to include their variabilities where they are known, and in any case estimate their uncertainties. Thus, for example, in the case of drinking water the range of ingestion factors and the possible impacts of inhalation and dermal exposure should be considered, since information is available in these areas. With respect to uncertainties in exposure, there should be at least a semi-quantitative assessment or judgement of the impact on the risk calculations. Where these uncertainties are very great, i.e., orders of magnitudes, as they are likely to be in some cases, a

good understanding of their effects is essential in ordering and prioritizing the problem areas.

### 3.3 Assessment of Toxicity

#### 3.3.1 Hazard Identification

The first step in risk assessment is the identification of a hazard, i.e., potential risk). This involves detailing the inherent toxicity (including carcinogenicity) of the substance or agent in question regardless of the actual level of exposure. Specifically, hazard identification is aimed at determining whether exposure to an agent can cause an adverse health effect (National Research Council/National Academy of Sciences, 1983). Evidence of inherent toxicity conventionally includes data on structure-activity relationships to known toxicants, in vitro or whole-animal short-term tests, chronic or long-term animal bioassays, human biomonitoring data, clinical studies, and epidemiology. A complete hazard identification process entails review of available information in these six categories in order to determine whether the next step--quantitative risk assessment--is warranted. The National Academy of Sciences has estimated that there are at least 25 components--of both a scientific and policy nature--in complete hazard identification (ibid).

By contrast, the Unfinished Business report was based on a foreshortened and largely undefined hazard identification process. Instead of carrying out complete hazard identification reviews according to clearly stated criteria, the working group relied largely on preexisting listings of candidate chemicals. Although these lists appear to have been driven by the non-availability of positive human and/or laboratory animal testing data, the criteria for hazard identification were never explicitly stated in the document. In any future attempt to rank risks of environmental toxicants, the hazard identification criteria should be explicitly stated. In line with the goal of disease prevention, they should include evidence of preclinical or subclinical effects of pollutants.

This lack of a consistent approach in selecting hazards is a serious limitation of the document. Yet it is easily understandable given the dearth of available toxicologic data on new and existing chemicals. The NAS has estimated that no toxicity data

are available for approximately 80% of the 48,000 chemicals in commerce (National Research Council, Toxicity Testing, National Academy Press, 1984).

This "Achilles heel" in hazard identification is no less evident when new chemicals are considered. Here, information on toxicity is woefully deficient. As stated in the Unfinished Business report, the Toxic Substances Control Act (TSCA) requires that industry submit to EPA data related to the health effects of new substance prior to its manufacture or importation. The data are claimed to be confidential by the submitters in the great majority of cases, however, so the premanufacturing notification (PMN) process allows EPA (but not the public) to identify potential risks presented by specific new chemicals (App. I, 8-63). EPA's own review of ten years experience with the PMN process under the TSCA indicates that only 60% of the new chemicals have any toxicological data (Auer, et al., 1988). The Subcommittee views the development of an adequate toxicological data base on existing and new chemicals as a priority--and a prerequisite--to any attempts to quantify comparative risks more precisely.

A third major weakness of the Report, flowing from the first, was the frequent reliance on a few selected surrogate contaminants to represent large categories of pollutants. For example, the Cancer Risk work group selected 4 agents--formaldehyde, methylene chloride, paradichlorobenzene, and asbestos as representative of the vast category of consumer product exposures. For non-cancer effects the Work Group relied on 3 pesticides to illustrate "pesticide residues on food," despite their acknowledgement that perhaps 160 pesticides may constitute potential risks. Similarly, only 6 of the hundreds or thousands of chemicals of concern in indoor air were evaluated (App. II, p. 2-I).

In summary, the present Subcommittee makes the following recommendations:

- a) The agency should develop and apply consistent criteria for hazard selection, since this process is the critical first step in risk assessment and determines the validity of the final product.
- b) Subclinical and preclinical adverse effects of pollutants should be included as endpoints of concern.

- c) EPA must make a concerted effort to improve its toxicological data base on both new and existing chemicals.
- d) EPA should expand its assessments of substances/agents within selected "problem categories" to encompass truly representative samples.

### 3.3.2 Dose-effect Characterization

A fundamental and basic tenet in toxicology is the existence of a dose-response relationship. To quote Paracelsus: "All substances are poison; there is none which is not a poison. The right dose differentiates a poison and a remedy." Dose-response data have, therefore, long been considered to be the cornerstone of risk assessment.

More recently, consideration of the dose-response relationship has become complicated by the recognition of at least two alternative dose-response models, defined in operational terms: the threshold dose-response model and the non-threshold dose-response model. All carcinogens are now assumed to be biologically active even at the lowest doses, without thresholds; thus there is no "right" dose at which they are considered harmless. On the other hand, for many effects other than cancer, dose-response relationships are known or presumed to have thresholds, with the result that the causative agents are considered to be ineffectual at sufficiently low doses. This dichotomy was reflected in the risk assessments presented in the UB report.

It should be emphasized that a conceptual problem with thresholds is the difficulty of identifying "safe" levels for a diverse human population expected to have significant inter-individual variations in biological response to toxicants. In the case of lead, neurodevelopmental effects are being observed at increasingly low levels of exposure. Recently, an extrapolation or a combined extrapolation/safety factor approach has been suggested for non-carcinogens such as reproductive or developmental toxicants (Gaylor and Kodell, 1980; Gaylor, 1989).

Another difficulty lies with our concepts of "threshold." Actually, we can envision that, for any given chemical, we might have to deal with several thresholds. One threshold can be defined by our present capabilities to detect the presence of a given

chemical. Progress in analytical techniques made over the last several decades has pushed this threshold to lower and lower levels, as documented several years ago in "The Case of The Vanishing Zero," (Zweig, 1970). Another threshold may be defined by limitations of our analytical capabilities with regard to access to materials to be analyzed. For example, many analytical procedures allow quantification of foreign compounds in easily accessible compartments such as body fluids. The same procedures are of much less, if any practical value to detect the same chemical in critical internal targets such as the brain or the kidneys without interfering seriously with normal organ structure and function. A third category of defining a threshold is time-dependent. Today's lesion often heals or is gone away tomorrow. On the other hand, a recent follow-up study has indicated long-term neurobehavioral effects from low-level exposures to lead (Needleman et al., 1990). There are many biological processes involved in repair and regeneration and reversibility vs. irreversibility is an important, but not sufficiently studied problem and must be considered whenever there is discussion of thresholds. There are, also, individual vs. population thresholds as well as "threshold-like" behavior. Finally, there is no clear-cut and generally accepted definition of what constitutes an untoward or "adverse" health effect. The only method for adequately judging if a threshold exists is an understanding of mechanism and of the biological system being affected.

If difficulties arise in the interpretation of dose-response data for risk assessment, the lack of sufficient data for precisely characterizing dose is often a limiting factor. Another problem may arise in linking dose to response and arriving at a judgement as to what the response means. Recent developments in the science and technology of "biomarkers" illustrate conceptual and practical problems in the Paracelsian approach to risk assessment. In lead poisoning, for example, biomarkers provide good evidence of exposure, and it is possible to link such specific biomarkers with some of the more florid manifestations of lead poisoning. Some years ago, a "threshold" could be defined, but more recent studies suggest that a "sub-threshold" dose for one untoward effect by no means constitutes a "sub-threshold" dose for another, potentially more deleterious effect (e.g., consequences of acute vs. chronic exposure; early vs. late signs of poisoning). Similarly, a blood alcohol level above a certain limit is predictive of impaired motor and sensory function, but of little value in

predicting chronic nervous system impairment or cirrhosis of the liver, to say nothing of fetal alcohol syndrome.

In view of present limitations in our ability to interpret and integrate dose-effect relationships in the low-dose domain, it is necessary to rely on informed assumptions for the purpose of risk assessment. There are several alternatives. One may adopt a conservative stance (i.e., to err on the side of being safe and to assume that any amount of a toxicant can increase the risk of disease in some individuals) or one can assume a human population threshold. The former assumption is justified by the observation of significant interindividual variability in response to toxicants, including carcinogens (Marquis and Siek, 1988; Harris, 1985; Perera et al., in press).

A few of the general problems that were inherent in the risk assessments contained in the UB report may be addressed as follows.

#### 3.3.2.1 Defining the Dose

The dose of a chemical is often defined as the amount of the substance that is administered under specific conditions; however a problem in defining the dose arises when the amount of the chemical is not known precisely as is the case with most environmental agents. In this situation, the dose is often related to, or equated with, the extent of exposure. For example, the concentration of a given chemical in air, water or food is equated roughly with the "dose". Epidemiological studies often implicitly rely heavily on this type of operational definition of dose, although there is always uncertainty about the extent to which exposure conditions (or concentrations) result in a given quantity of a chemical actually entering the body.

A second problem concerns estimation of the precise relationship between intake of a given amount of a chemical and the resultant effective dose. Every chemical entering the body is subject to the process of uptake, metabolism and elimination. Many chemicals are rapidly inactivated and eliminated, while others may accumulate or be activated. Dose depends thus not only on exposure conditions, but also on the interplay between intrinsic properties of the chemical and the capability of the organism to deal with the agent.

The third problem can be defined as "target dose" vs. "body dose." Many chemicals have no untoward effects unless they reach a critical biological target, i.e. the site where they can cause harm, in sufficient concentration to do so. Whether a chemical reaches its target or not is subject to many variables, such as route of exposure, toxicokinetic parameters and the capability of the exposed organ, tissue, or cell to deal with the agent. Ideally, the target dose should be known for a rational assessment of risk; however, in practically all instances this information remains unavailable for humans with the result that human risk assessment is correspondingly imprecise. Exposure "dose" is thus usually the best surrogate now available. Acceptable approaches for extrapolating from exposure conditions to "dose", be it total body dose or critical target site dose, may be developed through mathematical modeling based on appropriately designed laboratory experiments with animals. New developments with "biomarkers" applicable directly to human populations promise to yield additional approaches.

#### 3.3.2.2 Defining the Response

Response, or "endpoint," can be difficult to assess or to define. While certain endpoints, such as death, acute tissue injury, and cancer, are easily recognized, other responses may be much more difficult to detect or evaluate. During recent years, progress has been made in identifying so-called biomarkers of effect. The conceptual approach and techniques used, coupled with an understanding of the underlying biology (e.g., detection of DNA adducts) holds great promise for refining our analytical capabilities. The difficulty lies in answering the question: "What is truly a valid indication of an untoward health effect?" For neoplasia, any indication that an exposure may cause benign or malignant neoplasms is an unacceptable response. It is even more difficult to deal with non-cancer responses, that may include the more than 90 specific non-cancer health endpoints in the UB report. Some effort was made to classify these endpoints into various categories, from those of lesser concern to those that are severe, but the classification lacks logic and consistency. Some of the listed endpoints are true disease entities (e.g. pneumonia, herpes, increased heart attacks, mortality). Some are only signs of disease (e.g., angina, irritability, jaundice) or symptoms (e.g., headaches, learning disabilities). Still others are clinical or subclinical findings (e.g., decreased heme production, transient

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impairment might follow from a single episode of insecticide exposure, or exposure to high levels of a volatile solvent with anesthetic properties. It is not possible to judge the validity of the UB conclusions without a description of which exposure-effect scenarios were envisaged.

At present, defining health effects depends on recognizing deviations from normal structure and function, an approach that is driven by our analytical and diagnostic capabilities. Although we still lack an adequate understanding of the health significance of certain signs and symptoms, we must acknowledge that in the interest of disease prevention, validated early indices of risk such as chromosomal aberrations, gene mutations, certain enzyme alterations, reduction of lung function, and other preclinical indicators should be evaluated as elements in the spectrum of health endpoints of possible concern.

### **3.3.2.3 Defining Dose-response Relationships**

It must be remembered that any "response" defined and assessed in a dose-response analysis, represents the mean value of a set of responses that often follow a log-normal distribution in the exposed population. Within a large population there may exist families (defined by host characteristics) of dose-response curves, that are shifted to the right or left of the "ideal" curve and that have different slopes. The consequence of this phenomenon would be the inability to identify a "population threshold."

It may be concluded from the foregoing that ideal dose-response data for a toxicant should meet at least the following criteria: 1) the response should be a quantifiable endpoint and should be known to represent, in a health framework, an interpretable observation; its implications should be well enough understood for the making of meaningful predictions with reasonable accuracy; 2) it should be known to what extent the response depends on total (integrated) dose, single dose or multiple doses, and on the dose-rate; 3) qualitative information on the target site of action of the toxicant must be known, e.g. what organ, organ system, tissue, cell, or cellular mechanism is affected; 4) quantitative relationships between the amount of chemical at, and its effect on, the target must be known, both with regard to exposure conditions and with regard to the target/tissue dose; 5) because there are different exposure scenarios for different

toxicants, the interrelationships and correlations between different scenarios must be known well enough to allow extrapolation from one scenario to another; and 6) it should be known whether the response may be modified, or be subject to modification in subgroups of the population at risk, whether or not it is reversible, and whether it may be modified by other agents or by other biological circumstances (e.g. concomitant disease).

Although, in general, the above information is available on the acute effects of many chemicals, including drugs, pesticides, certain metals, inhalants (such as CO), and other agents of environmental concern, much less information is available on the chronic toxicity of such agents. Evaluation of chronic dose-response relationships entails additional problems as well, some of which are discussed briefly in the following.

Chronic dose-response data have usually been obtained, construed, or evaluated on the assumption that the relevant exposure has occurred continuously at a more or less constant level, and that the resulting effect has been cumulative and irreversible. Most animal studies dealing with chronic toxicity have been designed this way, and in the assessment of chronic effects in humans, the dose is usually estimated from exposure conditions and integrated over the presumed exposure time. Exceptions however, include studies providing the basis for some of the ambient air quality standards (e.g., ozone) where human dose-response data derived from acute exposures have been used to estimate the dose-response relationship and, more importantly, the no-effect level for chronic exposure (Lippmann, 1989). While this approach has its uses, one must not forget that it ignores the possible influence of the duration of exposure. Thus, estimation of chronic dose-response relationships is extremely complex for many reasons, not the least of which the influence of time.

There is a substantial body of knowledge on the pathogenesis, evolution and eventual outcome of chronic diseases in man. Cases in point include chronic obstructive lung disease, ischemic heart disease, certain degenerative lesions of the central and peripheral nervous systems, infectious diseases and the natural history of many cancers. Understanding of the relationship of exposure to environmental agents and causation of disease is fragmentary, however. Even for experimental animals, there is a comparative paucity of descriptive, let alone mechanistic, information on many

of the relevant disease entities. This is paralleled by the limited database on the toxicokinetics of most chemicals under conditions of chronic, low-level exposure. Few if any chronic studies address questions such as recovery of tissue damage or cellular repair mechanisms or the effects of intermittent-versus-continuous exposure conditions, factors that may well be critical determinants in inducing chronic disease states. In animal models generally, and in toxicology in particular, chronic disease is not thoroughly studied. Cancer may be the exception, at least in the pre-oncogene area.

Few experimental studies address the question of what happens once exposure to a given chemical ceases. Yet we know from the epidemiology of cigarette smoking that cessation of exposure may dramatically alter the risk of developing what might be an otherwise unavoidable outcome. Furthermore, chronic dose-effect estimates often fail to consider the importance of dose rate. It is generally assumed that chronic effects are proportional to the cumulative dose integrated over time. It is conceivable, however, that the rate at which exposure to a chemical occurs is more important in determining effects than is total cumulative dose. In low level ionizing radiation studies, dose-rate is an important determinant of the induced effects (Upton, 1984). It may become equally important to consider the role of dose-rate in assessing risk from exposure to such environmental agents as, for example, the criteria air pollutants.

Estimations of chronic dose-response relationships are usually based on the assumption that the toxicants in question act alone. Yet a given chemical may cause no untoward effects unless a second insult is superimposed. Most human exposures involve complex mixtures, but there are few data on the nature and magnitude of toxicological interactions between individual components (Waters et al., in press; Vainio et al., in press). Epidemiologic data on interactions which may modify risk estimates for cancer are limited to smoking in conjunction with asbestos, radon, and nickel (respectively). Animal experiments have shown significant interactions (e.g., between carbon tetrachloride and certain alcohols and between cancer initiating and promoting agents). However, the database here is limited as well. Thus, although the NOEL's or AID's for the latter usually include a safety factor of 100 or 1000, it is not known whether the effect of interactions, in combination with the many other variables theoretically "covered"

by safety factors, will exceed those margins of safety. On the other hand, some of the National Ambient Air Quality standards, such as those for ozone, have little or no margin of safety (CASAC, 1989, Lippmann, 1989) and modest degrees of interaction may be very important.

While efforts to estimate cumulative exposure through the measurement of biomarkers constitute a promising approach, major uncertainties in their utility continue to exist. Ideally, measurement of a biomarker of exposure dose or effect should provide an index of total exposure over a period of time. In pharmacokinetic studies, by comparison, it is not possible to estimate total exposure from one single measurement. Whether this will become possible with biomarkers remains an open question. Two major problems to be resolved concern the biological half-life of each biomarker (there is little information on the relevant repair and recovery mechanisms) and the extent to which a given biomarker is predictive of a subsequent biological effect.

#### 3.3.2.4 Summary

Some of the problems involved in the interpretation of dose-effect or relationship in risk assessment can be summarized as follows:

a) Cancer Although the database on dose-response relationships for carcinogens that has been obtained from both animal and human studies is comparatively strong, there is considerable uncertainty on how to extrapolate from high doses to low doses and from animals to humans. Currently accepted opinion recommends that a non-threshold model be used for assessing the carcinogenic risk that any chemical or physical agent may pose to the general population, but the validity of this model remains to be determined, as does the particular form of the model and species scaling factor that may be appropriate for a given form of cancer and for a given carcinogen (Upton, 1989). At intermediate-to-high dose levels, effects on cell proliferation kinetics may "promote" or otherwise enhance carcinogenesis in ways that do not occur at lower dose levels, thus complicating extrapolation to the low-dose domain. Unfortunately, it may never be possible to prove the absence or existence of thresholds as demonstrated by the so-called "ED<sub>01</sub>" study involving more than 20,000 rodents which was unable to confirm the shape of the low dose-response curve below a one

percent tumor incidence (Littlefield et al., 1979). In short, the scientific community is divided in its views of the feasibility of quantitative risk estimation for cancer, owing to the uncertainties involved.

b) Non-cancer The database for non-carcinogenic effects is extensive for acute exposures but much less extensive for chronic exposures. No conceptual problem precludes recognition and/or assumption of experimental thresholds for many such effects; however, as discussed above, major gaps in knowledge exist, concerning population thresholds. As far as animal studies are concerned, few chronic studies have been designed to deal with endpoints other than cancer. Also, there is a paucity of chronic toxicity data on the reversibility of the reaction process and on the importance of the dose rate in relation to the total cumulative dose. Human studies have been useful in detecting and confirming some types of health hazards, but the observations are often difficult to interpret because of scanty information concerning over-all dose, tissue dose, dose rate, existence of multiple endpoints, exposure, to additional chemical or physical agents, preexisting disease conditions, and other variables which contribute to interindividual variations. Given the existing gaps in our knowledge, caution should be exercised in qualitative and quantitative risk estimates.

Finally, consideration must also be given to the question as to how risks for non-cancer health effects are best elucidated. A possible strategy has been suggested by Doll and Peto (1981) for cancer. In their landmark paper, these authors discussed two possible strategies to explore the etiology (and, hence, risk) of cancer: the "mechanistic" strategy, that investigates the biology of cancer in order to make predictions, and the "black box" strategy that identifies the cancers that occur in the population and then looks for epidemiological clues as to their etiology. In the view of the authors, the "black box" approach was considered to be more likely to yield important clues quickly. It might be appropriate, therefore, to conduct a similar analysis of "environmentally caused," non-cancerous diseases, although the vital statistics for such diseases are relatively incomplete in comparison with those for cancer. Moreover, Doll and Peto themselves acknowledge the uncertainty in their "guesstimates" of the percent of human cancer attributable to various sources. In the absence of more complete information, the contribution of environmental

toxicants to the total burden of illness in the population will remain highly uncertain, as will the corresponding risk assessments, such as those presented in the UB report.

### 3.3.3 Assessment of Severity of Impact

#### 3.3.3.1 Introduction

The 1987 UB report, addressed four major types of risks: cancer risks, non-cancer health risks, ecological effects, and welfare effects. The report provided only a brief rationale for these categories; the four types of health and environmental risks were considered to be "major" and to be risks that were in existence at the time the report was prepared. No attempt was made to rank these four types of risk qualitatively or quantitatively against each other.

The cancer risk considered by the Cancer Risk Work Group was apparently overt malignancy and not intermediate indicators of carcinogenesis, such as dysplasia or metaplasia of epithelial membranes. The coverage of the Non-Cancer Risk Work Group was broad and included eleven types of effects: cardiovascular, developmental, hematopoietic, immunological, kidney, liver, mutagenic, neurotoxic/behavioral, reproductive, respiratory, and "other." The effects addressed by this group were heterogeneous, including indicators of exposure (e.g. mutagenicity), indicators of injury (e.g. lung injury), and the presence of frank disease and even death. Through the application of a ranking of organs with regard to importance to life and of the severity of the endpoints, an attempt was made to provide an overall ordinal grouping of the endpoints. The Welfare Risk Work Group also addressed a variety of effects, including aesthetic values.

In considering the approach used to develop the 1987 UB report, the overall choice of the four major risk categories noted earlier remains appropriate as does the decision to avoid a comparative ranking of the four types of risk. A process for establishing the ranking has not been developed, and appropriate criteria would not be wholly scientific or medical but would incorporate prevailing social values. For the health risks, placement of cancer and non-cancer risks within a single framework appears theoretically feasible, using indices of severity common to all diseases, such as extent of interference with function or

probability of mortality, as indices for comparison. However, one must question such functional and clinical criteria as not covering the full spectrum of adverse effects (i.e., excluding subtle pre-clinical manifestations of disease occurring at earlier time-points along the continuum between exposure to toxic substances and clinical diseases). As mechanistic information becomes available, it is likely that earlier occurring molecular or biochemical changes (such as alterations in oncogenes or enzyme inhibition in neurologic disease), will supplant conventional endpoints, allowing a preventive approach in priority-setting. Therefore, "interference with function" should be broadly defined to include biochemical or molecular alterations established as indicative of the disease process. This section considers measures of the impact of environmental risks on individuals and on populations.

### **3.3.3.2 Impacts on Individuals**

The effects of environmental pollutants on individuals may be assessed on distinct axes that measure effects such as comfort, functional status, and exposure status. While these axes overlap to an extent (e.g., the presence of disease necessarily signals the presence of a disease process), they offer a multidimensional framework for considering the impact of pollutants.

The relative risk of disease--that is, the rate of occurrence of disease in exposed persons, as compared with that in non-exposed persons--is the most widely applied measure of impact on individuals. The risk associated with exposure may also be expressed as the cumulative lifetime probability of disease, and contrasted with the lifetime risk in the absence of exposure. For individuals, the strength of the exposure-disease association is measured by the divergence of the relative risk from the no-effect value of unity. Small increments of risk, perhaps a few percent to about 20 percent, are not detectable in epidemiological studies because of statistical uncertainty. Thus, epidemiological data have generally provided direct evidence for adverse effects at increments of relative risk of about 50 percent or more. The consequences of exposures associated with lower levels of relative risk are often estimated by extrapolation. In considering the risks for specific individuals, factors determining susceptibility must be addressed, as specific host characteristics or exposure to other agents may have significant interactions with the exposure of interest from the biological and public health perspectives.

The occurrence of disease, or even death, in association with exposure to an environmental pollutant provides an unarguable indication of effect. On the other hand, a pathophysiological process may be detectable, even though overt disease is not present. For example, lung function decline over time in excess of the usual loss associated with aging might be detected in an individual who has no evidence of overt lung disease. Similarly, bronchoalveolar lavage may show an inflammatory response in asymptomatic subjects exposed to an inhaled pollutant (National Research Council, 1989).

Biological markers of exposure dose and effect represent another approach for characterizing the effects of pollutants on individuals (National Research Council 1989). Markers of exposure indicate only that an agent has entered a physiological compartment and their detection does not signal the presence of disease or necessarily of injury. Some markers have sufficient sensitivity and specificity to identify exposed persons with a high degree of certainty. For example, cotinine, the major metabolite of nicotine, can be readily measured in blood, saliva, and urine. High levels are produced by active cigarette smoking, whereas low levels may result from involuntary exposure to tobacco smoke; nonsmokers without any involuntary exposure to environmental tobacco smoke do not have detectable levels of cotinine in body fluids. A particular level of cotinine does not imply that a smoking-related disease has occurred or will occur. By contrast, a certain level of blood lead not only is indicative of exposure but likely predictive of disease.

Functional status provides an overall measure of the impact of exposure; the potential dimension of effect spans from minimal interference with performing one's job and activities of daily living to severity disability and death. Effects on well-being have become an increasingly prominent concern of the public. The range of impacts is broad, potentially including concern over aesthetic degradation of the environment, changes in behavior, and fear over the potential consequences of real or perceived exposure.

For any of these dimensions, the distinction between "adverse" and "non-adverse" effects needs to be made. The judgment concerning adversity incorporates not only medical criteria, but the predominant societal values at the time the decision is made. Thus, judgments as to the adversity of effects should not be regarded as

fixed, but as subject to change with social, political, and economic conditions.

For atmospheric pollutants, the language of the Clean Air Act forces consideration of the nature of an adverse effect health. For the criteria pollutants, the Administrator of the Environmental Protection Agency must set national primary ambient air quality standards that will protect the public health with "an adequate margin of safety." Section 112 of the 1977 Amendments requires the Administrator to regulate "hazardous air pollutants," those not covered by the primary standards but "... which may reasonably be anticipated to result in an increase in mortality or an increase in serious irreversible, or incapacitating reversible illness." The Clean Air Act does not explicitly define adverse effects on public health and welfare.

This ambiguity in the Clean Air Act has prompted both individuals and organizations to consider criteria for determining adverse health effects (Ferris 1978; Higgins 1983; American Thoracic Society 1985). Ferris (1978) noted the judgmental nature of this determination and the difficulty of achieving consensus for many effects. Higgins (1983) defined an adverse health effect as "... a biological change that reduces the level of well being or functional capacity." The report of an American Thoracic Society committee (1985) on adverse respiratory health effects turned to "medical significance" as the criterion for determining the adversity of an effect. The committee provided a hierarchical listing of potential respiratory effects without making a specific demarcation between adverse and non-adverse; the range of effects was from increased mortality to odors.

The issue of separating adverse from non-adverse health effects remains topical and arises throughout this report. The development of increasingly sensitive markers of exposure dose, preclinical effect and injury can result in the identification of potential effects of uncertain biological significance. The efforts of the American Thoracic Society and others to develop methodologies for establishing the adversity of health effects need to be continued. With a goal of prevention, there is a strong rationale for using the most sensitive indicators of early response that can be identified.

Epidemiological study designs are the principal approach used to directly characterize the effects of environmental pollutants on individuals (National Research Council 1985). For environmental pollutants, the most widely used designs are the descriptive study or survey, the case-control study, and the cohort study. While epidemiological studies have the advantage of directly examining disease risks in human populations, epidemiology has potential limitations that may constrain the interpretation of epidemiological data on environmental pollutants. Exposures of individuals to pollutants may be difficult to accurately measure; the resulting misclassification of the exposures of individuals may bias the results of studies towards not finding associations between exposure and disease. Moreover, many of the acute and chronic diseases of concern with regard to exposure to environmental pollutants are multifactorial in etiology. To accurately describe the effects of pollutant exposure, it is necessary to carefully measure and control for the effects of the other factors, e.g. cigarette smoking, and to consider interactions of the pollutant of interest with other factors.

This section considers the effects of environmental pollutants on individuals; it proposes dimensions along which these effects can be gauged as a basis for merging the diverse health endpoints along a single spectrum; and it considers the approach of the 1987 Unfinished Business report in this framework.

#### 3.3.3.2.1 Exposure Status

The continuing evolution of approaches for assessing exposure has led to increasing accuracy and sensitivity in the estimation of human exposures to environmental pollutants. Through the 1980s, estimates of exposure were often based on questionnaires, on measurements of pollution in large geographical regions, or on other surrogates for personal exposure. However, the development of new biological markers of exposure dose and effect, of personal exposure monitors for some pollutants, and of methods for characterizing the exposures of individuals in specific micro-environments has provided potentially more accurate measures that can be used to complement the older approaches (National Research Council 1989; Spengler and Soczek 1984; Wallace and Ott 1982).

The Non-Cancer Risk Work Group mingled mutagenicity, an indicator of exposure (or internal dose), with other health

endpoints in the 1987 report, but did not consider other exposure measures. More appropriately, markers of exposure should be handled independently from disease indicators. However, as discussed below, the consideration of risks for individuals and populations should be broadened to include markers of exposure.

### 3.3.3.2.2 Disease Status

Many of the endpoints considered by the Non-Cancer Risk Work Group were indicators of response to environmental pollutants, and not of overt disease that would produce symptoms or lead to a clinical diagnosis. For example, the list of endpoints included increased levels of liver enzymes, reduced corneal sensitivity, pulmonary irritation, nasal cellular irritation, and decreased midexpiratory flow rates. Many of the endpoints were histopathological abnormalities: tubular degeneration, hyperplasia, and hypertrophy of the kidney, histopathological alterations of the liver, and giant cell formation in the testes. While these endpoints provide clear indications of damage to target tissues, interpretation must be placed in the context of the relationship between each endpoint and the likelihood of developing disease. Measures of disease process should be handled separately from frank disease.

Indicators of disease status may be variably based on the presence of a clinical diagnosis, a specific physiological parameter (e.g., the diagnosis of anemia is based on reduction of the hematocrit, or another test. For some endpoints, the degree of diagnostic certainty is generally high, e.g. lung cancer or myocardial infarction, and the implications of the diagnosis for functional status and mortality are well characterized, e.g. Legionnaires' disease. The Non-Cancer Risk Work Group also addressed exacerbation of the status of persons with established disease, such as ischemic heart disease and asthma. Many of the endpoints considered by the Non-Cancer Risk Work Group were measures of effects that represented the final outcome of exposure, but were not disease states, e.g. low birth weight, oligospermia, and mucosal atrophy of the respiratory tract.

The heterogeneity of disease effects considered in the Unfinished Business Report was recognized by the Non-Cancer Risk Work Group. An attempt was made through the Toxicity Test Endpoint Severity Scores to rank the effects; an attempt was not made to

establish boundaries between adverse and not adverse. This aspect of the report would have been strengthened by a sharper separation of the various types of endpoints with a clearer demarcation between the causation of disease, the exacerbation of disease, and other effects. Within the category of effects, however, it is important to view individual endpoints as occurring along a continuum and to select those representing early sensitive effects of environmental toxicants.

#### **3.3.3.2.3 Functional Status**

The Non-Cancer Risk Work Group included measures of functional status among the other endpoints: pulmonary impairment, retardation, and learning disabilities. Functional impairment is a consequence of disease and the degree of impairment might have more appropriately been linked to the causative disease. This aspect of the 1987 report merits reconsideration and expansion.

#### **3.3.3.2.4 Welfare Effects**

The range of welfare effects is wide and reflective of societal responses to environmental degradation by pollution. The potential links between welfare and health effects should not be dismissed; noticeable environmental changes resulting from pollution or even the perception of exposure to pollution could have adverse impact by forcing behavioral modification (e.g. forgoing activities out-of-doors), altering mood, or causing stress (Evans et al. 1988). The public's increasing expectations of living in a risk-free environment undoubtedly fosters the potential for welfare effects.

#### **3.3.3.2.5 Functional Effects**

The capability of performing one's work and leisure activities, as well as routine activities of daily living, integrates both behavioral and non-behavioral consequences of pollutant exposure. At the extreme of adverse effects, impairment or even death obviously impact functional status; at the other extreme, subtle psychological effects may interfere with performance of routine tasks with consequences such as reduced productivity and increased absenteeism. This dimension of pollutant effects was not addressed in the 1987 Unfinished Business Report.

### 3.3.3.3 Impacts on Populations

The risks for populations should be addressed separately from the risks for individuals, although the dimensions of effect considered above for individuals remain relevant to populations. For individuals, concern focuses on the likelihood of developing disease following exposure; the relative risk indicates the strength of association at the individual level. The population's burden of disease integrates the distribution of exposure, the inherent susceptibility of the population, and the level of risk associated with exposure. It provides a measure of impact complementary to individual measures, such as the relative risk. From the public health perspective, exposures associated with relative risks that are of acceptable magnitude to many individuals might yield unacceptable disease burdens for the population as a whole. Or, conversely, as in the case of benzene air emissions, there may be a small number of excess cancer cases nationwide accompanied by high individual risks.

Epidemiological data can be used to describe directly the population's burden of disease associated with an exposure. The population attributable risk estimates the proportion of disease in a population resulting from exposure (Rothman 1986); its calculation requires information on the distribution of exposure in the population and on the excess relative risk associated with exposure. Risk assessment techniques can also be used to project the burden of disease caused by an environmental pollutant (National Research Council, 1983).

The distinction between individual and population risks was explicitly recognized by the Cancer and Non-Cancer Risk Work Groups. Both emphasized the population perspective, an approach that seems appropriate in light of the Environmental Protection Agency's public health charge. However, agents placing a small number of susceptible persons at particularly high risk also merit emphasis.

### 3.3.3.4 Synthesis

The selection of endpoints to characterize the impact of environmental pollutants on individuals and on populations poses a panoply of difficult choices. Exposure-effect relations need to be postulated and measurement approaches devised to validly detect the

anticipated effects. Choices must also be made among the various dimensions along which effects can be measured. For regulatory and risk management purposes, it may be necessary to separate "adverse" from "non-adverse" health effects or to rank effects in terms of overall impact. It may also be necessary to make judgments concerning the relative impacts of pollutant exposures on individuals and on populations. How can risks incurred by individuals be balanced against the population's burden of disease? The overall disease burden in a population may be the same for a rare exposure associated with a high relative risk as for a prevalent exposure associated with a low relative risk. [A definition of the term "adverse" and judgments about severity of effects are not purely scientific issues but involve consideration of social and ethical factors as well as public perception.]

Many of these issues were directly confronted in the Unfinished Business Report. The Work Groups left unsolved the difficult problem of grouping the various endpoints into a common framework. As discussed elsewhere in this report, this committee considers that this challenging task must be addressed. Potential scales for qualitatively ranking the various endpoints include the probability of developing disease (for exposure status or disease process), the degree of associated impairment (for disease status and welfare effects), and the probability of death (for exposure status or disease status). Ideally, these should be calculated for both the general population and for the most sensitive subgroups.

### 3.3.4 Susceptible/Critical Subgroups

#### 3.3.4.1 Introduction

In principle, efforts to characterize comprehensively the risks of environmental hazards to human health should consider the potential effects of variations in susceptibility among individuals, an issue that was not addressed in the 1987 UB report.

If one could depict the response of the entire U.S. population to each potentially hazardous environmental exposure, there would be, for each, a distribution characterized by individuals at each extreme of susceptibility. Because this report addresses public health, it focuses on those individuals who are the most, rather than least, susceptible.

One explanation for the increased susceptibility of some individuals, of course, is the "random" variation in physiologic make-up that is inherent in all biological systems. "Random", in this sense, refers to a quality of unpredictability.

Some variations, however, are predictable. They may be associated with an identifiable physiologic perturbation (e.g. an enzyme deficiency), and/or they may fall along distinct sexual, racial, ethnic, or other lines. The consequences of such variations are that the susceptible individuals receive a greater burden of risk in a risk area.

In an era in which we, as a society, are striving for racial and sexual equality, as well as sensitivity to the needs of the elderly and disabled, the prospect of achieving equal protection for all calls for sensitive scrutiny. In effect, the EPA acknowledged the need to focus on special populations at risk when it designated a separate risk area for occupational diseases. This designation constituted acknowledgment of the disproportionate burden of risk placed on certain occupational groups because of higher exposures to many hazards. It follows logically that we should make a distinction for other groups that bear a disproportionate burden of risk because of an identifiable susceptibility or consistent pattern of unequal exposure, as in the case of inner-city residents and lead, or rural fish consumers downstream from paper mills.

#### 3.3.4.2 Types of Susceptibility Variations

We advance here the concept of biological susceptibility versus susceptibility due to social/behavioral factors.

##### 3.3.4.2.1 Biological Variations in Susceptibility

This can be defined as susceptibility because of host factors (endogenous factors) that heighten an individual's risk of toxicologic injury to a given environmental exposure. Examples:

(a) Pregnant women, the fetus, and the nursing infant:

- (1) The developing fetal and infant nervous system is extremely sensitive to the effects of lead, which

freely crosses the placental barrier and is secreted into breast milk.

- (2) Other exposures that have been associated with birth defects include mercury, and PCBs. Embryonal and fetal tissues are extremely sensitive to ionizing radiation, especially during critical stages of organogenesis.
- (3) A number of toxicants are actively or passively transferred from plasma to breast milk, including mercury, cadmium, DDT, PCBs, and related halogenated hydrocarbons.

(b) Race or Ethnicity Factors:

Light-skinned whites, particularly those who tan poorly, are at greater risk for UV-induced skin cancer (Silverstone et al., 1970).

- (c) Elderly: By virtue of their physiology, the elderly are more susceptible to factors that affect the immediate physical surroundings. The higher prevalence of chronic diseases experienced by the elderly also indirectly increases their risk to many of the hazards listed earlier.

(d) Children:

- (1) In general, children can be seen as being more susceptible to toxins that require an extended latency time in order to express their effects, such as carcinogens.
- (2) The developing systems of children are generally viewed as more vulnerable than those of adults, as illustrated by the exquisite sensitivity of children's nervous systems to the toxic effects of lead.

(e) Chronic disease or other medical conditions:

- (1) Asthmatics: a broad range of air pollutants adversely affect persons with asthma.

- (2) Coronary Heart Disease: individuals with pre-existing coronary heart disease have increased susceptibility to exposure to carbon monoxide and noise (increased stress leading to increase in blood pressure, heart rate, circulating catecholamine and lipids.
- (3) Chronic liver disease: decreased ability to detoxify and increased susceptibility to a number of toxins, including chlorinated hydrocarbons, halogenated aromatics, etc.
- (4) Malnutrition: a diet deficient in calcium, magnesium, iron, or protein leads to increased dietary lead absorption (Mahaffey, 1981)
- (5) G-6-PD deficiency: more prone to methemoglobine-mia  
(e.g. from nitrate-contaminated well water, food high in nitrates or nitrites)
- (6) Decreased delta aminolevulinic acid dehydrase enzyme activity (d-ALA polymorphism): more prone to toxic effects of lead
- (7) Alpha<sub>1</sub> antitrypsin deficiency: more prone to the pulmonary effects of tobacco smoke, and grain dust (Chan Yeung, 1978).
- (8) Decreased activity of N-acetyltransferase: increased susceptibility to environmental bladder carcinogenesis (Cartwright, 1982).

#### 3.3.4.2.2 Susceptibility Variations Due to Social or Behavioral Factors

For a given risk area, particular population sub-groups are at increased risk because of social/behavioral factors that disproportionately increase their exposure. "Occupational groups" can be considered a category within this framework.

Geographical factors are also extremely important with respect to many hazards, such as living in high altitude or equatorial

regions which increases UV radiation exposure from ozone depletion. These distinctions are, in most cases, self-evident. In addition, for many of the EPA-defined "Risk Areas", geographical considerations are implicit in the construction of the Risk Area. For instance, individuals living on the coast in an industrial area are obviously the most susceptible to "Direct discharges to surface water"; likewise, exposure to "hazardous air pollutants" follows well-defined geographical distributions. Therefore, geographical factors are not considered directly within this framework unless they are accompanied by other factors that help distinguish particular population sub-groups (e.g., see section (2) on race below).

#### Examples:

- (1) Lifestyle factors (particularly with respect to cancer):  
Alcohol Ingestion: alcohol has been shown to enhance the toxicity (primarily hepatotoxicity) of several halogenated hydrocarbons, including carbon tetrachloride, chloroform, and methylene chloride (Hills and Venable, 1982). A synergistic interaction between alcohol ingestion and inhaled vinyl chloride for the induction of angiosarcoma of the liver has been reported in rats (Radike, et al., 1977).

Cigarette Smoking: increases cancer risk from radon and asbestos exposure (see Appendix section 8.1.2). It may also increase cancer risk from arsenic exposure (Steenland and Thun, 1986). There is a suggestion that heavy urban air pollution can add to the risk for lung cancer in smokers (Jadrychowski, 1983).

Dietary habits: (excluding malnutrition--see section 3.3.4.2.1 (e) (4)) in epidemiologic studies, intake of specific nutrients has been associated with varying risks for cancer, e.g., intake of vegetables and fruits has been inversely related to the risk of lung cancer in many studies, perhaps through the protective effects of beta-carotene (Willett, 1990). Nutritional intake may also modify the human response to environmental carcinogens, but little data is yet available to evaluate this possibility.

Sun exposure habits: total sun exposure increases the risk of non-malignant skin tumors and cataracts. "Bursts" of sun exposure increases the risk of malignant melanoma.

(2) Socio-economic Factors:

- (a) Rural Hispanics are disproportionately exposed to pesticides due to their concentration in agricultural jobs, and residence in areas heavily exposed to pesticide spraying.
- (b) Due to their concentrated residence in urban areas with deteriorating, old housing stock, African Americans and Hispanics are disproportionately exposed to lead (from lead paint).
- (c) Some groups live in subsistence economies relying heavily on fish. They would be disproportionately susceptible to hazards involving discharge pollution of estuaries, coastal waters, oceans, wetlands, surface water, etc.

3.3.4.3 Identifying Susceptible Subgroups According to Hazard of EPA "Risk Area"

It is difficult to append sections on special susceptible populations to the existing structure that EPA chose for organizing this risk reduction exercise. Some of the EPA-defined "Risk Areas" are very broad, and have a considerable amount of overlap with regards to specific toxins. Other Risk Areas are poorly defined with respect to specific substances.

3.4 Treatment of Uncertainty

From the foregoing, it is apparent that the assessment of environmental risks to human health is complicated at virtually every step by potentially large uncertainties in: 1) numerical values of measurement or other quantities affecting the risks; 2) the modeling of exposure and/or toxic responses; 3) temporal, spatial, and inter-individual variations in susceptibility; and 4) the quantification and comparison of societal and personal measures of risk. To the extent that the utility of a risk assessment may be limited by any or all of these uncertainties, each should be addressed explicitly in the design, conduct, interpretation, and reporting of the assessment. The relevant problems, many of which

are discussed in other sections of this report, have been considered in further detail elsewhere (eg, Finkel, 1990; Zackhauser and Viscusi, 1990).

#### 3.4.1 Parameter Uncertainty

Uncertainty in the numerical values of quantities affecting risks may result from: 1) errors in measurement, owing to imprecision in instruments or human mistakes; 2) misclassification of data; 3) random or sampling error; and 4) systematic errors in data-gathering or analytical techniques. Each of these sources of uncertainty has its own causes, the remedies for which must be addressed specifically.

#### 3.4.2 Model Uncertainty

In modeling exposure patterns or response to toxicants, error may result from: 1) failure to measure or include the correct quantities (e.g., "surrogate" variables); 2) exclusion or faulty treatment of significant (e.g., confounding) variables; 3) use of a model that is not of the correct form or structure (a major controversy in environmental risk assessment has concerned the selection of the appropriate model for estimating the risks attributable to low-level exposure to carcinogens; predictions derived from different models may differ by many orders of magnitude) (Krewski and Van Ryzin, 1981).

#### 3.4.3 Uncertainty Due to Inter-individual Variability

As noted above, inter-individual variations in exposure patterns and in susceptibility may be due to age, sex, occupation, socio-economic status, dietary practices, smoking habits, lifestyles, and other influences. For most environmental toxicants, knowledge of the effects of these variables on human susceptibility, and to a lesser extent on exposure, is still limited. As a consequence, risk assessments applicable to human populations involve uncertain assumptions about the distribution of differences among individuals.

#### 3.4.4 Uncertainty in Quantifying and Comparing Measures of Risk

Because risks can be expressed in different ways, which determines how they are perceived, there is frequently uncertainty

in the choice of the appropriate measure of risk to use in comparing different risks. If, for example, years of life lost were considered as a relevant measure of risk, then a fatal effect in a young person might be given more weight than the same effect in an older person. Similarly, a  $10^{-4}$  lifetime risk of death would predict no attributable fatalities in a population of 1,000 persons, but 25,000 attributable fatalities in the U.S. population as a whole. When the comparison among risks involves different kinds of health effects--e.g., cancer vs. mental retardation--the problem is complicated even further. Because ambiguity in the criteria for deciding which measure of risk is appropriate in a given situation will lead to uncertainty in the assessment, decision rules for addressing the problem have been proposed (e.g., Milvy, 1986; Machin, 1990).

#### 4.0

### Reducibility of Environmental Risks to Health

Although the risk to health from any given environmental toxicant can be lowered by reducing the extent of exposure to the toxicant, some toxicants--e.g., carcinogens--cause effects that may not become manifest until years or decades after exposure. With mutagens, likewise, the heritable damage to reproductive cells may affect offspring of the exposed person many generations later. In the case of toxicants causing such delayed health outcomes, therefore, cessation of exposure does not abolish risk immediately.

By the same token, stopping the release of a toxicant at its source does not suffice to prevent exposure to any levels of the toxicant that may have been previously released to the environment. In the case of long-lived toxicants, such as heavy metals, PCBs, asbestos, and long-lived radionuclides, indefinite persistence in the environment and the possibility of bioaccumulation in the food chain further complicate current risk-reduction efforts, as does persistence in the tissues of persons who may already have been exposed.

In light of the foregoing, evaluation of the reducibility of the environmental risk posed by a given environmental toxicant must take into account the time over which different risk-reduction strategies may be effective; the potential for long-term risk reduction must be weighed along with that for short-term reduction.

## 5.0 Review of The Health Risk Rankings in The "Unfinished Business Report"

### 5.1 Methodology

In the "Unfinished Business" Report, as noted above, various environmental problems were examined for their risks to the health of persons residing in the U.S. Two categories of risk were considered: 1) risks of contributing to the occurrence of cancer and 2) risks of causing other adverse health effects. The information used in that report was not based on new research undertaken expressly for the purpose, but was extracted from risk assessments conducted previously by EPA in support of other Agency activities.

The 31 environmental problems considered in the "Unfinished Business" report were selected primarily on the basis of their relevance to the Agency's regulatory mandates and programmatic organization. Because they included various sources of pollution, various pollutants themselves, various exposure media, and various situations involving human exposure (Table 2.1), their diversity complicated ranking them for their relative risks, as discussed below. The ranking was also complicated by inconsistencies in the methods and assumptions that had been used by the Agency in its earlier assessments of the different problems.

For virtually all problem areas, the risk assessments were severely limited by uncertainty about: 1) the relevant extent of human exposure (in some instances, the assessments were based on only a small percentage of pertinent chemicals); 2) the toxicity of the agents in question (eg, NAS, 1984); 3) the appropriate dose-response models to use for estimating the risk relevant to ambient exposure levels; 4) the extent of variations in susceptibility with species, age, sex, and other variables; 5) and the extent to which the relevant dose response(s) may be modified by exposure to other chemical or physical agents. All numerical estimates of numbers of individuals harmed need more careful examination to determine consistency and comparability for risk ranking purposes.

### 5.2 Rankings for Risks of Cancer

In spite of their large uncertainties, the estimated risks of cancer posed by the different problem areas were ranked in

<u>Environmental Problem</u>	<u>Rank Order</u>	<u>Estimated Magnitude of Risk</u>
<u>Category 1 (High Risk)</u>		
Worker exposure (#31)	1 (Tied)	250 cancers annually attributable to only four of the many chemical carcinogens in question. Risks to individuals may be high.
Indoor radon (#4)	1 (Tied)	5,000-20,000 lung cancers annually. Risks to individuals may be high.
Pesticide residues in foods (#25)	3	6,000 cancers annually, based on assessment of only 7 of 200 potentially oncogenic pesticides.
Indoor air (non-radon) (#5)	4 (Tied)	3,500-6,500 cancers annually (primarily from tobacco smoke). Risks to individuals may be high.
Exposure to consumer products (#30)	4 (Tied)	100-135 cancers annually from only 4 of the more than 10,000 chemicals in consumer products.
Other hazardous air pollutants (#2)	6	2,000 cancers annually from only 20 of the many pollutants in air. Risks to individuals may be high.
<u>Category 2 (Medium-to-High Risk)</u>		
Depletion of stratospheric ozone (7)	7	Possibly 10,000 cases annually by the year 2100.
Hazardous waste sites (inactive) (#17)	8	More than 1,000 cases annually.
Drinking water (#15)	9	400 to 1,000 cancers annually
Application of pesticides (#26)	10	100 cancers annually in small population exposed. Risks to individuals can be high.
Radiation other than radon (#6)	11	360 cancers annually, largely from building materials. Risks to individuals can be high.
Other pesticides risks (#27)	12	150 cancers annually. Estimate highly uncertain.
Hazardous waste sites (active) (#16)	13	Probably fewer than 100 cases annually. Risks to individuals can be high.
Industrial waste (non-hazardous) (#19)	14	No quantitative estimate, but judged less severe than hazardous waste sites.
New toxic chemicals (#28)	15	No quantitative estimate possible, but judged to pose moderate risks.

Table 5.2 "Unfinished Business" Report High and Medium-to High cancer risk rankings for the identified environmental problem areas

numerical order, problems estimated to pose the highest risks being assigned to category 1 and those judged to pose smaller risks being assigned to lower categories. Table 5.2 displays the UB report's category 1 "High Risk" and category 2 "Medium-to-High" assignments. Although in-depth reassessment or updating of the rankings was not

possible within the time that was available to the Subcommittee, each of the rankings was reviewed with care. For reasons discussed in previous sections, the rankings in the UB report were considered by the Subcommittee to be tenuous in view of present limitations in the methodology and databases needed for quantitative estimates of the cancer and non-cancer risks attributable to each category.

Salient comments, primarily addressing the "high" rankings, are summarized in the following section.

#### 5.2.1 Criteria Air Pollutants

Criteria air pollutants were ranked comparatively "low" for cancer risks in the "Unfinished Business" report, mainly because the air pollutants that were known to be carcinogens had been assigned to other problem areas. However, it should be noted that the same photochemical reaction sequence that leads to ozone formation in the atmosphere produces a broad range of vapors and particulates that are known carcinogens. In addition, inhaled nitrogen oxides contribute to nitrosamine formation *in vivo*, and lead is classified as a B2 carcinogen. While no cancer risk has yet been attributed conclusively to other criteria air pollutants, mechanistic studies, many of them with *in vitro* systems, suggest that ozone and perhaps other criteria air pollutants possess mutagenic and/or carcinogenic potential (Witschi, 1988). As far as ozone is concerned, the long-term National Toxicology Program bioassay of ozone is not yet complete, and earlier studies on the induction of lung tumors in mice are equivocal. Other studies have implied that under appropriate experimental conditions carcinogenesis in the respiratory tract of the rodent may be enhanced by ozone (Hasset et al., 1985; also see the Ozone Case Study in section 8.1.1) and, possibly also by SO<sub>2</sub>, although a recent experiment has failed to confirm the enhancing effects of the latter (Gunnison et al., 1988).

#### 5.2.2 Hazardous Air Pollutants

This problem area was ranked relatively high for cancer risk, on the basis of the estimate that 20 of the known human and animal carcinogens to which people may be exposed by inhalation can be expected to cause some 2000 cancers annually in the U.S. [It was also noted that individual risks can be high]. Although additional

information has since become available, it does not appear to affect the over-all qualitative assessment of high risk.

### 5.2.3 Other Air Pollutants

By definition in the UB report, this problem area, which included fluorides, total reduced sulfur, and other air pollutants not assigned elsewhere, excluded all substances posing known or suspected risks to human health. For this reason, it was not ranked for either cancer or non-cancer risks to health in the "Unfinished Business" report. It is noteworthy, however, that these air pollutants can exact health effects (e.g., sulfuric acid aerosol, both by inhalation and by mobilizing toxic metals in drinking water sources). Hence, they should be assessed.

### 5.2.4 Indoor Radon

A "high" cancer risk ranking was assigned to indoor radon in the "Unfinished Business" report, based on the estimate that it may cause 5,000-20,000 lung cancers annually in the U.S. This assessment, although uncertain, was considered reasonable by the Subcommittee (see Case Study on Indoor Radon, section 8.1.2).

### 5.2.5 Indoor Air Pollutants Other Than Radon

This problem area was ranked "high" for cancer risk, on the basis of the estimate that only seven specific pollutants (tobacco smoke, benzene, p-dichlorobenzene, chloroform, carbon tetrachloride, tetrachloro-ethylene, and trichloroethylene) may account for 3,500-6,500 cancers each year in the U.S. population. With the possible exception of environmental tobacco smoke however, the relevant exposure and exposure-response relationships are not well characterized for such pollutants.

### 5.2.6 Drinking Water

The cancer risk ranking assigned to this problem area in "Unfinished Business" was "moderate", on the basis of the estimate that only 23 of the known pollutants, may cause 400-1000 cancers annually in the U.S. population, most of which are attributable to radon (30-600) and trihalomethanes (322). Although the methodology used to estimate the risks was judged by the Subcommittee to be reasonable, the estimates must remain highly uncertain in the

absence of adequate information about exposure and the relevant exposure-response relationships. Furthermore, petroleum-related chemicals, such as benzene, xylene, toluene, and many pesticides, do not appear to have been considered, although they are found in drinking water not infrequently, especially in private wells. The risks should be reexamined using the new exposure data from EPA's recent groundwater pesticide survey.

#### 5.2.7 Pesticide Residues on Foods

A "high" cancer risk ranking was assigned to this problem area in "Unfinished Business", based on the estimate that about 6000 cancers per year in the U.S. population were attributable to the ingestion of pesticide residues on foods. This estimate, derived from assessing the risks of seven pesticides with oncogenicity for rodents, was extrapolated to cover all other pesticides in use, on the assumption that roughly one-third (200) of them were potentially oncogenic. The estimate, although not inconsistent with independent estimates based on similar methodology (e.g., NAS, 1987), rests almost entirely on uncertain extrapolation of carcinogenicity data from animal experiments, on fragmentary information about the extent of human exposure to the pesticides in question, and on uncertain assumptions about duration-of-life levels of intake of such substances. The UB analysis contained a number of simplifications. Limited data on a handful of pesticides was used to represent the more than 300 pesticides in use on food crops today. The report assumed that residues of pesticides in various foods were present at the maximum permissible concentrations (TMRC). It would have been preferable to use the TMRC times the percentage of crops treated, times consumption, based on the updated Tolerance Assessment System to indicate an upper bound on exposure. One should also estimate exposures to both the average and the most exposed populations (e.g., the infant and young child). The risk assessment did not include carcinogens such as methylene chloride, benzene, and vinyl chloride, which in some cases represent a significant percentage by weight of the relevant formulations.

#### 5.2.8 Application of Pesticides

This problem area was assigned a "moderate" ranking for cancer risk in the "Unfinished Business" report, based on the estimate that 100 cancers in pesticide applicators each year could be

attributed to their occupational exposure to carcinogenic pesticides, judging from risk assessments on 6 pesticides found to be oncogenic in rodents. Although the estimated number of cancers was small, the risks to individual workers were considered to be high. Because estimates of the carcinogenicity of pesticides for humans are based almost solely on uncertain extrapolations from animal data, the estimates are highly uncertain.

#### 5.2.9 Worker Exposure to Chemicals

The ranking assigned in "Unfinished Business" to this problem area was one of the highest, based on the estimate that 250 cancers each year in occupationally exposed workers are attributable to only four chemicals (formaldehyde, tetrachloroethylene, asbestos, and methylene chloride) of the more than 20,000 chemicals to which they may be exposed. Although the total number of all such occupationally related cancers was not calculated, the risks to some individual workers were judged to be high. The Subcommittee considered the UB report's ranking to be reasonable, especially in view of the fact that the workplace is a source of potentially toxic agents, so that when exposures occur there, they will tend to be higher, in general, than in environmental settings outside the workplace. At the same time, however, the estimates were judged to rest on relatively fragmentary exposure data and on inadequate knowledge of the carcinogenicity and carcinogenic potency of most of the chemicals and combinations of chemicals to which workers are currently being exposed.

In considering this ranking, the Subcommittee was cognizant of the previous estimate (Doll and Peto, 1981)<sup>1</sup> that 2-8 percent of all cancers in the U.S. population--namely, 10,000-40,000 fatal cases per year (with a "best" estimate of 20,000)--may be attributed to occupational exposure to carcinogens, with the attributable risks of all cancer in the worker population per se therefore approaching or exceeding 30 percent (Nicholson, 1984)<sup>2</sup>. Improvements in worker protection since these analyses suggest that

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<sup>1</sup>See Section 5 reference #2

<sup>2</sup>See Section 5 reference #16

the figures may no longer be applicable. Recent data<sup>3</sup> do not show this high an attribution for all cancers; however, they refer to only a small proportion of the worker population. While the data noted above do raise the question as to where cancer deaths occur (an important consideration for regulation), they do not, by themselves, contradict the overall Doll-Peto estimates. It would be useful if the assessment of carcinogenic risks to workers were to be updated.

#### 5.2.10 Consumer Product Exposure

A "high" cancer risk ranking was assigned in "Unfinished Business" to this problem area, based on the assessment that 100-135 cancers each year in the U.S. population are attributable to only four substances (formaldehyde, methylene chloride, p-dichlorobenzene, and asbestos) of the 10,000 chemicals estimated to be present in consumer products (many of which are also present in indoor air and other exposure media).

Neither detailed exposure data nor toxicological data were provided to support the assessment.

#### 5.2.11 Radiation Other Than Indoor Radon

A "medium" cancer risk ranking was assigned in "Unfinished Business" to this problem area, based on the estimate that 360 cancers each year in the U.S. may be attributed to ionizing irradiation from occupational exposures, consumer products (chiefly building materials), and industrial emissions. The exposure data on which the estimate was based are extremely limited, although somewhat better than the data for most environmental chemical toxicants. Similarly, the relevant dose-incidence relationship for radiation carcinogenesis is uncertain. The estimate was based on the National Academy's recommended risk models, that have been derived from analysis of cancer rates in irradiated human populations (e.g., NAS/BEIR, 1980) and have since been updated (NAS/BEIR, 1990). Depending on the assumptions employed, the new models would yield risk estimates that are higher by a factor of 2-4. In spite of these limitations, the Subcommittee considered the ranking to be reasonable.

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<sup>3</sup>See Section 5 references (3)-(6), (10), (14), (17) and (23)

### 5.2.12 Depletion of Stratospheric Ozone

A relatively high cancer risk ranking (seventh) was assigned in "Unfinished Business" to this problem, based on the estimate that an additional 10,000 deaths from skin cancer would result annually in the U.S. by the year 2100 if the levels of stratospheric ozone continue to be depleted at present rates during the interim. Although the estimate is based on uncertain projections, the Subcommittee considered the ranking to be appropriate at this time. Continued surveillance of the situation is called for, however, since a higher ranking would be warranted if the projections were to be supported by future trends in ozone depletion and skin cancer rates.

### 5.2.13 Hazardous Waste Sites

A moderately high relative risk rating was assigned to this problem area in "Unfinished Business, on the basis of the estimate, extrapolated from 35 of the 25,000 sites nationwide, that 1,000 cancers per year in the U.S. population are attributable to only six (trichloroethylene, vinyl chloride, arsenic, tetrachloroethylene, benzene, and 1,2-dichloroethane) of the many potentially carcinogenic substances known to be present at hazardous chemical waste sites. The ranking was also based on the assessment that the risks to some individuals can be high.

In the absence of data on the extent of human exposure to the chemicals in question, which were not provided in the UB report and which remain fragmentary, numerical assessment of any associated risks to human health is fraught with great uncertainty. The uncertainty is compounded by the fact that an increase in the incidence of human cancer attributable to residence in the vicinity of a waste site is yet to be demonstrated conclusively (Buffler, et al., Upton et al., 1989).

### 5.3 Rankings for Risks of Adverse Effects Other Than Cancer

The estimated relative risks for causing adverse effects other than cancer, although even more uncertain than the estimated risk for causing cancer, were ranked into three categories, 1) high, 2) medium, and 3) low, as shown in Table 5.3, below. Salient comments on the "high" rankings are summarized in the following.

### 5.3.1 Criteria Air Pollutants

This problem area was ranked comparatively "high" for non-cancer risk in the "Unfinished Business" report, and the Subcommittee agreed with this ranking. It merits a "high" classification even though levels of some of these pollutants have declined with the implementation of National Primary Ambient Air Quality Standards. While acute episodes are infrequent for SO<sub>2</sub>, TSP and O<sub>3</sub>, short-term concentrations can be high, and chronic effects of the criteria pollutants are still a concern. There was no discussion

of the neurotoxic/behavioral effects of lead in the UB report, although the latter are of far-reaching public health significance in view of evidence that the development of the human brain may be impaired by lead at levels resulting from concentrations widely prevalent in ambient air. On this basis alone, a "high" risk ranking would have been amply justified for criteria air pollutants. By and large, the human health effects of the other pollutants in this problem area are well known in terms of the "acute" effects

<u>Environmental Problem</u>	<u>Problem No.</u>	<u>Proportion of Problem Covered (%)</u>	<u>Level of Confidence in Ranking</u>
<u>High Risk</u>			
Criteria air pollutants	1	30-100%	High
Hazardous air pollutants	2	<3%	Medium
Other indoor air pollutants	5	30-100%	Medium
Drinking water	15	30-100%	High
Accidental releases of toxics	21	30-100%	High
Pesticide residues in foods	25	<3%	Medium
Application of pesticides	26	3-10%	High
Consumer product exposure	30	3-10%	Medium
Worker exposure to chemicals	31	<3%	High
<u>Medium Risk</u>			
Indoor radon	4	30-100%	Low
Radiation (non-radon)	6	30-100%	Medium
Ozone depletion by UV radiation	7	30-100%	Low
Indirect discharges (POTWs)	10	3-10%	Medium
Non-point discharges	11	?	?
Discharge to estuaries	13	30-100%	Medium
Municipal waste sites	18	10-30%	Medium
Industrial waste sites	19	30-100%	Low
Other pesticide risks	27	10-30%	Medium
<u>Low Risk</u>			
Direct discharges (industrial)	9	3-10%	Medium
Contaminated sludge	12	30-100%	Medium
Discharge to wetlands	14	?	?
Hazardous waste sites (active)	16	10-30%	Medium
Hazardous waste sites (inactive)	17	10-30%	Medium
Mining wastes	20	30-100%	Low
Releases from storage tanks	23	?	?
<u>Unranked</u>			
Other air pollutants	3	?	?
New toxic chemicals	24	?	?
Biotechnology	29	?	?
Greenhouse gases	8	?	?

Table 5.3 "Unfinished Business" Report non-cancer risk rankings of the various environmental problems

that they may produce during episodes of heavy pollution, and warrant a ranking of "high." Their chronic health effects are less well characterized, but are potentially of major health consequence. For example, inhibitory effects on pulmonary clearance mechanisms also have been documented experimentally (Driscoll et al., 1986; Schlesinger and Gearhart, 1987), and other experimental data suggest that interactions between such air pollutants, particularly acidic aerosols and oxidants such as ozone or NO<sub>2</sub>, may potentiate fibrogenesis and other long-term effects (Warren and Last, 1987; also see the Ozone Case Study, section 8.1.1).

Adverse effects of the pollutants on the "quality of life", that may result through the production of disagreeable odors, smog, haze, or irritation, were apparently not considered in the "Unfinished Business" report. Nevertheless, these effects, although difficult to evaluate quantitatively, can be stressful and can disturb mood and behavior.

#### 5.3.2 Hazardous Air Pollutants

Although, in general, their relevant health effects were not expected to be severe, this class of pollutants was ranked "high" in relative risk, in view of the large population that may be exposed to them and the projected non-cancer health impacts that were judged to be attributable to only six substances (estimated to be only 3 per cent) of the many potentially hazardous pollutants in question. This ranking was not explained in detail.

#### 5.3.3 Indoor Radon

A "medium" non-cancer risk ranking was assigned to indoor radon in the "Unfinished Business" report, based on the estimate that it may cause "200 cases per year of serious mutagenic and teratogenic effects;" however, the estimated radiation doses on which the assessment was based were not specified. The Subcommittee seriously questioned whether the relevant doses to the gonads and to the embryo are large enough to cause risks of the magnitudes projected (see the Case Study on Radon, section 8.1.2).

#### 5.3.4 Indoor Air Pollution Other Than Radon

The problem was ranked "high" for non-cancer risk in the "Unfinished Business" report on the basis of the large extent of

population exposure and the moderate-to-severe health effects that may be attributable to the types of agents in question.

However, with regard to risk assessment, the issue is still problematic. For most indoor air pollutants, the needed data on exposure are not available, the health effects are diverse, and the exposure-response relationships are not well characterized. It is noteworthy, however, that a possible exception to this generalization is environmental tobacco smoke, for which epidemiological investigations have described exposure-response relationships linking illnesses of the lower respiratory system and effects on lung development during infancy with maternal smoking.

#### 5.3.5 Drinking Water

A "high" non-cancer risk ranking was assigned to this problem area in "Unfinished Business", on the basis of the serious health effects that may be associated with ingestion of water pollutants such as lead, microbial pathogens, nitrates, and chlorine disinfectant by-products. Again, this ranking is based on limited exposure data. Lead used in plumbing may contaminate drinking water at high levels, and concern is increasing as more is learned about the toxicity of lead, especially at lower exposure levels. Also, as other sources of exposure to lead are eliminated, this source may be of greater importance even though water contamination is usually intermittent. Pathogens also continue to be a source of morbidity, especially in smaller systems that do not chlorinate or adequately filter surface water. The Subcommittee recommends that procedures be put into place to enable a better assessment of illness from this source.

#### 5.3.6 Pesticide Residues on Foods

A "high" non-cancer risk ranking was assigned to this problem area in "Unfinished Business", on the basis of assessments of the potential health effects attributable to only three (aldicarb, diazinon, and EPN) of the hundreds of pesticides to which large segments of the population are potentially exposed. The exposure and toxicological data necessary to support this ranking were not provided. In future ranking attempts, it is important to consider risks to children. As EPA recognizes, children are subject to higher exposures and constitute a more vulnerable population than do adults. A broad spectrum of effects should be considered,

including neurotoxicity, fetotoxicity, immunotoxicity, and enzyme alterations.

#### 5.3.7 Application of Pesticides

The problem area was ranked "high" for non-cancer risk in the "Unfinished Business" report, owing to the relatively large numbers of persons exposed (estimated at 10,000-250,000), the numbers of acute poisonings each year attributed to pesticides among pesticide applicators (e.g., 350 poisonings from ethylparathion and 100 from paraquat), and the risks of other severe toxic effects (e.g., fetotoxicity, teratogenicity) that may conceivably occur. Although the estimates cannot be evaluated critically in the absence of more detailed exposure data for the populations at risk, the Subcommittee considered the ranking to be reasonable.

#### 5.3.8 Worker Exposure to Chemicals

The non-cancer risk ranking assigned in "Unfinished Business" to this problem area was "high", based on the large population (at least 300,000 workers) estimated to be exposed to each of the four substances considered (2-ethoxyethanol, methylene chloride, perchlorethylene, and formaldehyde), and the high concentrations of the substances that may be encountered in the workplace; however, detailed data on the relevant exposure patterns and associated health consequences were not provided. On the basis of other assessments of the incidence of occupational disease--approximately 190,000 cases were reported in 1987 by the Bureau of Labor Statistics (Yancey, 1988; also see Levy and Wegman, 1988), and the Occupational Safety and Health Administration expects its new standards to reduce by 500,000 the number of workdays lost each year as a result of exposure to hazardous and toxic substances (King, 1989)--the Subcommittee considered the "high" risk ranking to be reasonable.

Although the Subcommittee concurred in the above risk rankings for occupational exposure, the uncertainties in its evaluation pointed to the need for several lines of effort to improve such assessments.

### 5.3.9 Consumer Product Exposure

A "high" non-cancer risk ranking was also assigned, based on consideration of three such substances (2-ethoxyethanol, methylene chloride, and formaldehyde), the large populations exposed, and the relatively high concentrations that may be encountered under certain circumstances. Neither detailed exposure data nor toxicological data were provided to support the assessment.

### 5.3.10 Radiation Other Than Indoor Radiation

A "medium" non-cancer risk ranking was assigned in "Unfinished Business", based on the estimate that 160-220 of the serious mutagenic and teratogenic effects occurring annually in the U.S. could be attributed to ionizing irradiation from consumer products and occupational sources; however, the radiation dose estimates and risk models on which the assessment was based were not presented. Without further documentation, the ranking cannot be evaluated critically. There are large uncertainties involved in assessing the genetic (heritable) and mutagenic risks attributable to low-dose irradiation (NAS/BEIR, 1990).

Excluded from consideration in "Unfinished Business" were the potential risks attributable to low-frequency electromagnetic radiation. These risks, although as yet equivocal (OTA, 1987), merit consideration in future assessments of the health hazards of environmental radiation, in view of the large populations that are exposed.

Noise was, similarly, excluded from consideration in "Unfinished Business." This form of energy, akin to non-ionizing radiation may also deserve inclusion in future assessments of environmental health effects insofar as it may, under appropriate conditions, cause hearing loss, stress, and impairment in the "quality of life," with consequent impacts on mood, behavior, and productivity.

### 5.3.11 Depletion of Stratospheric Ozone

A "medium" non-cancer risk ranking was assigned in "Unfinished Business", based on the estimate that the projected depletion of stratospheric ozone could eventually increase the incidence of senile cataracts in the U.S. by 10,000-30,000 cases per year, and

that it might also cause other adverse health effects, including disturbances of immunity.

#### 5.4 Merging of Cancer and Non-cancer Risk Rankings

Any attempt to combine into a single aggregate rank order the risk rankings for cancer (Table 5.2) and the risk rankings for health effects other than cancer (Table 5.3) would require appropriate weighting of the different risks for incidence and severity, as discussed below (Section 6.3). Because of the complexity of such a task, as well as the lack of the requisite data, the development of an aggregate ranking was not attempted by the Subcommittee. In Section 6.3 the Subcommittee proposes two possible methods for producing such merged rankings.

It is noteworthy, however, that if the 31 problems were to have been arranged merely on the basis of whether they represented either sources of environmental pollutants or environmental situations (or agents) involving direct human exposure, they would have appeared in categories such as those shown in Table 5.4. The order in which the rankings appear in Table 5.4. is not entirely unexpected since the public health impact of any toxicant depends not only on its toxicity but also on the relevant human exposure. Thus those problems representative of proximal exposure situations (Nos. 2, 4, 5, 15, 25, 26, 30, and 31) would logically be expected to receive relatively high risk rankings for cancer and/or other adverse health effects. It should be noted, however, that among such problems risk rankings for some (Nos. 2, 4, 5, 7, 15, 26, and 31) were supported more firmly by the available data than were the rankings for others.

Since the rankings shown in Table 5.4. are based on highly uncertain risk assessments, as noted above, the Subcommittee viewed the rank order with reservations. Sufficient time was not available, however, for in-depth reassessment of the rankings, that would probably have been of limited value in any case without more adequate information about the relevant levels of exposure and toxicity. For optimal refinement of the risk assessments, further effort must be directed toward developing the necessary databases, scientific understanding, and methodology, as recommended elsewhere in this report. Other comments that should be kept in mind in interpreting the table are as follows:

1) Risk estimates for different exposure and source categories or "problem areas" were not directly comparable because they were often based on different models and assumptions made by the various program offices involved.

2) In many cases, estimates of risks for a problem area were incomplete, covering only a few of the agents or exposures comprising the exposure or source category.

3) The assumption underlying the UB ranking was that existing programs would continue. Therefore, under that assumption, some problems appeared to

Situations and Agents Involving the Potential for Direct Exposure	Problem No.	Assigned Risks <sup>a</sup>	
		(Cancer)	(Non-cancer)
<b>Ambient air pollutants</b>			
criteria air pollutants	1	L	H
hazardous air pollutants	2	H	H
other air pollutants	3	-	-
<b>Indoor air</b>			
radon	4	H	M
other indoor air	5	H	H
Drinking water	15	M	H
Pesticide residues in food	25	H	H
<b>Occupational exposures</b>			
application of pesticides	26	M	H
worker exposures	31	H	H
Consumer products	30	H	H
<b>External radiation</b>			
radiation other than radon	6	M	M
<b>Sources of Environmental Pollution</b>			
<b>Atmospheric</b>			
substances depleting Strat. O <sub>3</sub>	7	H	M
greenhouse gases, CO <sub>2</sub> , etc.	8	-	-
<b>Surface water discharges</b>			
direct point source discharges	9	L	L
indirect point source discharges	10	L	M
non-point source discharges	11	L	M
discharges to estuaries	13	-	M
discharges to wetlands	14	-	L
<b>Multimedia discharges</b>			
contaminated sludge	12	M	L
hazardous waste sites (active)	16	M	L
hazardous waste sites (inactive)	17	H	L
nonhazardous waste sites (municipal)	18	M	M
nonhazardous waste sites (industrial)	19	M	M
mining wastes	20	L	L
accidental releases of toxics	21	L	H
accidental releases (oil spills)	22	L	-
releases from storage tanks	23	L	L
<b>Miscellaneous</b>			
Other ground water contamination	24	L	-
Other pesticide risks	27	M	M
New toxic chemicals	28	M	-
Biotechnology	29	-	-

<sup>a</sup> Risk rankings assigned in UB report; H = high, M = medium; L = low (see Tables 5.2, 5.3, and Section 8.2)

Table 5.4 Environmental Problems grouped by exposure and source categories with the risk rankings assigned in the UB Report because of the high rankings assigned in the UB Report levels of effort that had been devoted to controlling them (UB, p. 96). It is therefore important that future analyses state the scope of the problem without the control assumption.

In addition to these caveats it should be noted that the UB ranking system did not adequately address the goal of prevention of risk. This being the goal of EPA, future analyses should include assessment of subclinical or preclinical effects of environmental

agents and should give weight to effects that would affect future generations. In this regard, it is also important that risks be estimated both for the general population and for the most exposed or most sensitive sub-populations (e.g., children, those with preexisting disease, etc.) Also, certain factors were excluded from the UB analysis, including economic or technical controllability of the risks, the degree to which risks are voluntary or equitable, EPA's statutory or public mandate to deal with risks, etc. Translation of risk rankings into public policy should explicitly incorporate these factors in the future.

## 6.0 Approaches for The Long-term Development of Improved Risk Assessment Strategy

It has long been known that health risks can be associated with exposures to specific agents and combinations of agents, and that such risks can be lessened by reducing the exposures. It follows that the extent of the risks, and the benefits derived from risk reduction, can be determined from risk assessments based on reliable information about the distributions of exposures among population groups of interest and the exposure-response relationships for such groups. Furthermore, when such information is available for a variety of specific agents and mixtures, and for the severity of the various responses they produce, then the various risks can be ranked. The rankings can then be used in the development of overall risk reduction strategies.

Unfortunately, the straightforward logic outlined above requires more information than has previously been available. Section 6.1 outlines the problems with the UB framework and illustrates a conceptual plan to deconstruct the UB's 31 risk categories through a source--exposure--agent--effect matrix so that the information required for a more logical ranking scheme can be related to the information needs of Agency programs. It is followed by Section 6.2, which outlines the Subcommittee's recommended approach for developing risk assessments for specific toxicants. Using this approach, for example, the limited number of specific toxicants having credible risks could be ranked. Such rankings could then be used in developing optimal risk reduction strategies.

### 6.1 Alternative Models for Risk Reduction Targets

The problem areas defined in the Unfinished Business report are a mix of three very different types. The first typically represents agents that constitute direct sources of human exposure. These include indoor and outdoor air pollutants, radiation, pesticides, and consumer products. The second represents sources of emissions which in most cases must be transported to an exposure situation. The third type of problem area represents agents which must make contact with the human receptor before a toxic exposure can occur. Typical problem areas of this kind are worker exposure and drinking water. Also, in every source area, its impact is felt via agents in the first

SOURCES	PRIOR CATEGORIES	EXPOSURES						
		-1- SOIL	-2- FOOD	-3- WATER	-4- AMBIENT AIR	-5- MICRO ENVIRON.	-6- INDIRECT	-7- OCCUPATIONAL
-A- NATURAL SOURCES & PROCESSES	7, 8, 11, 13, 14	■	■	■	■	■	■	■
-B- LAND & WATER USE AND MANAGEMENT	11, 13, 14		■	■				
-C- AGRICULTURE	7, 8, 11, 13, 14, 28	■	■	■	■		■	■
-D- MINING & EXTRACTION	8, 13, 14, 20	■		■	■			■
-E- ENERGY	8, 9, 13, 14, 23			■	■		■	■
-F- TRANSPORTATION	7, 8, 9	■	■		■		■	
-G- MANUFACTURING	7, 8, 9, 13, 14, 23, 28			■	■		■	■
-H- WASTE STORAGE, DISPOSAL & TREATMENT	7, 8, 9, 12, 13, 14, 15, 17, 18, 19, 28	■		■			■	
-I- ACCIDENTAL RELEASES	9, 13, 14, 21, 22, 28	■		■	■			■
-J- CONSUMER & COMMERCIAL	7, 27, 28					■	■	

Table 6.1.1 Source and exposure matrix

category. Therefore, in conceptualizing the risks associated with the different problem areas it is important to understand their interactions so that the priorities of their relative impacts do not become confused or double-counted.

It is understood that the basis for the 31 risk categories in the UB report is the regulatory mandates and the administrative structure of the EPA. Nevertheless, in order to conceptualize the risks better and to understand the sources, and exposures that contribute to the risks, we find that the development of a matrix approach may be useful. An example of such a two-dimensional matrix is shown in Table 6.1.1. The vertical columns consist of direct exposure terms, that are the closest connections to the human exposures. These seven exposure terms or secondary vectors for the most part represent the routes via which humans are exposed, with the exception of Category 7, Occupational Exposure.

- A) Natural Sources and Processes** Includes constituents released naturally into the environment, even though their rates of release may be influenced anthropogenically. Radon seepage into homes or present in groundwater is an example; also, arsenic in groundwater from dissolution of bedrock. Included are natural processes that modify the chemical nature (and toxicity) of materials, such as methylation of mercury.
- B) Land and Water Use and Management** Examples are urban land use affecting constituents in water run-off such as road salt; emissions from the application of herbicides to control growth along highways; also, uncollected and untreated wastes from all non-commercial sources: e.g., homes, military installations, schools and universities, etc.
- C) Agriculture** Examples includes point and non-point emissions from fertilizer and pesticides.
- D) Mining and Extraction** Includes air and water emissions from mine tailings and on-site processing of minerals.
- E) Energy** Emissions of wastes from processing and production of coal, oil and nuclear energy. Includes petroleum refining, coal desulfurization, and stack emissions.
- F) Transportation** All waste emissions from transportation: includes air emissions from mobile sources (cars, trucks, airplanes); releases to water from ships.
- G) Manufacturing** Wastewater and air effluents, treated or untreated; fugitive emissions; deposition on land; injections to groundwater.
- H) Waste Storage, Disposal, and Treatment** Includes community, industrial, and individual owned wastewater treatment systems; landfills for hazardous and non-hazardous wastes; waste incinerators; ocean disposal; and industrial wastewater lagoons.
- I) Accidental Releases** All accidental releases, whether sudden or continuing: above or below ground storage tank ruptures or leaks; releases from train derailments and collisions of tank trucks; releases from explosions of chemical or power plants.
- J) Consumer and Commercial Products** Emissions from or contact with materials and products, other than the human exposures for which the product was intended. Examples are inhalation of emissions from products used in offices and homes, such as paint solvents and pesticides.

**Table 6.1.2 Source terms or primary vectors (A through J) of Table 6.1.1, representing the various activities, materials, or processes that constitute the recognizable sources of chemical and other emissions**

This can constitute a variety of possible routes of exposure, including dermal, inhalation, and oral.

A complete description of each of these categories, as well as the source terms represented by the horizontal rows is presented in Tables 6.1.2 and 6.1.3. These source categories or primary vectors represent the various activities, materials, or processes that can constitute recognizable sources of chemical and other emissions that are transported by various processes to human receptors. There are overlaps among these source vectors. For example, accidental releases can arise from transportation, waste storage, or manufacturing processes. However, because of their sporadic

1. Soil Direct human contact with contaminated soil, such as children playing in such soil.
2. Food Unintended contamination of food by anthropogenic chemicals.
3. Water Ground and surface water, potable or otherwise, contaminated with chemicals, radionuclides, and microorganisms.
4. Ambient Air All ambient (non-indoor) air
5. Micro-environment All indoor environments (homes, offices, transportation vehicles); includes indoor air, dust, consumer product contacts, and contact with materials; also outdoor environments influenced by activities in the immediate vicinity of people, such as garden use of pesticides.
6. Indirect Includes all indirect, non-occupational exposures. This includes radiation other than from radionuclides, such as UV-B radiation, since the intensity of such exposures can be affected by chemical emissions to the stratosphere. Also includes global warming from greenhouse effect.
7. Occupational Exposures Exposure of people in work environments to chemicals and other constituent generated or as a result of activities in the workplace.

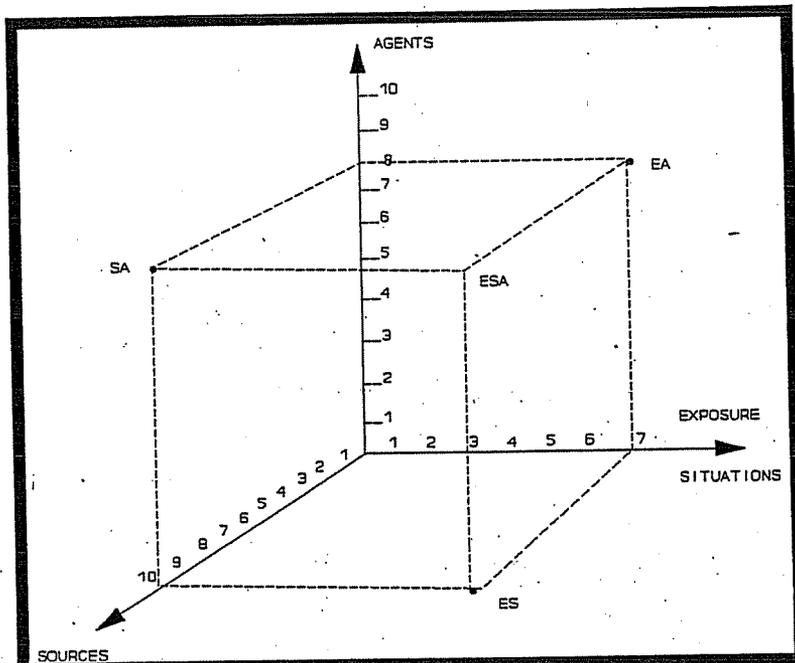
**Table 6.1.3 Exposure terms of Table 6.1.1 Terms 1-4 are media through which humans are exposed; Terms 5 & 7 are specific environments including these media; Term 6 includes ionizing radiation and indirect effects of anthropogenic activities**

nature, it may be useful to maintain Accidental Releases as a separate category in assessing the associated risks.

Note also in Table 6.1.1 the vertical column labeled "Prior Categories." These are the problem areas that were defined in the Unfinished Business report that are associated with each of the source terms. It is apparent that some are found in more than one source term. Thus, for example, Problem Area 8, CO<sub>2</sub> and Global Warming, is associated with emissions from source categories A, C, E, F, G, and H. At the same time, one could associate prior problem areas with the matrix exposure categories 1 through 7, although this is not shown in the matrix. An example of this would be exposure area 5, the Micro-environment. This would include the prior problem areas 4, Indoor Radon; 5, Indoor Air, Other than Radon; 30 Consumer Product Exposure; and 27, Other Pesticide Risks.

The way in which this matrix would be used most appropriately would involve consideration of the specific agents (chemicals and other emissions) from a given source term that might contribute to significant human exposures through each of the seven exposure categories. This has been done in a very preliminary fashion in Table 6.1.1 and is represented by the "block" markers in each element of the matrix. The presence of this symbol indicates that this element is likely to constitute a significant human exposure.

The next step would be to consider each of the exposure constituents in an element and assess the risk to the total U.S. population of the relevant endpoints. Only then could the final judgment of the health impact of each element in the matrix be addressed. The ultimate purpose would be to use this information to judge either the impact of a given source term by moving horizontally across a given row; or alternatively, to judge the health impact for a given exposure term by moving vertically through the matrix table for that exposure.



**Figure 6.1.1 Expansion of the two-dimensional matrix to include a third dimension--Agents**

given exposure term by moving vertically through the matrix table for that exposure.

Expanding the two dimensional source-exposure matrix to include a third factor, agents, is illustrated in Figure 6.1.1. Here, source #10 contributes to exposure situation #7; the intersection, corresponding to that of Table 6.1.1, is labeled ES. The figure also shows that source #10 contains agent #8, and thus source #10 contributes agent #8 to exposure situation #7 (intersection EA in the exposure situation/agent plane). The three dimensional intersection ESA brings all this information together.

Figure 6.1.2 expands further on the three dimensional concept, showing the interactions of a number of sources, exposure situations, and agents. Thus, source #5, containing agents #s 2, 4, and 7, contributes to exposure situations #s 3, 5, 6, and 7. Exposure situation #3 also receives agents #s 3, 5, 6, and 9 from other sources. This three dimensional matrix quickly discloses interactions and multiple contributions, and entering the matrix at any element of a dimension (for example, at agent #6) allows one to determine which other exposure situations are affected by agent #6 from which sources, etc... The three dimensional intersections, such as intersection ESA in Figure 6.1.2, are not shown, for

simplicity, but in setting up a computerized information system such as the one envisioned here they would be of major importance.

Lacking in this simplified three dimensional example, for purposes of an assessment of risk (risk of what endpoint(s)), is the fourth dimension, the endpoint or endpoints associated with each agent and therefore, with the sources and exposure situations associated with each agent.

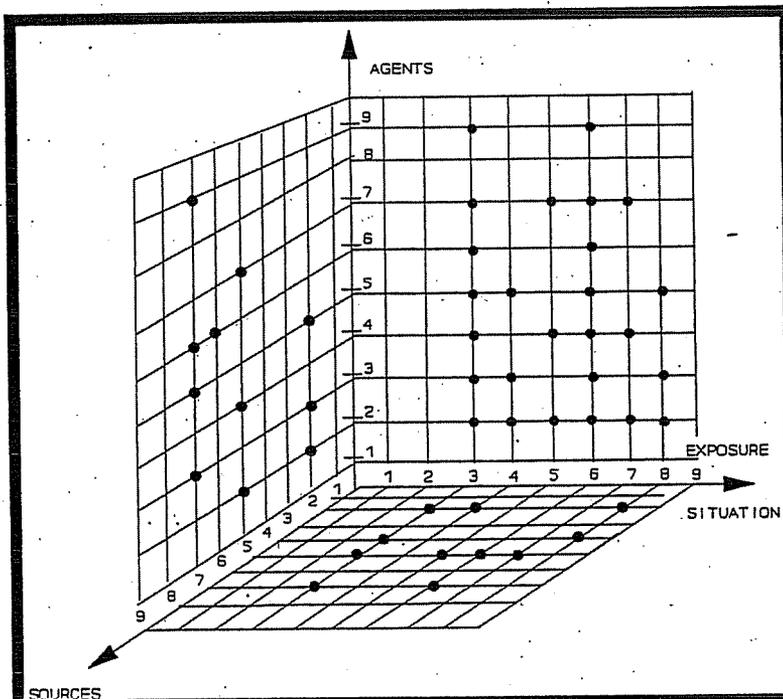


Figure 6.1.2 Expansion of 3-dimensional matrix, showing interactions of sources, exposures, and agents

Depicting this lacking information is not simply and directly possible on a two dimensional plane; three planes in addition to those shown in Figure 6.1.2, would be needed: Agent-endpoint, source/endpoint, and exposure situation/endpoint.

Given the four dimensional organization of information on sources, agents, exposure situations and endpoints, the work of rank-ordering different elements within each of these four dimensions, separately, for risk would be simplified and given consistency. It would also be possible to identify the three dimensional (ESA-type) intersections involved with other defined environmental problems, such as those in the UB report, and so to assist in rank ordering them.

In considering, then, how risk areas might be better defined and relevant information organized for ranking/assessment purposes, the Subcommittee proposes as a possible approach the development of a matrix the principal dimensions of which include sources, exposure situations, agents, and endpoints. Such a matrix can be entered via an element of any of the dimensions (for example, an agent or a source) and, via the intersections of that dimension with others, the appropriate relationship to the others can be

determined. Given such a matrix in computerized form exposure situations, sources or agents can each be ranked according to risk, bringing order to the problem of determining the most important steps to take to reduce health risks. Further, identifying the intersections relating to a risk area of interest to the agency would consistently identify the elements of each dimension relating to the risk area. Developing the matrix in usable form and entering information into it would be no small task; once even partially available, however, its utility would be great.

Developing and putting into practice the full information system required for insertion of relevant information now available, and new information as it is acquired, including the capability of tying into other existing information systems which already contain toxicity, physical and chemical property, exposure, dose response, or other information on agents, endpoints, exposure situations, and/or sources, is a very large task that would involve information system design specialists working closely with scientists, technologists and risk managers in the Agency, and possibly, outside of it. In essence, however, the information required can be structured as a relational data base design for which many commercial software products are available. The Subcommittee does not have an estimate of the numbers of workyears involved other than to say that it is expected to be large. In the final analysis, and, in a very real sense, the task will never be quite complete: whatever initial system is designed and put in place will undergo continual change, expansion, and development (as distinct from maintenance) as it is used and as experience is gained from cataloguing new information in it.

The Subcommittee recommends that that this strategy be implemented in small increments. At this early, conceptual stage the complexities and practical difficulties cannot be projected, but they will surely be there. Rather than address the design and implementation of the whole, ultimate system at the start, the Subcommittee recommends that a specific four dimensional system be developed and filled with information for a small number (three or four) of different but relatively widespread agents (tying in to pre-existing data bases (such as IRIS)), and used as a test case; this effort would take the form of a limited pilot project, the product of which would find immediate, practical utility, and it would serve to give practical guidance to the design of a more advanced version of the system suitable for the insertion of data

on many agents, endpoints, sources and exposures. Typical agents to be used in the pilot project would be, as examples from which to pick the small number to be used: Benzene, TCE, Lead, Ionizing Radiation, Arsenic, Chloroform, Dioxins, PCBs, Carbon Monoxide or Ozone. A step-wise, pilot-project-guided approach, the Subcommittee thinks, would produce a usable product even at the pilot stage, uncover what is needed to progress to a further stage of design and development, and increase the ultimate chances of achieving a successful four dimensional information organizing system or matrix. Progression to a further stage of development should also be restricted to a manageable project. The next stage is visualized as beginning by discovering what is encountered in the way of new problems, and how these are to be solved, by adding a larger but still limited number of agents, selected for ubiquity and potency, to the pilot project matrix. Such agents might be selected from already existing lists such as the list of agents for Community-Right-to-Know reporting under SARA, as well as new substances identified in the application of TSCA, Section 5.

The Subcommittee does not recommend a particular organizational approach to managing this project, either in the short or long term; it points out, however, that both short term and long term aspects should be considered in organizing for this undertaking. The Subcommittee recommends that a single, clear focus of responsibility be assigned at the start to provide planning (including budgetary planning), continuity, coordination, progress reporting and accountability for the project.

The four dimensions are not new to the risk assessor. The Subcommittee believes that conceiving of them formally as an interconnected system, as human health risk questions are addressed, will improve the risk assessment process, helping the risk assessors to think broadly and holistically when considering any particular problem. The Subcommittee believes that risk assessors within the Agency should be encouraged to consider the four dimensions as they pursue their work and to document, wherever possible, the four dimensions, their relationships, and the relevant risk information, as they do their work. Such documentation can become a source of information for insertion into the information system itself.

There is thus no need to wait to receive some benefit from this concept until the ultimate, or even the pilot, system is

established and implemented. As an aid to the thought process it can be useful.

We believe that this approach, although difficult to execute, would provide a perspective that could assist in prioritizing the efforts of the EPA in reducing the risks to the U.S. population. It could help identify the agents and activities that contribute to the greatest risks, as well as the exposure media of greatest concern.

## 6.2 Identification and Assessment of Specific Toxicants

From the foregoing it may be concluded that the initial step to be taken in environmental health risk assessment is the identification and tabulation of health effects of non-trivial concerns that are associated with those particular environmental pollutants which demonstrate both evidence of 1) toxicity following exposures of environmental relevance and 2) evidence of widespread or intense exposure to populations or to individuals. Most pollutants that meet these criteria will be specific agents, such as O<sub>3</sub>, chloroform, benzene etc, or mixtures containing a common active agent or functional group, such as Pb and its salts or nitrosamines. More complex mixtures, especially those that vary considerably in composition from place-to-place and/or from time-to-time are harder to rank. The possibility of synergism in such mixtures should be considered. An NAS-NRC report (1988) concluded that synergism is a relatively rare occurrence. However, there is a paucity of experimental and epidemiological data bearing on this question (Waters et al., in press; Vainio et al., in press). Based upon both experience and theoretical modelling it found that additivity of effect is the common rule, and that synergism generally occurs only when one component of the stressor or a co-stressor, is a potent toxicant present at a sub-threshold level or level that produces only a small yield of responses on its own. In some practical cases, the toxicity of a complex mixture can be characterized by the toxicity of its most active component that.

In theory, this approach can lead to lists containing hundreds, or possibly even thousands of agents. In practice, it is unlikely that as many as one hundred pollutants can meet the two entry criteria posed earlier. The pollutants that do cross the threshold can then be evaluated for risk levels according to the processes we have adopted for the following case studies. In this

manner the risks, and their uncertainties can be quantified and, if desired, ranked in order or by groups.

#### **6.2.1 Selection of Specific Pollutants**

The health impacts associated with environmental exposures can usually be attributed largely to individual chemical agents, such as ozone, most of which have been relatively well studied. Still, as the following case study on O<sub>3</sub> demonstrates<sup>4</sup>, there remain critical unknowns about exposure and exposure-response relationships which limit our ability to perform essential quantitative risk assessments.

Other health impacts are associated with classes of agents such as radon and its decay products, lead and its salts, the various nitrosamines, PCBs, dioxins, trihalomethanes, etc. In these groupings, there are variations in bioavailability and metabolism that result in widely varying toxicity according to the composition of the mixture and the influence of other materials in the exposure environment. The influence of such factors is demonstrated in the following case study on radon decay products<sup>5</sup>.

Even more difficult to evaluate are groupings such the products of incomplete combustion (PIC), municipal waste-treatment sludges, etc., where the materials are so diverse that they can range from highly toxic to essentially innocuous.

#### **6.2.2 Addressing Exposure Parameters**

The process of risk assessment depends on both the toxicity assessment and the exposure assessment. In most cases, the exposure assessment will be the limiting factor in the overall process. The increasing recognition of this limitation by EPA needs to be followed by positive action to address it. We strongly recommend that EPA continue to expand its capabilities for quantitative exposure assessment so that it can effectively utilize the growing data base of toxicity information.

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<sup>4</sup>See Appendix, Section 8.1

<sup>5</sup>See Appendix, Section 8.1.2

### 6.2.3 Summaries and Lessons Learned from the Case Studies

The two case studies presented in the Appendix (Sections 8.1.1 and 8.1.2) provide lessons that may help us deal with risk assessment problems in the future. Some of the lessons are:

#### 6.2.3.1 Ozone

1. Ozone in ambient air was not initially established as a human health hazard. Rather, it was considered primarily as a nuisance, as well as a plant pathogen. Ozone was grouped under the category "community or criteria air pollutant," which included demonstrated health hazards (e.g. the acidic pollutant mixtures that produced excess mortality and morbidity in Donora and London). Initially, concern with O<sub>3</sub> was thought to be limited to specific geographical locations, such as Los Angeles, rather than a widespread problem. As our concern has shifted from responses in terms of body-counts and clinical cases of disease, to risks of accelerated loss of lung function and/or avoidance of coughing and chest pain during outdoor exposure, O<sub>3</sub> came to be regarded as an important health hazard.

2. Early animal studies on O<sub>3</sub> clearly showed that it was capable of producing massive lung damage. However, it did so only at rather high doses. When experiments were conducted at levels of O<sub>3</sub> approaching ambient levels, animals no longer suffered detectable effects. As our ability to detect and quantify subtle changes in function and localized damage to airway linings improved, we began to recognize and appreciate the importance of gradual changes leading to disability or premature death late in life.

3. Although some early animal experiments indicated that O<sub>3</sub> would produce acute lung injury, little evidence for this was found in humans. The advent of sophisticated pulmonary function measurements eventually produced some evidence that O<sub>3</sub> would alter pulmonary function in humans at high ambient levels. The effects were modest and transitory, and were reduced in magnitude following repetitive daily exposures ("adaptation"). The laboratory studies in humans stimulated the undertaking of larger-scale field studies which provided further indication that a significant problem existed. They also stimulated the development and application of more sophisticated tests in the laboratory, such as broncho-

constrictor challenge, and assays of lung lavage fluids for cell number and function, and release of mediators.

4. The huge volume of health effects research on O<sub>3</sub> has not been adequate to define the extent of the human health risks associated with population exposures, demonstrating the need for a strategic research plan to address the critical knowledge gaps. These gaps include the role of repeated exposures over a season or a lifetime on the pathogenesis of chronic lung disease and the role of co-pollutants and other environmental factors on both short- and long-term responses.

5. We know a great deal about transient functional responses to single 1- and 2-hour exposures to O<sub>3</sub> under controlled conditions, including the enhancement of response due to increased ventilation during exercise. However, we have only recently learned that:

- The acute response syndrome involves other transient responses such as: 1) influx of inflammatory cells and mediators into the lung; 2) increased airway reactivity; 3) increased airway permeability; 4) altered rates of mucociliary particle clearance from the lung airways.
- The responses increase with duration of exposure for at least six hours, and dissipate with a similar time constant. This is important for people who remain outdoors, since O<sub>3</sub> exposures in most heavily populated regions have a broad daily plateau lasting 6-10 hours. Furthermore, peak O<sub>3</sub> exposures generally occur on many successive days during the summers, and exposures are often as high or higher in suburban and rural areas as in urban centers.
- Responses among children and healthy non-smoking adults engaged in normal outdoor recreational activities are greater than those observed in the controlled exposure studies with O<sub>3</sub> alone at comparable concentrations, suggesting that other constituents potentiate the characteristic O<sub>3</sub> responses, and that exposure-response relationships based on chamber studies underestimate the health impacts on natural populations.

- Acute responses among both laboratory and field study populations indicate large interindividual variations in sensitivity to O<sub>3</sub>. There is little known about the causes and correlates for this wide range of responsiveness. The data suggest that large numbers of individuals have symptomatic responses, as well as functional deficits large enough to constitute adverse effects, following natural exposures even on days when the current standard is not exceeded.

We clearly need to identify the constitutional factors that account for large variations in response among the population, so that the more susceptible people can know when to avoid outdoor exposures, and so prophylactic therapies can be designed to help susceptible individuals avoid the effects of excessive exposure.

6. We know relatively little about the long-term consequences of repetitive daily exposures of humans to O<sub>3</sub>. However, there are serious concerns based on the results of chronic exposure studies in laboratory animals showing that:

- Successive daily exposures of rats leads to progressive epithelial cell damage even when respiratory function changes are transient.
- Chronic exposure studies in rats and monkeys at high ambient O<sub>3</sub> concentrations produce functional and structural changes in the lung consistent with stiffening and/or premature aging of the lung.
- Rats are less sensitive than humans to O<sub>3</sub> in terms of acute functional response, and comparable to humans in their functional adaptation to multi-day exposures. The lesser functional responses are consistent with the dosimetry models for O<sub>3</sub> uptake along the airways of humans and rodents.

With so many people chronically exposed to O<sub>3</sub>, it is important to determine whether premature aging of the lungs is occurring, and if so, how the effects can be ameliorated.

### 6.2.3.2 Radon

A variety of important lessons emerge from an analysis of the findings in the radon case study.

1. The relatively large health risk of 5,000 to 20,000 lung cancer deaths per year from exposures to indoor radon was not well defined until NCRP (1984), EPA (1986), ICRP (1987) and NAS (1988) gave serious attention to general population risks as well as occupational exposure risks. Risks of this magnitude, which are larger than most regulated cancer risks, could have been predicted much earlier if any responsible authority has used available data from the uranium miner experience and the available evidence that a linear, non-threshold exposure-response model was appropriate.

2. EPA's advisory to the public on the risks from residential radon included advice on obtaining measurement kits and remediation services, providing effective guidance for individual home owner actions. This was made possible by EPA's prior research and development efforts in these areas.

3. Multiple sources of indoor radon may be important to residential exposure. While permeation of radon from subsurface soil is usually the dominant source, radon dissolved in potable water from wells can also be a significant source.

4. The risks to smokers are 6-10 times greater than for nonsmokers exposed to a given level of radon, a conclusion not generally communicated to the general public to help individual citizens decide about remediation.

5. The residual uncertainties about the risk of lung cancer from exposure to radon and daughters are quite small (30-50%). However, one major uncertainty is the contribution of exposure during childhood to the subsequent risk of disease.

### 6.2.3.3 Overall Lessons

In order to use quantitative risk assessment approaches for relative risk ranking, we will need to define the risks of concern and their overall impact on public health. A rich data base does not necessarily ensure that adequate risk assessments can be performed. The case study on ozone demonstrates that our knowledge

of the chronic health impacts of O<sub>3</sub> is extremely limited. We know virtually all we need to know about the acute functional responses in laboratory settings to O<sub>3</sub>. However, we also know that exposures in natural settings often produce much greater responses, limiting the applicability of the laboratory data for predicting population responses in natural settings. One lesson is that further research based on the use of conventional tests and assays and convenient durations of exposure should have lesser priority, while research focussed on the critical knowledge gaps should receive greater priority.

The radon case study demonstrates the importance of exposure assessment in complementing the well developed exposure-response relationships in the overall risk assessment. It also illustrates the importance of considering multiple sources, in this case the soil gas and radon dissolved in the potable water supply, as well as the strong role of cigarette smoking as a modifier of radon-induced cancer risk. Finally, it demonstrates how EPA can play an important and productive role in public health protection concerning an agent for which it has no direct regulatory authority.

### 6.3 Ranking Schemes

In the EPA's "Unfinished Business" Report (UB) thirty-one problem areas (Problems) were identified and ranked, separately, according to the cancer and non-cancer population risks believed, as a result of analysis and consensus, to be associated with each. The two rankings were not combined into a single population health risk ranking but were reported separately in the UB.

From the standpoint of providing inputs to a planning, budgetary, or resource allocation process, producing a combined health risk ranking to include cancer and non-cancer health effects in a single ranking would be useful. How to produce such a single ranking of Problems, of either the UB report's original thirty-one or of whatever different set may result from this study or future considerations, either (1) starting from scratch or (2) by combining separately derived rankings by cancer and non-cancer risks, is the question considered in this section. Both approaches to the question are explored, and frameworks are suggested for accomplishing the ranking task in each case. The second case is described in some depth in Section 8.2, along with an illustrative example of how the framework should be applied in merging the

rankings by cancer and non-cancer risks into a single health risk based ranking.

While two frameworks are described for accomplishing the development of health risk rankings, in neither of the two cases is the application of the frameworks a simple matter of applying a formula, nor can it be. The qualitative nature of much of the information used in ranking prevents this. At each major step scientific judgment, and preferably a consensus of knowledgeable scientists, is needed. The example given in Section 8.2 of merging two separate rankings into a single health risk based ranking is just that: an hypothetical example, an illustration of how the framework might be applied. It is not a final result of applying the framework in a consensus-generating fashion.

### 6.3.1 General Considerations on Ranking and Severity

In the original ranking of the thirty one problems for non-cancer risks as presented in the UB report the key variables were all considered to the extent possible: exposure, potency, incidence as derived from these two, numbers exposed, and severity of effect, and numerical estimates and scoring systems were developed and used, where possible, in addition to qualitative information and best guesses. Because quantitative information relevant to ranking was sparse, especially in the case of non-cancer effects, the basic factors to be considered in ranking had often to be taken into account by reaching consensus on the weights to be accorded to qualitative information combined with what quantitative indicators there were. This same problem exists today.

With the cancer and non-cancer risk rankings in the UB report done by different consensus groups, the ways in which information was considered, classified and used by each in arriving at their separate rankings, based on cancer and non-cancer risks, are not entirely consistent. More attention should be given to this factor in undertaking any new rankings. Also, ranking as a means of setting priorities for action is a common, well-used tool in many fields, including health. It would be useful, therefore, in any new undertaking, to review some of the ways in which rankings have been done in the past to ensure that what is good or useful in them is incorporated into the ranking method ultimately used. The well known medical practice of triage, used ordinarily under such

conditions of high demand for scarce resources as the battlefield or major disasters, is a good example of ranking for the purpose of allocating scarce resources in such a way as to save as many lives as possible. One reference well worth reviewing in considering possible improvements in the health risk ranking of Problems is the 1984 report of the National Research Council on strategies to determine needs and priorities for toxicity testing (see references). In this volume, a number of schemes utilizing different bases are reviewed in the course of reaching the conclusions of the study.

In ranking for non-cancer risk, severity of effect was considered by the participants in the UB project, and, with many apologies and qualifications, they developed an evaluation and scoring of the relative severities of a wide variety of non-cancer health effects as they were defined in the UB report. The method used was a technical one based on estimating the impacts that different apparent diseases or endpoints would have on different organs or systems and, in turn, the severities of those impacts on the individuals afflicted with the endpoints in question. In ranking the problems by cancer risk, severity of effect was not considered in the UB report. All types of excess cancers were considered to be of highly severe consequence to affected individuals. Whether "highly severe" meant more, or less, or of equal severity to the most severe of the non-cancer effects rated in the UB report is unknown; it is reasonable to assume that most cancers would be included in the highest of the seven severity levels (or possibly, some of them, in a new, higher level) defined in the UB report for non-cancer endpoints along with the most severe of the non-cancer endpoints, with only some falling into somewhat lower brackets.

In developing a merged ranking for different health endpoint risks, whether for a diverse set of non-cancer health effects or for cancer and non-cancer health effects combined, some way to consider severity is needed; otherwise, effects of low severity will be ranked as highly as those of high severity when they occur at the same frequency, a clearly unreasonable approach to maintaining or improving public health. The participants in the UB report effort recognized this and attacked the problem of severity, fully cognizant of the difficulty of the problem in the first place.

There is no universally acknowledged scoring system for severity of effect at the present time, certainly not for so broad a spectrum of diseases as falls under the heading of "non-cancer health effects," though the problems of establishing an index have been addressed in various contexts such as in the development of an Index of Harm for radiation induced effects [1,2]. There is little question that different diseases are of different degrees of severity of impact on the sufferers; it is only necessary to think of one's own response if asked which of two diseases one would prefer least to contract if that was the only choice available. What factors to consider and how to weigh and quantify such differences in ways satisfactory to most people presents major problems, however.

The technical approach used in the UB report must be regarded as a laudable effort to recognize the existence of differences in severity, but it may not give sufficient weight, in arriving at the severity scores, to either medical specialists, on the one hand, or to sufferers or potential sufferers on the other, nor to the process by which such a table of severity indexes might best be derived in the first place. In section 3.3.3 of this report, some of the broad factors that need to be considered in arriving at a characterization of severity are discussed in some depth. These factors range from scientific/technical factors to sociological/psychological ones. From the viewpoint of the sufferer or the potential sufferer, such factors as "loss of productive years of life" may not be of compelling interest; "When might I get it?;" "How bad is it--will I die, will I be in lifelong pain, or will I find it to be just a kind of nuisance?;" "How will it affect my family, my friends, my job, my finances?;" "Can it be cured or alleviated; does it progress or is it reversible?;" and "How distressing is the treatment?" are samplings of the kinds of questions laymen might ask when considering the severities of different diseases. Developing a translation of these kinds of questions into meaningful medical and scientific terms, and vice versa, may be a necessary first step in approaching severity from both the medical/technical and the lay perspectives in an integrated way; one possible way to accomplish this is through the use of lay and professional focus groups meeting separately and then together. The process by which this is done, whatever it may be, the way in which the views of informed potential sufferers (and how they become informed) and of medically and technically trained experts are brought together is critical to developing severity

factors or indices with any validity or credibility. Moreover, such factors must be reviewed and updated from time to time as new knowledge becomes available or as diseases become more curable or mitigatable.

### 6.3.2 Producing a Merged Health Risk Ranking: the Zero-Based Approach

We will consider, first, the problem of ranking starting from scratch, i.e., a zero-based approach.

An approach to the zero-based ranking for creating a single, merged health risk ranking would be to develop severity factors for both cancer and non-cancer effects, together, as was done in the case of non-cancer effects, only, in the UB report, but using groups of experts and lay persons as suggested in Section 8.2, both to develop the best set of variables to use in this exercise and to develop the relative severity factors. This amounts to starting over and, given the severity scores, having one consensus group then consider both types of effects as a single spectrum of health effects, connected to each other by the single severity factor table. To conduct this consensus ranking exercise most efficiently, it is suggested that expert individuals drawn partly from the UB ranking group and partly from outside sources, would be best suited to developing the new, merged, consensus ranking. This would help ensure that considerations raised in the present relative risk reduction project, new information, and new understandings or correlations of existing information would be fully utilized to avoid a full, duplicative refamiliarization with the information already utilized in the UB report.

The development of the severity table, the factors that need to be considered in defining severity, and how to combine the factors into severities, needs further thought and definition, as discussed in Section 8.2. Peer review of the result would ensure, to the maximum extent possible, its scientific quality and credibility. Such a value-laden process should include medical experts and ethicists, sociologists, and lay persons.

In the UB report, population risk appears to be the primary consideration in ranking, individual risk being only briefly mentioned. In a new zero-based aggregate health risk ranking effort, if consideration is to be given both to population and to

individual risk, the way these are to be weighted in reaching a conclusion on ranking must be defined and applied consistently to obtain a credible result; the same is true of any other particular factors such as individual or population subset sensitivity.

Long-term advantages to expending the resources needed to apply this full procedure is that (1) the most credible result would be produced, (2) a framework into which new information can be fitted to update the ranking would be brought into existence, and (3) the ranking, kept up to date, would provide useful, ongoing guidance for budgetary and resource allocation planning. The difficulties involved in establishing an agreed-upon severity table must not be underestimated; a method for merging pre-existing, separate rankings may prove to be more practical, in the immediate term, for producing a single aggregate health risk ranking.

### **6.3.3 Producing a Merged Health Risk Ranking: Merging Separate Rankings into One**

An alternative approach to the complete, start-from-scratch, zero-based approach is developed in some detail in Section 8.2. It builds on whatever may already have been done in ranking a set of Problems (the UB report Problems or another set of issues such as elements of one of the four dimensions described in Section 6.1) separately for cancer and non-cancer risk, copes with the lack of much quantitative information of any degree of precision and, starting from the two separate rankings, involves less total effort than the zero-based method, producing a preliminary merged risk ranking that may provide some assistance in considering planning alternatives.

A brief description of the principles involved in the merging of two qualitatively ranked separate rankings of problems or other defined issues according to cancer risks, on the one hand, and non-cancer risks, on the other, follows. For a fuller understanding, the reader is referred to the more detailed development in Section 8.2.

Figure 6.3.1 Shows a hypothetical linear (or cartesian) plot of items ranked for non-cancer risks versus the same items ranked for cancer risks as it would appear if the quantitative weights for each of the items, non-cancer and cancer, were known. In a real situation, the items might simply be ranked according to relative risk: High (H), Medium (M), or Low (L); in this situation, the

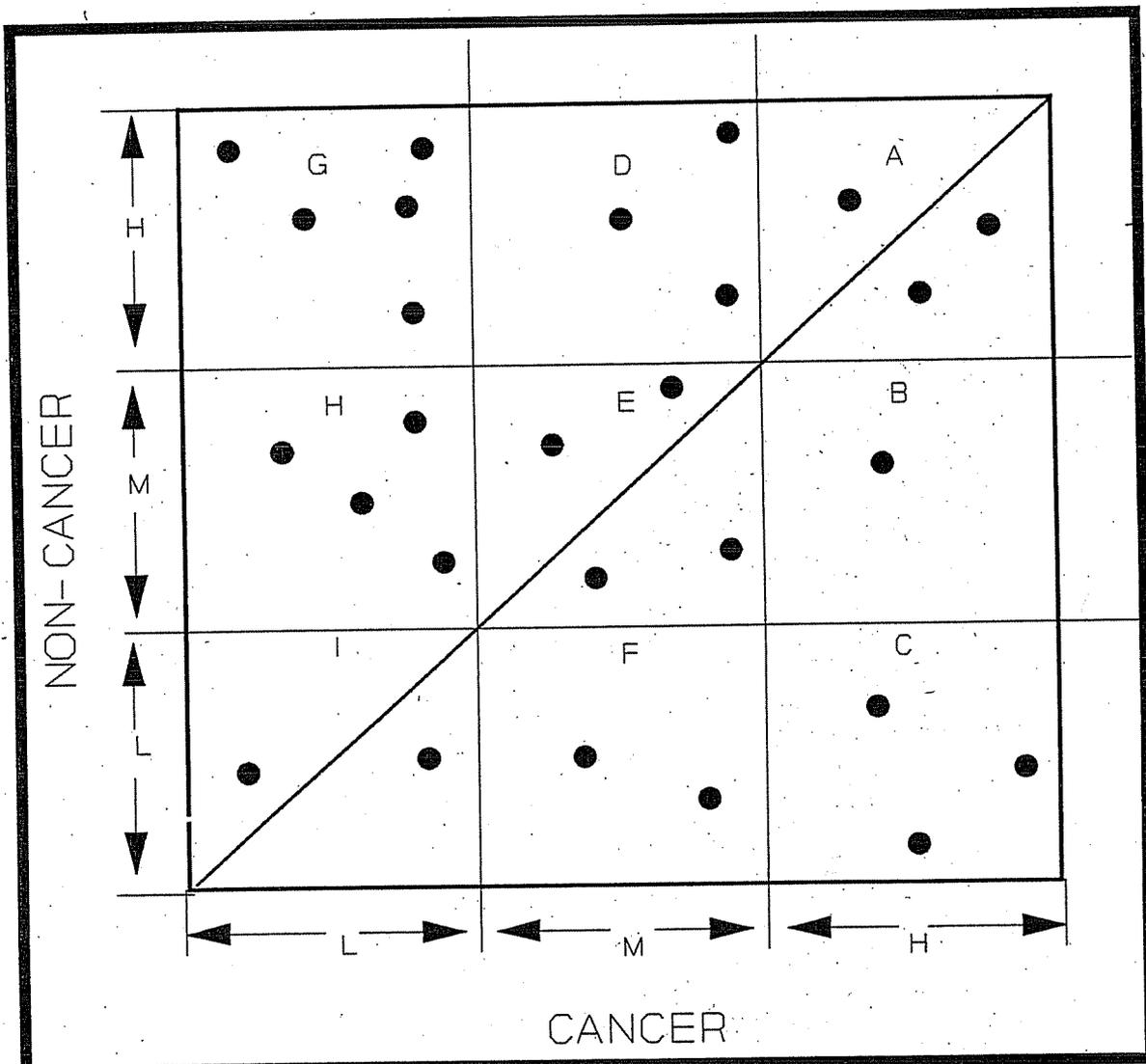


Figure 6.3.1 Plot of hypothetical risk rankings--non-cancer vs. cancer

precise locations of items within the grid squares in the figure would not be known: which of the items (such as the "problems" in the UB report) lie somewhere within which of the grid squares is all that would be known. From the figure it is obvious, assuming that the two qualitative rankings were meaningfully done in the first place, that items lying within grid squares A, E and I rank, for the two risks combined, as groups, in the order:  $A > E > I$ . In effect, these three sets of items are easily ranked according to the combined risks of cancer and non-cancer effects by a simple inspection of Figure 6.3.1.

The merging method suggested here provides the means for determining where the groups of items lying in the off-diagonal grid squares rank relative to those on the diagonal and to each other. Once this is accomplished a good start has been made on the merged ranking of the items themselves since those individual items which need to be compared to each other to arrive at a final ranking have been clearly identified.

No.	For*:	The ranking pattern is:**:
1.	Non-cancer Predominant	ADG > BEH > CFI
2.		A > D > G > B > E > H > C > F > I
3.		A > D > BG > E > CH > F > I
4.		A > D > B > G > E > C > H > F > I
5.	Cancer = Non-cancer	A > BD > CEG > FH > I
6.		A > B > D > C > E > G > F > H > I
7.		A > B > CD > E > FG > H > I
8.		A > B > C > D > E > F > G > H > I
9.	Cancer Predominant	ABC > DEF > GHI

\* Weight implied, overall, by the rank orders given.

\*\* Grid squares written together (e.g., BD or DEF) are of the same rank.

Table 6.3.1 Rankings possible for a three-by-three linear array

The method is based on the fact that for any of several models in which severity factors, in principle, can provide the link for comparing risks of different endpoints, there is only a limited number of sets of rankings of the groups of items in different grid squares to be compared with the risk information about the sets of items to determine which ranking is most consistent with the risk information. Models relevant to the items or problems of concern to the Agency include those which rank by individual risk, by population risk, or by combined individual and population risk, with or without taking account of other factors such as the sensitivities of individuals or of population subsets.

For three-by-three, linear arrays of risks such as the one plotted in Figure 6.3.1 the set of all possible rankings of the grid squares (and therefore of the items falling within them) is shown in Table 6.3.1. As shown in section 8.2, it is not necessary to determine which ranking is most compatible with the available information by a laborious comparison with each of the rankings shown; use can be made of the major rank reversals (for example, G and C in rankings 2., 3. or 4., versus 8., 7., or 6., respectively)

to reduce sharply the number of rankings where detailed comparison is necessary.

As shown in Section 8.2, Table 8.2.6.2, the number of possible rankings increases to seventeen if the array is symmetrical but nonlinear (for example, if the ranking coordinates are logarithmic) and also increases as the order of the array increases. Practical arrays for the merging of qualitatively ranked items are the three-by-three arrays, linear or nonlinear, in which the original rankings fall only into three categories: high, medium, and low. Four-by-four systems might work if the original information on the separate rankings is sufficiently complete and descriptive, but a more highly subdivided set rankings than that soon becomes cumbersome or outruns the ability of the information to discriminate. Generally speaking, too, when the final ranking has been achieved, it is desirable to express it in no more than the number of categories of the original two rankings; to use more would outrun the content of the original information.

One key point should be borne in mind: it is as true of the zero-based ranking method and of the separate ranking of items by cancer and non-cancer risks as it is of the process required to carry out rank merging that the various comparisons need to be made by appropriately chosen consensus groups for the comparisons, and the final result, to be as good in quality and as credible as possible.

From a practical standpoint, once that the possible ranking patterns are tabulated this rank merging process can be carried out without having to know or to decide whether cancer or non-cancer effects predominate, whether it has been explicitly determined what the relative severities might be, or whether the risk ranking scales the relative severities might be, or whether the risk ranking scales are linear or nonlinear. Comparison of the possible rankings with the available risk information to determine which is most in keeping with the information accomplishes this, accounting for whatever conscious or unconscious decisions may have been made by those doing the ranking. For this reason, as well as for its relative simplicity, the rank merging method is a preferable way to produce merged or aggregated health risk rankings until such time as a zero-based method can be put into practice.

#### 6.3.4 Further Comments and Recommendations

For the long term use of merged cancer and non-cancer risk ranking, the so-called zero-based procedure outlined early in this section, is best. Doing it once can form a solid basis for updating and revising it and, since it deals most directly with the problem in a manner as close as possible to the flexible and relatively inclusive models described in detail in Section 8.2, it is likely to yield the most correct and credible, and therefore reliable, result when it comes to budgeting and allocating resources to risk management activities and to research. It is recommended that this effort be undertaken as an investment in facilitating better planning and allocation.

One of the key missing sets of variables for producing a single, health risk based ranking of Problems is a single set of severities for cancer and non-cancer endpoints together. The experience already gained in attempting to grade the severities of different non-cancer endpoints in the UB report should help in the formulation of a method and a process for undertaking the task of producing a consensus on a health risk severity table including both cancer and non-cancer effects, and it is recommended that any updating of the UB report include this activity.

The procedure for merging separately ranked Problems (for cancer and non-cancer risk) is relatively easy to use, once the main possible rankings are tabulated (as for example, in Tables 8.2.6.1 and 8.2.6.2) and once separate cancer and non-cancer risk rankings are in hand. The consensus mechanism recommended is particularly useful not only in narrowing down the possible rankings to one best one but also in reaching the final merged ranking while ensuring that information that might have been lost along the way is utilized at the end.

#### 6.4 Development of Necessary Resources

Valid assessment of the health risks associated with environmental problems will require major improvements in the relevant exposure and toxicity data, as well as substantial strengthening of the underlying science base. To expedite the desired improvements, the following needs should be addressed:

Databases For most of the chemical and physical agents of environmental concern, the relevant data on human exposure are not sufficiently quantitative, comprehensive, or detailed to enable precise assessment of the associated risks to human health. Far more detailed and comprehensive exposure measurements are necessary, including data on tissue burdens as well as ambient exposure levels. Also needed are pertinent data on the uptake, distribution, metabolism, and excretion of the substances in question, as well as on the extent to which these parameters may vary with age, sex, diet, physiological state, and other variables. The data should also include, insofar as possible, information on the relevant biological and molecular markers of exposure, dose, and preclinical effects.

In addition to better exposure data, more adequate toxicological information also is needed, including more systematic data on the toxicity of the relevant agents for humans of different ages, more comprehensive assessment of their toxicity in surrogate toxicological test systems, and better understanding of the appropriate dose-response and trans-species scaling functions to be used in assessing their risks to human health.

Institutional Arrangements In order to develop exposure and toxicity databases of the richness needed, closer cooperation among different governmental and private institutions will be necessary. For example, development of the exposure databases should include, in addition to the data gathered by EPA itself, relevant information from other federal (e.g., NCHS, NIH, NIOSH, FDA, and DOE), State, and local agencies, as well as from the private sector.

Personnel Also in need of further development is scientific capability in the requisite disciplines. Furthermore, since assessment of the health risks of environmental agents requires the coordinated efforts of biologists, chemists, epidemiologists, mathematicians, physicians, toxicologists, and scientists of other disciplines, few institutions have the multidisciplinary teams needed for such research. Measures to develop such collaboration on a broader scale and to focus it on key problems deserve to be pursued. Inherent in the development of the needed scientific capability is the training of scientists with the necessary expertise. For this purpose, there is need for more long-term support of graduate and postgraduate training in toxicology,

epidemiology, and other disciplines crucial to progress in the field.

## 7.0 Conclusions and Recommendations

Toxicants that may pose significant risks to human health can be encountered in air, water, food, consumer products, the home, the workplace, and other environments. Although in some instances the risks from such toxicants have been adequately controlled by limiting human exposure to the agents in question, other environmental toxicant-related risks to health continue to exist, as reported in "Unfinished Business." It is important, therefore, to assess any such risks and to develop measures for controlling them.

In order to set appropriate priorities for allocating resources to different environmental risk problems, the relative importance of each problem must be evaluated. For this purpose, some sort of comparative risk assessment is required. At present, however, such assessments must be interpreted with caution, in view of their large uncertainties.

Among the most serious sources of uncertainty is the inadequacy of available data on the extent of human exposure to the toxicants in question. In few cases has the concentration of a given toxicant in the relevant exposure media been characterized well enough in time and space to enable precise estimation of the patterns and extent of human exposure to the agent in question. In even fewer cases have environmental exposure measurements of a toxicant been accompanied by systematic analyses of its uptake, distribution, metabolism, and retention in the tissues of persons differing in age, sex, dietary habits, lifestyle, occupation, and other potentially important variables. In the absence of such information, quantitative estimation of the extent of human exposure to most toxicants, and of the exposure-dose relationships relevant to assessment of their risks to human health, must remain highly tenuous.

To provide exposure-dose data of the quantity and quality needed for more adequate assessment of environmental risks to human health, there is need for far more systematic monitoring of the environment and of human tissues, including the use of biomarkers and other newly-developing measures of exposure and effects. Toward this end, expanded research and data collection are

recommended, including closer interagency cooperation and data-linkages to facilitate development of the requisite networks and databases.

Another serious limitation in risk assessment results from the uncertainty inherent in evaluating the toxicity of virtually any environmental toxicant under conditions of chronic low-level exposure. For relatively few environmental agents has toxicity for humans been observed directly, even at relatively high doses, and in these instances the relevant dose-response relationships and mechanisms of toxicity have not been defined well enough to enable risk assessment without reliance on uncertain dose-effect models for extrapolation to the low dose domain. In these cases the assessments also involve uncertain assumptions about the influence of age, sex, and other factors on the susceptibility of the exposed persons, as well as the extent to which the effects of a given toxicant may be modified by the action of other environmental agents. For the majority of environmental toxicants, human data are lacking altogether, with the result that assessment of their potential risks must be based on extrapolation from studies of laboratory animals and other surrogate test systems, that involves uncertainty about species differences as well as the other uncertainties mentioned above. For thousands of additional chemicals to which humans may be exposed, no toxicological data of any kind are available as yet, precluding even the most rudimentary assessment of their potential impacts on human health.

In order to improve the assessment of environmental risks to human health, the following steps must be taken to strengthen the underlying toxicological science, methodology, and database: 1) further research on the development and validation of toxicological testing methods, including analyses of structure-activity relationships and other correlational techniques, short-term in vitro and in vivo tests, and long-term and inter-generational animal bioassays; 2) use of these testing methods to screen new chemicals before they enter commercial use and to test expeditiously existing chemicals identified as possible hazards; 3) expanded epidemiological study of human populations, with particular reference to populations at increased risk because of elevated levels of exposure or heightened susceptibility; 4) studies to elucidate the mechanisms and dose-response relationships of the various types of health effects that may be associated with low-level exposure to different toxicants and combinations of toxicants; and 5) inter-

national, national, and local interagency cooperation in the collection of vital statistics and other data, record-linkage, and networking, so as to enlarge the toxicological database as rapidly as possible.

In view of the above limitations in the available exposure and toxicity data, the risk rankings that were assigned in "Unfinished Business" must be regarded as provisional. Whether the rankings could be improved greatly in the absence of more adequate data is problematic. Pending better data and scientific knowledge, it may be inferred that those environmental problem areas involving the highest probability of proximal human exposure to toxicants are likely to pose the largest potential risks to human health. Such situations include those encountered by the general population through exposure to pollutants in ambient outdoor air, indoor air, drinking water, food, and consumer products, and those encountered by workers in the workplace. It is not illogical, therefore, that the environmental problems assigned the highest relative risk rankings for cancer and/or other adverse health effects in "Unfinished Business" were representative of such exposure situations; i.e., criteria and hazardous air pollutants, indoor air pollution and indoor radon exposure, drinking water, pesticide residues on food, pesticide application, consumer product exposure, and occupational exposure to chemicals.

Among the latter problems, however, it should be noted that the "high" risk rankings for the following problems are supported more firmly by the available data than are the rankings for others:

- criteria air pollutants
- hazardous air pollutants
- indoor air pollutants (excluding radon)
- indoor radon
- drinking water
- pesticide application
- occupational exposure to chemicals)

Another factor seriously complicating the comparative ranking of environmental risks to health is the diversity of the health outcomes that are involved. While cancer is clearly a serious health outcome, a cancer occurring in a 90-year-old man could be considered less serious than mental retardation in a newborn infant. In any case, however, quantification of the health impacts

of different types of toxicant-induced effects is complicated, since it must take into account both the aggregate numbers of all persons who are affected, including those affected indirectly as well as those affected directly, and the severity of the effects judged in terms of their physical, psychological, social, and economic impacts. Detailed consideration of these ramifications calls for more detailed analyses than have been conducted thus far and may not be feasible without further refinement in the data.

In addition to the relative magnitudes of the health impacts of different environmental risks, their controllability must also be considered in evaluating alternative risk-reduction strategies. It must not be forgotten, therefore, that the adverse health outcomes caused by certain environmental toxicants--such as carcinogens--may not appear until decades after exposure, with the result that termination of exposure to the toxicants does not suffice to abolish risk in those who have already been exposed. It is also noteworthy that certain environmental toxicants--such as heavy metals, PCBs, and long-lived radionuclides--tend to persist indefinitely in the environment and may gradually become concentrated in certain components of the human food chain. Consequently, such toxicants may continue to pose a threat to human health long after their release into the environment has been halted.

It must also be recognized that, in many instances over the past 20 years, EPA has undertaken programs to reduce risks attributable to specific substances in the environment, either through legislative mandate (as in the case of PCBs under TSCA) or through utilizing regulatory powers (as in the case of lead in gasoline). However, none of these risk reduction programs has been complete in terms of absolutely banning all production and use (including in situ uses as with PCB containing electrical equipment) of these substances. Residual risks remain associated with these continued uses, including waste disposal. Nevertheless, EPA has already devoted considerable efforts to identify the risks of these substances, through epidemiological studies, other research on toxicity, and exposure assessments. Similarly, the private sector has already invested in partial control technologies or substitute materials. Thus the major expenses of risk reduction may in these cases have already been incurred (e.g., capital investment in catalytic cracking units at oil refineries to produce additives for unleaded gasoline). In these cases, the cost of

further risk reduction--even risk elimination--may be relatively small, as compared to undertaking risk reduction de novo for substances and exposures not previously addressed in any substantial fashion. EPA should consider these factors in evaluating strategies for relative risk prioritization and for implementing risk reduction measures.

Limited as the existing data may be for assessing recognized risks to health, our capacity to predict future risks and to respond to emerging problems is even more severely limited. There is need, therefore, for the establishment of a formal mechanism for risk anticipation, including an in-house expert committee, peer oversight, and a means of supporting long-range research on emerging problem areas. Emerging problems that merit attention at this time would appear to include the potential risks associated with low-level exposure to 60 Hz magnetic fields.

Finally, the development of any long-range strategy to improve environmental risk assessment and risk reduction will require provision for developing and sustaining the needed scientific capability and workforce. This will necessitate programs for graduate and postgraduate training in the relevant disciplines, as well as the development of measures to enlist and nurture the participation of the scientific community in the kinds of interdisciplinary research that are required.

8.0

Appendices

8.1 Case studies

8.1.1 Ozone Case Study

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### 8.1.1.1 Introduction and Background

Ozone ( $O_3$ ) was recognized by Schonbein (1851) as a powerful lung irritant soon after its initial synthesis (Bates, 1989). It was first listed among the American Conference of Governmental Industrial Hygienists (ACGIH) list of Threshold Limit Values (TLVs) for occupational exposure in 1946, with an eight-hour time weighted average (TWA) concentration limit of 1 ppm. In 1954, the TLV was reduced to 0.1 ppm TWA. The current ACGIH TLV of 0.1 ppm, as a ceiling value, was adopted in 1989.

Health effects among the general community were first reported among high school athletes in California, in terms of lesser performance on high exposure days (Wayne et al., 1967). The initial National Ambient Air Quality Standard (NAAQS) of 1971 was 0.08 ppm of total oxidant. The NAAQS was revised in 1979 to 0.12 ppm of  $O_3$ , and was based upon clinical studies by DeLucia and Adams (1977) showing that exercising asthmatic adults exposed for 1 hr to 0.15 ppm in a test chamber had increased cough, dyspnea, and wheezing, along with small, but nonsignificant reductions in pulmonary function (U.S. EPA, 1986). A small margin of safety was applied to protect against adverse effects not yet uncovered by research and effects whose medical significance is a matter of disagreement. In its May 1, 1989 closure letter to the EPA Administrator on its reviews of the 1986 Ozone Criteria Document (CD), the 1988 CD Supplement, and the Agency Staff Paper of 1988, the Clean Air Scientific Advisory Committee (CASAC) split on its recommendation to the Administrator concerning a scientifically supportable upper bound to the range for a revised 1 hr NAAQS, with half the members accepting 0.12, and the other half recommending a reduced upper bound (CASAC-1989).

The effects of concern with respect to acute response in the population at large are reductions in lung function and increases in respiratory symptoms, airway reactivity, airway permeability, and airway inflammation. For asthmatics, there are increased rates of medication usage and restricted activities. Margin of safety considerations include: 1) the influence of repetitive elicitation of such responses in the progression of chronic damage to the lung of the kinds seen in chronic exposure studies in rats and monkeys; and 2) evidence from laboratory and field studies that ambient air co-pollutants potentiate the responses to  $O_3$ .

O<sub>3</sub> is almost entirely a secondary air pollutant, formed in the atmosphere through a complex photochemical reaction sequence requiring reactive hydrocarbons, nitrogen dioxide (NO<sub>2</sub>) and sunlight. It can only be controlled by reducing ambient air concentrations of hydrocarbons, NO<sub>2</sub>, or both. NO and NO<sub>2</sub> are primary pollutants, known collectively as NO<sub>x</sub>. In the atmosphere, NO is gradually converted to NO<sub>2</sub>. One of the major sources of hydrocarbons and NO<sub>x</sub>, i.e., motor vehicles, has been the major target of control efforts, and major reductions (> 90%) have been achieved in hydrocarbon emissions per vehicle. NO<sub>x</sub> from stationary source combustion has increased, and there has also been major increases in vehicle miles driven. The net reduction in exposure has been modest at best. In 1986-1988, there were high levels of ambient O<sub>3</sub> with exceedances of the current NAAQS recorded in 101 communities with a total population of 112 million people.

The risks remain very high for demonstrable acute responses, and potentially very high for the still poorly defined chronic health risks, especially premature aging of the lungs.

#### 8.1.1.2. Current Knowledge on Exposure and Sources

##### A. Exposures

1. Personal Air No personal monitors have been available; hence there are no data.

##### 2. Microenvironmental Air

a. Ambient Air Extensive data are available from continuous monitors at many urban and some rural sites since the early 1970's. Most readily available data are on one hour maximum concentrations and numbers of exceedances of the one hour NAAQS of 0.12 ppm. Data on distributions of concentrations over various averaging times are not normally reported.

b. Indoor Air Relatively few data are available. A recent review by Weschler et al. (1989) indicates that indoor/outdoor ratio (I/O) varies from 0.2 to 0.8, averaging about 0.5.

c. Transportation O<sub>3</sub> within motor vehicles is generally lower than in outdoor air because of efficient scrubbing by tailpipe NO in transportation corridors. O<sub>3</sub> in cabins of jetliners flying in the stratosphere can be quite high due to high concentrations in compressed stratospheric air used to ventilate the cabins (NRC, 1988).

d. Other Electrostatic air cleaners generate O<sub>3</sub> that can be distributed widely through ducts to occupied spaces. Xerographic copying machines can elevate O<sub>3</sub> in rooms containing them. A major source of occupational exposure is arc welding.

3. Ingestion Not applicable to O<sub>3</sub>

4. Dermal Not applicable to O<sub>3</sub>

5. Overall Exposure Biomarkers Not applicable to O<sub>3</sub>

#### B. Populations Exposed

1. Healthy Adults With children, healthy young adults are the most sensitive to the acute effects of O<sub>3</sub> especially those engaged in active exercise out-of-doors (McDonnell et al., 1983; McDonnell et al., 1985).

2. Infants and Children No data on infants. Children and adolescents are, with young adults the most responsive to acute effects. Children may be at greater risk because of more time out-of-doors.

3. Elderly Healthy elderly adults are less responsive than younger people to O<sub>3</sub> in terms of acute effects (Drechsler-Parks et al., 1987; Reisenauer et al., 1988).

4. Susceptible Subgroups Healthy children and young adults are the most responsive to O<sub>3</sub> in terms of acute functional decrements, and no biomarkers of susceptibility have yet been identified. Since exercise during exposure potentiates acute responses, healthy individuals exercising out-of-doors are an especially susceptible group.

Another susceptible subgroup are asthmatics, based on reports of increased medication usage and restricted activities during high

O<sub>3</sub> days. Whittemore and Korn (1980) reported that daily asthma attack rates were increased on days with high oxidant levels in Los Angeles area communities. Holguin et al. (1985) reported a similar association for asthmatics in Houston.

### C. Factors Modifying Effective Dose

1. Activity Level The effect of ventilation rate on acute functional response has been summarized by Hazucha (1987). Response increases progressively with minute ventilation over the range of available data (0-68 L/min). However, at levels above 80 L/min, increasing ventilation reduces the response (Spektor et al., 1988).

2. Pre-existing Disease No data available.

3. Constitutional Factors Affecting Uptake and Retention Studies of regional particle deposition in healthy humans show a large degree of variability in conductive airway caliber, affecting the distribution and depth of penetration of tidal air (Bohning et al., 1975; Chan et al., 1980). Combined with O<sub>3</sub> dosimetry models (Miller et al., 1978; Overton et al., 1987). These differences could account for unexplained variability in acute responsiveness to O<sub>3</sub> among healthy persons.

4. Constitutional Factors Affecting Metabolic Transformation Not applicable to O<sub>3</sub>

### D. Sources

1. Energy Production Sources of hydrocarbons and nitrogen oxides vary greatly by region, season, and time of day. Stationary fossil fuel combustion accounts for almost half of ambient NO<sub>x</sub>.

2. Transportation Motor vehicles account for almost 31% of NO<sub>x</sub> emissions and some 26% of the hydrocarbons. Transportation in total accounted for 41% of the NO<sub>x</sub> and 33% of hydrocarbons.

3. Other Sources of Hydrocarbons Other sources of hydrocarbons vary greatly according to region and season. In the southeastern U.S. in the summer the transpiration of trees and shrubs can be the dominant source. Other significant sources are fugitive emissions from petrochemical plants, sewage treatment plants, agricultural operations and consumer product usage.

#### 8.1.1.3 Toxicity and Health Effects

##### A. Human - Clinical Studies

1. Laboratory Studies The major focus of the extensive body of data on the health effects of a single day's maximum hourly exposure to ambient O<sub>3</sub>. The 1971 and 1979 NAAQS for photochemical oxidants were based on the maximum 1 hr concentrations as the relevant index of exposure, and this, in turn, has focused most of the clinical research on exposure protocols involving either 1 or 2 hours of exposure. However, recent research has shown that effects can be produced with exposures as short as 5 minutes (Fouke et al., 1988), and that various effects become progressively larger as exposures at a given concentration are extended out to 6.6 hours (Folinsbee et al., 1988; Horstman et al., 1989).

There are more data on respiratory function responses than on any of the other coincident responses to short-term O<sub>3</sub> inhalation. The major debate about very small, but statistically significant, decrements in function from such studies is how to interpret their health significance (Lippmann, 1988).

The inhalation of O<sub>3</sub> causes concentration dependent mean decrements in exhaled volumes and flow-rates during forced expiratory maneuvers, and the decrements increase with depth of breathing (Hazucha, 1987). There is a wide range of reproducible responsiveness among healthy subjects (McDonnell et al., 1985), and functional responsiveness to O<sub>3</sub> is no greater, and usually lower, among cigarette smokers (Kagawa, 1984; Shephard et al., 1983), older adults (Drechsler-Parks et al., 1987; Reisenauer et al., 1988), asthmatics (Koenig et al., 1987; Linn et al., 1983), and patients with chronic obstructive pulmonary disease (COPD) (Linn et al., 1983; Solic et al., 1982). The only exception is that patients with allergic rhinitis had greater changes in airway resistance (McDonnell et al., 1987).

The effects of O<sub>3</sub> on respiratory function accumulate over time. Folinsbee et al. (1988) undertook a chamber exposure study of 10 adult male volunteers involving 6.6 hours of O<sub>3</sub> exposure at 120 ppb. Moderate exercise was performed for 50 min/h for 3 hours in the morning, and again in the afternoon. They found that the functional decrements become progressively greater after each hour of exposure, reaching average values of 400 ml for forced vital capacity (FVC) and 540 ml for forced expiratory volume in one second (FEV1) by the end of the day. Follow-up studies by Horstman et al. (1989) were done on 21 adult males with 6.6 hour exposures at 80, 100, and 120 ppb. The exposures at 120 ppb produced very similar responses, e.g., a mean FEV1 decline of 12.3 percent while those at 80 and 100 ppb showed lesser changes that also became progressively greater after each hour of exposure.

The time scale for the biological integration of O<sub>3</sub> exposure can also be deduced from the rate at which the effects dissipate. Folinsbee and Hazucha (1989) studied 18 young adult females exposed to 350 ppb O<sub>3</sub> for 70 min, including two 30 min periods of treadmill exercise at 40 L/min. The responses were highly variable, from zero to 40%. Their mean decrement in FEV1 at the end of the exposure was 21 percent. After 18 hours, their mean decrement was 4 percent, while at 42 hours it was 2 percent.

In summary, it is now clear that the respiratory function effects can accumulate over many hours, and that an appropriate averaging time for transient functional decrements caused by O<sub>3</sub> is 6 hours. Thus, there is less scientific basis for the current health based exposure limit with an averaging time of 1 hour than previously believed. Since O<sub>3</sub> exposures in ambient air now can have broad peaks with 8 hour averages equal to 90 percent of the peak 1 hour averages (Rombout et al., 1986), the functional decrements associated with ambient concentrations are likely to be much greater than those predicted on the basis of the responses in the chamber studies following 1 to 2 hour exposures.

Respiratory symptoms have been closely associated with group mean pulmonary function changes in adults acutely exposed in controlled exposures to O<sub>3</sub>. However, Hayes et al. (1987) found only a weak-to-moderate correlation between FEV1 changes and symptoms severity when the analysis is conducted using individual data.

Exposure to O<sub>3</sub> can also alter the responsiveness of the airways to other bronchoconstrictive challenges as measured by changes in respiratory mechanics. For example, Folinsbee et al. (1988) reported that airway reactivity to the bronchoconstrictive drug methacholine for the group of subjects as a whole was approximately doubled following 6.6 hour exposures to 120 ppb O<sub>3</sub>. On an individual basis, Folinsbee et al. (1988) found no apparent relationship between the O<sub>3</sub>-associated changes in methacholine reactivity and those in FVC or FEV<sub>1</sub>. The follow up tests by Horstman et al. (1989), involving 6.6 hour exposures to 80, 100 and 120 ppb indicated 56, 89 and 121 percent increases in methacholine responsiveness respectively.

Koren et al. (1989) reported that an inflammatory response, as indicated by increased levels of PMN, was also observed in BAL fluid from subjects exposed to 100 ppb O<sub>3</sub> for 6.6 hours. The 6.6 hours at 100 ppb O<sub>3</sub> produced a 4.8x increase in PMNs at 18 hours after the exposure. Since the amount of O<sub>3</sub> inhaled in the 100 ppb protocol was -2.5 µg, while it was -3.6 µg in a prior 400 ppb protocol (Koren et al., 1989), we might have expected a  $2.5/3.6 \times 8.2 = 5.7$  times increase in PMNs. The close correspondence of the observed to expected ratio suggests that lung inflammation from inhaled O<sub>3</sub> also has no threshold down to ambient background O<sub>3</sub> levels.

Foster et al. (1987) studied the effect of 2-hour exposures to 200 or 400 ppb O<sub>3</sub> with intermittent light exercise on the rates of tracheobronchial mucociliary particle clearance in healthy adult males. The 400 ppb O<sub>3</sub> exposure produced a marked acceleration in particle clearance from both central and peripheral airways, as well as a 12 percent drop in FVC. It is of interest that the 200 ppb O<sub>3</sub> exposure produced a significant acceleration of particle clearance in peripheral airways, but failed to produce a significant reduction in FVC, suggesting that significant changes in the ability of the deep lung to clear deposited particles take place before significant changes in respiratory function take place.

The weight of the evidence from these results, showing both functional and biochemical responses that accumulate over multiple hours and persist for many hours or days after exposure ceases, is clear and compelling.

2. Field Studies Spektor et al. (1988a) found that children at summer camps with active outdoor recreation programs had greater decrements in lung function than children exposed to O<sub>3</sub> at comparable concentrations in chambers for 1 or 2 hours. Furthermore, their activity levels, although not measured, were known to be considerably lower than those of the children exposed in the chamber studies while performing very vigorous exercise. Since it is well established that functional responses to O<sub>3</sub> increase with levels of physical activity and ventilation (Hazucha, 1987), the greater responses in the camp children had to be caused by other factors, such as greater cumulative exposure, or to the potentiation of the response to O<sub>3</sub> by other pollutants in the ambient air. Cumulative daily exposures to O<sub>3</sub> were generally greater for the camp children, since they were exposed all day long rather than for a 1 or 2-hour period preceded and followed by clean air exposure.

A follow-up (Spektor et al. 1988b) study addressed the issue of the potentiation of the characteristic functional response to inhaled O<sub>3</sub> by other environmental cofactors. It involved healthy adult nonsmokers engaged in a daily program of outdoor exercise with exposures to an ambient mixture containing low concentrations of acidic aerosols and NO<sub>2</sub> as well as O<sub>3</sub>. Each subject did the same exercise each day, but exercise intensity and duration varied widely between subjects, with an average minute ventilation of 79 liters, and with duration of daily exercise averaging 29 min. Respiratory function measurements were performed immediately before and after each exercise period. O<sub>3</sub> concentrations during exercise ranged from 0.021 to 0.124 ppm. All measured functional indices showed significant (p<0.01) O<sub>3</sub> associated mean decrements. It was concluded that ambient cofactors potentiate the responses to O<sub>3</sub>.

## B. Human - Epidemiology

1. Acute Effects Kinney et al. (1988) studied school children in Kingston and Harriman, Tennessee, whose lung function was measured in school on up to six occasions during a 2-month period in the late winter and early spring. Child specific regressions of function versus maximum 1-hour O<sub>3</sub> during the previous day indicated significant associations between O<sub>3</sub> and function, with coefficients similar to those seen in the summer camp studies of Lippmann et al. (1983) and Spektor et al. (1988a). Since children in school may be expected to have relatively low

activity levels, the relatively high response coefficients may be due to potentiation by other pollutants or to a low-level of seasonal adaptation. Kingston-Harriman is notable for its relatively high levels of aerosol acidity. As shown by Spengler et al. (1989), Kingston-Harriman has higher annual average and higher peak acid aerosol concentrations than other cities studied, i.e., Steubenville, Ohio; St. Louis, Missouri; and Portage, Wisconsin. Alternatively, the relatively high response coefficients could have been due to the fact that the measurements were made in the late winter and early spring. Linn et al. (1988) have shown evidence for a seasonal adaptation, and children studied during the summer may not be as responsive as children measured earlier in the year.

2. Chronic Effects Epidemiologic studies of populations living in Southern California suggest that chronic oxidant exposures do affect baseline respiratory function. Detels et al. (1987) compared respiratory function at two points in time five years apart in Glendora (a high oxidant community) and in Lancaster (a lower oxidant community-but not low by national standards). Baseline function was lower in Glendora, and there was a greater rate of decline over 5 years. The annual change in lung function in Glendora was much greater than that in Lancaster, that, in turn, was much greater than that in Tucson, Arizona (Knudson et al., 1983) for a comparable population of Caucasian non-smokers. The second highest 1 hour  $O_3$  concentrations in Tucson in all of 1981, 1982, and 1983 were 100, 120 and 110 ppb (EPA, 1986). In Lancaster there were 58 days in 1985 with 1 hr  $O_3$  maxima greater than 120 ppb, while in Azusa, adjacent to Glendora, there were 117 days in 1985 with 1 hr  $O_3$  maxima greater than 120 ppb. Thus, the three different rates of function decline appear to suggest an exposure-response relationship with potentially significant health importance.

Further evidence for chronic effects of  $O_3$  were recently reported by Schwartz (1989) based upon an analysis of pulmonary function data in a national population study in 1976-80, i.e., the second National Health and Nutrition Examination Survey (NHANES II). Using ambient  $O_3$  data from nearby monitoring sites, he reported a highly significant  $O_3$  associated reduction in lung function for people living in areas where the annual average  $O_3$  concentrations exceeded 40 ppb. On the other hand, there were no significant correlations with other indices of  $O_3$  exposure, and the results should be interpreted cautiously at this time.

### C. Animal Toxicology

1. Acute Effects Studies in laboratory animals have examined the roles of O<sub>3</sub> concentration and exposure time on biochemical and cellular responses. Rombout et al. (1989) exposed mice and rats to 380, 750, 1250, and 2,000 ppb O<sub>3</sub> for 1, 2, 4, and 8 hours, and measured broncho-alveolar lavage (BAL) protein with both daytime and nighttime exposures. Observation times extended from 1 to 54 hours. The responses varied with O<sub>3</sub> concentration, duration of exposure, time after the start of the exposure, and minute volume, with time of exposure having a greater than proportional influence. For 4 and 8-hour exposures, the protein content of BAL peaked at 24 hours, and remained at elevated levels even at 54 hours. As indicated previously, Koren et al. (1989) found increased BAL protein in humans 18 hours after an exposure to 100 ppb O<sub>3</sub> for 6.6 hours.

The effects of O<sub>3</sub> on mucociliary particle clearance have been studied in rats and rabbits. Rats exposed for 4 hours to O<sub>3</sub> exhibited a slowing of particle clearance at 800 ppb (Frager et al., 1979; Kenoyer et al., 1981). Rabbits exposed for 2 hours at 100, 250 and 600 ppb O<sub>3</sub> showed a concentration dependent trend of reduced clearance rate with increasing concentrations, with the change at 600 ppb being - 50 percent and significantly different from control (Schlesinger and Driscoll, 1987).

Phipps et al. (1986) examined the effects of acute exposure to O<sub>3</sub> on some of the factors that affect mucociliary transport rates in studies in which sheep were exposed to 500 ppb O<sub>3</sub> for 2 hours on two consecutive days. The exposures produced increased basal secretion of sulfated glycoproteins, but had no effect on ion fluxes. Their histological examination indicated a moderate hypertrophy of submucosal glands in the lower trachea, and they concluded that the exposure caused airway mucus hypersecretion.

Studies of the effects of O<sub>3</sub> on alveolar macrophage mediated particle clearance during the first few weeks have also been performed in rabbits. Rabbits exposed to 100, 600, or 1200 ppb O<sub>3</sub> once for 2 hours had accelerated clearance at 100 ppb and retarded clearance at 1200 ppb. Rabbits exposed for 2 hours/day for 13 consecutive days at 100 or 600 ppb O<sub>3</sub> had accelerated clearance for the first 10 days, with a greater effect at 600 ppb (Driscoll et al., 1986).

The responses of the alveolar macrophages to these exposures was examined by Driscoll et al. (1987). These studies demonstrated significant alterations in the numbers and functional properties of alveolar macrophages as a result of single or repeated exposure to 100 ppb ozone, a level frequently encountered in areas of high photochemical air pollution.

Both in vivo and in vitro studies have demonstrated that O<sub>3</sub> can affect the ability of the immune system to defend against infection. Increased susceptibility to bacterial infection has been reported in mice at 80 to 100 ppb O<sub>3</sub> for a single 3 hour exposure (Coffin et al., 1967; Ehrlich et al., 1977; Miller et al., 1978). Related alterations of the pulmonary defenses caused by short-term exposures to O<sub>3</sub> include: impaired ability to inactivate bacteria in rabbits and mice (Coffin et al., 1968; Coffin and Gardner, 1972; Goldstein et al., 1977; Ehrlich et al., 1979), and impaired macrophage phagocytic activity, mobility, fragility and membrane alterations, and reduced lysosomal enzymatic activity (Witz et al., 1983; Dowell et al., 1970; Hurst and Coffin, 1971; Hurst et al., 1970; Goldstein et al., 1971a; Goldstein et al., 1971b; McAllen et al., 1981; Amoruso et al., 1981). Some of these effects have been shown to occur in a variety of species including mice, rats, rabbits, guinea pigs, dogs, sheep, and monkeys.

Other studies indicate similar effects for short-term and subchronic exposures of mice to O<sub>3</sub> combined with pollutants such as SO<sub>2</sub>, NO<sub>2</sub>, H<sub>2</sub>SO<sub>4</sub> and particles (Gardner et al., 1977; Aranyi et al., 1983; Ehrlich, 1980; Grose et al., 1980a; Grose et al., 1980b; Phalen et al., 1980). Similar to human pulmonary function response to O<sub>3</sub> activity levels of mice exposed to O<sub>3</sub> has been shown to play a role in determining the lowest effective concentration that alters the immune defenses (Illing et al., 1980). In addition, the duration of exposure must be considered. In groups of mice exposed to 200 ppb O<sub>3</sub> for 1, 3, or 6 hours, superoxide anion radical production decreased 8, 18, and 35%, respectively, indicating a progressive decrease in bacteriocidal capacity with increasing duration of exposure (Amoruso and Goldstein, 1988).

The major limitation of this large body of data on the influence of inhaled O<sub>3</sub> on lung infectivity is that it requires uncertain interspecies extrapolating in order to estimate the possible effects of O<sub>3</sub> on infectivity in humans.

2. Chronic Effects It is well established that repetitive daily exposures, at a level which produces a functional response upon single exposure, result in an enhanced response on the second day, with diminishing responses on days 3 and 4, and virtually no response by day 5 (Farrell et al., 1979; Folinsbee et al., 1980; Hackney et al., 1977). This functional adaptation to exposure disappears about a week after exposure ceases (Horvath et al., 1981; Kulle et al., 1982). The adaptation phenomenon has led some people to conclude that transient functional decrements are not important health effects. On the other hand, recent research in animals has shown that persistent damage to lung cells accumulates even as functional adaptation takes place. Tepper et al. (1987) exposed rats to 350, 500, or 1000 ppb O<sub>3</sub> for 2.25 hours on five consecutive days. Carbon dioxide (8%) was added to the exposure during alternate 15 min periods to stimulate breathing and thereby increase O<sub>3</sub> uptake and distribution. Tidal volume, frequency of breathing, inspiratory time, expiratory time and maximal tidal flows were affected by O<sub>3</sub> during day 1 and 2 at all O<sub>3</sub> concentrations. By day 5, these O<sub>3</sub> responses were completely adapted at 350 ppb, greatly attenuated at 500 ppb, but showed no signs of adaptation in the group exposed to 1000 ppb. Unlike the pulmonary function data, light microscopy indicated a pattern of progressive epithelial damage and inflammatory changes associated with the terminal bronchiole region. These data suggest that attenuation of the pulmonary functional response occurs while aspects of the tissue response reveal progressive damage.

The effects of multi-day O<sub>3</sub> exposures of laboratory animals on particle clearance from the lungs and on lung infectivity were reviewed previously. They also show that O<sub>3</sub>-induced transient effects often become greater with repetitive exposures.

Last (1989) reported synergistic interaction in rats, in terms of a significant increase in lung protein content, following 9 day exposures at 200 ppb O<sub>3</sub> with 20 or 40 µg/m<sup>3</sup> H<sub>2</sub>SO<sub>4</sub>, and a non-significant increase for 9 days at 200 ppb O<sub>3</sub> with 5 µg/m<sup>3</sup> H<sub>2</sub>SO<sub>4</sub>.

The highest O<sub>3</sub> dose is received at the acinus, where the terminal bronchioles lead into alveolar ducts, and a series of studies has shown that the effects of inhaled O<sub>3</sub> on lung structure is also greatest in this region. Using morphometric techniques selectively focussed on this limited region of the lung. Barry et al. (1985) showed that significant changes occurred in the alveoli

just distal to the terminal bronchioles in rats exposed for 12 hr/day for 6 or 12 weeks to 120 or 240 ppb O<sub>3</sub>. From physiological studies of rats that were simultaneously exposed Raub et al. (1983) reported that there were significant increases in the vital capacity and end expiratory volume that suggested alterations in distensibility of the lung tissue.

The plausibility of accelerated aging of the human lung due to chronic O<sub>3</sub> exposure is greatly enhanced by the results of recent chronic animal exposure studies in rats and monkeys, especially those in rats of Huang et al. (1988) and Grose et al. (1989) using a daily cycle with a 180 ppb average over 9 hrs superimposed on a 13 hr base of 60 ppb, and those in monkeys of Hyde et al. (1989) and Tyler et al. (1988) using 8 hr/day of 150 and 250 ppb. The persistent cellular and morphometric changes produced by these exposures in the terminal bronchioles and proximal alveolar region, and the functional changes consistent with a stiffening of the lung reported by Raub et al. (1983) and Tyler et al. (1988) are certainly consistent with the results of the epidemiological studies.

There has long been interest in the possible role of O<sub>3</sub> in lung cancer because of its radiomimetic properties. A comprehensive review of these issues has recently been prepared by Witschi (1988). His analysis indicated that there is, to date, no epidemiological or experimental evidence to support the hypothesis that O<sub>3</sub> is a pulmonary carcinogen. There are data that show that O<sub>3</sub> increases the incidence of lung tumors in strain A mice, but the tumor yield can be either increased or decreased depending on the exposure protocol. Also, the proliferation of pulmonary neuroendocrine cells, the precursor cells for small cell lung cancer can be altered by O<sub>3</sub> exposure. Witschi concluded that there is little evidence to implicate O<sub>3</sub> as a pulmonary carcinogen, but that it might modify and influence the carcinogenic process in the lung.

3. Mechanistic Studies investigating mechanisms of O<sub>3</sub> toxicity in animals have been included in the previous discussions. The best discussion on the mechanisms of the acute functional responses in humans was recently presented by Hazucha et al (1989).

#### D. In-Vitro Assays

1. Genotoxic Effects An EPA Criteria Document (Air Quality Criteria for Ozone and Other Photochemical Oxidants, 1986) reviewed the genotoxic effects of ozone. It noted that "the mutagenic properties of O<sub>3</sub> have been demonstrated in procaryotic and eucaryotic cells. Only one study, however, (Hamelin and Chung, 1975a, with E. coli) investigated the mutagenic effect of O<sub>3</sub> at concentrations of less than 1 ppm. The results clearly indicate that if cells in cultures are exposed to sufficiently high concentrations of O<sub>3</sub> for significantly long periods, mutations will result. The relevance of the presently described investigations to human or even other mammalian mutagenicity is not apparent. Additional studies with human and other mammalian cells will be required before the mutagenic potency of O<sub>3</sub> toward these species can be determined."

A more recent review of the pathobiology of O<sub>3</sub>-induced damage at the cellular and molecular levels by Steinberg et al., (1990) concluded that O<sub>3</sub> linearizes circular DNA and induces O<sub>3</sub> sensitive pneumocytes to repair its DNA. DNA adducts from O<sub>3</sub> exposure free radical damage effect--aging, cellular transformation, mutagenesis, carcinogenesis, and cell death. DNA-binding proteins are potent positive and negative regulators, enhancers, or silencers of gene expression. Part of their action, may be related to their ability to initiate the binding sequence of DNA transcription proteins and thus form complexes. Alteration of DNA-binding sites by O<sub>3</sub> adducts may affect mRNA transcription due to altered binding by DNA-binding proteins.

In a recent study by Harder et al., (1990) the effect of in vitro O<sub>3</sub> exposure on human peripheral blood natural killer (NK) cell activity was measured using K562 tumor target cells. The NK activity was inhibited in a time-dependant manner with marked suppression observed after 6 hours at three different levels of O<sub>3</sub> exposure (1.0, 0.5, and 0.18 ppm) and effector cell:target (E:T) ratios (50:1, 25:1, and 12.5:1) compared to air controls (p < 0.05). The capacity of O<sub>3</sub> exposed NK cells to kill tumor cells decreased in a linear fashion as the level of O<sub>3</sub> increased from 0.18 to 1.0 ppm (p = 0.006 at 50:1; 0.004 at 25:1). Unexposed cells treated with supernatant from O<sub>3</sub> exposed cells showed no decrease in NK activity.

2. Cellular Function Leikauf et al. (1988) investigated the hypothesis that oxidant damage to the tracheal epithelium may result in elaboration of various eicosanoids. To examine eicosanoid metabolism after exposure to 100 ppb to 10.0 ppm ozone, epithelial cells derived from bovine trachea were isolated and grown to confluency. Monolayers were alternately exposed to ozone and culture medium for 2 hours. There were O<sub>3</sub>-induced increases in cyclooxygenase and lipoxxygenase product formation. Ozone concentrations as low as 100 ppb produced an increase in prostaglandin F<sub>2α</sub>. Thus, ozone can augment eicosanoid metabolism in airway epithelial cells.

In a study focussed on the effects of the 6 week exposures at 250 ppb on the terminal bronchioles, Barry et al. (1988) reported that exposure to O<sub>3</sub> produced alterations in the surface characteristics of ciliated and nonciliated (Clara) cells in rats.

Rats were also exposed to O<sub>3</sub> in tests in which there was a daily cycle with a baseline of 60 ppb for 13 hr with a 5 day/week broad peak for 9 hr averaging 180 ppb and containing a 1 hr maximum of 250 ppb for a period of 3 or 12 weeks. Combining the results of all these tests, Huang et al. (1988) reported that hyperplasia of type I alveolar cells in the proximal alveoli was linearly related to the cumulative O<sub>3</sub> exposure. Thus, there is no threshold for cumulative lung damage and any future standard to protect against chronic health damage from O<sub>3</sub> should have a seasonal or annual averaging time.

Rats exposed for 6 weeks to clean air or to O<sub>3</sub> using the daily cyclic exposure regimen used by Huang et al. (1988) were exposed once for 5 hr to an asbestos aerosol by Pinkerton et al. (1988). When sacrificed 30 days later, the fiber count in the lungs of the O<sub>3</sub> exposed animals were 3 times greater than in the sham exposed animals. Thus, subchronic O<sub>3</sub> exposure can increase the effective dose of insoluble particles that may have toxic and/or carcinogenic effects.

One year of O<sub>3</sub> exposure to the same daily cycle caused: (1) functional lung changes indicative of a "stiffer" lung; (2) biochemical changes suggestive of increased antioxidant metabolism; and (3) no observable immunological changes (Grose et al., 1989).

Studies at relatively low  $O_3$  concentrations have also been done in monkeys. Hyde et al. (1989) exposed them to  $O_3$  for 8 hr/day for 6 or 90 days to 150 or 300 ppb. Responses included ciliated cell necrosis, shortened cilia, and secretory cell hyperplasia with less stored glycoconjugates in the nasal region. Respiratory bronchiolitis observed at 6 days persisted to 90 days of exposure. Even at the lower concentration of 150 ppb  $O_3$ , nonciliated bronchiolar cells appeared hypertrophied and increased in abundance in respiratory bronchioles.

For some chronic effects, intermittent exposures can produce greater effects than those produced by a continuous exposure regime that results in higher cumulative exposures. For example, Tyler et al. (1988) exposed two groups of 7 month old male monkeys to 250 ppb  $O_3$  for 8 hr/day either daily or, in the seasonal model, on days of alternate months during a total exposure period of 18 months. A control group breathed only filtered air. Monkeys from the seasonal exposure model, but not those exposed daily, had significantly increased total lung collagen content, chest wall compliance, and inspiratory capacity. All monkeys exposed to  $O_3$  had respiratory bronchiolitis with significant increases in related morphometric parameters. Even though the seasonally exposed monkeys were exposed to the same concentration of  $O_3$  for only half as many days, they had larger biochemical and physiological alterations and equivalent morphometric changes as those exposed daily. Lung growth was not completely normal in either exposed group. Thus, long-term effects of oxidant air pollutants that have a seasonal occurrence may be more dependent upon the sequence of polluted and clean air than on the total number of days of pollution, and estimations of the risks of human exposure to seasonal air pollutants from effects observed in animals exposed daily may underestimate long-term pulmonary damage.

The preceding chronic animal exposure studies were performed at concentrations that occur frequently in ambient air, at least in Southern California. Thus, the effects observed may be considered directly relevant to human health, especially in view of our knowledge that humans receive even greater local doses of  $O_3$  in the vicinity of the acinus than do rats.

A number of other interesting chronic exposure studies have been done in animals with  $O_3$  concentrations in the range of 300 to

1000 ppb. Those of them that appear to provide useful insights into mechanisms of toxic action have been reviewed by Lippmann (1989).

E. Structure-Activity Relationship Not applicable to O<sub>3</sub>

F. Biomarkers of Response Not applicable to O<sub>3</sub>

G. Overall Toxicity Assessment In terms of functional effects, single O<sub>3</sub> exposures to healthy non-smoking young adults at concentrations in the range of 80-200 ppb produce a complex array of pulmonary responses including decreases in respiratory function and athletic performance, and increases in symptoms, airway reactivity, neutrophil content in lung lavage, and rate of mucociliary particle clearance. Responses to O<sub>3</sub> in purified air in chambers occur at concentrations of 80 or 100 ppb when the exposures involve moderate exercise over 6 hr or more and require concentrations of 180 or 200 ppb when the duration of exposure is 2 hr or less. On the other hand, mean FEV1 decrements 5% have been seen at 100 ppb of O<sub>3</sub> in ambient air for children exposed all day at summer camps and for adults engaged in outdoor exercise for only 1/2 hr. The apparently greater responses to peak O<sub>3</sub> concentrations in ambient air may be due to the presence of, or prior exposures to, acidic aerosol, but further investigation of this tentative hypothesis is needed.

Further research is also needed to establish the interrelationships between small transient functional decrements, such as FEV1, PEF, and mucociliary clearance rates, that may not in themselves be adverse effects, and changes in symptoms, performance, reactivity, permeability and neutrophil counts. The latter may be more closely associated with adversity in themselves or in the accumulation or progression of chronic lung damage.

Successive days of exposure of adult humans in chambers to O<sub>3</sub> at current high ambient levels leads to a functional adaptation in that the responses are attenuated by the third day, and are negligible by the fifth day. On the other hand, a comparable functional adaptation in rats does not prevent the progressive damage to the lung epithelium. Daily exposures of animals also increase other responses in comparison to single exposures, such as a loss of cilia, a hypertrophic response of Clara cells, alterations in macrophage function, and alterations in the rates of particle clearance from the lungs.

For children exposed to O<sub>3</sub> in ambient air there was a week-long baseline shift in peak flow following a summer haze exposure of four days duration with daily peak O<sub>3</sub> concentrations ranging from 125 to 185 ppb (Lioyatch, 1985). Since higher concentrations used in adult adaptation studies in chambers did not report such effects, it is possible that baseline shifts require the presence of other pollutants in the ambient air.

Chronic human exposures to ambient air appear to produce a functional adaptation that persists for at least a few months after the end of the O<sub>3</sub> season, but which dissipates by the spring. Several population-based studies of lung function indicate that there may be an accelerated loss of lung function associated with living in communities with persistently elevated ambient O<sub>3</sub>, but the limited ability to accurately assign exposure classifications of the various populations in these studies makes a cautious assessment of these provocative data prudent.

The plausibility of accelerated aging of the human lung due to chronic O<sub>3</sub> exposure is greatly enhanced by the results of a series of chronic animal exposure studies in rats and monkeys. There is little reason to expect humans to be less sensitive than rats or monkeys. On the contrary, humans have a greater dosage delivered to the respiratory acinus than do rats for the same exposures. Another factor is that the rat and monkey exposures were to confined animals with little opportunity for heavy exercise. Thus humans who are active outdoors during the warmer months may have greater effective O<sub>3</sub> exposures than the test animals. Finally, humans are exposed to O<sub>3</sub> in ambient mixtures. The potentiation of the characteristic O<sub>3</sub> responses by other ambient air constituents seen in the short-term exposure studies in humans and animals may also contribute toward the accumulation of chronic lung damage from long term exposures to ambient air containing O<sub>3</sub>.

#### 8.1.1.4 Risk Characterization

##### A. Combining Exposure and Toxicity Assessments

1. Individual Risks Individual risks are highly variable. In terms of acute functional and symptomatic responses they vary enormously among healthy individuals for reasons that are currently unknown. Prolonged daily exposures to some healthy individuals engaged in moderate exercise at concentrations within

the current NAAQS produce as much as 40% loss in forced vital capacity, while others show little, if any response. Since function decrements greater than 10% are considered adverse (Lippmann, 1988), and since many millions of people are subject to such exposures while exercising one or more times each year, there is a very high, but unquantitated risk of a marginally significant acute response to large numbers of people.

The concomitant changes in lung reactivity and inflammation that these widespread exposures also produce are potentially quite important in terms of an accelerated aging of the lung. However, the risk of such an effect cannot be quantitated.

2. Population Risks The population risks are the summation of the individual risks. Since the latter cannot be quantitated at this time, neither can the former.

#### B. Descriptions of Risk

1. Absolute risk levels for acute responses have been calculated in the 1988 O<sub>3</sub> Staff Paper. However, these risk levels are undoubtedly too low since they were based largely upon the results of 1 and 2 hour chamber exposures to O<sub>3</sub> in purified air. This is due to the greater cumulative outdoor exposures and the likelihood that outdoor air contains factors that potentiate the characteristic O<sub>3</sub> response.

2. Relative and Marginal Relative and marginal risks cannot be determined for a ubiquitous pollutant such as O<sub>3</sub>. There is no evidence for a threshold exposure for acute response, and no population which can be considered unexposed.

#### C. Risk Projections

1. With Current Controls Exposures are not likely to decline significantly. New motor vehicles emit less hydrocarbons and NO<sub>x</sub> than those being scrapped, but the projected increases in vehicle miles travelled should at least partially balance the reduced unit rate of emissions.

2. With Enhanced Controls The effects will depend on the kinds of controls implemented. Further hydrocarbon emission controls on anthropogenic sources can have only a modest effect of

ambient O<sub>3</sub>, unless there are also major reductions in NO<sub>x</sub> emissions. Natural hydrocarbons, combined with uncontrollable small sources will still combine with NO<sub>x</sub> to produce O<sub>3</sub> at levels that produce measurable acute responses. On the other hand, tight controls on

tailpipe and power plant stack emissions of NO<sub>x</sub> could substantially reduce ambient O<sub>3</sub> concentrations.

3. With Relaxed Controls Exposures and effects would rapidly increase.

8.1.2 Radon Case Study

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8.1.2.1 Introduction

A. Initial Evidence for Effects on Human Health

Of the various sources of ionizing radiation to which the general population is exposed, indoor radon contributes the greater part of the average dose (NCRP, 1987), and is thought to be the most important from the standpoint of risk to human health (Table 8.1.2.1, Figure 8.1.2.1). The role of radon in the causation of lung cancer in underground miners has been recognized for decades. Although iron, zinc, silver, and uranium mines contain other potential carcinogens, the high radon levels in the air of such mines have been implicated as the main cause of the increased rates of lung cancer in the miners (NAS/BEIR, 1989).

While the average levels of radon in the air inside buildings tend to be only a fraction of the levels in current

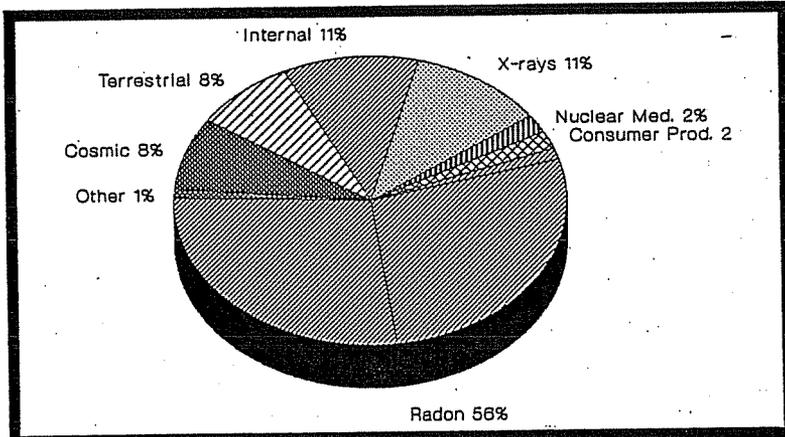


Figure 8.1.2.1 The percentage contribution of different sources of radiation to the average total effective dose equivalent to members of the U.S. population (From NCRP, 1987)

Study Population	Average Cumulative Exposure (WLM) <sup>a</sup>	Excess Relative Risk (WLM)	Reference
U.S. uranium miners	1,180 <sup>b</sup>	0.45	Thomas, et al., 1985 NAS/BEIR, 1988
Czech uranium miners	313	1.92	Thomas, et al., 1985
	226	1.5	Svec, et al., 1988
Ontario uranium miners	40-90	0.15-1.3	Muller, 1985
Saskatchewan uranium miners	20.2	1.4	NAS/BEIR, 1988
Malmberget iron miners	81.4	3.28	Howe, et al., 1986
Newfoundland fluorspar miners	382.8	2.6	NAS/BEIR, 1988
		3.6	Radford and Renard, 1984
		1.4	NAS/BEIR, 1988
		0.9	Morrison, et al., 1988

\* 1 WLM = 1 WL for 170 Hr =  $2 \times 10^{-5} \text{ J m}^{-3} \times 170 \text{ Hr} = 3.4 \times 10^{-3} \text{ J Hr m}^{-3}$

<sup>a</sup> In miners, exposure to radon decay products are expressed in units of working levels (WL), which are measures of the concentration of decay products in air recorded in working level months (WLM), one WLM representing exposure to an air concentration of 1 WL for a working month of 170 hours.

<sup>b</sup> Subsequently reported as 834 uWLM.

Table 8.1.2.1 Mortality from lung cancer in major cohorts of underground miners (from Puskin and Nelson, 1989)

underground mines, the epidemiological data on miners imply that radon may pose some risk of lung cancer even at the low levels customarily encountered in private houses (NAS/BEIR, 1988). Moreover, many homes have been identified with concentrations comparable to those in mines where workers have been found to be at increased risk of lung cancer. Thus, the recent recognition that radon is present in all homes and at unacceptably high concentrations in many houses and other buildings has prompted concern about the health hazard that radon may pose to the public (NCRP, 1984a, 1984b).

## B. History of Regulation/Guidelines

Radiation protection guidelines for radon, established initially to prevent the excessive occupational exposure of underground miners, were extended to the general U.S. population in 1984, when the National Council on Radiation Protection and Measurements (NCRP, 1984a) recommended that the annual exposure of members of the public not exceed 2 WLM per year<sup>6</sup>. This was followed by the recommendation from EPA, in 1986, that the average annual concentration of radon in the indoor air of houses not exceed 4 pCi l<sup>-1</sup> (EPA, 1986), and by the recommendation from ICRP, in 1987, that the concentration of radon in the indoor air of new and existing houses not exceed 7 and 14 Pci l<sup>-1</sup> (100 and 200 Bq m<sup>-3</sup> EEC), respectively (ICRP, 1987). In parallel with these developments at the national and international levels, similar attempts to limit exposure to radon have been made by agencies at the State and local levels (e.g., Reilly, 1988; Nichols and Stearns, 1988; Roessler, 1988).

### 8.1.2.2 Current Knowledge Of Exposures

The radiation dose from radon is delivered by short-lived, alpha-emitting decay products, a large fraction of which is attached to the inhaled background aerosol. Both attached and unattached decay products deposit in the respiratory tract. The resulting radiation dose, delivered to critical sites along the lining of the respiratory tract, is highest in the bronchial airways, the sites at which most lung cancers arise.

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<sup>6</sup> 1 WLM = 1 WL for 170 Hr =  $2 \times 10^{-5} \text{ J m}^{-3} \times 170 \text{ Hr} = 3.4 \times 10^{-3} \text{ J Hr m}^{-3}$ .

Exposure of the U.S. population to radon first became a matter of public concern in Grand Junction, Colorado, where uranium milling wastes containing radium were used as fill. Concern later developed in areas of Florida and Montana where phosphate rock was mined. Subsequently, surveys in other parts of the country made it evident that homes in many areas contained elevated levels of naturally occurring radon. Although the Reading Prong area in Pennsylvania, New Jersey, and New York has received special attention, many other areas have a significant proportion of homes in excess of the 4 Pci l<sup>-1</sup> action guideline recommended by EPA.

Radon is the immediate decay product of radium, that is present at low concentrations (40 Bq kg<sup>-1</sup>; 1 Pci g<sup>-1</sup>) in most soils and rocks. The average rate of release of radon from the soil--about 0.2 Bq m<sup>-2</sup> (0.5 Pci m<sup>-2</sup>) per second--can be calculated to cause an average concentration of radon in the overlying outdoor air of about 8 Bq m<sup>-3</sup> (0.2 pCi l<sup>-1</sup>). Radon, with a half-life of 3.8 days, is released from soil near the ground surface and is dispersed upward by convection. Under inversion conditions, however, the upward dispersion of radon is limited, so that most locations show concentrations rising at night and falling in the morning. Seasonal cycles also occur, depending on location, freezing of the ground, rainfall, and other factors. The radon decay products are at about 70 percent of equilibrium outdoors, the unattached fraction being somewhat below 10 percent of the total radon daughter concentration. With this degree of equilibrium, the estimated average outdoor concentration (8 Bq m<sup>-3</sup>, or 0.2 pCi l<sup>-1</sup>) corresponds to a WL of about 0.001 and thus an annual exposure of 0.05 WL<sup>7</sup> for anyone remaining outdoors all of the time.

Radon released into an enclosed space, as in a mine or building, cannot disperse into the atmosphere and therefore gradually increases in concentration. The major source of radon in the air inside a building and the soil beneath and adjacent to the building, although release from the water supply may also be significant in some locations. The observed values of indoor radon show a log-normal distribution (Tables 8.1.2.2 and 8.1.2.3), the numbers of buildings with concentrations 10-100 times the average value being disproportionately large compared with the numbers expected from a normal distribution (NCRP, 1984b), and the percentages of buildings with high concentrations varying among

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<sup>7</sup> (2 x 10<sup>-4</sup> Jh m<sup>-3</sup>)

surveys (Table 8.1.2.4)

The highest indoor radon concentrations have been measured in the basements of single-family houses, concentrations on higher floors decreasing somewhat. The concentrations in high-rise apartments and public buildings have generally been much lower, largely because of their greater ventilation and more substantial foundations, and physical separation from basement air.

As discussed by Robkin (1987), radon concentrations in the air of homes in the U.S. have been measured widely. Geometric mean air concentrations for single-family homes are about 1 Pci/L. This has been estimated to be about equivalent to 0.005 working levels (WL). However, some homes have been found to have concentrations greater than or equal to one WL.

Generally surveys show that the concentrations are distributed approximately log-normally (see Fig. 8.1.2.2 from the Robkin article). Such distributions from surveys in the eastern part of

Radon Level X (Pci/L)	Portion of Houses Above X <sup>a</sup>	Average Radon Level in Houses Above X <sup>a</sup> (Pci/L)	Percent of Risk Associated with Houses Above X <sup>a</sup>
0	1.0 x 10 <sup>0</sup>	1.5	100
1	4.6 x 10 <sup>-1</sup>	2.7	82
2	2.2 x 10 <sup>-1</sup>	4.2	60
4	7.4 x 10 <sup>-2</sup>	7.0	33
10	9.7 x 10 <sup>-3</sup>	15	9
20	1.3 x 10 <sup>-3</sup>	28	2
50	4.8 x 10 <sup>-5</sup>	65	0.2
100	2.4 x 10 <sup>-6</sup>	130	0.01

<sup>a</sup> Based on log-normal distribution of radon levels estimated by Nero, et al., 1986. (GM = 0.9 Pci/L, GSD = 2.8).

Table 8.1.2.2 Distribution of houses and radon-induced lung cancer risk with respect to radon concentration (Distribution I, Puskin and Nelson, 1989)

Radon Level X (Pci/L)	Portion of Houses Above X <sup>a</sup>	Average Radon Level in Houses Above X <sup>a</sup> (Pci/L)	Percent of Risk Associated with Houses Above X <sup>a</sup>
0	1.0 x 10 <sup>0</sup>	1.8	100
1	4.6 x 10 <sup>-1</sup>	3.3	86
2	2.5 x 10 <sup>-1</sup>	4.9	68
4	1.0 x 10 <sup>-1</sup>	8.0	44
10	1.9 x 10 <sup>-2</sup>	17	6
20	3.8 x 10 <sup>-3</sup>	31	0.9
50	2.8 x 10 <sup>-4</sup>	70	0.1
100	2.6 x 10 <sup>-5</sup>	130	0.1

<sup>a</sup> Based on log-normal distribution of radon levels estimated by Nero, et al., 1986. (GM = 0.9 Pci/L, GSD = 3.2).

Table 8.1.2.3 Distribution of houses and radon-induced lung cancer risk with respect to radon concentration (Distribution II, Puskin and Nelson, 1989)

	Average Radon Concentration Bq m <sup>-3</sup> (Pci l <sup>-1</sup> )	Percent Greater Than 150 Bq m <sup>-3</sup> (4 Pci l <sup>-1</sup> )
MCRP (1984b)	37 (1.0)	3
Nero et al., (1986)	55 (1.5)	7
Alter & Oswald (1987)	260 (7.1)	23
Cohen (1988)	120 (3.3)	19

Table 8.1.2.4 Reported distribution of radon in U.S. living areas.

the U.S. show that the means and slope of the distribution curves can, however, vary considerably regionally (George and Hinchliffe, 1987), as shown in Figure 8.1.2.3. Even in a given community indoor air concentrations vary, as do concentrations in different parts of the house, and by season (see their Figure 8.1.2.4).

One would expect that air-infiltration rates would have a substantial effect on indoor-air concentrations of radon. However, because source rates and other controlling factors operate as well, the effect of ventilation rates may not be great, as shown by Nero et al. (1983). Figures 8.1.2.5 and 8.1.2.6 show a wide scatter of radon concentration among homes when plotted against ventilation rate. However, when a frequency distribution plot is made of the product of air concentrations and ventilation rates

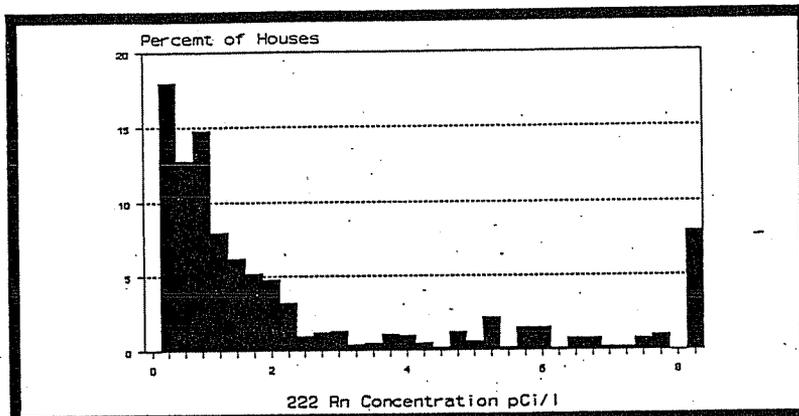


Figure 8.1.2.2 Distribution of radon 222 concentrations in single-family homes for 552 sites (after Robkin, 1987, based on Nero, 1984)

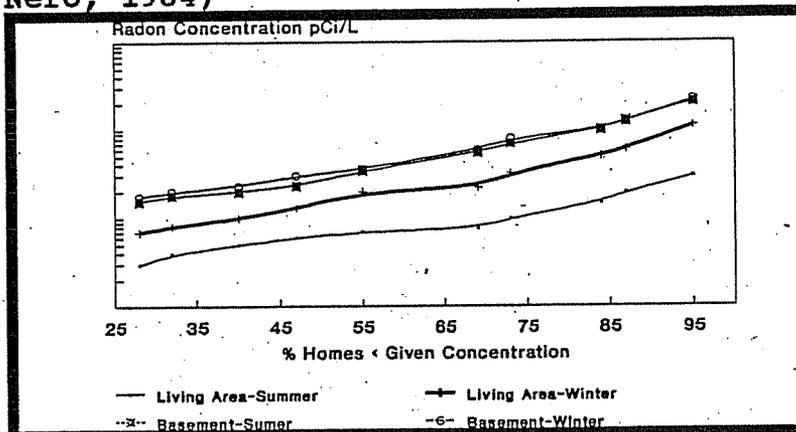


Figure 8.1.2.3 Distribution of radon concentration in residential buildings in Morris County, New Jersey (after George and Hinchliffe, 1987)

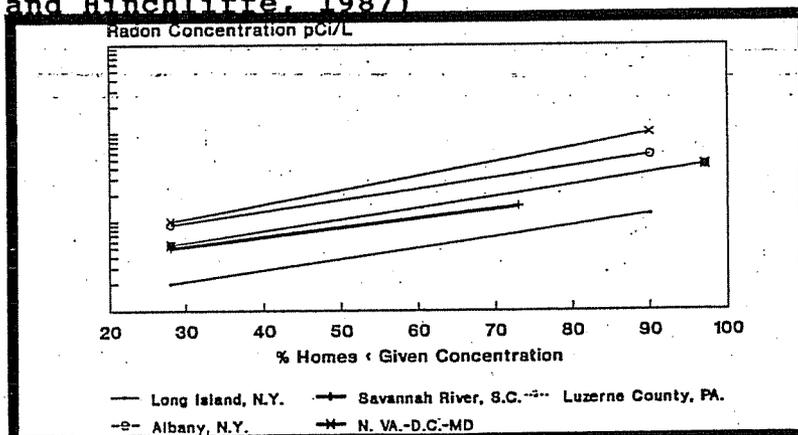


Figure 8.1.2.4 Distribution of radon concentrations in living areas during winter in different geographical locations (after George & Hinchliffe, 1987)

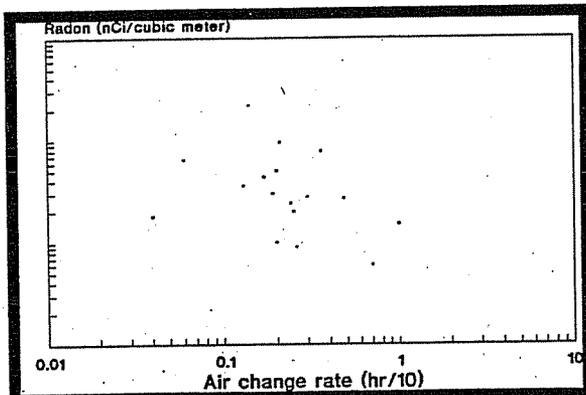


Figure 8.1.2.5 Radon-222 concentrations vs. ventilation rates in 17 "energy-efficient" houses (after Nero, 1983)

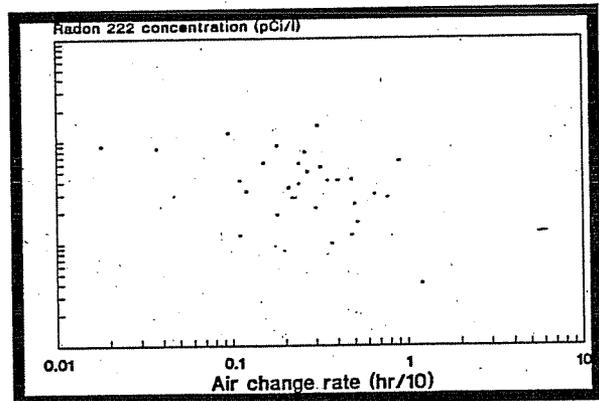


Figure 8.1.2.6 Radon-222 concentrations vs ventilation rates in 29 houses in the San Francisco area (after Nero, 1983)

(Figure 8.1.2.7), there seems to be a distribution around a mean. Such variations could result from differences in the nature of the sources from house to house, and from differences in design and construction, as well as temporal fluctuations in the source.

Radon has been surveyed in groundwaters of the U.S. (Longtin, 1988). Table 8.1.2.5 summarizes the population-weighted averages for radon concentrations (Pci/L) in various states. This displays data from two sources, one an EPA National Inorganics and Radionuclides Survey (NIRS) of 1000 U.S. public groundwater supply systems randomly selected from four population categories. The two surveys indicate that the U.S. state-average concentrations (600-800 Pci/L) for sites with populations <1000 were higher than those for the sites >1000 (about 200 Pci/L). There was a large range in average concentrations among the states. As shown in Figure 8.1.2.8, a very small number of supplies have radon concentrations greater than 10,000 Pci/L in water, and about 80% have less than 500 Pci/L.

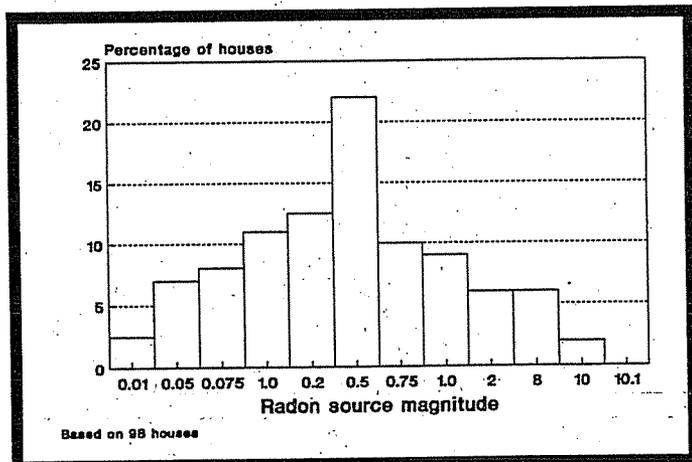


Figure 8.1.2.7 Frequency distribution of radon source magnitudes calculated from the data in Figs. 8.1.2.5 and 8.1.2.6 by taking the product of  $^{222}\text{Rn}$  concentrations and ventilation rate (After Nero, 1983)

STATE	Sites with <1,000 People		Sites With >1,000 People	
	Cothorn*	NIRS	Cothorn	NIRS
Alabama	160 (40)+	2,025 (5)	160 (35)	171 (26)
Alaska	100 (47)	129 (44)	100 (47)	
Arizona	120 (44)	1,302 (7)	320 (17)	1,610 (1)
Arkansas	75 (51)	75 (50)	100 (42)	
California	500 (18)	538 (18)	500 (10)	161 (28)
Colorado	380 (23)	336 (29)	380 (14)	317 (12)
Connecticut	1,500 (3)	3,328 (1)	770 (4)	646 (2)
Delaware	100 (48)	116 (48)	126 (42)	126 (35)
Florida	1,000 (9)	393 (25)	148 (40)	118 (35)
Georgia	1,100 (6)	419 (24)	150 (37)	583 (4)
Hawaii	50 (52)		50 (51)	
Idaho	256 (30)	431 (22)	256 (25)	438 (9)
Illinois	100 (49)	136 (40)	167 (34)	198 (20)
Indiana	105 (45)	136 (41)	105 (45)	195 (22)
Iowa	250 (31)	166 (35)	200 (29)	130 (32)
Kansas	250 (32)	365 (27)	106 (44)	370 (11)
Kentucky	250 (33)	148 (39)	10 (43)	220 (19)
Louisiana	180 (39)	116 (49)	180 (31)	107 (41)
Maine	10,000 (1)	1,228 (9)	2,000 (1)	
Maryland	700 (15)	2,161 (4)	450 (11)	112 (36)
Massachusetts	1,500 (4)	253 (33)	770 (5)	596 (3)
Michigan	105 (46)	370 (26)	105 (46)	164 (27)
Minnesota	210 (36)	342 (28)	210 (28)	397 (10)
Mississippi	150 (4)	133 (32)	82 (49)	100 (43)
Missouri	300 (24)	125 (46)	100 (48)	148 (30)
Montana	500 (19)	535 (19)	328 (16)	112 (37)
Nebraska	300 (25)	291 (31)	290 (19)	444 (8)
Nevada	550 (17)	743 (12)	550 (9)	
New Hampshire	1,400 (5)	2,674 (3)	1,183 (2)	
New Jersey	150 (42)	737 (13)	300 (18)	125 (34)
New Mexico	200 (37)	423 (23)	180 (32)	250 (16)
New York	500 (20)	647 (14)	132 (41)	173 (25)
North Carolina	1,100 (7)	2,876 (2)	278 (21)	100 (44)
North Dakota	300 (26)	125 (47)	150 (38)	109 (40)
Ohio	200 (38)	164 (36)	169 (33)	177 (24)
Oklahoma	250 (34)	164 (37)	160 (36)	158 (29)
Oregon	300 (27)	130 (43)	264 (23)	112 (38)
Pennsylvania	1,000 (10)	467 (20)	720 (6)	535 (5)
Rhode Island	3,400 (2)	1,170 (10)	1,151 (3)	
South Carolina	1,100 (8)	1,260 (8)	276 (22)	196 (21)
South Dakota	300 (28)	334 (30)	290 (20)	273 (15)
Tennessee	100 (50)	128 (45)	24 (52)	112 (39)
Texas	150 (43)	264 (32)	150 (39)	138 (31)
Utah	500 (21)	157 (38)	360 (15)	238 (18)
Vermont	250 (35)	1,533 (6)	656 (8)	497 (7)
Virginia	700 (16)	952 (11)	450 (12)	313 (13)
Washington	300 (29)	238 (34)	264 (24)	520 (6)
West Virginia	1,000 (11)	459 (21)	720 (7)	240 (17)
Wisconsin	750 (14)	540 (17)	234 (27)	300 (14)
Wyoming	880 (12)	558 (16)	415 (13)	
Puerto Rico	500 (22)			200 (30)
US average	780 (13)	602 (15)	240 (26)	194 (23)

\*Based on data of Hess et al.  
+Numbers in parentheses are relative rankings.

Table 8.1.2.5 Population-weighted averages for radon activity (Pci/L) (After Longtin, 1988)

Prichard and Gesell (1981) have estimated population exposures to radon volatilized indoors from water. They estimated that the average radon indoor air concentration emanating from 1000 Pci/L in water might vary from 0.01 to 0.1 Pci/L in air, depending on the nature of the dwelling. The water use-weighted volatilization rate of radon from water is typically 50%. Others have estimated that the ratio of the air-to-water concentrations in U.S. homes,  $C_A/C_W$ , would be typically  $10^{-4}$ , consistent with the high estimate of Prichard and Gesell.

Andelman and co-workers have measured the volatilization of chemicals from indoor uses of water, and have shown that these inhalation exposures from

showers, baths and other water uses is at least comparable to those from the direct ingestion of water (Andelman, 1985). In a recent assessment of such exposures it was judged that a whole house inhalation exposure for an adult spending 24 hours in a home would be given by

$$E = (0.2 \text{ to } 10) C_w$$

where E is the inhalation exposure (in the case of radon, Pci/day) and  $C_w$  the concentration in water, Pci/L (Andelman, 1990). Thus, for example, if the water supply concentration contains 1000 Pci/L, this would constitute a 24-hr predicted inhalation exposure expected to range from 200 to 10,000 Pci. For comparison, a typical U.S. indoor-air concentration of 1 pCi/L would lead to an inhalation exposure of about 20,000 pCi/day. It should be emphasized that "inhalation exposure" refers to the quantity of radon inhaled.

It has also been shown by Andelman (1990), that the inhalation exposure from a shower alone is substantial, such that E is about equal to  $C_w$ . A shower using water containing 1000 pCi/L radon would lead to an inhalation exposure of about 1000 pCi. This is in addition to the exposure in the home from all water uses.

One can conclude that radon is ubiquitous in U.S. homes, the concentrations vary considerably regionally, locally, seasonably, and temporally. Also ventilation and other individual home characteristics, and location within the home will affect the concentrations. Water as a source can add to the exposures, and localized point source exposures, such as showering, can be important.

Although the overall risks on a national basis may be estimated from national survey data, the variability of exposure and, therefore, risk can be expected to be substantial.

The average exposure of members of the U.S. population has

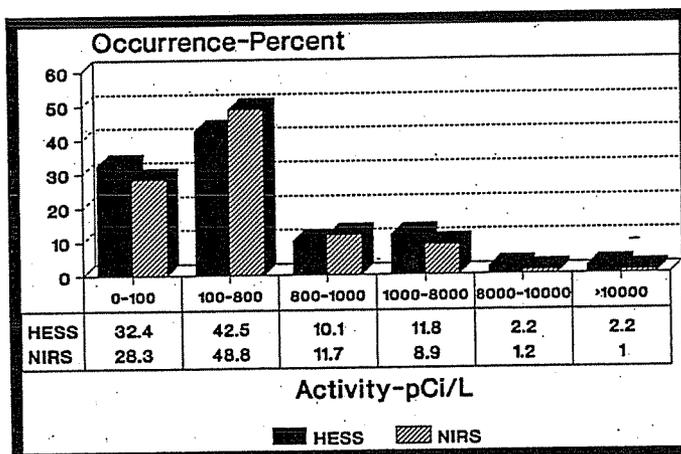


Figure 8.1.2.8 Occurrence of radon in drinking water

been estimated to range from 0.2 WLM per year (NCRP, 1984b) to 0.25 WLM per year (Puskin and Nelson, 1989), or possibly higher (NCRP, 1987). The many radon measurements that have been made are of only limited value for exposure estimation, however, since they have been designed primarily to determine the maximum potential concentrations of radon in houses rather than the actual levels to which occupants are exposed. The commercial measurements are also biased by the fact that the customers requesting them usually have had reasons to suspect high concentrations of radon in their homes (Cohen, 1988). Hence there is a need for a statistically stratified program of radon sampling to estimate the average level of exposure in the United States (NCRP, 1984b, 1989). EPA is currently implementing such a survey. Without a more accurate estimate of the average exposure of the U.S. population, a precise assessment of the magnitude of the health risks from radon is not possible.

#### 8.1.2.3 Toxicity And Health Effects

A. Human Epidemiology The major studies of underground miners reported thus far are listed in Table 8.1.2.1; however, a number of problems complicate the interpretation of these studies. First, the exposures of the miners were documented to a varying extent and the estimates are subject to misclassification. Exposures were not measured at all for many of the early miners. Second, the contribution of smoking to the observed excess of lung cancer is difficult to evaluate, especially since smoking histories of the miners were not available in most of the studies. Third, selection of an appropriate control population is subject to uncertainty, although internal analyses are most appropriate for estimating exposure-response relationships.

Many epidemiological studies are under way in the general population to estimate directly the risk of indoor radon, they are also subject to limitations from exposure misclassifications, inadequate sample size, and the possible confounding effects of extraneous risk factors. Because the general population has had lower levels of exposure than the miners, and, consequently, smaller effects are anticipated, the statistical power of the studies may be inadequate for the detection of small effects. At present, therefore, estimates of the risks to the general

population from exposure to radon have been based on extrapolation from the data on miners.

From the lung cancer mortality reported in various cohorts of miners, the exposure-response relationship for lung cancer appears to be linear in the low-to-intermediate dose range. On the basis of this epidemiological evidence, supporting animal studies, and biological considerations, the frequency of lung cancer is assumed to increase linearly with exposure below 50 WLM. To assess the total magnitude of the radon risk, however, it is necessary to predict the lifetime lung cancer mortality in the various mining populations, many members of which still survive. For this purpose, neither the simple absolute risk model (which predicts a constant additional risk of death per year following a given exposure) nor the simple relative risk model (which predicts a constant percentage increase in the annual age-dependent baseline risk following a given exposure) adequately describe the observed patterns of mortality. Instead, either a modified absolute risk

model, in which the risk is reduced with time after exposure (NCRP, 1984a), or a modified relative risk model in which the risk varies as a function of age and time after exposure, (NAS/BEIR, 1988), would seem preferable (Table 8.1.2.6). A model of the latter type has been adopted by EPA for its radon risk assessment (Puskin and Nelson, 1989).

Source of Estimate	Lifetime Risk(%)	Projection Model
NCRP (1984b)	0.9	Modified absolute risk
ICRP (1987)	1.6	Constant relative risk
	1.1	Absolute risk
BEIR IV (NAS, 1988)	3.4 men 1.4 women	Modified relative risk
EPA (1989)*	2.0	Relative risk

\* Puskin and Nelson (1989)

Table 8.1.2.6 Estimated lifetime risk of lung cancer attributable to 0.02 WL (4 pCi l<sup>-1</sup>) exposure to radon, assuming the short half-life decay products are in 50% equilibrium with the radon

The use of risk models for estimating risks to the general population from the data on miners involves additional uncertainties owing to differences in age-and sex-distribution, and potential differences between continuous exposure over a lifetime and short-term occupational exposure during working-hours only. Other uncertainties complicating the assessment relate to estimation of the actual dose delivered to the lung, owing to

differences in breathing rate and to differences in aerosol particle size, degree of radioactive equilibrium of the decay products in the atmosphere, and other variables (NCRP, 1984a; Harley and Cohen, 1987). Also uncertain is the form of the interaction between the effects of smoking and those of radon; assessment of this interaction is possible in only a few studies. The strongest evidence is available from the study of Colorado plateau uranium miners, that suggests a somewhat less than multiplicative interaction (NAS, 1988). If the multiplicative interaction model is correct (e.g., NAS, 1988), the absolute lifetime risk for a given level of radon exposure would be 6-10 times higher in smokers than in non-smokers.

The apparent decrease in risk with time after cessation of radon exposure has not been precisely established. Since lung cancer is rare before the age of 40, exposure during childhood may possibly contribute little to the subsequent risk of the disease (BEIR, 1990); however the ICRP (1987) has considered risks to be greater for exposure during childhood.

B. Animal Toxicology Radon and radon decay products have been shown to increase the incidence of benign and malignant tumors of the respiratory tract in rats exposed to these radionuclides by chronic inhalation (Cross et al., 1982; Chameaud et al., 1984), the magnitude of the increase varying, depending on the dose and on the influence of other factors, such as inhalation of dusts or cigarette smoke (Table 8.1.2.7). The lifetime risk of lung cancer has been calculated from such experiments to approximate  $1-5 \times 10^{-4}$  WLM<sup>-1</sup> (Bair, 1986; Cross, 1988).

#### 8.1.2.4 Risk Characterization

The average level of exposure to radon in members of the U.S. population has not been characterized in a large nationwide survey. However, data from diverse sources suggest a mean concentration in U.S. homes of about  $1.5 \text{ pCi l}^{-1}$ . If annual exposure is assumed to approximate 0.25 WLM per year (Puskin and Nelson, 1989), as noted above, the lifetime risk of mortality from lung cancer can be calculated with the use of the risk models cited (Table 8.1.2.8, Figure 8.1.2.9). With the use of such models, the lifetime risk of lung cancer from exposure to radon in the U.S. population can be estimated to range from roughly 0.4 to 1.8 percent. By the same token, exposure to radon can be estimated to account for some

Factor	Tumorigenic Potential <sup>a</sup>
Radon-daughter cumulative exposure	Increases approximately linearly with exposure
Radon-daughter exposure rate	Increases with decrease in exposure rate (approximately 200 to 400% increase from about 500 to 50 WLM/week. The 500-, the 50-, and the 5-WLM/week data are not significantly different at approximately 300-WLM exposures.)
Radon-daughter unattached fraction	Increases with increase in unattached fraction (approximately 50% increase per WLM exposure from 2 to 10% <sub>a</sub> ) <sup>b</sup>
Radon-daughter disequilibrium	Increases with increase in disequilibrium (approximately 30% increase per WLM exposure (borderline significance) from 0.4 to 0.1F) <sup>c</sup>
Concomitant exposure to cigarette smoke	Decreases if smoking alternates on same day with radon-daughter exposure. Increases if smoking following cumulative radon-daughter exposures. No effect if smoking precedes cumulative radon-daughter exposures

<sup>a</sup> Data pertain to raw tumor-incidence data uncorrected for time-related factors and life span differences from control animals.

<sup>b</sup>  $f_a$  is the percentage of  $^{218}\text{Po}$  that is unattached. When expressed as percentage of radon concentrations, they are 1.3 and 5.2%, respectively.

<sup>c</sup> Equilibrium factor (F) is the ratio of the non-equilibrium concentration of short-lived daughters in air to the equilibrium equivalent concentration.

Table 8.1.2.7 Salient factors influencing the tumorigenic potential of radon-daughter exposures in rats (from Cross, 1988)

Study	Lifetime Excess Lung Cancer Deaths/10 <sup>6</sup>
	WLM
UNSCEAR, 1977	200-450
BEIR III, 1980	730
NCRP, 1984	130
ICRP, 1987	170-230 <sup>a</sup>
BEIR IV, 1988	350
EPA, 1989	360 <sup>c</sup>

<sup>a</sup> Relative risk with ICRP Ref. population.

<sup>b</sup> Relative risk with BEIR IV U.S. Ref. population.

<sup>c</sup> Based on average of BEIR IV and ICRP 50 risk models (confidence interval of 140-730)

RR approximately constant with age at exposure (but decreased with time after exposure).

Table 8.1.2.8 Life time risk estimates for lung cancer due to lifetime exposures to radon

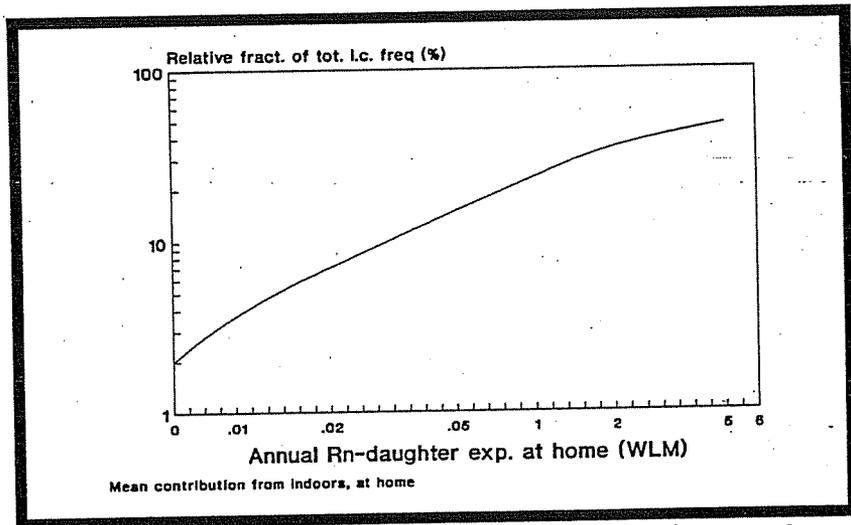


Figure 8.1.2.9 Expected relative percentage of the total lung cancer attributable to indoor exposure to Rn daughters, as a function of the mean level of Rn daughters in indoor air at home (after Jacobi, 1986)

5,000-40,000 deaths from lung cancer each year in the U.S., or about 4-30 per cent of all lung cancer deaths in the U.S. population (Puskin and Nelson, 1989).

The above estimates strongly suggest that radon exposure presents a significant public health problem. The uncertainties in the exposure levels and in the risk estimates are large, however, and vigorous efforts to refine the levels and the risk estimates are needed.

These analyses illustrate that risk assessment techniques can be used, even when definitive data are not available, to estimate the extent of an environmental disease risk. In the case of radon, a number of uncertainties affect the projected risk. The range of these uncertainties can be specified however; most analyses indicate that extrapolation from the studies of miners to the indoor environment introduces only a relatively small degree of uncertainty, ranging up to 30 percent. Thus, even in the face of uncertainty, radon must be considered an important public health problem. The use of risk assessment can provide an indication of harm (numbers of cancer deaths), which is useful for a ranking process.

8.2 Ranking Schemes: Detailed derivation of Rank-merging

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### 8.2.1 Formulation of the Basic Model

Considering the total possible set of endpoints (both cancer and non-cancer) that may be caused by agents in the environment, E in number, and the total set of agents in the total environment (specific substances and types of radiation), A in number, that may cause, individually, anywhere from none to many of the endpoints, the weight to be accorded the jth of the Problems (thirty-one in number in the case of the UB report) in ranking that Problem in comparison to the others, based on population risk, is proportional to  $W_j$ , where

$$W_j = N_j \sum_{i=1}^E \sum_{k=1}^A S_i f_{ijk} \quad (1)$$

$W_j$  may also be written in the form,

$$W_j = N_j \sum_{i=1}^E \sum_{k=1}^A S_i D_{jk} P_{ik}(D_{jk}) \quad (2)$$

In these equations  $N_j$  is the number of individuals comprising the population relevant to the jth Problem, S is severity, P is potency, f is the fraction of the population that exhibits an endpoint (the response to the exposure to an agent) at exposure D, and the subscripts i and k designate, respectively, the ith endpoint and the kth agent. E, to reiterate, includes all possible endpoints that might be considered, caused by whichever agents, and A includes any and all agents (not just those known to be associated with the j-th Problem) present in any way and in any and all parts of the environment. In the case of endpoints that respond proportionally to exposure/dose (that are said to be "linear" in dose), P is independent of D; in the case of endpoints whose responses are curvilinear or that exhibit thresholds or threshold-like behavior, P is a function of D (as shown here in the general case). Thus,  $f_{ijk}$  is the fraction of the population relevant to the jth Problem affected by the ith endpoint if caused, in turn, by the kth agent; the product of  $N_j$  and  $f_{ijk}$  is the number of individuals affected by that (ith) endpoint as caused by the one (kth) agent, and is thus a measure of the excess population risk of that endpoint from that agent. If the kth agent does not exist in the jth Problem, or if it does not cause the ith endpoint, or both,

then  $f_{ijk}$ , corresponding to that particular agent and/or endpoint, is zero. The same endpoint may also be caused by other agents and the same agent may cause other endpoints. Multiplying by  $S_i$  weights the population risk according to severity, for the  $i$ th endpoint, and the summations over  $i$  and  $k$  give the weighted sum of the excess risks of all endpoints of every kind for the  $j$ th Problem,  $W_j$ . Equation (1) is for cases when  $f_{ijk}$  can be obtained directly from epidemiologic information when available at appropriate exposure levels. Equation (2) is the form of equation (1) necessary when such direct data may not be adequate and when estimates of dose response may have to be used (from human or animal data); this is the more usual case. If one knew all of the factors in either equation (1) or (2), then ranking would be easy: the Problem with the highest value of the weighted sum would be the highest ranking, and so forth. Independent action by agents is assumed.

As written, the two equations suppose that in those cases where the same individuals exhibit more than one endpoint the aggregate severity is the sum of the  $S_i f_{ijk}$  products, with no special allowance for the fact that some individuals may exhibit more than one endpoint. In many instances this is probably a reasonable assumption; however, there may be instances in which the true severity of affliction by two endpoints is greater than would be indicated by the sum and others in which it is less. An example of the latter case would be if the result of each endpoint is certain death in about the same time period and under similar circumstances: two such deaths, for the same individual, are no more severe than one. Because of the smallness of the values of the  $f_{ijk}$  for the usually encountered levels of human exposure and the smallness of the fraction of individuals involved, out of the total, with endpoints such as those described,  $W_j$  will be only slightly overestimated using this model. It should also be noted that  $S$  is not considered to be a function of exposure in the first two equations whereas it may be so in real cases. In the case of carcinogens, for example, not only does the number of subjects exhibiting at least one tumor increase with exposure but so, usually, does the number tumors per individual, on average, a factor that may be deemed, in different instances, to impact  $S^8$ .

While the above equations represent real simplifications of the actual situation (exposures, for example, are not represented

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<sup>8</sup>If  $S_i$  is a function of exposure, equation (3), derived later, still applies and the merging method proposed is still valid.

in actual fact, for any one agent, by a single value, D, independent of time, place, individual circumstance, or other factors), they contain the main variables of importance in an appropriate relationship and they would provide, from the outset, given reasonable estimates of the levels of the variables, consistent, merged rankings for both cancer and non-cancer risks taken as a spectrum of health risks. Thus, if all of the quantitative values of the variables in either equation (1) or equation (2) were available, developing a merged health risk ranking would be a simple matter of calculation; indeed, the ranking, itself, would be directly quantitative and not merely a listing of rank order.

One of the key missing sets of variables for producing a single, health risk based ranking of Problems is a single set of severities for cancer and non-cancer endpoints together. The experience already gained in attempting to grade the severities of different non-cancer endpoints in the UB report should help in the formulation of a method and a process for undertaking the task of producing a consensus on a health risk severity table including both cancer and non-cancer effects, and it is recommended that any updating of the UB report include this activity.

It is highly desirable to utilize the above two equations and the operations they depict to the maximum extent possible when developing a merged health risk ranking procedure because of their scientific basis and the mutual consistency across the different kinds of endpoints that they therefore automatically provide. Although the same lack of information that prevented a more rigorous approach in the UB report prevents the straightforward utilization of the above equations, any approach should approximate as nearly as possible the above equations so as to provide the best basis for merging the rankings.

### 8.2.2 Merging Separately Established rankings: General Discussion

The "merging of separate rankings" procedure depends, as discussed below, on certain characteristics of three-by-three grid arrays (see Figures 8.2.2.1 and 8.2.2.2) when combined with an algebraic expression described below that, in turn, is based on equation (1). These characteristics lead to the conclusion that there are only a finite number of ranking patterns that need to be considered in the merging process, a fact that reduces the problem

of selecting sets of Problems for consideration of their combined risks. The same is true of larger arrays but, while four-by-four or larger arrays of grids might be used, for example, the procedure rapidly becomes cumbersome because of the increase in the number of ranking patterns that must be considered as the order of the grid array used increases.

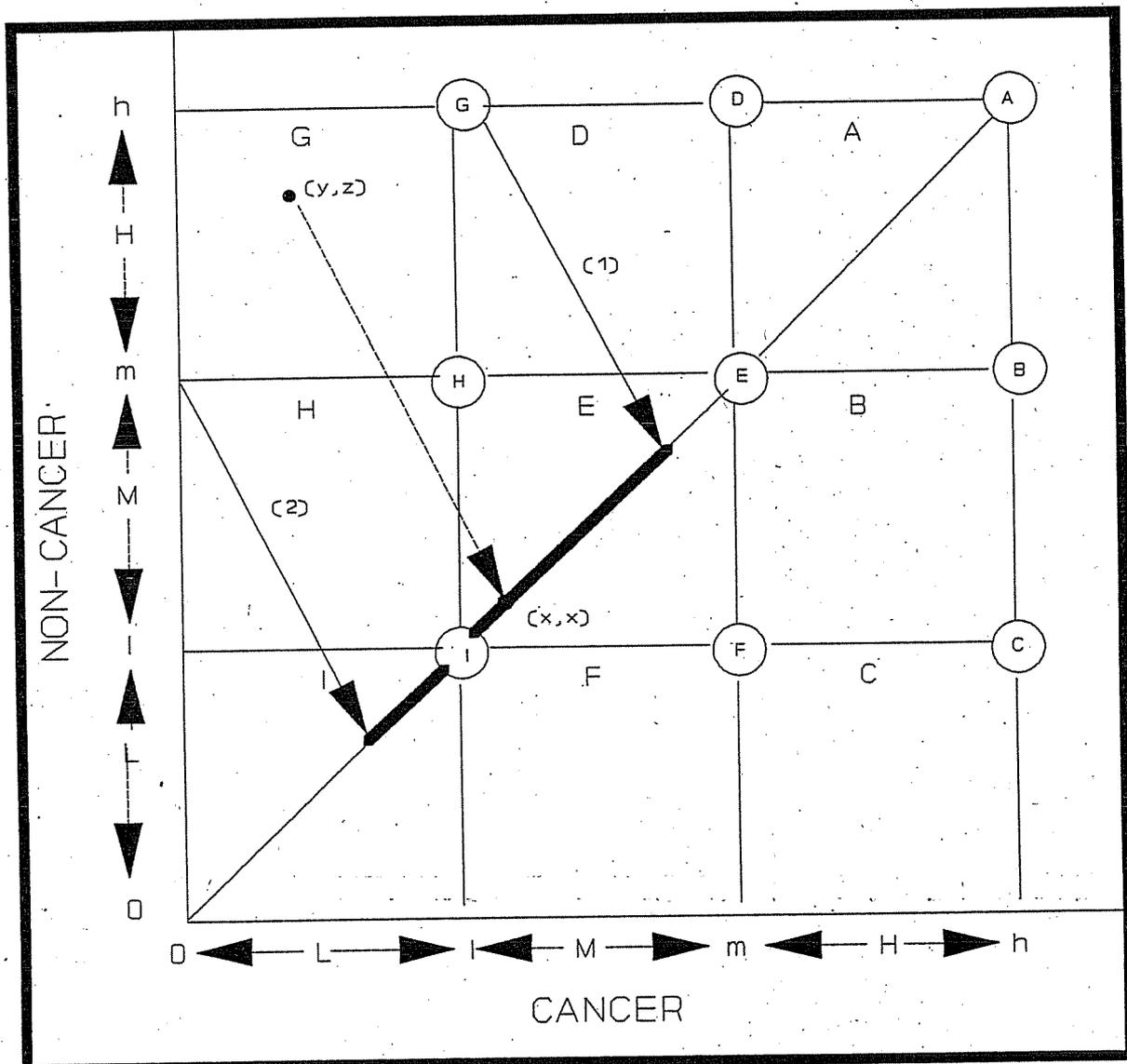


Figure 8.2.2.1 Projecting a grid square--linear array

The use of a three-by-three grid array means that the rankings of Problems for cancer and non-cancer risks must first be grouped into three qualitative risk categories: high (H), medium (M) and low (L). Each of these levels may be thought of as bounded by quantitative risk values,  $h$ ,  $m$ , and  $l$ , as shown in Figure 8.2.2.1,

where  $h > m > l$ . Thus, a Problem judged to be of high risk for cancer, and so categorized as H, would have a quantitative risk value lying between  $m$  and  $h$  on the cancer axis, if its risk could be quantified in some manner; and similarly for Problems categorized as H, M or L, on either axis. Plotted, each Problem

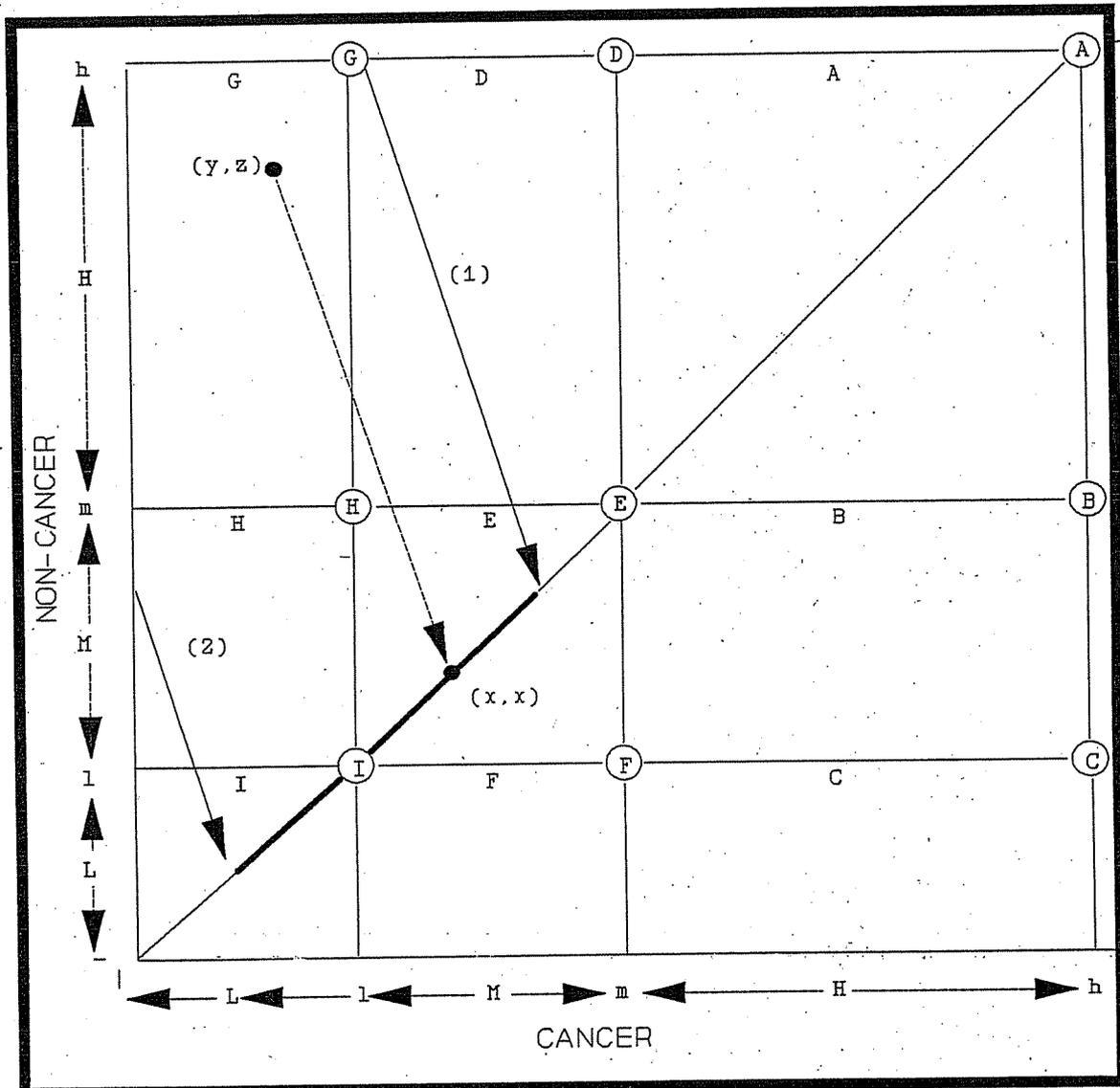


Figure 8.2.2.2 Projecting a grid square--nonlinear array

would appear as a point within an appropriate grid square; thus a Problem categorized as H for cancer and M for non-cancer would fall somewhere within grid square B in Figure 8.2.2.1 or 8.2.2.2. As shown in the Figures, each of the grid squares is labeled A through I, for identification, and one of nine nodes (denoted by circles) is associated with each of the grid squares by being given the same letter designation as its corresponding grid square.

With three risk categories for each of the two sets of rankings, nine pairs of categories, nine grid squares, and up to nine risk levels, are possible for merging the rankings of those Problems ranked for both cancer and non-cancer risks as seen in Figures 8.2.2.1 and 8.2.2.2. In this section, the type of array in Figure 8.2.2.1 in which  $h - m = m - 1$  is called a linear array. Depending on how the individual risk factors are taken into account in the separate rankings by cancer and non-cancer risks, the actual array of risks may be linear or it may be nonlinear; in this section the only type of nonlinear array to be considered is the one in which  $h - m > m - 1$  and in which the array is symmetrical around the diagonal (see Figure 8.2.2.2); linear arrays, by nature, are symmetrical about the diagonal.

Under whatever system is employed, the merged ranking of the Problems lying within grid square A (or (H,H)) and of those within grid square I (or (L,L)) is clear enough: grid square A contains the Problems of the highest merged risks and grid square I contains those of the lowest; moreover, grid square E (or (M,M)), and its Problems, falls unambiguously between them. Geometrically, as seen in the Figures, these three grid squares are rank ordered as they fall along the diagonal,  $A > E > I$ ; the question is, then, how to project the off-diagonal grid squares, and their corresponding problems, such as grid square D (or (M,H)), onto the diagonal so as to know where they fit in the resulting ranking against the three grid squares already athwart (or, "on") the diagonal. This is best seen by considering the projection of a single, off-diagonal Problem (or point) onto the diagonal.

### 8.2.3 The Principle of Projection onto the Diagonal

An equation of the following form may be derived, starting from equation (1) (see Section 8.2.11):

$$w_j = w_{cj} + v w_{Nj} \quad (3)$$

where

$$v = \frac{w_{NH}}{w_{CH}} = \frac{N_{NH} S_{NH} F_{NH}}{N_{CH} S_{CH} F_{CH}} \quad (4)$$

In equation (3)  $w_{cj}$  is the weight for ranking purposes of the  $j$ th Problem that may fall into one of the three categories, H, M or L, for cancer, and  $w_{Nj}$  is the same, separately, for non-cancer; and all

weights are scaled so that the highest quantitative level is h on each axis. In other words, the two weights represent the quantitative risk rankings, for cancer risk only, on the one hand, and for non-cancer risk only, on the other. The two weights are therefore the coordinates of points plotted within one or another of the grid squares and the sum,  $w_{jt}$ , is just the merged ranking score, for the point in question. As shown in Section 8.2.11, the coefficient  $v$  takes into account the differences in number exposed, the fractions of those exposed who suffer harm (potencies of and exposures to agents) and their relative severities, cancer versus non-cancer; it represents the weight given to non-cancer versus cancer risks. In equation (4),  $W_{NH}$  and  $W_{CH}$  are the weights (see equation 7) for cancer risk and non-cancer risk, respectively, of the problems having the highest such weights without respect to  $j$  (that is, the two weights need not correspond to the same Problem) and the  $S$  and  $F$  values are the mean values of severity and of the fraction of the relevant population affected corresponding to these same highest weights; the  $N$  values are the numbers exposed, also corresponding to the same highest weights. Note that  $v$  is a constant for the ranking of a particular set of problems; for a different set (or subset) in which the highest weights correspond to different Problems and are therefore likely to be different, a different value of  $v$  is likely to obtain.

The way in which equation (3) governs the slopes of the projection vectors, and the sets of possible rankings that can result, is described in more detail below. A brief description is given here for convenience.

Referring to Figure 8.2.2.1, if a point on the diagonal, with coordinates  $(x,x)$ , is the projection of an off-diagonal point, with coordinates  $(y,z)$ , that means that the value of  $w$  at  $(x,x)$  is equal to the value at  $(y,z)$ . That is, by equation (3),

$$(1 + v)x = y + vz \tag{5}$$

from which the value of  $v$  required to yield the projection of  $(y,z)$  onto the diagonal at  $(x,x)$  is obtained in terms of  $x$ ,  $y$  and  $z$ . Conversely, given a value of  $v$ , the projection of any point or node onto the diagonal is known, where points or nodes already on the diagonal are their own projections. The order in which such projected points or nodes appear on the diagonal is therefore their rank order in terms of the combination of both cancer and non-cancer risks.

It is shown below that the slopes of the projection vectors are all the same for projections from the off-diagonal points or nodes onto the diagonal for the value of  $v$  pertaining to the particular set of ranked groupings, whatever that value of  $v$  may be. Moreover, the slopes are all equal to  $-1/v$ ; that is, the slopes are all negative (since  $v$  is not less than zero), and the projection vectors, for a given  $v$ , are all parallel. Thus, continuing with our example in Figure 8.2.2.1, any off-diagonal point within any grid square will project onto the diagonal along a vector parallel to that joining  $(y,z)$  and  $(x,x)$ , so long as  $(x,x)$  is the projection of  $(y,z)$ , and vectors (1) and (2) thus define the projections of node G and of the vertex diagonally opposite to node G in grid square G. Moreover, every point or Problem contained within grid square G lies on a line segment or range on the diagonal lying between the intersections of vectors (1) and (2) with the diagonal. Generalizing, the projection of any grid square is such a line segment or range, and the projections of all grid squares constitute a set of overlapping ranges, the positions of which on the diagonal with respect to each other (or their rank orders), and degrees of overlap, are dependent on the value of  $v$ . In the case of Problems that are qualitatively but not quantitatively rank ordered, as in the UB report, the coordinates of the Problems within a particular grid square are not known; however, the projection of the grid square itself onto the diagonal gives the range within which those problems must lie, narrowing the range of comparisons that must be made to arrive at an ultimate rank ordering of Problems on the basis of total health risk. Because of the overlaps, some of the Problems within individual ranges may ultimately be rank ordered oppositely to the rank ordering of their ranges. How this is accounted for in achieving the final rank order is described further on.

#### 8.2.4 Derivation of the Possible Ranking Patterns for Grid Squares and Ranges

Consideration of the projections of all the grid squares onto the diagonal as was done in the case of grid square G in Figure 8.2.2.1 shows that the rank orders of the resulting ranges, including those of grid squares lying athwart the diagonal in the first place, are the same as the rank orders of the projections of their corresponding nodes (or of any other conveniently defined point within the grid squares). To derive the possible rank orders of the ranges for different values of  $v$ , it is possible and

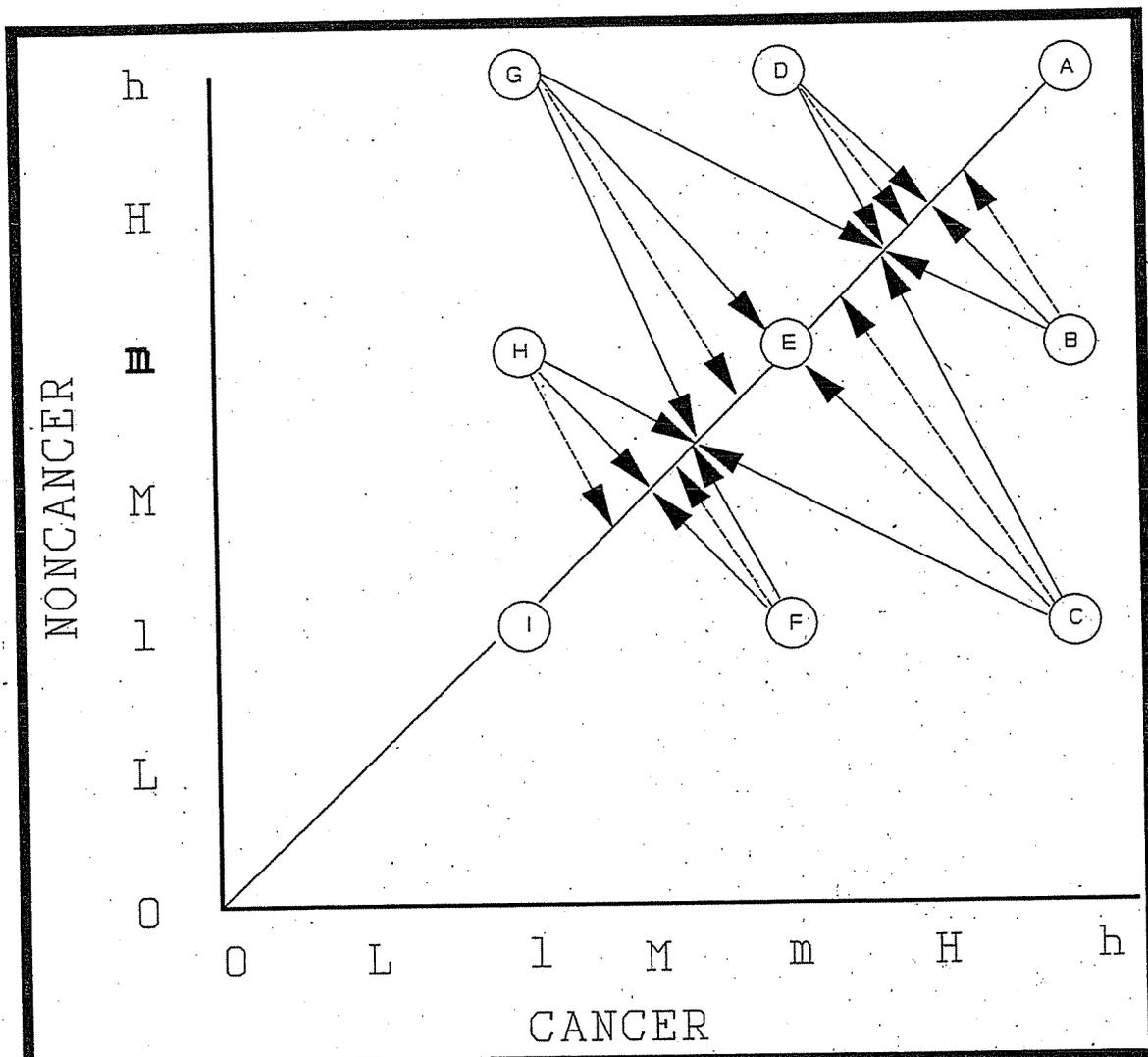
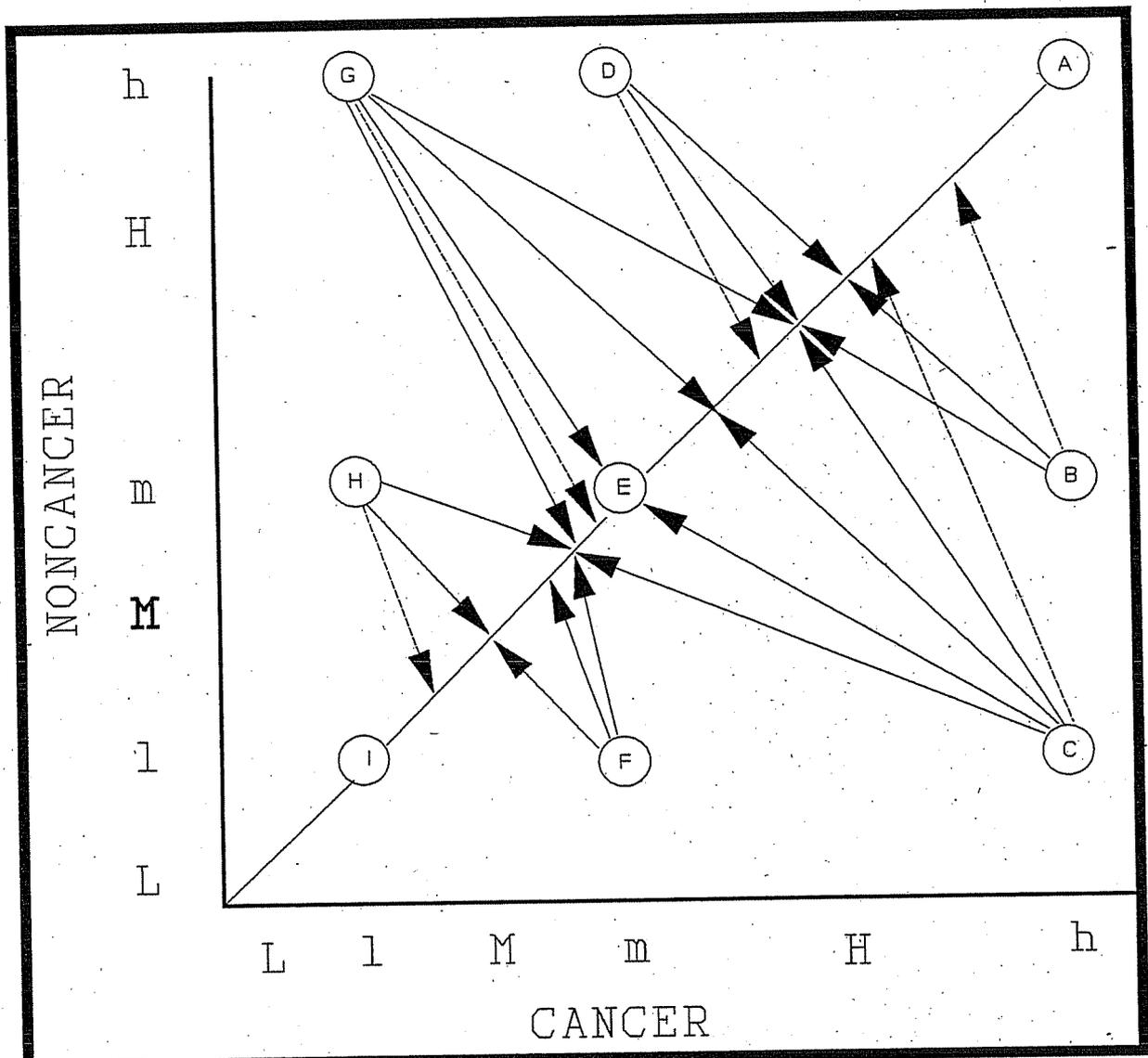


Figure 8.2.4.1 Linear array of nodes

convenient to do so by considering those of the nodes. The plot of nodes only, corresponding to the grid squares and their nodes in Figure 8.2.2.1, is shown in Figure 8.2.4.1.

In Figure 8.2.4.1, two kinds of vectors can be distinguished: (1) those that project more than one off-diagonal node onto the same point on the diagonal (vectors drawn with continuous black lines are examples of these such as the vectors connecting nodes H and C, D and C, etc...) and (2) the dashed-line vectors that project only one node onto the diagonal. Imagining the dashed-line vectors to rotate around their off-diagonal nodes so as to pass through points where more than one node is projected (common projections), the order (the rank order) of the projections (of the merged risk rankings) changes: one order occurs when a dashed-line



**Figure 8.2.4.2 Nonlinear array of nodes**

vector is on one side of a common projection, a reversal of order occurs on the other side, and an order unique to the common point occurs at the common point. The same observation pertains to nonlinear arrays, an example of which is shown in Figure 8.2.4.2.

For linear arrays, it is found that, in addition to the physically trivial cases where  $v$  is equal to either zero or infinity, there are three values of  $v$  that yield common points and four ranges of  $v$  that do not; these yield seven different rankings, all that are possible for a three-by-three, linear array: three for  $v > 1$ , three for  $v < 1$ , and one for  $v = 1$ . For a three-by-three nonlinear array of the type considered in this report regardless of the values of  $h$ ,  $m$  and  $l$ , again excluding the physically trivial

cases, there are at most fifteen possible rankings: seven for  $v > 1$ , seven for  $v < 1$ , and one for  $v = 1$ . Two such rankings are listed in Tables 8.2.6.1 and 8.2.6.2, including the trivial cases for completeness; only the non-trivial cases are numbered for reference in each table. Note that for a four-by-four linear array, the number of rankings that must be considered jumps to fifteen; hence the practical importance of using the three-by-three array.

The practical meaning of all of this is that even if it is not known whether the rankings are linear or nonlinear, what the values of  $h$ ,  $m$  and  $l$  are, or what the value of  $v$  is, the number of possible rankings of ranges that need to be considered and compared for consistency with the information available on their separately ranked Problems is no more than seven for linear three-by-three arrays and fifteen for nonlinear ones as defined here.

#### 8.2.5 Comparing Range Rankings With Data

If it can be decided whether  $v > 1$  or  $v < 1$  (the most important considerations) or whether  $v = 1$  (or close to it), then the number of possible range rankings that must be considered to obtain a first rough ranking of Problems associated with the rankings is further reduced. Since there are certain features among the possible rankings such as specific reversals of ranking of ranges between pairs of rankings for different values of  $v$ , or cases in which certain ranges are of equal rank, there are additional ways in which the number of rankings that must be compared with the information in any detail in any given case can be reduced; moreover, these types of comparisons yield an answer to the question of the value of  $v$  relative to unity without requiring any direct attempt to evaluate  $v$ .

A final ranking of ranges (each with its contained Problems) chosen by using the properties of three-by-three arrays, as governed by equation (3), becomes the basis for further, detailed comparison of Problems contained within overlapping rankings, using the information available, to introduce changes in the rankings of individual Problems if these seem necessary.

The actual comparison of any two ranges to determine their relative ranking requires that available data or information on the risks associated with the Problems associated with (contained within) one of the two ranges be compared with the information on

the Problems in the other to determine where the two sets of Problems, on balance, appear to lie in terms of relative rank order: one generally above other (recognizing that some individual Problems may rank differently than their ranges because of overlap), one generally below the other, or that the two sets are generally similar in rank (the ranges have roughly equal rank). There will generally be small (and different) numbers of Problems associated with any two ranges, a fact that does not make the comparison easy since the ranges are relatively broad (see, for example, Figure 8.2.2.1) and there is no way of knowing, quantitatively, where the Problems lie within ranges. Of some small help is the fact that the projections of Problems will tend to be grouped centrally within the ranges rather than uniformly, even if one supposes the Problems to be drawn from a uniform distribution of Problems over the area of the grid squares, except as  $v$  becomes either very large or very small. For  $v$  equal to zero or infinity, the distribution of projections of Problems within ranges will be uniform.

#### **8.2.6      Steps in the Process for Producing a Merged Health Risk Ranking**

Given that the possible ranking patterns of ranges for three-by-three linear and nonlinear arrays are now established (Tables 8.2.6.1 and 8.2.6.2), the following are the steps to be taken in arriving at a merged health risk ranking for a set of Problems that have been ranked separately according to the risks associated with two different classes of health effects (cancer and non-cancer effects, in this case):

- (1) List the Problems that have been ranked for both cancer and non-cancer risks.
- (2) For those Problems that have been ranked for both, group the cancer and non-cancer rankings separately into three qualitative risk levels: high (H), medium (M) and low (L) if this is not the way they have been ranked already. This is best done by an appropriately selected, knowledgeable, consensus group.
- (3) List the Problems that lie within each of the nine possible grid squares of the three-by-three risk array; plotting them helps visualize the information.

(4) Make an initial decision as to how  $v$  relates to unity if the information available permits; in any case, whether this is possible or not, check major rank reversals between pairs of rankings for different values of  $v$  (see Tables 8.2.6.1 and 8.2.6.2 for examples of major rank reversals as  $v$  changes;

No.*	For:	The ranking pattern is:
	$v = \text{infinity}$	ADG > BEH > CFI
11.	$v > 1$	A > D > G > B > E > H > C > F > I
12.	"	A > D > BG > E > CH > F > I
13.	"	A > D > B > G > E > C > H > F > I
14.	$v = 1$	A > BD > CEG > FH > I
15.	$v < 1$	A > B > D > C > E > G > F > H > I
16.	"	A > B > CD > E > FG > H > I
17.	"	A > B > C > D > E > F > G > H > I
	$v = 0$	ABC > DEF > GHI

\* Only the physically non-trivial rankings are numbered.

Table 8.2.6.1 Rankings possible for a linear three-by-three array (versals of C and G, B and D, and F and H) to either select  $v$  or confirm the selection made. This is best done by the same consensus group.

- (5) Using the result of step (4), select from the possible range rankings for the linear array (Table 8.2.6.1) the rankings in keeping with that result.
- (6) Compare the rankings in step 5) with the information available on individual Problems, as described above, to conclude, on balance, which ranking is most in keeping with the information. This is best done by the same consensus group.
- (7) Use the result of step (6) as guidance to select rankings for nonlinear arrays (e.g., Table 8.2.6.2) for comparisons such as have been made for linear arrays in step (6) (Check the selection of  $v$  against this array of rankings, also).
- (8) Of the sets of rankings now in hand, select the best one, overall, from the two types of arrays. This is best done by the same consensus group.

(9) Rank order the problems within each of the ranking groups obtained in step (8) if, and to the extent which, this is possible. This is best done by the same consensus group.

(10) Check the nearly final ranking, Problem by Problem, against the information available on each Problem to see if any specific Problems need to be moved upward or downward in rank in the nearly final ranking. If step (9) has been carried out, step (10) can be made easier by comparing Problems at the high end of one range with those at the low end of the next higher ranking range first, and vice versa. This, too, is best done by the same consensus group.

No.*	For:	The ranking pattern is:
	$v = \text{infinite}$	ADG > BEH > CFI
N1.	$v > 1$	A > D > G > B > E > H > C > F > I
N2.	"	A > D > G > B > E > HC > F > I
N3.	"	A > D > G > B > E > C > H > F > I
N4.	"	A > D > G > B > EC > H > F > I
N5.	"	A > D > G > B > C > E > H > F > I
N6.	"	A > D > GB > C > E > H > F > I
N7.	"	A > D > B > G > C > E > H > F > I
N8.	$v = 1$	A > DB > GC > E > HF > I
N9.	$v < 1$	A > B > D > C > G > E > F > H > I
N10.	"	A > B > DC > G > E > F > H > I
N11.	"	A > B > C > D > G > E > F > H > I
N12.	"	A > B > C > D > GE > F > H > I
N13.	"	A > B > C > D > E > G > F > H > I
N14.	"	A > B > C > D > E > GF > H > I
N15.	"	A > B > C > D > E > F > G > H > I
	$v = 0$	ABC > DEF > GHI

\* Only the physically non-trivial rankings are numbered.

Table 8.2.6.2 Rankings possible for a non-linear three-by-three array

When step (10) is completed, the final ranking is in hand. This final step, not taken in the illustrative example, is very important; it is the final opportunity to correct the joint ranking, exposing and correcting not only the overlaps already described but even, possibly, any errors made in the original rankings.

A note of caution: this discussion should not imply that one would require a high ranking for both cancer and non-cancer health effects to consider an exposure to be of high priority.

### 8.2.7 An Illustration of the Merging of Separate Rankings into One

The UB report represents an extensive study in which a set of Problems, thirty-one in number, significant to the U.S. EPA, was defined and ranked in two separate rankings according to their cancer and non-cancer effects population risks. In this section the UB report problems are referred to using the same numbers, from 1 to 31, as used in the report. Although the Human Health Subcommittee of the Relative Risk Reduction Steering Committee of the Science Advisory Board has reservations about the definitions and rankings of the Problems in the UB report (see elsewhere in this report for discussions and recommendations), it was concluded that the thirty-one Problems in the UB report, with some modification, and the information in the UB report relative to those Problems, could be used to illustrate how the risk merging procedure is applied.

The modifications involve a regrouping of the thirty-one Problems and one additional one (electromagnetic fields) under three main headings: Situations and Agents Involving the Potential for direct Exposure, Sources of Environmental Pollution, and Miscellaneous (see section 5.4 and Table 5.4.1). Further subgroupings within these categories were proposed. Thus, for example, Occupational Exposures included Worker Exposures (Problem # 31) and Application of Pesticides (#26). In the proposal a number of individual Problems as defined in the UB report appeared to be better combined as new Problems (an example is the possible combination, for purposes of health risk ranking of Discharges to Estuaries, #13, and Discharges to Wetlands, #14). In the case of Occupational Exposures, although the proposal groups them together, the two types of exposures Application of Pesticides and Worker Exposures) are so very different (different populations, different physical conditions, different kinds of remedial actions possible, etc...) that it would not be useful to consider them as one Problem. However, Indoor Air-Radon (#4) and Indoor Air-Other (#5) are readily redefined as a single Problem, Indoor Air (#4/5); here the same population is affected, the exposure situation is physically well defined, and many of the remedial methods apply to more than one agent present.

In this illustrative example of how the merging process is carried out, only one pair of Problems, Indoor Air-Radon (#4) and

Indoor Air-Other (#5) will be combined into a new Problem, Indoor Air (#4/5), leaving the other Problems as in the UB report.

In the UB report, Problems are already grouped as H, M or L for non-cancer risk, the consensus group that created that ranking having concluded that no finer subdivision was possible. In the case of cancer risks, all but five of the thirty-one problems were ranked, qualitatively, one above the other, a few pairs being given the same ranking; here, the existing ranking had to be reduced to three levels as is already the case for non-cancer risk ranking.

### 8.2.7 Grouping the Cancer Risk Ranked Problems into Three Risk Groupings

An examination of the ranking on the basis of cancer risks and of the factors considered in the UB report leads to the conclusion that a reasonably natural boundary between the "high" and the "medium" levels for cancer risks lies between the eighth and ninth ranked Problems; similarly, the boundary between the "medium" and "low" levels lies reasonably naturally between the seventeenth and eighteenth ranked Problems. The three rankings for cancer risk that result are as follows (with Indoor Air combined as #4/5, as above):

<u>Rank Level</u>	<u>Problem Numbers</u>
High (H)	2, 4/5, 7, 17, 25, 30, 31
Medium (M)	6, 12, 15, 16, 18, 19, 26, 27, 28
Low (L)	1, 9, 10, 11, 20, 21, 22, 23, 24

Among the H-ranked Problems, nos. 31 and 4/5 stand out relative to the rest as, in effect, "extra high." Please note that this is a tentative grouping into H, M, and L categories for illustrative purposes only; this grouping in no way represents a consensus of the current Subcommittee as to the relative risk to human health from any of the "Problem Areas" as set forth in the original UB Report. In any actual case of ranking Problems, however defined, or by using any methodology, such a ranking should be subjected to a broad consensus process.

Table 8.2.7.1 shows the above Problems, ranked H, M or L for cancer risk together with the H, M or L rankings for non-cancer risks. Only twenty-two Problems, as defined here, were ranked

simultaneously for both cancer and non-cancer risks. The rest of this example considers how to merge the rankings for these twenty-two Problems, only, to produce a rank order list based on both cancer and non-cancer risks.

The information in Table 8.2.7.1 is plotted in Figure 8.2.7.1; the numbers near each of the nodes indicate which Problems lie within the corresponding grid squares, their actual locations within the grid squares being unknown. Table 8.2.8.1 shows the same information, with the problems listed in the same order, from left to right, as in their cancer risk ranking so as not to lose sight of this information.

Problem Number	Cancer Rank	Non-cancer Rank
2	H	H
4/5	H	H
7	H	M
17	H	L
25	H	H
30	H	H
31	H	H
6	M	M
12	M	L
15	M	H
16	M	L
18	M	M
19	M	M
26	M	H
27	M	M
28	M	-
1	L	H
9	L	L
10	L	M
11	L	M
20	L	L
21	L	H
22	L	-
23	L	L
24	L	-
3	-	-
8	-	-
13	-	M
14	-	L
29	-	-

Table 8.2.7.1 High, Low, and Medium rankings for UB problem areas

8.2.8 The Value of v Relative to 1.0

A direct estimate of  $v$ , even to the extent of concluding whether it is above or below one, cannot be made with any reasonable degree of certainty. The severities of cancers, on average, are well above those of the aggregation of non-cancer endpoints considered in the UB report so that, unless the fraction of the population affected by non-cancer endpoints is very much higher than that for all cancers, as related to relevant agents in the environment,  $v$  is more probably less than one than it is above one. The consideration of the consistency of the information in the UB report on individual Problems with respect to reversals of rankings of ranges from one possible ranking to another for different values of  $v$  (Tables 8.2.6.1 and 8.2.6.2) is a surer indicator of where  $v$  lies in this case. These comparisons are described in the next subsection. In any case, where  $v$  lies with respect to one is not to be chosen arbitrarily but, rather, on the basis of what the information itself demonstrates it to be.

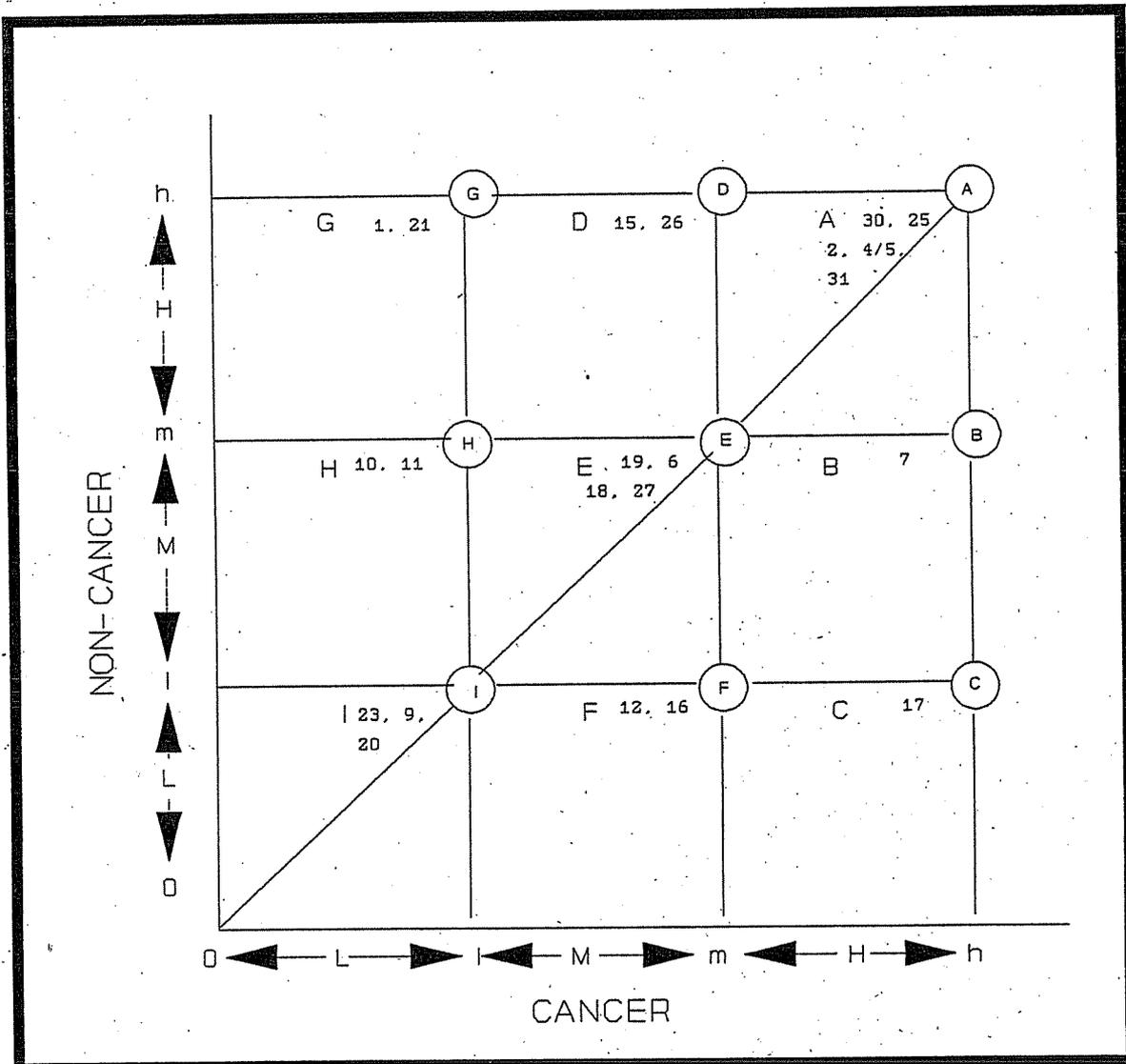


Figure 8.2.7.1 Actual Problems

**8.2.9 Consideration of Possible Rankings for Consistency with Available Information: Selection of a Ranking of Ranges**

The simplest approach is to examine the linear array rankings in Table 8.2.6.1 before passing on to considering the nonlinear rankings in Table 8.2.6.2. The results of considering linear rankings first, despite the fact that it would seem more reasonable to choose the nonlinear ones first, can serve as guides when nonlinear rankings are examined; moreover, it is not in fact known what the original ranking teams had in mind insofar as linearity or non-linearity is concerned, nor what their unconscious choices

might have been, as they ranked the Problems for cancer and non-cancer risks.

The assumption that  $v < 1$ , for a linear array was first tested by examining rankings where large reversals of rank of pairs of ranges in Table 8.2.6.1 occur. The reversals of B and D, F and H, and C and G between the rankings for  $v < 1$  and  $v > 1$  are striking. Examining the descriptive information in the UB report on the Problems contained in these three ranges (see Table 8.2.8.1) shows clearly that  $B > D$ ,  $F > H$ , and  $C > G$  is more consistent with the information than the reverse and thus the conclusion that  $v < 1$  is the reasonable one.

Grid Square	Problems
A	31, 4/5, 25, 30, 2
B	7
C	17
D	15, 26
E	6, 27, 19, 18
F	16, 12
G	1, 21
H	11, 10
I	20, 23, 9

Table 8.2.8.1 Problems Contained in each range, in order of cancer risk (left-to-right)

With  $v < 1$ , Table 8.2.6.1 gives the following possible rankings for further consideration:

L5        A > B > D > C > E > G > F > H > I

L6        A > B > CD > E > FG > H > I

L7        A > B > C > D > E > F > G > H > I

Ranges shown grouped together are of equal rank.

Examining the information given in the UB report for the Problems contained in ranges C and D, the information is inconsistent with the order  $C > D$ ;  $D > C$  is only weakly supported; and lumping C and D is the best choice. Moreover, on balance, the arguments for lumping F and G appeared to be better than those for keeping them separate; thus, merged risk ranking number L6 was selected of the three possible ones given above for a linear array. Other inequalities in L6 appear consistent with the information in the UB report, although B and D appear to be closely ranked; H and I also appear to be close together, though not so close as B and D; one has to bear in mind the overlapping nature of the ranges. For the moment, pending examination of possible rankings for nonlinear arrays (e.g., as in Table 8.2.6.2), L6 will be the ranking of choice.

Considering the nonlinear array rankings against L6, rankings N9 and N10 appear to be the best to examine first, in particular the relationships of E, G and F that, in L6, are in the order  $E > FG$  but in N9 and N10 are in the order  $G > E > F$ . It is found that  $E > F$  and  $E > G$  is consistent with the information in the UB report; and, since it was already determined that lumping F and G was more reasonable than not, L6 appears as the best choice of all for the ranking to be examined in detail, problem by problem. Note that N14 is not a good choice since lumping C and D, and F and G, is preferable. Table 8.2.9.1 shows this ranking with the Problems within each of the ranges listed, from left to right in their cancer risk order and with their non-cancer rankings shown in parentheses. The fact that the linear rather than the non-linear array produced the most consistent result does not force the conclusion that the array is indeed linear. It may be not too highly nonlinear, the uncertainty of the information and its qualitative nature being such as to not make too close a discrimination possible; or the array may be nonlinear but not exactly symmetrical about the diagonal; or other deviations of the real example from the theoretical model may cause the appearance of near linearity.

Range(s)	Problems
A	31(H), 4/5(H), 25(H), 30(H), 2(H)
B	7(M)
DC	17(L), 15(H)/26(H)
E	6(M), 27(M), 19(M), 18(M)
GF	1(H), 21(H)/16(L), 12(L)
H	11(M), 10(M)
I	20(L), 23(L), 9(L)

Table 8.2.9.1 Selected rankings for further expansion and consideration (in order of cancer risk, left-to-right; non-cancer risk ranking in parentheses)

In Table 8.2.9.1, in all but DC and GF the, non-cancer rankings are the same; thus, recognizing that with new information the non-cancer rankings may alter this conclusion, for the moment the cancer ranking order appears to prevail within each of these ranges. In DC and GF, consideration of the information in the UB report on each of the individual Problems shows that ranking them in cancer risk order is consistent with that information. In GF, the fact that the two highest in cancer order are both ranked H for non-cancer risk and the lower two, in cancer order, are ranked L for non-cancer risk is consistent with this finding. Table 8.2.9.2 shows the information in Table 8.2.9.1, with the Problem descriptions included. In this form the tabulation is, to all intents and purposes, a nearly final illustrative merged health risk ranking, by problem, of the twenty-two original problems, as previously ranked in the UB Report,

separately by cancer and non-cancer population risk. This ranking is based on the original UB report scores for the 31 categories of problem areas, and in no way reflects the view of this Subcommittee. It serves only to illustrate a the application of a theoretical approach to merged risk ranking.

This last ranking is called nearly final because this is the ranking that now should be examined, Problem by Problem, for overall consistency with the available information to see if any Problems need to be exchanged in rank order or rank ordered equally because of the overlap of ranges already discussed. A cursory examination does not indicate the need for changes, though a few pairs of Problems are probably better shown to be of equal rank as opposed to their ranking in Table 8.2.9.2. The examinations of the pairs of ranges above, and of this nearly final ranking for consistency with the available information should be by consensus of experts for the soundest results. When completed, the results, to be consistent with the input information, should be reported as "high," "medium," and "low" risk groups (though some may stand out within these groupings as, for example, nos. three and four/five).

Range(s)	Problem	Description of Problem
A	31 *	Worker exposure to chemicals
	4/5 *	Indoor air
	25	Pest. res. on food eaten by humans/wildlife
	30	Consumer product exposure
	2	Hazardous/toxic air pollutants
B	7	Stratospheric ozone depleting substances
DC	17	Hazardous waste sites -- inactive
	15	Drinking water at the tap
	26	App. of pest. (applicators, consumers, etc)
E	6	Radiation -- other than radon
	27	Other pest. risks (leaching, runoff, etc)
	19	Nonhazardous waste sites -- industrial
	18	Nonhazardous waste sites -- municipal
GF	1	Criteria air pollutants (stat. & mobile src.)
	21	Accidental releases -- toxics (all media)
	16	Hazardous waste sites -- active
	12	Contaminated sludge (municipal and scrubber)
H	11	Non-point surface discharges to surface wat.
	10	Indir. pt. src. disch. (POTWs) to surf. wat.
I	20	Mining waste (inc. oil & gas extraction)
	23	Rel. from stor. tanks (on/above/underground)
	9	Direct point discharges to surface waters

\*Essentially of equal rank, high relative to the others in this range.

**Table 8.2.9.2 Hypothetical "Nearly Final" merged risk rankings (illustrative), based on the unmodified UB Report information**

Problem by Problem, for overall consistency with the available information to see if any Problems need to be exchanged in rank order or rank ordered equally because of the overlap of ranges already discussed. A cursory examination does not indicate the need for changes, though a few pairs of Problems are probably better shown to be of equal rank as opposed to their ranking in Table 8.2.9.2. The examinations of the pairs of ranges above, and of this nearly final ranking for consistency with the available information should be by consensus of experts for the soundest results. When completed, the results, to be consistent with the input information, should be reported as "high," "medium," and "low" risk groups (though some may stand out within these groupings as, for example, nos. three and four/five).

### 8.2.10 Further Comments and Recommendations

For the long term use of merged cancer and non-cancer risk ranking, the so-called zero-based procedure outlined early in this section is best. Doing it once can form a solid basis for updating

and revising it and, since it deals most directly with the problem in a manner as close as possible to equation (1) and its alternate form in terms of P and D, equation (2), it is likely to yield the most correct and credible, and therefore reliable, result when it comes to budgeting and allocating resources to risk management activities and to research. It is recommended that this effort be undertaken as an investment in facilitating better planning and allocation.

The procedure for merging separately ranked Problems (for cancer and non-cancer risk) is relatively easy to use, now that the possible rankings are tabulated in Tables 8.2.6.1 and 8.2.6.2 and once separate cancer and non-cancer risk rankings are in hand. The consensus mechanism recommended is particularly useful not only in narrowing down the possible rankings to one best one but also in reaching the final merged ranking while ensuring that information that might have been lost in reducing the cancer risk based rankings to three levels is utilized at the end.

#### 8.2.11 Derivation of $w_j = w_{cj} + vw_{nj}$ and of $v$

Numbering the cancer endpoints from 1 to C and the non-cancer endpoints from C + 1 to E, equation (1) may be rewritten in the following form:

$$W_j = N_j \sum_{i=1}^C \sum_{k=1}^A S_i f_{ijk} + N_j \sum_{i=C+1}^E \sum_{k=1}^A S_i f_{ijk} \quad (6)$$

that in turn may be written in the form

$$W_j = W_{cj} + W_{nj} \quad (7)$$

Here, the three terms correspond to the parallel three terms in equation (A1). The first term on the right represents the aggregate weight of cancers and the second term that for all non-cancer endpoints, all appropriately scaled for severity, potency and exposure (see, too, equation (2) in the body of the report).  $W_j$ , as before, then represents the weight to be used for ranking purposes to rank the  $j$ th problem with respect to the other problems being considered.

The terms in these equations are not directly known, in the present case, cancer risks having been ranked against cancer risks,

only, non-cancer risks against non-cancer risks, only, and the relative scaling of the two types of risks not having been addressed. The rankings are qualitative, too, not quantitative. Equation (7), to be useful here, must be recast in terms relevant to the present case.

Defining  $w_{cj}$  as the weight to be used for ranking the  $j$ th Problem against other Problems on the basis of cancer risk only, scaled so that the weight of the problem of maximum cancer risk is  $h$ , then

$$w_{cj} = hW_{cj}/W_{ch} \quad (8)$$

Similarly, for non-cancer risk ranking,

$$w_{nj} = hW_{nj}/W_{nh} \quad (9)$$

Here  $W_{ch}$  is the weight for cancer risk, as defined for equations (6) and (7), of the Problem in the set of Problems considered for ranking according to cancer risk that has the highest weight (and therefore would be ranked first for cancer if the weight were known, quantitatively), and  $W_{nh}$  is the same but for the Problem that ranks highest for non-cancer risk. The Problems need not be the same in the two cases.

Equation (7), combined with equations (8) and (9) and multiplied by  $h/W_{ch}$  becomes

$$(h/W_{ch})W_j = w_{cj} + vW_{nj} \quad (10)$$

$$\text{where } v = W_{nh}/W_{ch} \quad (11)$$

a constant for the particular set of problems being ranked; note that  $v$  may take a different value for another set of problems or for subsets of the original set of problems if  $W_{nh}$  and  $W_{ch}$  or their ratio is not the same from one set to the other.

Since  $h$  is a constant, and since  $W_{ch}$  is a constant for the particular set of ranked problems under consideration, then the left hand side of equation (10) is the weight to be accorded the combination of cancer and non-cancer risks in ranking the  $j$ th problem against the other problems in its set,  $w_j$ . Thus equation (10) becomes

$$W_j = W_{Cj} + vW_{Nj} \quad (12)$$

This is the key equation in the rank merging method. Though it is derived in this instance for the case in which the separate rankings are made on the basis of population risk (as is the derivation of  $v$  which follows), the same form of equation is obtained if either individual risk or a mixture of individual and population risk is used. In these latter two cases the definition of  $v$  is different, in each case, from the one derived below, but this has no impact on the number and nature of the possible rankings derived later on. Special factors, suitably formulated, such as for individual or population sensitivity, may also be included in the derivation without altering the form of the key equation.

From equations (6) and (7),

$$W_{CH} = N_{CH} \sum_{i=1}^C \sum_{k=1}^A S_i f_{ijk} \quad (13)$$

where here  $j$  is for the Problem with the highest cancer risk

$$\text{and } W_{NH} = N_{NH} \sum_{i=C+1}^E \sum_{k=1}^A S_i f_{ijk} \quad (14)$$

where here  $j$  for the Problem with the highest non-cancer risk. The average severity of cancers in the Problem with weight  $W_{CH}$  is  $S_{CH}$ , where

$$S_{CH} = \frac{\sum_{i=1}^C \sum_{k=1}^A S_i f_{ijk}}{\sum_{i=1}^C \sum_{k=1}^A f_{ijk}} \quad (15)$$

and a similar expression is obtained for the average severity of non-cancer endpoints,  $S_{NH}$ , in the Problem with weight  $W_{NH}$ . Substituting these terms into equations (13) and (14),

$$W_{CH} = S_{CH} N_{CH} \sum_{i=1}^C \sum_{k=1}^A f_{ijk} \quad (16)$$

and 
$$W_{NH} = S_{NH} N_{NH} \sum_{i=C+1}^E \sum_{k=1}^A f_{ijk} \quad (17)$$

The double summation in equation (16) is an estimate of the fraction of all exposed subjects in the highest cancer risk Problem who exhibit cancerous endpoints,  $F_{CH}$  (note that the fraction of those who exhibit at least one endpoint--those showing any effect - is slightly less, but the difference is small because the individual  $f$ -values are small). Similarly, fraction  $F_{NH}$  is defined for the Problem with the highest non-cancer risk. Then

$$v = \frac{N_{NH} S_{NH} F_{NH}}{N_{CH} S_{CH} F_{CH}} \quad (18)$$

The two fractions,  $F$ , are functions of the potencies of the agents and of exposures to them; equation (18) thus indicates the factors, and their relationships, that determine the value of  $v$  for a particular set of points being ranked.

#### 8.1.12 Derivation of Some of the Characteristics of Three-By-Three Arrays as Governed by Equation (3)

Suppose that for some value of  $v$  both nodes C and G project onto the diagonal at E (see the solid arrows indicating this in Figure 8.2.4.1. This means that the  $w_{CNj}$ -values for C, E and G are equal. Similarly to equation (5),

$$h + vl = m + vm = l + vh \quad (19)$$

from which it follows that  $v = 1$  for this case. Similarly, if F and H project onto the diagonal at some common point and B and D do so at another common point, then

$$m + vl = 1 + vm \quad (20)$$

and  $h + vm = m + vh \quad (21)$

and in each case  $v = 1$ . Thus for  $v = 1$ , the merged risk rank order is, for a linear array:

$$A > BD > CEG > FH > I \quad (22)$$

giving a total of five risk levels since some of the nodes are of the same relative rank, as indicated. For a nonlinear array, the  $v = 1$  rank order becomes:  $A > BD > CG > E > FH > I$ ; here, C, E and G are not co-linear (see Figure 8.2.4.2).

Consider nodes F and G in Figure 8.2.4.1, projected onto the diagonal at a common point. Here,

$$m + vl = 1 + vh \quad (23)$$

from which

$$v = \frac{m - 1}{h - 1} < 1 \quad (24)$$

Designating the value of  $v$  by the letters corresponding to the off-diagonal nodes projected onto common points on the diagonal, referring to Figure 8.2.7.1,

$$v(FH) = v(CG) = v(BD) = 1 \quad (25)$$

and  $v(FG) = \frac{m - 1}{h - 1} < 1 \quad (26)$

By similar reasoning,

$$v(CD) = \frac{h - m}{h - 1} = 1 - v(FG) < 1 \quad (27)$$

$$v(BG) = \frac{h - 1}{h - m} = 1/v(CD) > 1 \quad (28)$$

$$\text{and } v(CH) = \frac{h - 1}{m - 1} = 1/v(FG) > 1 \quad (29)$$

This kind of treatment gives the values of  $v$ , and the relationships between them, for which off-diagonal nodes can be projected onto common points on the diagonal for linear and nonlinear arrays. For linear arrays, regardless of the values of  $h$ ,  $m$  or  $l$ , it turns out that not only does  $v(FH) = v(CG) = v(BD) = 1$ , but  $v(CD) = v(FG) = 0.5$  and  $v(BG) = v(CH) = 2.0$ , and these are the three values of  $v$  leading to common projections. For nonlinear arrays, the same common projections lead to  $v = 1$ ; however  $v(CD)$  and  $v(FG)$  are not equal, and nor are the pairs  $v(BG)$  and  $v(CH)$  or  $v(CG)$  and  $v(EG)$ . In the nonlinear case, there are therefore seven values of  $v$  that lead to common projections.

For projections onto any point on the diagonal, with coordinates  $(x,x)$ , from an off-diagonal node with coordinates  $C'$  (for cancer) and  $N'$  (for non-cancer), the equality of the two  $w_{CNj}$  values at the two points requires that

$$x + vx = C' + vN' \quad (30)$$

$$\text{or, } v = \frac{C' - x}{x - N'} \quad (31)$$

The slope of the vector connecting  $(C',N')$  with  $(x,x)$  is

$$\text{slope} = - \frac{N' - x}{x - C'} = - \frac{- N'}{C' - x} \quad (32)$$

Thus, for any such vector,

$$\text{slope} = -1/v \quad (33)$$

Considering the above, it is expected that for linear arrays there will be seven possible rankings (three for the values of  $v$  leading to common projections and four more corresponding to values of  $v$  between and on each side of the highest and lowest of the three common projection values, excluding the physically trivial cases of  $v$  equal either to zero or infinity) and fifteen possible rankings for the nonlinear case (seven for the common projections and eight other, again excluding the two trivial cases). These are tabulated in Tables 8.2.6.1 and 8.2.6.2. An alternative to deriving the rankings by considering, geometrically, the rotations of the vectors around the nodes so as intersect the diagonal is to assign values to  $v$ . For either the linear or nonlinear arrays, values of  $v$  for the common points plus arbitrarily chosen values of  $v$  between and to either side of these makes it possible to calculate the weights, and therefore to derive the rank orders, corresponding to each of these values of  $v$ ; thus the possible sets of rank orders are derived. For the linear case, the common-point values of  $v$  are 0.5, 1.0 and 2.0, whereas for the nonlinear case these values depend on the  $h-m/m-1$  ratio; however, common-point values of  $v$  based on any arbitrarily chosen value of this ratio, (or of the values of  $h$ ,  $m$ , or  $l$ ) plus other values of  $v$  falling between and to either side of the common-point values, may be used to make the weight calculation with the same result regardless of the choices; in the case of three-by-three nonlinear arrays, whatever the value chosen for  $h-m/m-1$ , the rank order patterns derived will be the same. For four-by-four and higher nonlinear arrays, more than one set of rankings will be obtained depending on the specific values of  $v$  or ranges of values of  $h$ ,  $m$ , or  $l$ .

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Section 8.1.1--Appendix

OZONE CASE STUDY

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#### Section 8.1.2--Appendix

##### RADON CASE STUDY

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