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Volume 1. Introduction and Epidemiology

Clement Associates, Inc., Ruston, LA

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Investigation of Cancer Risk Assessment Methods:

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16. ABSTRACT The major focus of this study is upon making quantitative comparisons of carcinogenic potency in animals and humans for 23 chemicals for which suitable animal and human data exists. These comparisons are based upon estimates of risk related doses (RRDs) obtained from both animal and human data. An RRD represents the average daily dose per body weight of a chemical that would result in an extra cancer risk of 25%. Animal data on these and 21 other chemicals of interest to the EPA and the DOD are coded into an animal data base that permits evaluation by computer of many risk assessment approaches.

This report is the result of a two-year study to examine the assumptions, other than those involving low dose extrapolation, used in quantitative cancer risk assessment. The study was funded by the Department of Defense [through an inter-agency transfer of funds to the Environmental Protection Agency (EPA)], the EPA, the Electric Power Research Institute and, in its latter stages, by the Risk Science Institute.

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Section 1

INTRODUCTION

BACKGROUND

In recent years there has been a growing awareness of the potential health hazard from chemicals encountered in environmental or occupational settings. Paralleling this awareness has been an increasing interest in the characterization of human health risks resulting from exposures to potentially hazardous chemicals. Often, such characterizations (risk assessments) must rely solely on experimental animal data because of lack of relevant epidemiological studies. Lifetime animal bioassays are frequently used to identify adverse health effects and to estimate risk to humans. Risk assessments based on animal data involve a series of assumptions concerning such issues as the dose response model, the appropriateness of the animal data, and dose conversion factors between animals and humans.

Carcinogenicity bioassays are usually designed as screening procedures with the primary focus being identification of potential human hazards, rather than human risk assessment. In these studies, a limited number of animals may be exposed to the maximum tolerated dose, which is a level often several orders of magnitude higher than the doses encountered by man. To estimate human risk from such studies requires both the extrapolation of results from high doses to low doses and from animals to humans. The present study focuses upon extrapolation from animals to humans, which has not been studied as extensively as extrapolation from high to low dose.

Extrapolation from animals to humans involves a number of components, each requiring a choice among several possible approaches. The approaches to the components reflect the assumptions that are made with respect to conditions likely to provide biological comparability of

animals and humans. The choice of a particular approach can have a considerable effect upon the resulting quantitative estimates. Although these components are based on scientifically sound biological principles insofar as possible, it is unfortunately the case that for most of the components of risk analysis there is often no scientifically defensible "correct" procedure. The NAS Committee on the Institutional Means for Assessment of Risk to Public Health (1) listed the components of risk assessment, and discussed possible approaches for each component. The Committee also recommended that "detailed" but "flexible" guidelines be developed for addressing each component of risk assessment.

STUDY GOALS

This study is designed to provide a detailed and systematic investigation of the components, other than low-dose extrapolation, that relate to estimation of human carcinogenic risk from animal bioassay data. Several components of quantitative risk assessment using animal models are listed in Table 1-1. Those components relate to the choices that must be made during the course of a risk assessment and involve such things as experimental design, analysis of data, and choice of studies to use when more than one is available. Components reflecting selection of appropriate experimental protocols include the route of administration and the duration of dosing and observation. Analysis of an experiment depends on the mathematical model relating dose and biological response. Average dose levels can be calculated in several ways and expressed in many units; the units chosen are those assumed to provide human and animal equivalence with respect to carcinogenic response. Response parameters depend on choice of site and type of tumor and calculation of response rates. When more than one study is available, one must determine which studies will be used and how they will be combined. Such choices may be based on selections of particular species, studies, or sex of test animals. A multitude of analysis procedures are possible, all of which may be more or less equally supported by scientifically defensible arguments.

An empirical approach has been taken in the present study to investigate the issue of human risk estimation based on animal carcinogenicity data.

Table 1-1

COMPONENTS OF RISK ASSESSMENT: CHOICES TO BE MADE

A. Requirements for a Study

1. Length of the experiment
2. Length of dosing
3. Route of exposure

B. Analysis of a Study

1. Dose

   a. Units assumed to give human-animal equivalence
   b. Expression of dose level values

2. Response

   a. Animals to use in analysis
   b. Malignancy status to consider
   c. Particular tumor type to use

3. Dose-Response model

C. Multiplicity of Studies

1. Sex to use
2. Study to use
3. Species to use

Having identified the steps in risk assessment at which crucial choices must be made (Table 1-1), alternative approaches have been identified for each of the steps (with the exception of the selection of a dose-response model, which has been studied extensively elsewhere in connection with the low-dose extrapolation problem). The approaches selected (Table 1-2) either have been used in past assessments, seem potentially useful, or seem particularly plausible because of biological considerations. The goal is to derive estimates of risk from the bioassay data by various combinations of the approaches selected and to compare those estimates to risk estimates derived from epidemiologic data (cf. Volume 3). Section 2 of this volume describes the manner in which the human-based estimates are determined. These represent our best estimates of risk to humans derived solely from epidemiological data; they are the "targets" at which the bioassay-based estimates are aimed and the standards against which they are judged.

The detailed evaluation of the different methods of analysis of the bioassay data allows one to address the question of uncertainty in animal-to-human extrapolation. Examination of a wide range of methods provides a range of risk estimates that are based on different but scientifically acceptable assumptions, and so will aid in the development of guidelines for presenting uncertainty. That examination also allows identification of the set of assumptions, those relating to the components of risk assessment as well as those relating to the quality of the data (e.g. with respect to sample size), that produce the best correlation of risk estimates between humans and animals. It is also possible to study the uncertainty attributable to each component; by including single-component variations of a standard protocol (i.e. those that differ from the standard only in selection of an alternative approach for one component, all other components remaining fixed) we obtain ranges of risk estimates that relate to the uncertainty associated with each of the components. In all these respects, we provide information about the extrapolation from animals to humans and the uncertainty that is involved. Additional research may be warranted in those areas that are less well characterized, i.e. those showing considerable variability or uncertainty.

Table 1-2

APPROACHES TO RISK ASSESSMENT COMPONENTS

1. Length of the experiment

   a. Use data from any experiment but correct for short observation periods.
   b. Use data from experiments which last no less than 90% of the standard experiment length of the test animal.

2. Length of dosing

   a. Use data from any experiment, regardless of exposure duration.
   b. Use data from experiments that expose animals to the test chemical no less than 80% of the standard experiment length.

3. Route of exposure

   a. Use data from experiments for which route of exposure is most similar to that encountered by humans.
   b. Use data from any experiment, regardless of route of exposure.
   c. Use data from experiments that exposed animals by gavage, inhalation, any oral route, or by the route most similar to that encountered by humans.

4. Units assumed to give human-animal equivalence

   a. mg/kg body wt/day.
   b. ppm in diet.
   c. ppm in air.
   d. mg/kg body wt/lifetime.
   e. mg/m^2 surface area/day.

5. Expression of dose-level values

   a. Doses expressed as average dose up to termination of experiment.
   b. Doses expressed as average dose over the first 80% of the experiment.

6. Animals to use in analysis

   a. Use all animals examined for the particular tumor type.
   b. Use animals surviving just prior to discovery of the first tumor of the type chosen.

Table 1-2 (continued)

APPROACHES TO RISK ASSESSMENT COMPONENTS

7. Malignancy status to consider

   a. Consider malignant tumors only.
   b. Consider both benign and malignant tumors.

8. Particular tumor type to use

   a. Use combination of tumor types with significant dose-response.
   b. Use total tumor-bearing animals.
   c. Use response that occurs in humans.
   d. Use any individual response.

9. Sex to use

   a. Use each sex within a study separately.
   b. Combine the results of different sexes within a study.

10. Study to use

   a. Consider every study within a species separately.
   b. Combine the results of different studies within a species.

11. Species to use

   a. Combine results from all available species.
   b. Combine results from mice and rats.
   c. Use data from a single, preselected species.
   d. Consider all species separately.

IDENTIFICATION OF THE CHEMICAL DATA BASE

To accomplish the goals of this investigation, a suitable collection of chemicals is needed. Both human epidemiological and animal bioassay carcinogenicity data are required for these chemicals. Moreover, the data from those tests need to be available and adequate to support a quantitative approach to risk assessment in both humans and animals.

Table 1-3 lists the chemicals for which were found at least minimal human and animal data capable of supporting the comparative analysis that is the goal of this study. This list has been compiled by review of the literature, starting with the monographs produced by the International Agency for Research on Cancer (IARC). Studies by the National Academy of Science (2) and Crouch and Wilson (3) that made similar comparisons of bioassay- and epidemiology-based risk estimates were also reviewed. Primarily, however, the list has been developed by perusal of the literature on specific cancer types, on chemical carcinogenesis in general, and on individual epidemiological investigations in particular. It is almost always the case that the availability of adequate, quantitative human data is a key factor for determining whether a chemical could be included in the study, so thorough review of the epidemiologic literature was essential. (Only one chemical, treosulfan, had human data suitable for a quantitative approach but lacked animal bioassay data.) We are grateful to a number of persons who suggested potentially useful substances, some of which were found to be acceptable for our quantitative analysis.

For a chemical to be included in the comparative analysis, the animal data or the human data, but not necessarily both, had to provide reasonably strong evidence of carcinogenicity. Note in this regard, that IARC considers the evidence for the carcinogenicity of each chemical listed in Table 1-3 (except methotrexate) to be either "limited" or "sufficient" for either animals or humans. On the other hand, chemicals that are carcinogenic in neither humans or animals provide no information on the comparison of risk estimates and, hence, are not useful for this investigation. For example, although methotrexate has been the subject of both bioassay and epidemiologic investigations which provide the necessary quantitative information for risk assessment, methotrexate is

Table 1-3

CHEMICALS FOR WHICH MINIMAL HUMAN AND ANIMAL DATA EXIST FOR QUANTITATIVE RISK ESTIMATION

Chemical	Evidence for Carcinogenicity (IARC designation) In Humans	In Animals
Benzene	Sufficient	Limited
Benzidine	Sufficient	Sufficient
Trichloroethylene	Inadequate	Limited
Vinyl Chloride	Sufficient	Sufficient
Aflatoxin	Limited	Sufficient
Arsenic	Sufficient	Insufficient
Nickel	Limited	Sufficient
Asbestos	Sufficient	Sufficient
Chlorambucil	Sufficient	Sufficient
Estrogens (conjugated)	Sufficient	Insufficient
Isoniazid (isonicotinic acid hydrazide)	Inadequate	Limited
Melphalan	Sufficient	Sufficient
Methotrexate	Inadequate	Inadequate
Phenacetin (analgesics containing phenacetin)	Sufficient	Limited
Reserpine	Inadequate	Limited
Tobacco smoke[a]	- -	- -
Diethylstilbestrol (DES)	Sufficient	Sufficient
Ethylene oxide	Inadequate	Limited
Saccharin	Inadequate	Limited
Chromium	Sufficient	Sufficient
Polychlorinated Biphenyls	Inadequate	Sufficient
Methylene Chloride	Inadequate	Sufficient[b]
Epichlorohydrin	Inadequate	Sufficient
Cadmium	Limited	Sufficient

[a]Not considered in IARC monographs, although acknowledged by IARC as a known human carcinogen.

[b]Although classified as "Inadequate" by IARC (4), results of studies completed since IARC evaluation indicate that the evidence for the carcinogenicity of methylene chloride in animals is now "Sufficient" (5).

not used in this study because neither the animal nor human studies provide evidence of carcinogenicity for methotrexate.

It is important to note that it is neither necessary nor sufficient that a chemical be unequivocally carcinogenic in humans in order that that chemical be included in the present investigation. Thus, a chemical such as saccharin, which has been associated with cancer only in laboratory rodents, is included while bis(chloromethyl) ether is not included, even though sufficient evidence apparently exists to establish that bis(chloromethyl) ether is carcinogenic in humans (4). Of the 23 chemicals or chemical groups that IARC considered in 1982 to have "sufficient" evidence of human carcinogenicity, 12 are included in this study (including cigarette smoke). Eleven other chemicals have been included; three were considered to provide "limited" evidence and eight to provide "inadequate" evidence in support of human carcinogenic effects.

We feel that it is essential to include in the study chemicals for which carcinogenicity in humans is not yet established. One of the ultimate goals of the study is to compare the predictions of carcinogenic potency of chemicals derived from animal data with the corresponding potency in humans. Bias could result if such comparisons were restricted to confirmed human carcinogens: the ability of the animal data to predict human results might be overestimated. The same would be true if the study were restricted to confirmed animal carcinogens. Although a similar study by the National Academy of Sciences was restricted to confirmed human carcinogens, the authors recognized the potential for bias in this approach (2). Negative epidemiological studies can be used in some cases to establish upper limits on the potential carcinogenic potency of chemicals, and such limits can be evaluated for compatibility with carcinogenic potencies estimated from animal data. These limits are also useful for regulatory and other purposes. On the other hand, we recognize the potential for misinterpretation of results derived from data on chemicals not established to be carcinogenic in humans. We have attempted, in the analyses and discussions which follow, to minimize the possibilities for such misinterpretations.

In addition to the twenty-three chemicals that have appropriate epidemiological data, the contractor (the Environmental Protection Agency and

the Department of Defense) supplied a list of 24 other substances that are of interest or concern with respect to possible carcinogenicity (Table 1-4). The available animal carcinogenicity bioassay data have been collected for all the chemicals in Tables 1-3 and 1-4. When available, IARC monographs, EPA criteria documents, EPA health assessment documents, EPA Carcinogen Assessment Group (CAG) assessment documents, and National Cancer Institute (NCI) or National Toxicology Program (NTP) technical reports have been consulted for references to animal carcinogenicity bioassays. Computerized data bases were also checked for suitable experimental studies. The data bases searched for references include Medline, Chemical Exposure, Biosis, Embase, and National Technical Information Service (NTIS). In addition, research articles were checked for references to earlier bioassay data. The NCI and NTP reports were particularly helpful in terms of supplying rodent carcinogenicity bioassay data for many chemicals, as was the data base published by Gold *et al.* (6). All bioassays listed by Gold and her associates for the chemicals of interest have been collected.

The chemical data base is described in detail in Volumes 1 and 2. Section 2 of this volume presents the epidemiological data that determine the direct estimates of cancer risk. Volume 2 devotes attention to the content of the animal data base. Finally, Volume 3 presents the comparison of the two sets of risk estimates, human and animal, and discusses the implications of the results, especially with respect to uncertainty and predictiveness of bioassay-based risk assessment.

Table 1-4

OTHER CHEMICALS FOR WHICH DATA HAS BEEN COLLECTED[a]

Acrylonitrile	Formaldehyde
Allyl chloride	Hexachlorobenzene
4-Aminobiphenyl	Hydrazine
Benzo(a)pyrene	Lead
Carbon tetrachloride	Mustard gas
Chlordane	2-Naphthylamine
Chlornaphazine	Nitrilotriacetic acid
Chloroform	2,4,6-Trichlorophenol
3,3-Dichlorobenzidine	TCDD
1,2-Dichloroethane	Tetrachloroethylene
Diphenylhydrazine	Toxaphene
Ethylene dibromide	Vinylidene chloride

[a]Requested by the Environmental Protection Agency and the Department of Defense.

REFERENCES

1. National Research Council (1983). Risk Assessment in the Federal Government: Managing the Process. National Academy Press. Washington, D.C.

2. National Academy of Sciences Executive Committee (1975). Contemporary Pest Control Practices and Prospects. Pest Control: An Assessment of Present and Alternative Technologies, Vol. 1.

3. Crouch, E. and Wilson, R. (1979). Interspecies comparision of carcinogenic potency. Journal of Toxicology and Environmental Health 5:1095-1118.

4. International Agency for Research on Cancer (1982). Chemicals, industrial processes and industries associated with cancer in humans. IARC Monographs on the Carcinogenic Risk of Chemicals to Humans Supplement 4.

5. Environmental Protection Agency (1985). Addendum to the Health Assessment Document for Dichloromethane (Methylene Chloride). Office of Health and Environmental Assessment, Washington, D.C. EPA-600/8-82-004FF.

6. Gold, L., Sawyer, C., Magaw, R., Backman, G., de Veciana, M., Levinson, R., Hoooper, N., Havender, W., Bernstein, L., Peto, R., Pike, M., and Ames, B. (1984). A carcinogenic potency database of the standardized results of animal bioassays. Environmental Health Perspectives 58:9-319.

Section 2

EPIDEMIOLOGY

ion 1, the risk estimates derived from epidemiologi-
the basis for comparison of the bioassay analyses.
at yield predictions of risk that are closest to the
rived directly from the epidemiological data are deemed
analyses that do not match the direct estimates as
estimates of carcinogenic potency based on epidemiologic
only as guides for evaluating the accuracy of estimates
mal bioassay data; they are of fundamental importance in
ght. A realistic program for the protection of humans from
enic effects of chemicals should take into account the
rmation on potency in humans provided by the epidemiologic
or those chemicals with human data suitable for quantitative
ation of risk, we have provided detailed analyses of their carcino-
ic potency in humans.

The data reported in the epidemiologic literature varies greatly in format and quality. Three types of studies are represented in the data we have analyzed: prospective cohort studies (including clinical trials), case-control studies, and (in the case of aflatoxin) a cross-sectional comparison of cancer rates and levels of exposure in different populations. Even within one of these categories, the individual studies often differ in their handling of dose groups, latency, and expected numbers of cancers. Such variation within the epidemiologic literature makes our goal of a common, balanced treatment of all the chemicals difficult to achieve. It has been necessary to tailor the

analyses to some extent, so as to be able to take advantage of the particular data available. Because of the wide variations in epidemiological studies, a systematic, standardized method of recording the human data (like that developed for the bioassay data base) is not considered feasible. The epidemiologic data for each chemical is considered as a whole and risk estimates have been developed using general guidelines. Those guidelines, described in this section, have been developed so that, to the extent possible, the methodology 1) can be employed with a minimal amount of data, 2) makes best use of the data, and 3) ensures that risk estimates made from data of differing types and quality are comparable. While these requirements can be at odds with one another, the approaches we describe have been able to accommodate without modification all the chemicals listed in Table 1-3 with the exceptions of asbestos, cigarette smoke, and aflatoxin. The modifications necessary for these exceptions are described in the sections pertaining specifically to these chemicals.

METHODS

An epidemiological study provides adequate data for the analyses performed in the course of this investigation if dose can be estimated quantitatively, if the observed numbers of responses (cancers) for each dose group is known, and if a measure of the expected numbers of responses for each dose group is available. The measure of expected response varies according to the format of the study; for a prospective study, expected numbers will be based on the response rate in a reference population and for a case-control study the control series provides the appropriate comparison groups. Regardless of the study format, however, the major factor limiting the number of studies that are suitable for a quantitative analysis is the sparsity of exposure data. With very few exceptions, the amount of substance to which study parti-

cipants have been exposed is incompletely known. The single major uncertainty affecting the estimates of risk from an epidemiological study is often this uncertainty in the dose variable. We have attempted to quantitatively incorporate that uncertainty, as described below. Also described below are the details of the methods used to estimate risk from prospective and case-control studies and a description of the approach used to determine the final risk related dose (RRD) estimates for each chemical.

Uncertainty in Exposure Estimates

There are many sources of uncertainty in exposures in the epidemiologically studied populations. For example, exposures in occupational cohorts are often measured infrequently and those measurements that are made are sometimes of uncertain relevance to exposures of specific workers. It was considered to be important for this study to quantify these uncertainties, even though such quantification is difficult. The approach adopted is to estimate uncertainty factors α and γ (to be described in detail below) that represent our impression of the uncertainty of the dose estimates for any given study, and which are developed from subfactors associated with different sources of uncertainty. Some degree of subjectivity is unavoidable when determining these factors. To promote uniformity, the subfactors discussed below and the intervals from which they are chosen were formulated *a priori*. A single investigator (B.A.) developed the bounds for each chemical for each study. As additional studies were analyzed, the uncertainty bounds derived earlier were reviewed and occasionally revised. All of the analyses of the epidemiological data were performed independently of the analyses of the animal data.

A set of three dose measures is estimated for each dose group in each epidemioligical study used in this investigation. Let d_i represent the

best estimate of cumulative dose for group i determined from the data presented in a specific study. The two other dose estimates associated with group i are upper and lower bounds on d_i, labeled $d_{i,U}$ and $d_{i,L}$, respectively, and are defined by

$$d_{i,U} = d_i \cdot \gamma$$
$$d_{i,L} = d_i / \alpha$$

where

$$\gamma = 1 + \gamma_1 + \gamma_2 + \ldots + \gamma_8$$
$$\alpha = 1 + \alpha_1 + \alpha_2 + \ldots + \alpha_8.$$

The factors, α and γ, are uncertainty factors determined by the eight subfactors as shown. Those subfactors correspond to eight sources of potential uncertainty that may be present in a study. The following describes the considerations that determine the magnitude of the subfactors, each of which is estimated independently for each dose group.

1. Length of exposure: α_1 and γ_1. It is often the case that there is some uncertainty about length of exposure to the substance in question. This might arise in a case-control study because recollection by the patient (or his relatives or friends) may be uncertain. Or, in a prospective study, length of exposure may be completely undocumented, in which case we assume a default value of 7 years. Most often, however, length of exposure will be categorized but average duration values for the categories will not be available. If duration of exposure is completely unknown, then α_1 and γ_1 are set equal to 1.5. Otherwise, α_1 and γ_1 are assigned values from the interval [0, 0.3]. The specific values selected depend on the width of the intervals defining the duration categories (the wider the

intervals, the larger are α_1 and γ_1) and on additional information pertinent to the estimation of average length of exposure.

2. Measurement of exposure early in the exposure period: α_2 and γ_2. In prospective, occupational studies it is often the case that concentrations of the chemical under investigation that prevailed in the more distant past are not well documented. Similarly, recall problems may entail greater uncertainty about early exposure experiences in a case-control setting. To account for such possibilities, α_2 and γ_2 are selected from the interval [0, 0.8]. The estimation of these subfactors depends on descriptions of process changes affecting exposure, on the length of time without adequate exposure documentation, and on the method used to compensate for the lack of early measurements. If, for instance, early concentrations are known to have been higher than more recent concentrations but no extrapolation that estimates those higher concentrations is performed, then α_2, the subfactor contributing to the lower bound, would be set equal to zero (the uncertainty here does not affect the lower bound, since exposures are underestimated) but γ_2 would be positive.

3. Completeness of measurements (aside from the early exposure period; cf. 2 above): α_3 and γ_3. These subfactors pertain to the extent to which exposures have been measured and documented. Considerations such as the number of samples taken, the amount of variability seen in the samples, and the completeness of the sampling with respect to different areas or departments of a facility (in an occupational setting), and with respect to different periods of time are relevant to the determination of α_3 and γ_3. These subfactors are chosen from the interval [0, 0.5].

4. Categorization of exposure: α_4 and γ_4. As with duration of exposure, intensity of exposure (or cumulative exposure) can be

categorized into groups and presented without average values for those groups. Both α_4 and γ_4 are selected from [0, 0.3]. In this case also, the specific values depend on the presence or absence of data pertinent to the estimation of those average values.

5. Recording biases: α_5 and γ_5. The presence of biases in the format of the presentation of results is a major contributor to uncertainty. Common sources of bias include classification of study participants by their maximum exposure and, more subtly, duration and intensity of exposure being reported separately, rather than cross-classified. In the former instance (classification by maximum exposure) γ_5 would equal zero but α_5 would be positive. Both α_5 and γ_5 may be positive in the second case -- we may not know if those with less intense exposure were exposed for longer or shorter periods, on average, than those with more intense exposure. The subfactors, α_5 and γ_5, are chosen from the interval [0, 1.0], based on the estimated degree of bias.

6. Applicability of reported exposures: α_6 and γ_6. Unless every study participant had personal sampling performed during the period of exposure, there is bound to be some uncertainty with respect to the applicability of the reported exposures. That uncertainty may be fairly minor, as when area as opposed to personal concentration measurements determine an individual's degree of exposure. In other cases, the uncertainty may be more substantial, as when respirator use is not considered or concentrations from some different, though similar, facility are used to estimate exposure. The subfactors α_6 and γ_6 are chosen from the interval [0, 0.3].

7. Conversion of units: α_7 and γ_7. In several instances it has been necessary to convert from one set of units to another. This most often involves conversion of concentrations of a

chemical found in the urine of exposed individuals to atmospheric concentrations of the substance under investigation. Such conversions involve both biological and statistical variability. Whatever is known about that variability is used to select α_7 and γ_7 from the interval [0, 1.0].

8. Expected numbers of cancers: α_8 and γ_8. Uncertainty with respect to the expected numbers of cancers is included here even though it does not relate directly to bounds on the dose values. Because epidemiology studies are observational in nature rather than being carefully controlled experiments, it is always possible that exposures to other substances or other confounding effects may have been partly responsible for the quantitative findings of a study. Whenever possible, we restrict our analyses to cohorts or subcohorts with minimal opportunity for exposure to multiple chemicals. Otherwise, we can do little in the secondary analyses we conduct to directly mitigate this problem, aside from noting those exposures that may influence the results and to include them in the uncertainty calculations, via the subfactors α_8 and γ_8.

   Other features contributing to α_8 and γ_8 include the use of national rates, rather than local or industrial control rates, to calculate expected numbers of cancers. In a case-control study, no expected numbers are calculated. But, a corresponding uncertainty is related to the selection of the control series. An evaluation of the appropriateness of the controls forms the basis for the determination of α_8 and γ_8 in the case-control setting. Whatever the cause of the uncertainty in the expected numbers, α_8 and γ_8 are selected from the interval [0 and 0.5].

The bounds on the estimates of dose that result from the application of the uncertainty factors are employed, as are the best estimates of dose, in the dose-response models fit to the epidemiological data. In this way, uncertainty with respect to exposure is incorporated in the derivation of risk estimates consistent with the data.

Dose-Response Models

A dose response model is used to relate the observed response to a measure of cumulative dose for each group in a specific study. Both prospective and case-control studies have been analyzed in such a way as to provide a consistent approach to dose response and the subsequent risk estimation.

Prospective Studies. The minimum amount of information required for an analysis of a prospective study consists of a single group with known cumulative dose (expressed in ppm-years, for example), an observed number of cancers, and an expected number of cancers. Additional information on observed and expected responses categorized by exposure group is accommodated by the same approach and may provide better estimates of carcinogenic potency.

The basic analytical treatment is as follows. Suppose we have data divided into n groups ($n \geq 1$). For each group, i, we know the observed number of cancers (O_i), the expected number of cancers (E_i) and a measure of cumulative exposure (d_i). A potency parameter, β, is estimated by maximum likelihood methods, assuming O_i has a Poisson distribution with mean

$$E_i(1+\beta d_i).$$

Thus, a linear relationship is assumed between dose and relative risk. The background cancer risk (i.e., risk assuming no exposure to the chemical), P_o, is calculated by a life table method from vital statistics data for the cancer of interest.

The first method, to be known as Basic Method 1, for calculating a risk related dose (RRD) corresponding to a given lifetime extra risk, π, involves assuming that lifetime risk is a function of the total cumulative dose received during life but is independent of the timing of exposure. If that is the case, then the lifetime risk of cancer from dose d is given by

$$P(d) = P_o(1+\beta d) \tag{2-1}$$

and the extra risk from dose d is defined as

$$\frac{P(d)-P_o}{1-P_o} = \frac{\beta d}{P_o^{-1}-1} \tag{2-2}$$

The dose corresponding to extra risk π (RRD) is then

$$RRD = \pi\frac{(P_o^{-1}-1)}{\beta} . \tag{2-3}$$

The assumption of risk being independent of timing of exposure is obviously an oversimplification. Basic Method 2 does not make this assumption but rather assumes only that Eq. 2-1 holds for each 5 year age group with the dose used being the cumulative dose up to the 5-year age interval in question. Since the estimated risk depends upon the timing of exposure, risk is estimated for a specific exposure pattern thought to be typical of occupational exposures: exposure for 240 days per year for 45 years starting at age 20. Hence, the dose variable up to age 20 will have the value zero; for the next nine five-year age groups it will increase linearly, at which point it will level off. The work day exposure that corresponds to a given extra risk, π, is our

estimate of RRD.

The cancer endpoints used in the analyses depend on what is known about the chemical in question. In every case possible, analyses are performed using all malignant neoplasms. Any types of cancer known to be or suspected of being related to exposure (e.g., leukemia and benzene exposure) are analyzed also.

Case-Control Studies. In a case-control study, cases of disease are located and then suitable controls, often matched to the cases, are found. Level of exposure to the substance under investigation is subsequently determined for each case and control. Data from such a study can be expressed as follows:

Average Dose	No. of Cases	No. of Controls
d_1	x_1	y_1
d_2	x_2	y_2
$\vdots$	$\vdots$	$\vdots$
d_g	x_g	y_g

To determine an appropriate analytic approach, consider the following 2x2 table:

	Cases	Controls
d_1	p_{11}	p_{12}
d_2	p_{21}	p_{22}

where the p_{ij}'s represent the proportions of the population in the various categories. In a prospective study persons are selected randomly from the dose groups and then checked for disease status (the disease status is the random variable). In that case, the relative risk of those in dose group 2 compared to those in dose group 1 is given by

$$[p_{21}/(p_{21} + p_{22})]/[p_{11}/(p_{11} + p_{12})] \approx p_{21}p_{12}/(p_{11}p_{22}),$$

the approximation being valid whenever, as is usually the case, cases

are much rarer than controls. The right side of this expression is called the odds ratio. This approximate relative risk can be estimated from a retrospective study, also. In fact, $x_2y_1/(x_1y_2)$ is an estimate of

$$([p_{21}/(p_{21} + p_{11})][p_{12}/(p_{12} + p_{22})])/([p_{11}/(p_{11} + p_{21})][p_{22}/(p_{12} + p_{22})]) = p_{21}p_{12}/(p_{11}p_{22}).$$

This and related considerations lead to the conclusion that it is an adequate approximation to analyze a retrospective study as if the data had been collected prospectively (1).

Moreover, if the population sampled is composed of persons all the same age, then the p's refer to rates of occurrences given that that age is attained -- that is, the relative risk being estimated is the incidence of disease in the exposed group at that age divided by the corresponding incidence in the unexposed group. Thus, this relative risk has exactly the same interpretation as the relative risk calculated from prospective studies in the manner described earlier.

The basic assumption to be used is that the risk to dosed individuals relative to unexposed individuals is the same for a given cumulative dose independent of age. This same assumption is made in the recommended analysis of prospective studies. If age is confounded with dose then an analysis of a retrospective study should be stratified on age. Otherwise biases may occur even if the assumption of the same relative risk for all ages holds (1). Since we will generally have access only to the published data, we can use a stratified approach only if the published analysis took such an approach. As this generally will not be the case, we will present only an unstratified method here. However, a stratified approach is preferred and should be used whenever possible.

As stated above, assuming the data were collected prospectively is an adequate approximation. Therefore, the log-likelihood to be used is the prospective one,

$$L = \sum_i [x_i \log(P(d_i)) + y_i \log(1-P(d_i))],$$

where P(d) is the conditional probability of disease during the age interval given survival to that age. With this notation the odds ratio is given by

$$P(d)(1-P(0))/[P(0)(1-P(d))].$$

In order to be consistent with the approach taken with prospective studies we wish to have the odds ratio (the approximate relative risk) given by

$$1 + \beta d.$$

For that to be case, P(d) must be expressed as

$$P(d) = \alpha(1 + \beta d)/(1 + \alpha + \alpha\beta d).$$

The potency parameter, β, is estimated by maximum likelihood techniques using this expression and the log-likelihood given above. The parameters so estimated are applied with Basic Methods 1 and 2 to derive RRD estimates, as described above for prospective studies.

Calculation and Selection of RRD Estimates

The methods discussed above in the context of prospective and case-control studies estimate 90% upper confidence bounds and 90% lower confidence bounds as well as the maximum likelihood estimate of β. As a means of incorporating this statistical variability and the exposure

uncertainty into the analysis, a set of three potency parameters is estimated for each carcinogenic response in each study. A lower bound for the potency, β_L, is estimated by the lower statistical confidence limit obtained when using the upper bounds on dose, the $d_{i,U}$'s. Similarly the upper bound for potency, β_U, is estimated by the upper confidence limit derived using the lower bounds on dose, the $d_{i,L}$'s. These potencies, β_L, β_U, and β, the MLE estimate of potency using the best estimates of dose, are applied in Basic Methods 1 and 2 to derive RRD_U, RRD_L, and a maximum likelihood estimate of RRD, respectively.

Thus, at this point, an interval (RRD_L to RRD_U) with a "midpoint" (the MLE estimate of RRD) is defined for each carcinogenic response in each study analyzed. These intervals are not statistical confidence intervals; they combine statistical uncertainty with exposure uncertainty and hence represent what might be called "reasonable limits" on the doses corresponding to specific levels of extra risk. The triples of RRD estimates have been calculated for extra risks of 10^{-6} and 0.25.

RRD's derived from the epidemiological literature are converted to a mg/kg/day equivalent, assuming 240 days of exposure per year (in accordance with the assumed exposure scenario, 45 years beginning at age 20). So, for example, a RRD estimate derived from a study in which the dosing is continuous is converted to the desired format by multiplying by 365/240. Or consider a RRD expressed in terms of ppm. At standard temperature and pressure, dry [STPD], 22.4 liters of a pure gas is equal in weight to its molecular weight, W, in grams. Therefore, one cubic meter weighs

$$(1000/22.4) \times W \times 1000 \text{ mgs.}$$

Since a pure vapor is 10^6 ppm,

$$1 \text{ ppm} = \frac{(1000/22.4) \times W \times 1000}{10^6} \text{ mg/m}^3.$$

Converting to 25°C,

$$1 \text{ ppm} = \left[\frac{(1000/22.4) \times W \times 1000}{10^6}\right] \times \frac{273}{298} = 0.041 \times W \text{ mg/m}^3.$$

This value is converted to mg/kg/day by assuming 10 m^3 of air breathed during an eight-hour work shift and a 70 kg body weight.

In many cases, more than one RRD interval for a chemical is available from the epidemiologic literature either because of more than one study or more than one carcinogenic response analyzed. Rather than combining results for different responses or from different studies, a single triple of RRD estimates is selected to represent the potency of a given chemical. The triple that is selected is one that corresponds best with the consensus of opinion about the carcinogenic effect of the chemical determined from all the literature that was reviewed. However, the results from a study or particular response in a study are not used if the dose-response model provided a poor fit to the data or if the study is deemed to be markedly inferior to other studies that have analyzed a particular response. In the case of vinyl chloride, for example, a liver cancer response is chosen since angiosarcoma of the liver is considered to be undeniably linked to vinyl chloride exposure whereas respiratory cancer, another endpoint analyzed, is not so clearly linked. Another example is provided by isoniazid. Overall, the literature on isoniazid does not conclusively demonstrate its carcinogenicity in humans let alone indicate any particular site of action. Hence, the response selected is all malignant neoplasms, and, moreover, the triple chosen is one that has an infinite upper bound (consistent with no carcinogenic effect), since one meeting that criterion is available from our quantitative estimation.

RESULTS

Following below are the descriptions of the epidemiological data relating human exposure and carcinogenic response for the chemicals listed in Table 1-3. Each analysis of a particular chemical includes a brief review of background information and a description of the human carcinogenicity data as a whole. The latter of these is important in light of the method, described above, of selecting the specific response to represent the epidemiological risk estimation; i.e., we select the response most representative of the entirety of the human cancer data base for each substance. Derivations of the RRD estimates and discussions of the uncertainties relevant to those derivations conclude each analysis.

The epidemiological assessments are intended to be independent, self-contained examinations of the individual chemicals. Consequently, RRD estimates are presented in the same units used by the authors of the published reports, except that exposures reported in terms of total dose (e.g. in total milligrams consumed) have been converted to cumulative doses (e.g. milligram-years). Following the individual chemical write-ups is a summary of the results for all the chemicals, specifying the responses chosen and the conversions to the standard units of dose, mg/kg/day.

Aflatoxin

The aflatoxins are naturally occurring contaminants of food stuffs produced by species of the fungus Aspergillus. According to the International Agency for Research on Cancer (IARC) (2) aflatoxin B_1 is a potent mutagen and forms the same DNA adducts in human cells as in rodent cells. Aflatoxin ingestion has been linked to primary liver cancer so, in accordance with the analysis guidelines described above, risk estimates will be based on liver tumors.

Primary liver cancer appears to be most prevalent in tropical areas, those areas in which aflatoxin contamination of food is a problem but also the areas where hepatitis B virus is common (3, 4). However, in 13 of 15 cases of liver cancer studied in Czeckoslovakic (5) some trace of aflatoxin B_1 was found in or around the tumor. Aflatoxin intake in the southeastern United States from 1910 to 1960 was estimated to be about 100 times greater than in the north and west of the United States (6). Stoloff concluded that the excess primary liver cancer rate in the southeast (10%), given the much greater aflatoxin contamination, was not as large as expected from studies in Africa and Asia and that the excess may not have been attributable to aflatoxin. Perhaps factors present in Africa and Asia (hepatitis B virus, for example) may interact with aflatoxin to enhance the rate of primary liver cancer in those areas. The study by Wang *et al.* (4) suggests that this may be the case.

Several studies (7-9) have reported conditions most conducive to development of aflatoxin contamination of food and the types of foods commonly found to be contaminated. Traditional harvesting and storage techniques appear to be conducive to *Aspergillus* growth and a variety of vegetable foodstuffs contain detectable levels of aflatoxin. Groundnuts (peanuts) appear to be particularly susceptible; all peanut samples were

contaminated in Pakistan (9) and samples from Mozambique averaged 1936 μg of aflatoxin per kilogram of peanuts (7).

Studies in Swaziland (10) and China (4) report good correlation between the pattern of liver cancer and the percentage of food samples found to be contaminated with aflatoxin. In an occupational setting in the Netherlands, 71 workers exposed to aflatoxin at a plant extracting oil from peanuts were estimated to have respiratory exposures ranging from 0.04 μg to 2.5 μg of aflatoxin per week (11). Although no liver cancers were reported, all cancers and respiratory cancers were overrepresented in this small cohort.

Bulatao-Jayme *et al.* (12) describe the results of a case-control study in the Philippines. Based on mean aflatoxin loads of food samples collected around the country and dietary histories collected from cases with primary liver cancer and from matched controls, the authors calculated the mean daily aflatoxin intake for each individual (Table 2-1). No individual's food was sampled, but rather a total of 3510 analyses for aflatoxin in over 100 food items was used to estimate the average aflatoxin content of food eaten by the individuals studied.

The remainder of this write-up reviews studies of aflatoxin intake and current primary liver cancer incidence in Kenya, Swaziland, Mozambique, or Thailand. In each case, it must be assumed that levels of aflatoxin intake estimated in the studies have persisted for long enough so that they correspond to the incidence rates observed. As all the areas investigated represent traditional, third-world population groups, this is probably a safe assumption, though one that introduces some uncertainty. Further uncertainty is due to the setting of these studies: diagnostic capabilities are not uniform over all the areas (even within a country) and may not be as complete as in the U.S. Additional caution must be exercised because of the design of the studies; cause and effect

are difficult to determine in cross-sectional investigations.

Nevertheless, all these reports document a positive correlation between estimated aflatoxin intake and primary liver cancer incidence. Table 2-2 presents intake and incidence data for those studies that used ready-to-eat food samples to determine aflatoxin dose. Linsell and Peers (13) consider the reported aflatoxin intake values to represent minimal ingestions. The yearly and life-time cancer rates are the crude rates.

These data are not in any of the forms assumed in our standard approaches to quantify risk; a special analytic method is required. Suppose that a yearly crude rate of liver cancer, c_i, can be expressed as a linear function of aflatoxin intake (ng/kg/day), d_i; i.e.,

$$c_i = \alpha + \beta d_i \ .$$

Then, for any of the studies described in Table 2-2 for which the population size is available, one would expect to observe $c_i \cdot N_i \cdot y_i$ liver cancers, where N_i is the population size and y_i is the number of years of observation. If we assume that the observed liver cancers are distributed as a Poisson distribution with the indicated expected value, likelihood methods applied to the data in Table 2-2 allow estimation of α and β and calculation of related confidence bounds (Table 2-3). Table 2-3 also displays the bounds on the dose values that are used to investigate the sensitivity of the analysis to selection of the dose levels. The upper bounds are arbitrarily set at 5 times the best estimate; the lower bounds are 3 times smaller than the best estimate. The bound is wider above the best estimates because, as suggested by Linsell and Peers (13), the values given in Table 2-2 may reflect only minimal aflatoxin intake levels.

Given an annual crude rate of liver cancer, $c_i = \alpha + \beta d_i$, a lifetime probability of liver cancer can be calculated as

$$P(d_i) = (\alpha + \beta d_i) \cdot F$$

for some factor F. In this case, extra risk attributable to aflatoxin is

$$\frac{\beta \cdot d_i \cdot F}{1 - \alpha F} .$$

The choice of the factor F is open to some question. Carlborg (14) uses a value of F equal to the life expectancy of the study population. This may be too small, however, if we consider that in any given year a large fraction of the population is under the age of 15, especially in the third-world populations included in these calculations. This segment of the population is essentially at no risk from liver cancer so that the N_i values used to estimate α and β are too large. To compensate, the following procedure is suggested.

Let a_j be the proportion of the population in age group j, which consists of all individuals with ages in an interval (j) years in length. Suppose also that individuals in age group j experience an all-cause yearly mortality rate of b_j. The values a_j, b_j, and δ_j are available from international demographic sources. Let l_j be the liver cancer rate in group j without exposure to aflatoxin. This is not, in general, known but we will assume that

$$l_j = l_{us,j} \cdot f$$

where $l_{us,j}$ is the liver cancer rate in the U.S. in group j. This assumption is made despite the fact that liver cancer in the U.S. appears to have a substantially different age pattern than in the

populations included in this study. The different pattern may very well be attributable to the aflatoxin intake and hence not pertinent to evaluation of the assumption. In any case, the background liver cancer risk, α, estimated above, can be expressed as

$$\alpha = \Sigma_j a_j l_j = \Sigma_j a_j l_{us,j} \cdot f,$$

which will serve to define f.

By lifetable methods, the lifetime probability of liver cancer in the presence of an aflatoxin dose d is

$$P(d) = \Sigma_j \left[\prod_{k=0}^{j-1} (1-b_k)^{\delta(k)} \right] \delta(j) l_j(d)$$

where $l_j(d)$ is the liver cancer rate in the jth age group with dose d. The variable $l_j(d)$ can be estimated, on the basis of the crude rates originally approximated, to be

$$l_j(0)(1 + (\beta/\alpha)d) = l_{us,j} \cdot f(1 + (\beta/\alpha)d).$$

Since P(d) is assumed to equal $(\alpha + \beta d)F$, solution for F in the equation for P(d) yields

$$F = \frac{\Sigma_j \left[\prod_{k=0}^{j-1} (1-b_k)^{\delta(k)} \right]}{\Sigma_j a_j l_{us,j}} .$$

Typical values for a third-world population (Thailand in 1960) (15) have been used to obtain a_j, b_j, and $\delta(j)$, and the 1978 U.S. liver cancer rates (Table 2-4) were combined to give a value of F equal to 215. This value is considerably larger than the average life span of the population, which was used by Carlborg (14), but we believe a value of 215 is more appropriate.

RRD estimates based on the derivation above are shown in Table 2-5. These apply to a scenario corresponding to life long exposure to aflatoxin. To crudely approximate the RRDs associated with our standard exposure scenario (45 years exposure starting at age 20) we have multiplied the estimates in Table 2-5 by (75/45), where 75 is the assumed life span over which exposure occurs. These results are displayed in Table 2-6.

Table 2-1

DISTRIBUTION OF FILIPPINO CASES AND CONTROLS WITH RESPECT TO DAILY AFLATOXIN INTAKE[a]

Daily Aflatoxin Intake(μg)	Primary Liver Cancer Cases	Matched Controls
0-3 (1.5)[b]	20	74
4-6 (5)	15	4
7+ (8.5)	55	12

[a]From Bulatao-Jayme *et al.* (12).
[b]Assumed average for the group.

Table 2-2

DATA FROM CROSS-SECTIONAL STUDIES OF AFLATOXIN INTAKE AND PRIMARY LIVER CANCER INCIDENCE

Region	Mean Dose of Aflatoxin (ng/kg/day)	Population Size	Years of Observation	Yearly Risk ($x10^5$)	Life Expectancy[a] (yr)	Lifetime Risk ($x10^5$)
Thailand[b]						
Songkhla	5.0	97867	1	2.0	54	108.0
Ratburi	45.0	99537	1	6.0	54	324.0
Kenya[c]						
High	3.5	46279	7	1.2	47	56.4
Middle	5.9	187514	7	2.5	47	117.5
Low	10.0	174525	7	4.0	47	188.0
Swaziland[d]						
Highveld	5.1	100719	5	2.2	41	90.2
Middleveld	8.9	151430	5	3.8	41	155.8
Lowveld	43.1	91471	5	9.2	41	377.2
Lebombo	15.4	18747	5	4.3	41	176.3
Mozambique[e]						
Inhambane	222.4	?	?	13.0	41	533.0

[a]From Carlborg (14).
[b]From Shank *et al.* (16).
[c]From Peers and Linsell (17).
[d]From Peers *et al.* (18).
[e]Cited in Linsell and Peers (13).

Table 2-3

DOSE AND RESPONSE DATA ESTIMATION OF α AND β

Dose (ng/kg/day)			
Lower Bounds	Best Estimates	Upper Bounds	Observed Number of Liver Cancers
1.2	3.5	17.5	4
1.67	5.0	25.0	2
1.7	5.1	25.5	11
2.0	5.9	29.5	33
3.0	8.9	44.5	29
3.3	10.0	50.0	49
5.1	15.4	77.0	4
15.0	45.0	225.0	6
14.4	43.1	215.5	42

Parameter Estimates:

Using:	90% Lower Limit on β	MLE	90% Upper Limit on β
Lower Bounds on Dose	α = .20E-4 β = .40E-5	α = .16E-4 β = .54E-5	α = .12E-4 β = .68E-5
Best Estimates of Dose	α = .20E-4 β = .13E-5	α = .16E-4 β = .18E-5	α = .12E-4 β = .23E-5
Upper Bounds on Dose	α = .20E-4 β = .27E-6	α = .16E-4 β = .36E-6	α = .12E-4 β = .45E-6

Chi-squared goodness-of-fit statistic (7 d.f.): 5.5.

Table 2-4

POPULATION STATISTICS USED FOR CALCULATION OF F

Age Group	Proportion of Population[a]	All-Cause Death Rate[a]	Liver Cancer Death Rate ($x10^6$)[b]
<1	.023	.07683	1.56
1-4	.138	.01092	1.97
5-9	.152	.00331	0.296
10-14	.118	.00192	0.538
15-19	.095	.00211	0.809
20-24	.092	.00296	0.839
25-29	.079	.00337	1.11
30-34	.067	.00414	1.45
35-39	.052	.00562	2.92
40-44	.043	.00706	5.48
45-49	.037	.00871	9.77
50-54	.031	.01123	16.5
55-59	.025	.01437	25.4
60-64	.018	.02131	38.2
65-69	.012	.02856	58.7
70-74	.008	.04383	68.4
75-79	.004	.05973	79.6
80-84	.002	.09247	75.0
85+	.002	.12989	68.9

[a]Based on data from Thailand, 1960 (15).
[b]Based on data from the U.S., 1978 (19).

Table 2-5

RRD ESTIMATES FOR LIFETIME EXPOSURE TO AFLATOXIN (ng/kg/day)

	Level of Extra Risk					
	10^{-6}			0.25		
Method	RRD_l	MLE	RRD_u	RRD_l	MLE	RRD_u
Using F=47 (life expectancy)	3.13E-3	1.19E-2	7.78E-2	7.82E+2	2.98E+3	1.97E+4
Using F=215.4 (life table method)	6.81E-4	2.59E-3	1.71E-2	1.70E+2	6.47E+2	4.28E+3

Table 2-6

RRD ESTIMATES FOR AFLATOXIN (ng/kg/day)[a]

	Level of Extra Risk					
	10^{-6}			0.25		
Method	RRD_l	MLE	RRD_u	RRD_l	MLE	RRD_u
Using F=47 (life expectancy)	5.22E-3	1.98E-2	1.30E-1	1.30E+3	4.97E+3	3.28E+4
Using F=215.4 (life table method)	1.14E-3	4.32E-3	2.85E-2	2.83E+2	1.08E+3	7.13E+3

[a]Converted so as to apply to the standard exposure scenario: 45 years of exposure starting at age 20.

Arsenic

The metal arsenic and its compounds have had many uses. Elemental arsenic is used as an alloying additive and in electronic devices. Various compounds containing arsenic have been used as medicines, as defoliants, as intermediates in several manufacturing processes, as pesticides, and as pigments (20). Human exposures have been associated with ingestions of arsenic-containing medicines and drinking water contaminated with arsenic, with insecticide operations (especially in sheep dipping), and with certain smelting operations (20, 21).

The association between arsenic exposure and cancer in humans has been known for some time. A preponderance of skin cancers was noted by Neubauer (21) to be related to use of arsenic-containing medicines. More recently, case reports of hepatic angiosarcoma attributed to use of Fowler's solution (potassium arsenite) have appeared (22, 23). Skin cancers have been reported to be in excess in areas in which the drinking water contains high levels of arsenic. Neubauer (21) reports anecdotal information on increased frequency of skin cancer in a German town whose drinking water contained 1.22 mg percent arsenic due to gold smelting operations that released arsenical fumes. Many reports (21) document typical arsenic-associated skin cancers in an area of Argentina whose wells had 0.28 - 0.48 mg percent arsenic. Tseng *et al.* (24) and Tseng (25) present similar findings for an area in Taiwan that had arsenic in well water averaging 0.5 mg/ℓ.

The mechanism by which arsenic causes cancers in humans is not entirely clear. Arsenic does not appear to be mutagenic in the systems so far tested (2). Reports of tests in human cells, however, document arsenic's effect on chromosomal damage. Paton and Allison (26) describe the results of *in vitro* tests in which chromosome damage in leucocytes and fibroblasts was enhanced in the presence of arsenic salts.

Chromatid breaks were frequent. In a case-control study, Petres *et al.* (27) found more chromosomal aberrations in individuals who had been exposed to arsenic (via psoriasis treatment or pesticides) than in unexposed controls. These authors also found arsenic to impair nuclear division, to reduce incorporation of thymidine in DNA (although the effect on RNA uridine incorporation was not as severely affected), and to decrease hyperdiploidism in PHA-stimulated lymphocytes.

The observations reported above have lead to the suspicion that arsenic may be inhibiting DNA repair mechanisms. This may be accomplished by interfering with the enzymes which are responsible for that operation, especially those with sulfhydryl groups (27, 28). Another possibility is that arsenic reduces, or competitively inhibits, the uptake of phosphorus into the DNA chain. The arsenic would then cause weak spots in the chromosomes that could lead to more frequent breakage (26, 27). An argument against this mechanism is the fact that, while the trivalent forms of arsenic appear to have the highest carcinogenic potency, the pentavalent form would be more likely to substitute for phosphorus in DNA (29). No definitive conclusion about the mechanism of action of arsenic in carcinogenesis has been reached.

Numerous investigations of occupationally exposed workers have implicated arsenic as a human carcinogen. In an early proportional mortality study, Hill and Faning (30) found an excess proportion of cancer deaths among employees of a factory handling arsenicals. There was a suggestion that lung and skin cancers were over represented. A case-control study in Japan (31) strongly suggested that employment as a copper smelter, which entails arsenic exposure, was closely linked to lung cancer. A retrospective cohort study of those copper smelters (32) confirmed the excess lung cancer risk and demonstrated a clear dose-response relationship between lung cancer and a qualitative measure of exposure to arsenic.

Ott *et al.* (33) investigated the proportional mortality experience of industrial workers manufacturing insecticides containing arsenic, primarily lead and calcium arsenate. Nearly 2000 white males who died between 1940 and 1972 were included in the study. Relative risks for highly exposed workers were as high as 7.0. A retrospective cohort study by the same authors confirmed a strong relationship between arsenic-containing insecticide exposure and respiratory cancer mortality.

Two cohorts of workers have been used to quantitate the relationship between arsenic exposure and cancer: workers employed at the ASARCO smelting plant in Tacoma, Washington, and copper smelters in Montana working for the Anaconda Company. These cohorts form the basis of the analysis reported below.

The ASARCO copper smelter in Tacoma, Washington is one of the nation's largest, producing, at times, 10% of the refined copper in the U. S. The copper it smelts has been traditionally high in arsenic (34). Several studies of workers and retirees from the plant have been conducted. Pinto and Bennett (35) studied the proportional mortality of 229 decedants who had worked in the refinery. Excesses in the proportions of lung cancers and of breast and genito-urinary cancers were found. Pinto *et al.* (36) studied 527 retirees who had had some degree of arsenic exposure. A dose-response trend was evident for respiratory cancer as related to an estimated cumulative exposure based on urinary arsenic levels. These authors also reported that atmospheric concentrations could be related to urinary concentrations: air levels (in $\mu g/m^3$) were 0.304 times the urine levels (in $\mu g/\ell$).

Enterline and Marsh (34, 37) defined a cohort of ASARCO workers who were employed a year or more during the period 1940 through 1964 and studied

its mortality experience through 1976. A total of 2802 men were included in the cohort. Exposure information was based on the urinary arsenic concentrations measured in 1948-1952 and 1973-1975. The average concentrations for a department were assumed to apply to each worker stationed in that department. Levels measured in 1948-1952 were assumed to reflect earlier exposures and linear interpolation was used to estimate the values for the years 1953 through 1972. Cumulative dose was expressed in terms of μg-years/liter of arsenic.

Table 2-7 displays the dose and response data for this cohort. The cumulative dose values have been converted to cumulative atmospheric exposures using the factor 0.304 determined by Pinto *et al.* (36). As indicated in Table 2-7, reasonable bounds on dose (used to investigate the sensitivity of the analysis to uncertainty in the estimates) are derived from the best estimates of exposure and uncertainty factors $\alpha = 2.35$ and $\gamma = 2.75$. The major uncertainties influencing those bounds include the following:

1. Although the smelter has been in operation since 1913, the first measurements of urinary arsenic occurred in 1948. Exposures prior to 1948 are estimated to be equal to those measured in the period 1948-1952, even though the authors believe this to underestimate those exposures. Consequently, γ_2 has been assigned a value of 0.4, whereas $\alpha_2 = 0$.
2. Even after 1948, few measurements of urinary arsenic were available, none between 1952 and 1972. Since linear interpolation was used to estimate the exposures between 1952 and 1972, uncertainty is contributed to both upper and lower bounds. Both α_3 and γ_3 have been set equal to 0.4.
3. The levels of urinary arsenic assumed to be appropriate to the different departments were determined from samples of workers in those departments. Thus, the applicability of the values

used to estimate cumulative exposure is uncertain. Both α_6 and γ_6 are given a value of 0.3.

4. Conversion of urinary to atmospheric concentrations of arsenic is accomplished by one fixed conversion factor. This factor undoubtedly varies from individual to individual and, perhaps, with concentration level. A factor of 0.6 is assumed for α_7 and γ_7.
5. Finally, expected values were based on U.S. national rates. A nominal value of 0.05 is assumed for α_8 and γ_8 to account for uncertainty in the expected numbers.

The second cohort of workers that can supply quantitative risk estimates is that employed by the Anaconda Company in Montana. The first report on this cohort was that by Lee and Fraumani (38). A total of 8,047 white males who worked at least one year before 1957 were observed from 1938 through 1963. In this report, only relative exposures to arsenic ("heavy", "medium", and "low") were discussed. An excess of respiratory cancer was discovered that was related to relative exposure to arsenic trioxide and also to SO_2.

Lubin *et al.* (39), reporting on that portion of the Lee and Fraumani (38) cohort alive in 1964, state that the mean arsenic levels in the "heavy", "medium", and "low" exposure areas were 11.3, 0.58, and 0.29 mg/mg^3, respectively. Respirators were used, intermittently, especially in the heavy exposure areas; the authors estimate this effect by reducing the pertinent concentration in the heavy exposure jobs by a factor of ten.

The follow-up of the 5,403 survivors through 1977 yielded 64,315 person-years of observation. Multivariate analyses revealed an association between arsenic concentrations and respiratory cancer. SO_2 did not appear to be related to respiratory cancer although its interaction with

arsenic could not be ruled out.

A pilot study (40) and a larger sampling (41) of the Lee and Fraumani (38) cohort investigated the reported association between arsenic and respiratory cancer, especially as it relates to cigarette smoking. Although the cohort members were more likely to be smokers than men in the general U. S. population, smoking could not be considered to confound the relationship between arsenic and lung cancer. Dose-response trends were observed among smokers as well as nonsmokers; no interaction between smoking and arsenic exposure was apparent.

Finally, Lee-Feldstein (42) published an update of the original Lee and Fraumani (38) study. Follow-up was extended through most of 1977. Classification of a cohort member, as in the original study, was based on the maximum exposure category (heavy, medium, light) experienced by the worker. This tends to overestimate the actual exposures encountered and complicates the calculation of cumulative dose. Table 2-8 displays the distribution of respiratory cancer deaths cross-classified according to this classification and length of employment. Using the estimates of average airborne arsenic concentrations for the qualitative exposure categories given by Lubin et al. (39) and average lengths of exposure for the groups defined in Table 2-8 yields cumulative dose and response data as displayed in Table 2-9. It has been assumed that the category into which the men were placed reflects their average exposure. Cumulative exposures for those in the medium and heavy groups are apt to be overestimated in this case. However, estimated exposures for those in the low category may be representative because a person in this category had all of his work experience in low exposure areas.

The uncertainties pertinent to the Lee-Feldstein (42) study are summarized as follows:

1. Length of exposure is grouped into three categories. The categories are presented without average values and so we have used midpoints of the intervals defining the groups. This contributes some uncertainty; α_1 and γ_1 are both given values of 0.2.
2. The arsenic concentrations that have been used to quantify the exposure groups were measured between 1943 and 1958 (39). There is some potential for underestimation of exposure, since the plant has been in operation since before 1925 and some members of the Lee-Feldstein cohort worked during this early period. Consequently, $\alpha_2 = 0$ and $\gamma_2 = 0.6$.
3. The completeness of the concentration measurements is not documented. Both α_3 and γ_3 are set equal to 0.3.
4. The most serious uncertainty relates to recording biases: cohort members have been classified by their maximum exposure, resulting in overestimates in the "heavy" and "medium" groups. As a result, γ_5 has been equated with 0.1 for all groups. For the "low" group $\alpha_5 = 0.1$ as well; for the other groups $\alpha_5 = 0.8$.
5. In the "heavy" exposure group, some account has been taken of respirator use, by dividing the actual concentrations by 10 to obtain effective concentrations. However, respirator use was not universal so this conversion may be too extreme. We have set α_6 to 0.1 and γ_6 to 0.2, for the high dose group only, to account for this uncertainty.
6. Finally, since respiratory cancer is the endpoint of interest, a value of 0.1 is assumed for α_8 and γ_8 because smoking-specific expected values are not available.

The resulting uncertainty factors are dose-group dependent, as follows:

"heavy" exposure: $\alpha = 2.5$, $\gamma = 2.5$

"medium" exposure: $\alpha = 2.4$, $\gamma = 2.3$

"low" exposure: $\alpha = 1.7$, $\gamma = 2.3$

Table 2-9 displays the bounds on cumulative dose that result when these factors are applied.

Welch *et al.* (41) consider a subset of the original Lee and Fraumani cohort, a total of 1800 white males. Follow-up was continued to 1978. Welch and her colleagues calculated and presented cumulative exposure estimates based on measurements of arsenic concentrations prevalent between 1943 and 1965 (Table 2-10). Data presented in Welch *et al.* (41) indicates an average cumulative exposure for their cohort of about 26,500 μg-yrs/m^3. We assume that the midpoints of the intervals displayed in Table 2-10 represent average exposures in the first three groups (i.e. 250, 1250, and 7000 μg-yrs/m^3, respectively). Employing the fact that the entire cohort averaged 26,500 μg-yrs/m^3 and weighting the exposure groups on the basis of their expected numbers of respiratory cancers (in lieu of actual numbers of men), we estimate the average for the highest cumulative dose group to be 85,000 μg-yrs/m^3. It should be noted that Welch *et al.* have not considered the effect of respirator use on reduction of exposure.

The following features of the Welch *et al.* study affect uncertainty estimation:

1. The same lack of measurements of concentrations before 1943 as was seen in the Lee-Feldstein (42) study contributes a value of 0.6 to γ_2. Again $\alpha_2 = 0$.
2. Between 1943 and 1965, 818 samples were taken in 18 of the 35 smelter departments. Estimates for departments with no

measurements were made by analogy to departments with known concentration. Both α_3 and γ_3 have been set equal to 0.3.

3. Average values for the cumulative exposure groups had to be estimated. The knowledge of the average for the entire cohort aided in estimation of the average for the highest dose group, so α_4 and γ_4 both equal 0.2.
4. Welch *et al.* do not consider respirator use when accumulating dose. As they say, "Interviews with men who had worked in the plant before 1964 ... indicated that respirator usage was sporadic at best during that time. It does not seem that respirators would have made an important difference in the concentrations to which the vast majority of men were exposed." Nevertheless, the numbers presented by these authors are probably overestimates of exposure; $\alpha_6 = 0.3$ and $\gamma_6 = 0$.
5. Although substantial discussion of smoking status and its effect on respiratory cancer is provided by Welch *et al.*, this analysis did not consider that variable. Both α_8 and γ_8 are assumed to be 0.1, as they were for the Lee-Feldstein study.

The uncertainty factors, $\alpha = 1.9$ and $\gamma = 2.2$, determine the bounds on cumulative dose, as seen in Table 2-10.

The respiratory cancer potency estimates for the three studies are given in Table 2-11. Unfortunately, the relative risk model does not fit any of these data sets. Crump and Ng (43) analyzed occupational arsenic exposure data and found that an absolute risk model fit the data much better than a relative risk model but that the risk estimates did not differ greatly from one model to the other. We have continued to use the relative risk model to compute RRD estimates (Table 2-12), knowing that some error is thereby introduced.

Table 2-7

DOSE AND RESPONSE DATA FOR THE COHORT OF WORKERS EXPOSED TO ARSENIC AT THE TACOMA, WASHINGTON SMELTER

Dose (μg-yrs/m^3)			Respiratory Cancer Deaths	
Lower Bound	Best Estimate	Upper Bound	Observed	Expected
39.1	91.8	252	8	4.0
112	263	723	18	11.4
281	661	1818	21	10.3
588	1381	5000	26	14.1
1741	4091	11250	31	12.7

[a]From data presented in Enterline and Marsh (34).

Table 2-8

OBSERVED AND EXPECTED DEATHS FROM RESPIRATORY CANCER, BY MAXIMUM EXPOSURE TO ARSENIC AND LENGTH OF EMPLOYMENT, ANACONDA EMPLOYEES[a]

Years of Exposure	Maximum Exposure to Arsenic (12 or more months)					
	Heavy		Medium		Light	
	Observed	Expected	Observed	Expected	Observed	Expected
25+	13	2.7	49	7.2	51	16.2
10 - 24	12	1.9	23	6.7	25	13.0
1 - 9	8	1.8	21	6.8	60	29.6

[a]From Lee-Feldstein (42).

Table 2-9

DOSE AND RESPONSE DATA FOR ANACONDA EMPLOYEES, FROM THE LEE-FELDSTEIN (42) CATEGORIZATION

Years of Exposure	Maximum Exposure Category	Cumulative Dose (μg-yrs/m^3)	Observed Respiratory Cancer Deaths	Expected Respiratory Cancer Deaths
25+[a]	Heavy[b]	39550 (15820, 98875)[c]	13	2.7
	Medium	20300 (8458, 46690)	49	7.2
	Light	10150 (3759, 23345)	51	16.2
10 - 24[d]	Heavy	19436 (7774, 48590)	12	1.9
	Medium	9976 (4157, 22944)	23	6.7
	Light	4988 (1847, 11472)	25	13.0
1 - 9[e]	Heavy	4656 (1862, 11640)	8	1.8
	Medium	2390 (996, 5497)	21	6.8
	Light	1195 (443, 2748)	60	29.6

[a]The average length of exposure for this group is assumed to be 35 years, the average of 25 and an assumed maximum of 45 years.
[b]The airborne concentration for the "heavy" category has been reduced to 1.13 mg/m^3 to account for possible respirator use.
[c]In parentheses are the lower bounds and upper bounds on dose for each dose group.
[d]The average length of exposure for this group, 17.2, is based on the 1138 men with 15-24 years employment (20 years average) and 678 men with 10-14 years employment (12.5 years average).
[e]The average length of exposure for this group, 4.12, is based on the 1082 men with 5-9 years employment (7.5 years average) and 3248 men with 1-4 years employment (3 years average).

Table 2-10

DOSE AND RESPONSE DATA FOR THE WELCH *ET AL.* (41) COHORT OF ANACONDA WORKERS

Cumulative Arsenic Exposure (μg-yrs/m^3)	Respiratory Cancer Deaths	
	Observed	Expected
< 500 (132, 250, 550)[a]	4	5.8
500 - 2000 (658, 1250, 2750)	9	5.7
2000 - 12000 (3684, 7000, 15400)	27	6.8
12000+ (44737, 85000, 187000)	40	7.3

[a]In parentheses are the lower bounds, best estimates, and upper bounds, respectively, for cumulative exposure in each dose group.

Table 2-11

RESPIRATORY CANCER POTENCY PARAMETER ESTIMATES FOR ARSENIC

Study	Dose Measure	Potencies ($(\mu g\text{-}yrs/m^3)^{-1}$) Lower Limit[a]	MLE	Upper Limit[a]
Enterline and Marsh (34) (chi-squared (4) > 10.8)	Upper Bounds	1.14E-4*	1.58E-4	2.07E-4
	Best Estimates	3.30E-4	4.59E-4*	6.04E-4
	Lower Bounds	7.757E-4	1.08E-3	1.42E-3*
Lee-Feldstein (42) (chi-squared (8) > 37.0)	Upper Bounds	8.80E-5*	1.00E-4	1.13E-4
	Best Estimates	2.08E-4	2.37E-4*	2.67E-4
	Lower Bounds	5.24E-4	5.97E-4	6.75E-4*
Welch *et al.* (41) (chi-squared (3) > 32.9)	Upper Bounds	2.25E-5*	2.87E-5	3.57E-5
	Best Estimates	4.95E-5	6.31E-5*	7.85E-5
	Lower Bounds	9.40E-5	1.20E-4	1.49E-4*

[a]90% confidence limits are shown.
*An asterisk marks the parameters used to derive RRD estimates.

Table 2-12

RRD ESTIMATES[a] FOR ARSENIC ($\mu g/m^3$)

Study	Estimation Method	Level of Extra Risk 10^{-6} RRD$_l$	MLE	RRD$_u$	0.25 RRD$_l$	MLE	RRD$_u$
Enterline and Marsh (34)	1	1.92E-4	5.92E-4	2.38E-3	4.79E+1	1.48E+2	5.96E+2
	2	2.21E-4	6.84E-4	2.75E-3	6.81E+1	2.11E+2	8.47E+2
Lee-Feldstein (42)	1	4.03E-4	1.15E-3	3.09E-3	1.01E+2	2.87E+2	7.72E
	2	4.65E-4	1.33E-3	3.56E-3	1.43E+2	4.09E+2	1.10E+3
Welch et al. (41)	1	1.82E-3	4.31E-3	1.21E-2	4.56E+2	1.08E+3	3.03E+3
	2	2.10E-3	4.97E-3	1.40E-2	6.48E+2	1.53E+3	4.30E+3

[a]Based on the risk of respiratory cancer.

Asbestos

With the exception of cigarette smoke and radiation, asbestos has probably been more unequivocally linked with human carcinogenesis than any other risk factor. Exposure to asbestos in the workplace has been clearly shown in a number of studies to place workers at increased risk of lung cancer, particularly among smokers, of plural and peritoneal mesothelioma, and possibly of other cancers of the pulmonary and gastrointestinal tracts. Several of these studies have data suitable for quantitative risk assessment, and a number of risk assessments for asbestos have been carried out by various individuals and governmental agencies (44-49).

Despite the fact that the carcinogenicity of asbestos in human populations has been thoroughly documented and studied, there are some unique difficulties associated with estimating risk to humans from exposure to asbestos. First of all, the carcinogenic risk from asbestos depends heavily upon fiber type and dimension. Risk of cancer from exposure to asbestos in mines and mills is less than that from most other occupational exposures, including exposures in manufacturing plants, textile mills, and in insulation applications. The potency of chrysotile asbestos for causing lung cancer in Canadian miners, for example, is 1/100 of the corresponding risk in workers exposed to amosite asbestos in a manufacturing plant during World War II (44). Risk of mesothelioma appears to be much less after exposure to chrysotile than to a comparable level of amosite or crocidolite (50).

Thus, a single carcinogenic potency for asbestos may not be appropriate for all applicatons; different fiber clouds can entail different risks. For purposes of setting regulatory policy, regulatory agencies have calculated an average potency over a range of exposure conditions. We shall take this approach here also.

Asbestos fiber clouds used in animal studies of carcinogenicity are generally created by hammer milling or ball milling raw asbestos. These processes create fibers which may not be representative of those to which humans have been exposed. This means that discrepancies in carcinogenic potencies obtained for asbestos from animal and human data may be due to differences in the types and dimensions of fibers to which animals and humans are exposed rather than to fundamental differences between animals and humans in their in susceptibility to the carcinogenic effects of asbestos.

Because of these limitations of the asbestos data, no detailed review of the epidemiological literature will be carried out here and a detailed risk assessment will be not be conducted for asbestos. Instead, risk estimates will be adapted from risk assessments already available in the literature. Several U.S. governmental agencies have conducted risk assessments for asbestos; these include the Consumer Product Safety Commission (44), the Occupational Safety and Health Administration (45), and the Environmental Protection Agency (46). The risk assessment conducted by the CPSC is specifically relied upon here, although the differences among these risk assessments are minor.

Asbestos has been shown unequivocally to cause lung cancer and mesothelioma (both pleural and peritoneal). There is also evidence that asbestos can cause other types of cancer, including various cancers of the gastrointestinal tract, although evidence for such a cause and effect relationship are more limited.* Following our guidelines for selection of cancer types for quantitative estimates, separate estimates

*The CPSC Panel, for example, could not agree on the interpretation of the evidence on these other cancers. "Some members [of the Panel] thought it possible that these excesses could conceivably be due to a combination of misdiagnosis of peritoneal mesothelioma and the use of inappropriate expected numbers. Others members thought that after allowance is made for these possible errors that some of the observed excess must be attributable to asbestos (43)."

of risk will be made for lung cancer and mesothelioma. Estimates will also be made for all cancer, including lung cancer, mesothelioma and other types of cancer that may be related to asbestos.

Due to the synergistic relationship that apparently exists between asbestos and cigarette smoke in causing lung cancer (51), the risk of lung cancer from asbestos is appreciably greater in smokers that in nonsmokers. To account for this difference in susceptibilty, separate estimates of risk for lung cancer and total cancer will be made for smokers and nonsmokers.

Table 2-13 shows potency parameters for lung cancer (K_L's) estimated by CPSC (44) from 11 occupational studies, and corresponding potency parameters for mesothelioma (K_M's) obtained from 4 studies. K_M and K_L are parameters from the lung cancer model and mesothelioma model, respectively, used by CPSC and represent the potency of asbestos for causing these effects. OSHA (45) and EPA (46) used these models, also. Because of differences in the lung cancer and mesothelioma models, K_M and K_L are in different units and consequently their magnitudes are not directly comparable.

CPSC used a range of values of 0.3×10^{-2} to 3.0×10^{-2} for K_L to estimate lung cancer risk. The midpoint of the range for K_L, 1.0×10^{-2}, is about the geometric average of the K_L's in Table 2-13 after omitting the K_L's obtained from studies of miners and millers (52-54). Although lung cancer risk is generally lower in mining and milling operations, the fiber types encountered in these operations are probably not representative of either those encountered in manufacturing and insulation operations or those studied in animal bioassays.

There are only four estimates of K_M in Table 2-13 and these come from studies for which the corresponding estimates of K_L are somewhat larger

than the geometric average of 1.0×10^{-2}. CPSC used a range of values of $K_M = 0.3 \times 10^{-8}$ to 3.0×10^{-8} to estimate risk of mesothelioma. OSHA justified using the middle of this range, 1.0×10^{-8}, because the ratios K_M/K_L for the four studies for which K_M's are available are closely distributed about 1.0×10^{-8} and an value of 1.0×10^{-2} was used for K_L on the basis of eight studies. However, using data from three studies in which exposure was primarily to chrysotile, Crump (55) estimated K_M's that were much lower than 1.0×10^{-8}; consequently the approach used by CPSC and OSHA may overestimate the risk of exposure to chrysotile. Nevertheless, we will follow the CPSC and OSHA approaches in the present analyses and use $K_L = 1.0 \times 10^{-2}$ and $K_M = 1.0 \times 10^{-8}$ (or, equivalently, use the middle of the range of risks estimated by CPSC).

CPSC (44) estimated risks for lung cancer and mesothelioma in nonsmoking and smoking males and females separately for continuous exposure to 0.01 f/cc beginning at ages 0, 10, 20, 30 and 50, and lasting for 1, 5, 10, and 20 years. These results are contained in CPSC's Table J-8A. In the current analysis we are interested is estimating risk from occupational exposure beginning at age 20 and lasting for 45 years. The scenario nearest this in terms of exposure durations considered by CPSC is 20 years of exposure beginning at age 20. The risk of mesothelioma in male smokers, for example, is 12.3×10^{-5} to 123.5×10^{-5}. Taking the geometric mean of this range, 3.90×10^{-4}, and converting to a risk corresponding to 45 years of exposure by multiplying by the ratio of risk of mesothelioma estimated by OSHA (45) for 45 years of exposure to that for 20 years of exposure, namely 82/73 (from exposure to 0.1 f/cc; this ratio does not depend critically on the exposure level assumed), yields a risk of 4.38×10^{-4}. Applying this same approach to male nonsmokers and female smokers and nonsmokers yields risks of 5.58×10^{-4} (male nonsmokers), 6.54×10^{-4} (female smokers), and 7.18×10^{-4} (female nonsmokers); the average of these 4 risks is 5.92×10^{-4}. This risk will be used to derive RRDs for mesothelioma. The differences in the four individual risks are

due to differences in longevity between males and females and, more importantly, between smokers and nonsmokers.

The continuous exposure assumed by CPSC is equivalent to an occupational exposure (8 hours per day, 240 days per year) of

$$(0.01\ f/cm^3)(24\ h/8\ h)(365\ d/240\ d) = 0.046\ f/cm^3.$$

Assuming a daily (8 hour) occupational breathing rate of 10 m^3 per day, the total exposure is

$$(0.046\ f/cm^3)(1.0\times10^6\ cm^3/m^3)(10\ m^3/d)(240\ d/yr)(45\ yr) = 5.0\times10^9\ \text{fibers}.$$

The corresponding RRD for a risk of 1×10^{-6} is therefore

$$(5.0\times10^9/5.92\times10^{-4})(1.0\times10^{-6}) = 8.39\times10^6\ \text{fibers}.$$

The same approach will be used to estimate RRDs corresponding to a risk of 0.25. Although this method does not fully account for attenuation of risks at such a high risk level due to asbestos-related deaths, such an adjustment would be very minor compared to the other sources of uncertainty in these estimates.

This approach is also used to estimate lung cancer RRDs, the only difference being that risks are estimated separately for smokers and nonsmokers. Similar methods are also used to estimate RRDs for total cancer. Following OSHA (45), cancer risks other than lung cancer and mesothelioma are assumed to be 10% of the risk of lung cancer in smokers.

Table 2-14 contains the resulting RRD estimates for asbestos in units of total fibers. The number of fibers counted depends upon the equipment

used and the method of counting. The estimates in Table 2-14 refer to fibers longer than 5 microns as measured by an optical microscope.

It is necessary to convert RRD estimates based on numbers of fibers to those based on a weight measure of asbestos exposure. The Ontario Royal Commission (47) estimated that there are 30 fibers longer than 5 microns (measured by optical micorscope) per nanogram of asbestos (measured with a transmission electron microscope). Experiments they performed suggested conversion factors ranging from 9.1 to 770 fibers per nanogram (conversions from samples in buildings ranged from 20 to 102 fibers per nanogram), so variability is considerable. Table 2-15 displays RRDs converted to units of milligrams per day.

Also shown in Table 2-15 are the bounds on the RRD estimates. Uncertainty in this asbestos analysis has been handled differently from that for other chemicals. We have arbitrarily chosen a factor of 6 to specify the bounds, hoping to account for such uncertainties as the conversion between number of fibers and weight of asbestos, the different types of and setting for asbestos exposure, the range of potency estimates obtained by CPSC, and possible differences in action of the various forms of asbestos.

Table 2-13

VALUES OF K_L AND K_M OBTAINED IN THE ANALYSIS OF ELEVEN STUDIES OF ASBESTOS WORKERS (44)

Mortality Study	K_L [a]	K_M [b]
McDonald *et al.* (52)	6×10^{-4}	
Henderson and Enterline (56)	$3.3\text{-}5.0 \times 10^{-3}$	
Weill *et al.* (57)	3.1×10^{-3}	
Dement *et al.* (58)	$2.3\text{-}4.4 \times 10^{-2}$	
Rubino *et al.* (54)	1.7×10^{-3}	
Berry and Newhouse (59)	6×10^{-4}	
Peto (60)	1.0×10^{-2}	0.7×10^{-8}
Finkelstein *et al.* (61, 62)	4.8×10^{-2}	12.0×10^{-8}
Nicholson *et al.* (53)	1.2×10^{-3}	
Seidman *et al.* (63)	6.8×10^{-2}	5.7×10^{-8}
Selikoff *et al.* (64)	1.0×10^{-2}	1.5×10^{-8}

[a] In f-yr/mℓ.
[b] Increase in SMR per f-yr/mℓ/100.

Table 2-14

RRD ESTIMATES FOR ASBESTOS (TOTAL FIBERS)

Neoplasm	Population	Level of Extra Risk 10^{-6}	.25
All malignant	Nonsmokers	6.5×10^{6}	1.6×10^{12}
	Smokers	3.6×10^{6}	9.0×10^{11}
Lung	Nonsmokers	5.5×10^{7}	1.4×10^{13}
	Smokers	6.9×10^{6}	1.7×10^{12}
Mesothelioma	All	8.4×10^{6}	2.1×10^{12}

Table 2-15

RRD ESTIMATES FOR ASBESTOS (mg/day)

		Level of Extra Risk					
		10^{-6}			.25		
Neoplasm	Population	RRD_l	MLE	RRD_u	RRD_l	MLE	RRD_u
All Malignant	Nonsmokers	3.3E-6	2.0E-5	1.2E-4	8.3E-1	4.9	2.9E+1
	Smokers	1.8E-6	1.1E-5	6.6E-5	4.7E-1	2.8	1.7E+1
Lung	Nonsmokers	2.8E-5	1.7E-4	1.0E-3	7.2	4.3E+1	2.6E+2
	Smokers	3.5E-6	2.1E-5	1.3E-4	8.7E-1	5.2	3.1E+1
Mesothelioma	All	4.3E-6	2.6E-5	1.6E-4	1.1	6.5	3.9E+1

Benzene

The aromatic hydrocarbon benzene (CAS No. 71-43-2) has been produced from coal or petroleum for over one hundred years. At one time benzene was blended with gasoline, but now it is used primarily as a chemical intermediate (as ethylbenzene) in plastic manufacture and as a solvent in the paint and rubber industries (65). Although benzene has been tested in a number of systems, it does not appear to be mutagenic. It has, however, induced chromosome anomalies in some rodent species and in occupationally exposed people (2).

The literature describing the human benzene experience is extensive. Several studies (65-68) document the metabolic fate of inhaled benzene. Apparently, in addition to short-term excretion of benzene in expired air and in urine (as phenol, primarily), some of the chemical accumulates in the body, probably in the fat, and is only slowly eliminated.

Studies by McMichael *et al.* (70), Arp *et al.* (71) and Checkoway *et al.* (72) review the health of workers in the rubber industry. These workers are exposed to a variety of solvents, among which is benzene. Leukemia is the cancer most commonly associated with benzene exposure. The first two studies, along with the review article by Infante and White (73), examine the distribution of leukemia types. Checkoway *et al.* (72) claim a stronger association exists between lymphocytic leukemia and solvents other than benzene (notably carbon disulfide and carbon tetrachloride) than between lymphocytic leukemia and benzene. In the case reports provided by Vigliani and Saita (74) and Vigliani (75), none of the leukemia deaths associated with benzene exposure were lymphocytic. Data from France (75) reveal only 8 of 44 benzene-related leukemia deaths of the lymphocytic type.

The series of articles from Turkey (76-83) corroborates these observations: only 9% of the benzene-exposed population with leukemia had lymphocytic leukemia, as opposed to 26% of nonexposed leukemia patients (81). These articles also suggest a relationship of benzene exposure to malignant lymphoma, myeloid metaplasia, multiple myeloma, Hodgkins disease, and possibly lung cancer. Aksoy and his associates also discuss the possibility that genetic factors may influence the predisposition to, or expression of, benzene-induced leukemia. Unfortunately, in none of these reports is a cohort of exposed individuals defined or followed-up, so no risk analysis was performed on these studies.

Two articles (84, 85) document the occupational standards for and exposures to benzene in recent years. It is concluded that occupational exposures *per se* have been substantially reduced. However, background levels of benzene as an atmospheric pollutant are present, especially in urban areas. These studies apply primarily to Scandinavia and the United States.

The three cohort studies for which exposure estimates have been derived (86-88) will serve as the basis of our risk assessment. As leukemia is the only generally accepted carcinogenic response associated with benzene exposure, that outcome and all malignant neoplasms will be the endpoints analyzed, in accordance with our guidelines. Similar risk estimates have recently been developed from these data sets by two of us (89). The exposure estimates contained in Appendix B of that report were used in this document without change.

A cohort of 594 individuals employed by Dow Chemical was identified by Ott *et al.* (86). Three production areas, two consuming benzene in manufacture and the other using benzene as a solvent, were in operation from the 1930's. The cohort consisted of employees who worked in those areas from 1940 to 1973. Individual job histories were available, as were

estimates of benzene concentrations in the three production areas. Most of the measurements of atmospheric benzene were obtained subsequent to 1964, with none before 1944. Exposures before 1944 were assumed to parallel those in the earliest periods for which industrial hygiene measurements were available. If one accepts that levels may have been somewhat higher during World War II and earlier, exposure estimates may tend to be somewhat low for people employed during the earlier years. Job categories were classified by exposure level, as depicted in Table 2-16. Through the courtesy of Mr. Ott, we had access to a computer listing of the data for this cohort, including work histories and the exposure classification, so that cumulative dose (in ppm-years) and expected deaths were calculable (Table 2-17). Age- and calendar-year-specific mortality rates for United States white males were employed in the calculation of expected numbers of deaths.

Uncertainty considerations for this study are summarized as follows:

1. Measurements of atmospheric benzene concentrations did not occur before 1944, and in some departments not before 1952. The authors claim, however, that few process changes occurred in the earlier time periods so that the concentrations measured in 1944 are probably representative of earlier exposures. We have assigned a value of 0 to α_2 and 0.4 to γ_2.
2. To cover the uncertainties associated with use of area concentration samples and with use of national death rates to estimate expected numbers of deaths, $\alpha_6 = \gamma_6 = 0.1$ and $\gamma_8 = \gamma_8 = 0.05$.

The resulting factors, $\alpha = 1.15$ and $\gamma = 1.55$, are relatively small because of the availability of job histories that include exposure estimates and of fairly complete documentation of the benzene concentration history of the plant. Table 2-17 displays the bounds obtained from the

application of these factors to cumulative dose estimates.

The cohort identified by Rinsky *et al.* (87) consists of white, male employees of three facilities producing rubber hydrochloride at two locations in Ohio. Through the courtesy of Mr. Rinsky, a computerized listing of the cohort was obtained. It included detailed job histories, mortality information, and follow-up through 1978. A total of 1713 white males employed between 1940 and closure of the plants (1965 in one location, 1976 in the other) were examined.

Mr. Rinsky was also kind enough to supply us with the data necessary to relate job codes in the cohort data tape to work areas, for which exposure estimates were available. The occupational hygiene measurements given in the original paper could then be used to estimate exposures encountered in each job over the years (Tables 22 and 23). Note that past exposures to high concentrations have been documented; the industrial hygiene data for these plants was generally good and reasonably complete for many years, including most of the follow-up period. No exposures to other potentially carcinogenic chemicals have been reported.

As with the Ott *et al.* cohort, detailed dose calculations were possible owing to the availability of the individual job histories. The relationship between cumulative dose (in ppm-years) and occurrence of leukemia and all malignant neoplasms is displayed in Table 2-20. A total of 8 leukemias were observed; all of them were nonlymphocytic. The expected numbers of deaths were calculated from age- and calendar-year-specific rates.

The uncertainties in this investigation are much like those reported above for the Ott *et al.* (86) study. The contributing features are as follows:

1. Benzene measurements were obtained only after 1945. However, the plants supplying cohort members began operations in 1937 and 1939, so relatively little time of exposure is not documented. In this case, $\alpha_2 = 0$ and $\gamma_2 = 0.3$.
2. Fewer concentration measurements were performed at the plants in the second location. Rinsky *et al.* state that "there is no evidence to suggest that exposures between the two locations differed widely either in type or severity." The concentrations presented in their paper corroborate that claim; α_3 and γ_3 have been given a value of 0.1.
3. Once again, $\alpha_6 = \gamma_6 = 0.1$ and $\alpha_8 = \gamma_8 = 0.05$ to reflect uncertainty in the applicability of area samples and of U.S. national mortality rates.

The resulting bounds, shown in Table 2-20, are derived from the uncertainty factors $\alpha = 1.25$ and $\gamma = 1.55$.

The cohort described by Wong (88) is taken from seven chemical manufacturing plants. The 7676 workers who worked for at least six months between 1946 and 1976 and who were followed up to the end of 1977 were classified on the basis of their exposure to benzene: nonexposed (control), intermittently exposed, and continuously exposed. For each job which involved continuous exposure, estimated time-weighted average benzene concentrations were derived. The method of derivation was based on a uniform task approach: each job was broken down into 34 possible tasks by the proportion of time spent performing the tasks. Each task was associated with some level of atmospheric benzene. The benzene concentrations were presumably estimated from occupational hygiene measurements taken at one or more of the seven plants. The concentrations were calendar-time specific. The author did not describe the source of the concentration estimates assigned to each task, nor did he

state how far in the past measurements were taken.

Workers in the continuously-exposed group (so assigned if they worked at one continuously exposed job, regardless of duration) were further divided by cumulative exposure. This dose estimate was calculated using all jobs held, those involving no exposure to benzene as well as those associated with benzene exposure. Unfortunately, average exposures in each group were not reported; the values we have estimated are presented in Table 2-21.

Table 2-21 also lists observed and expected numbers of deaths for leukemia and all cancers. Note that the comparison group (no exposure) experienced substantially fewer leukemias than were expected. A total of six leukemias were observed in the group of men who at one time were continuously exposed to benzene. Expected mortality was based on age- and calendar-year-specific rates.

As shown in Table 2-21, the bounds on dose for this investigation are wider than those in the two previously-reported benzene studies. The following features contribute to the outcome:

1. Very little is said about the occupational hygiene measurements that defined the exposure estimate associated with each job title. We assume that some measurements in at least some of the facilities formed the basis of those exposure estimates, but beyond that we lack documentation. To account for possible underestimation of early exposures, $\gamma_2 = 0.5$, and to cover the possibility of not very complete measurement even in more recent times (a very real possiblity, given the fact that seven different plants were included) α_3 and γ_3 have been assigned a value of 0.5.

2. The cumulative exposure groups were presented without average values. Both α_4 and γ_4 equal 0.2 to address uncertainty in the estimation of the average.
3. As in the previous two studies, we assumed a value of 0.1 for α_6 and γ_6 and a value of 0.05 for α_8 and γ_8 in consideration of the use of area samples and national mortality rates.

The overall uncertainty factors are $\alpha = 1.85$ and $\gamma = 2.35$.

The potency parameter estimates from the three studies discussed are displayed in Table 2-22. These have been calculated for leukemia and for all malignant neoplasms. The corresponding RRDs are shown in Table 2-23. Despite the fact that benzene is fairly specifically linked to leukemia, the lower bounds on RRD are smaller when studying all neoplasms than when studying leukemia alone, within each study. Nevertheless, two of the studies (the weakest two -- Ott *et al.* and Wong) are consistent with a hypothesis of no effect of benzene on either leukemogenesis or carcinogenesis in general. This is indicative of the variability and uncertainty associated with epidemiologic studies of cancer.

Table 2-16

CLASSIFICATION OF JOB TITLES IN THE OTT *ET AL.* (86) COHORT, BY EXPOSURE TO BENZENE

Exposure Category	Range (ppm)	Estimated Average (ppm)
Very Low	<2	1
Low	2-9	5
Moderate	10-24	17
High	≥25	30

Table 2-17

OBSERVED AND EXPECTED NUMBERS OF DEATHS IN THE OTT *ET AL.* (86) COHORT, BY CUMULATIVE DOSE OF BENZENE

Cumulative Dose (ppm-years)	Person-years of Observation	Cause of Death: All Malignant Neoplasms Observed	All Malignant Neoplasms Expected	Leukemia Observed	Leukemia Expected
0-5 (1.29, 1.48, 2.29)[a]	3533	2	3.5	1	0.18
5-20 (9.48, 10.9 16.9)	2961	9	4.6	0	0.20
20-80 (39.0, 44.8, 69.4)	3758	10	7.4	1	0.31
80-200 109.5, 125.9, 195.1)	1790	7	3.6	0	0.14
200+ (306.9, 352.9, 547.0)	1229	3	3.4	0	0.13

[a]In parentheses are the lower bound, best estimate, and upper bound, respectively, for cumulative exposure for each dose group.

Table 2-18

BENZENE EXPOSURE (ppm) BY OPERATION CODE
AND YEAR FOR LOCATION 1, RINSKY *ET AL*. COHORT

	Year						
Operation Code	-'46	'47	'48	'49-'57	'58-'63	'64-'69	'70+
11	62	62	30	22	10	10	2
03,07,17	60	60	30	21	2	2	2
12	56	56	28	20	10	6	2
06,33	51	51	26	18	18	11	2
04	111	111	56	39	34	18	11
27	31	31	16	11	8	8	4
01,08,31	259	114	59	42	31	31	10
05	259	118	61	44	32	32	11
15	259	108	54	38	22	22	6
02,13	76	54	27	19	14	9	3
09,10,14,16, 18,19,20,21, 22,23,24,25, 26,28,29,30,34	5	1	1	1	1	1	1
32,35	--	--	--	--	--	--	--

Table 2-19

BENZENE EXPOSURE (ppm) BY OPERATION CODE
AND YEAR FOR LOCATION 2, RINSKY *ET AL*. COHORT

Operation Code	Year -'46	'47	'48	'49-'57	'58-'63	'64-'69
18,56	63	63	31	22	12	18
03,16,46,47	60	60	30	2	2	2
05	56	56	28	20	10	6
21,40,52	51	51	26	18	18	11
12	43	43	21	15	15	3
22	111	111	56	39	34	18
34	31	31	16	11	8	8
10,14,35,54	259	240	120	42	31	31
07,08,27,28, 44,48,57	259	249	129	44	32	32
29,30,55	259	240	120	36	20	20
01,02	76	70	36	19	14	9
04,06,09,11,13, 15,19,20,23,24, 25,26,31,32,33, 36,37,38,39,41, 43,45,49,50,51 53,59,60,61,62,63	5	5	5	1	1	1

Table 2-20

OBSERVED AND EXPECTED NUMBERS OF DEATHS IN THE RINSKY *ET AL.* COHORT, BY CUMULATIVE DOSE OF BENZENE

Cumulative Dose (ppm-years)	Person-years of Observation	Cause of Death			
		All Malignant Neoplasms		Leukemia	
		Observed	Expected	Observed	Expected
0-5 (0.96, 1.20, 1.86)[a]	19239	28	26	2	1.2
5-20 (8.8, 11.0, 17.0)	8098	15	13	0	0.55
20-80 (33.8, 42.2, 65.4)	7003	7	13	0	0.52
80-200 (103.2, 128, 200.0)	3746	5	7.9	0	0.32
200-1000 (336.4, 420.5, 651.8)	3363	15	8.8	5	0.34
1000+ (1186, 1482, 2297)	457	3	1.4	1	0.051

[a]In parentheses are the lower bounds, best estimates, and upper bounds for cumulative exposure in each dose group.

Table 2-21

OBSERVED AND EXPECTED NUMBERS OF DEATHS IN THE WONG COHORT, BY CUMULATIVE DOSE OF BENZENE

Cumulative Dose (ppm-years)	Cause of Death			
	All Malignant Neoplasms		Leukemia	
	Observed	Expected	Observed	Expected
0	53	82.5	0	3.40
0-15 (4.05, 7.5, 17.6)[a]	56	54.6	2	2.07
15-60 (20.3, 37.5, 88.1)	45	34.8	1	1.28
60+ (42.8, 79.2, 186)	22	28.3	3	1.09

[a]In parentheses are the lower bounds, best estimates, and upper bounds for cumulative exposure in each dose group.

Table 2-22

BENZENE POTENCY PARAMETER ESTIMATES

Study	Response	Dose Measure	Potencies ((ppm-yrs)$^{-1}$) Lower Limit[a]	MLE	Upper Limit[a]
Ott *et al.* (86)	All Malignant Neoplasms (chi-squared (4) = 7.99)	Upper Bounds	-5.35E-4*	7.61E-4	2.53E-3
		Best Estimates	-8.38E-4	1.18E-3*	3.93E-3
		Lower Bounds	-9.52E-4	1.36E-3	4.52E-3*
	Leukemia (chi-squared (4) = 5.75)	Upper Bounds	-1.06E-2*	0.00	1.16E-2
		Best Estimates	-1.64E-2	0.00*	1.80E-2
		Lower Bounds	-1.89E-2	0.00	2.07E-2*
Rinsky *et al.* (87)	All Malignant Neoplasms (chi-squared (5) = 5.89)	Upper Bounds	1.40E-4*	5.86E-4	1.15E-3
		Best Estimates	2.16E-4	9.09E-4*	1.78E-3
		Lower Bounds	2.70E-4	1.14E-3	2.23E-3*
	Leukemia (chi-squared (5) = 4.61)	Upper Bounds	6.27E-3*	1.22E-2	2.05E-2
		Best Estimates	9.73E-3	1.88E-2*	3.18E-2
		Lower Bounds	1.22E-2	2.35E-2	3.97E-2*

Table 2-22 (continued)

BENZENE POTENCY PARAMETER ESTIMATES

Study	Response	Dose Measure	Potencies ((ppm-yrs)$^{-1}$) Lower Limit[a]	MLE	Upper Limit[a]
Wong (88)	All Malignant Neoplasms (chi-squared (3) = 14.98)	Upper Bounds	-1.33E-2*	0.00	1.05E-3
		Best Estimates	-3.11E-3	0.00*	2.46E-3
		Lower Bounds	-5.75E-3	0.00	4.56E-3*
	Leukemia (chi-squared (3) = 4.11)	Upper Bounds	-1.74E-4*	6.05E-3	1.56E-2
		Best Estimates	-4.08E-4	1.42E-1*	3.67E-2
		Lower Bounds	-7.62E-4	2.63E-2	6.78E-2*

[a]90% confidence limits shown.
*An asterisk marks the parameters (β_L, β, β_U) used to derive RRDs for each study and response.

Table 2-23

RRD ESTIMATES FOR BENZENE (ppm)

Study	Response	Estimation Method	Level of Extra Risk 10^{-6} RRD_L	MLE	RRD_L	0.25 RRD_L	MLE	RRD_U
Ott et al. (86)	All Malignant Neoplasms	1	1.74E-5	6.67E-5	∞	4.36	1.67E+1	∞
		2	2.29E-5	8.78E-5	∞	7.34	2.81E+1	∞
	Leukemia	1	1.33E-4	∞	∞	3.32E+1	∞	∞
		2	1.50E-4	∞	∞	5.03E+1	∞	∞
Rinsky et al. (87)	All Malignant Neoplasms	1	3.53E-5	8.66E-5	5.64E-4	8.83	2.17E+1	1.41E+2
		2	4.65E-5	1.14E-4	7.42E-4	1.49E+1	3.65E+1	3.27E+2
	Leukemia	1	6.95E-5	1.46E-4	4.39E-4	1.74E+1	3.66E+1	1.10E+2
		2	7.85E-5	1.65E-4	4.97E-4	2.63E+1	5.54E+1	1.66E+2
Wong (88)	All Malignant Neoplasms	1	1.73E-5	∞	∞	4.32	∞	∞
		2	2.27E-5	∞	∞	7.28	∞	∞
	Leukemia	1	4.06E-5	1.94E-4	∞	1.02E+1	4.85E+1	∞
		2	2.59E-5	2.19E-4	∞	1.53E+1	7.35E+1	∞

Benzidine

The aromatic amine, benzidine, is an intermediary in the dyestuff industry and has been used as a hardener in the rubber industry. According to the International Agency for Research on Cancer (2), benzidine is mutagenic when metabolically activated. Moreover, occupational exposure to benzidine has been causally associated with bladder cancer in humans. Risk estimation, in accordance with the analysis guidelines described above, is based on bladder tumors.

Several studies (90-95) report occupational exposures to benzidine and other aromatic amines, principally β-naphthylamine. The incidence of bladder tumors is increased in those workers exposed to benzidine. Bladder cancer appears to be particularly aggravated by exposure to β-naphthylamine in addition to benzidine. There is a suggestion of increased occurrence of some second primary cancers following joint exposure (92). Moreover, it appears that exposure to azo-dyes made from benzidine carries a carcinogenic risk to the bladder (93, 94). Walker and Gerber (96) review data relating to that association and the reaction of OSHA to the potential hazard. Unfortunately, none of these occupational studies can document benzidine exposure levels.

Two reports (97, 98) relate physiological characteristics to aromatic amine bladder carcinogenesis. Horton and Bingham (97), studying the cohort defined by Zavon et al. (99) (see below), found that bladder tumor occurrence was related to the serum properdin levels in exposed men. Lower *et al.* (97) suggest that the genetically-determined ability to acetylate arylamines influences aromatic amine-induced bladder carcinogenesis; slow acetylators may be at increased risk.

Only the occupational study by Zavon *et al.* (99) gives and response data essential for quantitative treatment of risk. This paper describes a

cohort of workers engaged in the manufacture of benzidine. The number of workers was quite small, 25, but 11 of them developed bladder carcinomas and 2 had benign bladder tumors. Some of these men were exposed to other chemicals. In fact, 3 men were exposed to β-naphthalamine (including the 2 with benign tumors).

The analysis presented below is based on the Zavon *et al.* (99) cohort. All 25 men are included; exclusion of 3 men exposed to β-naphthalamine, for example, would not exclude any observed carcinoma responses but would decrease the expected number and hence elevate the relative risk. Only one of the cases was terminal (1 man died from metastases to the abdomen); expected morbidity was determined from the age-specific incidence rates of malignant bladder tumors presented in the SEER report (100), Table 11E. These rates apply to the period 1973-1977; they would tend to slightly overestimate the risks from the period 1958 to 1970, judging by the trend in urinary system cancer mortality. The cohort was followed up for a maximum of 13 years, for a total of nearly 200 person-years. Follow-up was terminated when death or bladder cancer occurred. Roughly 0.05 bladder cancers would have been expected. With 11 cancers observed, the relative risk is 220.

Concentrations of benzidine measured at the manufacturing plant are presented in Table 2-24. If we assume that workers rotated through each work station and that only one employee at a time worked at the shoveling location while the other 24 were spread evenly at the other jobs, then a weighted arithmetic average concentration that these employees encountered was 0.80 mg/m^3.

Zavon *et al.* also present data on urinary benzidine concentrations in the workers. They found an average of about 0.04 mg/ℓ after the shift, 0.01 mg/ℓ before the shift, and 0.003 mg/ℓ on Monday morning. Assuming a linear increase in urine concentration during work gives an average

concentration of (0.01 + 0.04)/2 = 0.025 mg/ℓ during the 9 hours spent at work, assuming an exponential decay during non-work hours gives an average concentration of -0.04(1 - 0.25)/ln(.25) = 0.022 mg/ℓ. This results in an average concentration in urine during work days of about 0.023 mg/ℓ. Assuming that 100% of the benzidine inhaled by humans is taken up by the body, that humans excrete 1.4% of the inhaled benzidine in urine (rhesus monkeys excrete this percentage of ingested benzidine in urine, (101)), and that humans breathe 10 m^3 per 8-hour work day, the resulting estimate of benzidine exposure is

$$(0.023\ mg/\ell)(1.5\ \ell/day)(1/0.015)/(10\ m^3/day) = 0.23\ mg/m^3.$$

By comparison, the National Academy of Sciences report (102) estimates of exposure in this cohort correspond to a level of 0.38 mg/m^3. However, NAS assumes an average urine benzidine level of 0.05 mg/day as opposed to the value

$$(0.023\ mg/\ell)\cdot(1.5\ \ell/day) = 0.034\ mg/day$$

that we have estimated. IARC (2), using the measurements of atmospheric benzidine presented in Table 2-24, calculates an upper limit on concentration of 0.5 mg/m^3. The value 0.23 mg/m^3 appears reasonable; it was used in the calculations reported.

The men were exposed for an average of 11.24 years. Considered as a whole, then, the cohort was exposed to an average cumulative dose of

$$(0.23\ mg/m^3)\cdot(11.24\ years) = 2.59\ mg\text{-}yrs/m^3\ .$$

Uncertainty in this study stems from the following sources:

1. Relatively few urine benzidine measurements were obtained, and these occurred late in the history of the plant. There is a possibility that higher exposures further in the past were not documented although the authors state that they were assured that the conditions they describe were typical of those that prevailed over the past few years. We assigned a value of 0.2 to γ_2 ($\alpha_2 = 0$) and a value of 0.3 to α_3 and γ_3 to account for the lack of extensive exposure determinations.
2. The largest uncertainty is associated with the conversion from urine concentration to atmospheric concentration. First of all, the percentage of benzidine excreted (1.5%) was based on a study of gavaged monkeys. Secondly, that study measured benzidine and mono-acetyl benzidine excretion; it is not known if the mono-acetyl moiety was included in the Zavon *et al.* measurements of urine concentration. In this case $\alpha_7 = 1$ and $\gamma_7 = 1.5$, the latter factor being larger to reflect the last-mentioned concern, which would tend to make the atmospheric concentration estimates larger if mono-acetyl benzidine was not measured.
3. Expected numbers of bladder cancers were based on data from 1973 to 1977, after the follow-up period ended. A factor of 0.2 is assigned to α_8 and γ_8.

The uncertainty factors, $\alpha = 2.5$ and $\gamma = 3.2$, determine the lower and upper bounds on cumulative exposure, 1.04 and 8.29 mg-yrs/m^3, respectively. Potency parameters based on these values, and the best estimate of dose, are given in Table 2-25.

Since the expected number of bladder cancers is so small, we considered an alternative to our standard analysis approach. Suppose the lifetime

probability of these cancers, when exposed to the indicated cumulative doses is 11/25 = 0.44 as suggested by the Zavon *et al.* study. The binomial 90% bounds on this probability are 0.31 and 0.57. The dose-dependent probability of cancer is expressed as

$$P(d) = 1-\exp(-\alpha-\beta_2 d) \qquad (2\text{-}4)$$

The parameter α is calculated from the expected number of bladder cancers, 0.05, if there had been no exposure. That is,

$$P(0) = 0.05/25$$

and

$$P(0) = 1-\exp(-\alpha).$$

Hence $\alpha = 0.002$. Use of the best estimates of dose and lifetime probability, 2.59 mg-yrs/m^3 and 0.44, respectively, yields a best estimate, β_2, of

$$-\frac{\ln(1-0.44) + 0.002}{2.59} = 0.22$$

The corresponding reasonable upper and lower bounds on potency, β_{2U} and β_{2L}, respectively are

$$-\frac{\ln(1-0.57) + 0.002}{1.04} = 0.81$$

and

$$-\frac{\ln(1-0.31) + 0.002}{8.29} = 0.045$$

These potency parameters arise from a model different from the standard model and have different interpretations. They should not be compared

directly to the parameters in Table 2-25, but only by reference to the corresponding RRD estimates (Table 2-26). Basic Methods 1 and 2 use the parameters shown in Table 2-25 and calculate virtually safe doses based on the methods outlined in earlier in this setion. The binomial method is based on equation 2-4. If any more of the 25 men have developed bladder cancer since Zavon *et al.* studied that cohort, the binomial method gives underestimates of risk and, consequently, overestimates of RRDs.

Table 2-24

CONCENTRATIONS OF BENZIDINE IN ATMOSPHERE AT DIFFERENT LOCATIONS OF BENZIDINE MANUFACTURING PLANT[a]

Sampling Location	Benzidine Concentration, mg/m^3
Reducers	<0.007
Conversion tubs	<0.007
Clarification tub	0.005
Filter press	0.072 - 0.415
Salting-out tub	0.152
Centrifuge	<0.005
Location for shoveling benzidine into drums	17.600

[a]From Zavon *et al.* (99).

Table 2-25

BLADDER CANCER POTENCY PARAMETER ESTIMATES FOR BENZIDINE, FROM DATA IN ZAVON *ET AL.* (99)[a]

Dose Measure	Potencies ($(mg\text{-}yrs/m^3)^{-b}$)		
	Lower Limit[b]	MLE	Upper Limit[b]
Upper Bounds	1.55E+1*	1.93E+1	4.15E+1
Best Estimates	4.96E+1	6.19E+1*	1.33E+2
Lower Bounds	1.24E+2	1.54E+2	3.31E+2*

[a]Zero degrees of freedom are available to assess goodness-of-fit.
[b]90% confidence limits are shown.
*An asterisk marks the parameters used to derive RRD estimates.

Table 2-26

RRD ESTIMATES[a] FOR BENZIDINE (mg/m^3)

Estimation Method	Level of Extra Risk 10^{-6}			0.25		
	RRD_L	MLE	RRD_U	RRD_L	MLE	RRD_U
1	2.35E-9	1.26E-8	5.02E-8	5.89E-4	3.15E-3	1.26E-2
2	2.60E-9	1.39E-8	5.54E-8	8.42E-4	4.50E-3	1.80E-2
Binomial[b]	8.24E-8	3.03E-7	1.48E-6	7.89E-3	2.91E-2	1.42E-1

[a]Based on the risk of bladder cancer and the data in Zavon *et al.* (99).

[b]In this method, the model for lifetime probability of bladder cancer is $P(d) = 1-\exp(-\alpha-\beta d)$. Forty-five years of exposure is assumed.

Cadmium

The metal, cadmium, is a relatively rare element found in the earth's crust. It is produced for use mainly by sintering flue dusts and roasting zinc ores. Cadmium and its compounds are used in metal plating, in plastics stabilizers, in pigments, in pesticides, and in the manufacture of batteries (103).

Short-term tests of cadmium have been equivocal. Although it was not mutagenic in one test on *Drosophila*, it produced chromosomal anomalies in human and mammalian cells *in vitro*. There are conflicting reports about the production of chromosomal aberrations in exposed people (2). The kidney is the critical organ with respect to noncancer, systemic effects (104).

The epidemiologic literature contains several descriptions of the human cadmium experience. Pharmacokinetic studies (104, 105) indicate that ingested or inhaled cadmium is rapidly transported to the liver. It is slowly released from the liver and appears in the kidneys where it again resides for extended periods. The half-life for cadmium in the human body may be as long as 30 years. Another study (106) indicates that iron deficiency may increase the absorption of dietary cadmium. This study also estimates the half-time of cadmium to be 93 to 202 days, significantly shorter than the 30 years mentioned above.

Various types of studies have suggested carcinogenic effects of cadmium. A case-control study (107) collected data on three main sources of cadmium exposure -- diet, cigarette smoking, and occupation -- and determined that renal cancer was associated with such exposure. A geographical investigation in Alberta, Canada (108) found that areas with high cadmium concentrations in water, soil, and grains tended to have higher incidences of prostate cancer. In a geographical investigation of trace

metals in the water supplies of various parts of the United States, Berg and Burbank (109) found an association between cadmium levels and several tumors including cancers of the esophagus, large intestine, and lung.

Studies of occupational cadmium exposure are also represented in the literature. Potts (110) described conditions in an alkaline battery factory. The employees were exposed to cadmium oxide dust. Of seventy-four men exposed for at least 10 years, three prostatic cancer deaths were noted. Further evidence of a link between cadmium and cancer of the prostate was provided by Kipling and Waterhouse (111). In their survey of 248 workers exposed for at least one year to cadmium oxide, 4 prostate cancers were observed whereas 0.58 would have been expected.

Lemen *et al.* (112) followed up retirees from a cadmium smelter. The 292 white males who worked at least two years between 1940 and 1970 experienced cadmium concentrations that were, for the most part, on the order of 1 to 1.5 mg/m^3. Excursions into areas that had concentrations up to 31.3 mg/m^3 were documented. Follow-up to the beginning of 1974 revealed 4 prostate cancers (1.15 expected) and, moreover, an excess of respiratory system cancers (12 observed vs. 5.11 expected).

Kjellstrom *et al.* (113) have presented preliminary results on two groups of workers exposed to cadmium: 269 workers in a battery factory and 94 exposed employees at a copper-cadmium alloy smelter. All members of the cohort were exposed for at least 5 years. The first group, followed from 1959 to 1975, showed a significant excess of nasopharnyx cancer cases and nonsignificant excesses of prostate, lung, and colorectal cancers. The second group was followed for prostate cancer deaths only, from 1940 to 1975. Four were observed; 2.69 were expected. Exposures in these cohorts ranged from 1 mg/m^3 to 50 $\mu g/m^3$ and perhaps down to 5 $\mu g/m^3$ in recent times in the battery factory. In a recent update

(114) with an expanded cohort and additional follow-up, nasopharyngeal cancer was no longer significantly overrepresented. The nonsignificant excesses of prostate, lung and colorectal cancers were still apparent. Similar excesses of pancreatic and bladder malignancies were found.

Armstrong and Kazantzis (115) identified a cohort of 6995 men from 17 English plants processing cadmium. These men were born before 1940 and had at least one year of employment between 1942 and 1970. The cohort was categorized by the maximum exposure category ("high", "medium", or "low") in which they were employed for a year or more. Unlike other studies, prostatic cancer deaths were underrepresented (23 observed and 23.3 expected). A slight, but nonsignificant excess of lung cancers (199 observed, 185.6 expected) was said to be unrelated to the exposure grouping.

Sorahan and Waterhouse (116) provide an update and expansion of the investigations by Potts (110) and Kipling and Waterhouse (111). The cohort they described includes 3025 employees of the nickel-cadmium battery factory who began work between 1923 and 1975 and who were employed for a least one month. Mortality was investigated for the period January 1, 1946 to January 31, 1981. Although exposure to nickel hydroxide was not separable from cadmium exposure, the authors tentatively conclude that there exists some indication of a risk of respiratory system cancer due to cadmium exposure. Prostate cancer was associated with cadmium exposure also, but no new evidence of that association was found over and above that presented by Kipling and Waterhouse (111).

Unfortunately, the occupational studies described above provide very little information on magnitudes of exposures, certainly not enough to define quantitative dose measures. The study by Thun *et al.* (117) does include mortality analyses by cumulative exposure and, hence, will serve

as the basis for a quantitative assessment of risk due to cadmium exposure.

The cohort identified by Thun *et al.* is an extension of the cadmium production workers cohort described by Lemen *et al.* (112). In the update, the cohort included all hourly employees who worked a minimum of 6 months in a production area of the plant between 1940 and 1969. A total of 602 white males were followed up through 1978.

Calendar-year-specific cadmium concentrations were determined for each department in the plant (Table 2-27). These were based on historical area monitoring data, which began in 1940, but these have been adjusted in two ways. First a correction was applied to convert area samples to personal samples, based on the ratios of those two values found in measurements taken from 1973 to 1976. Second, in those departments where respirators were used, personal exposures were divided by 3.9, the mean respirator protection factor determined in a plant survey. Detailed job histories allowed computation of cumulative exposures over time for each cohort member.

The total of 41 malignant neoplasms observed differed only slightly from the 36.46 expected. On the other hand, the 20 respiratory system cancers were significantly in excess of the 12.15 expected. Four of the 20 were hired before 1926, when the plant functioned as an arsenic smelter. When the analysis is limited to the subcohort hired on or after January 1, 1926, and so presumably with little or no arsenic exposure, a dose-response trend for lung cancer was observed (Table 2-28). Lung cancer is the only carcinogenic response categorized by cumulative exposure, so the risk estimates are limited to that endpoint.

Table 2-28 presents the averages assumed for each exposure group -- 1.22, 7.30, and 18.16 -- and the bounds derived for those averages. The

bounds were obtained by applying the factors α and γ, both of which have the value 1.65 relating to the following uncertainties:

1. Industrial hygiene measurements began in 1940, but exposures began as early as 1926. It is not known how concentration estimates were extrapolated to this early period. The value 0.3 is assigned to α_2 and γ_2.
2. Also not documented is the completeness of the measurements used to estimate concentrations post-1940. The data in Table 2-27 indicates that is was possible to estimate exposures that differed from department to department and over time. A nominal value of 0.1 is assumed for α_3 and γ_3.
3. The cumulative exposure groups defined by Thun *et al.* (Table 2-28) were presented without average values. The groups are fairly narrow (except for the last) so a relatively small value of 0.1 is assigned to α_4 and γ_4.
4. The authors did an excellent job constructing exposure estimates pertinent to individual inhalation by taking account of respirator use and the difference between area and personal samples. Some small amount of residual uncertainty with respect to that conversion entails a value of 0.05 for α_6 and γ_6.
5. The endpoint of interest is lung cancer, one very sensitive to smoking behavior. A retrospective assessment of smoking patterns in the cohort demonstrated little difference between the cohort and national values with respect to percentage of smokers. Some of the cohort members were exposed to arsenic, a known lung carcinogen. It would have been ideal if expected values of lung cancer deaths could have been derived with these factors in mind, but the effect is probably small. Both α_8 and γ_8 have been given a value of 0.1.

The averages and bounds have been used to estimate the parameters β, β_U, and β_L. These estimates are shown in Table 2-29. When applied to the standard exposure scenario -- forty-five years exposure starting at age 20 -- RRD estimates can be derived. Those corresponding to the estimated potency parameter and its bounds are given in Table 2-30.

Table 2-27

ESTIMATES OF CADMIUM INHALATION EXPOSURE, BY PLANT DEPARTMENT AND TIME PERIOD[a]

Time Period	Plant Department									
	Sampling	Roaster	Mixing	Calcine	Solution	Tank House[b]	Foundry	Retort	Pigment	Offices[c] and Laboratories
Pre-1950	1.0	1.0	1.5	1.5	0.8	0.04	0.8	1.5	0.2	0.02
1950-54	0.6	0.6	0.4	1.5	0.8	0.04	0.1	0.2	0.2	0.01
1955-59	0.6	0.6	0.4	1.5	0.4	0.04	0.1	0.2	0.04	0.01
1960-64	0.6	0.6	0.4	0.4	0.4	0.02	0.1	0.2	0.04	0.007
1965-76	0.6	0.6	0.4	0.15	0.04	0.02	0.04	0.2	0.04	0.007

[a]Data presented in Thun et al. (117).
[b]Tank house estimates also used for nonproduction plant departments that were not measured directly, e.g., the repair shops.
[c]Office estimates also were used for nonplant areas that were not measured directly, e.g., areas patrolled by the plant guard.

Table 2-28

DOSE AND RESPONSE DATA FOR THE CADMIUM-EXPOSED COHORT STUDIED BY THUN *ET AL.*

Cumulative Exposure ($mg\text{-}yrs/m^3$)[a]	Lung Cancer Deaths	
	Observed	Expected[b]
≤2.43 (0.74, 1.22, 2.01)[c]	2	3.77
2.43 - 12.17 (4.42, 7.30, 12.04)	7	4.61
≥12.17 (11.07, 18.26, 30.13)	7	2.50

[a]The original authors presented cumulative exposures in units of mg-days/m^3. These have been converted by assuming that 240 days per year are spent on the job, i.e. by dividing by 240.
[b]Expected values have been calculated from observed numbers and SMRs.
[c]In parentheses are the lower bounds, best estimates, and upper bounds for cumulative exposures, respectively. These were not presented by the original authors; see the text.

Table 2-29

CADMIUM LUNG CANCER POTENCY ESTIMATES ($(mg\text{-}yrs/m^3)^{-1}$), FOR THUN *ET AL.* (117) COHORT

Dose Measure	Lower Limit[a]	MLE	Upper Limit[a]
Upper Bounds (chi-squared (2) = 1.21)	2.09E-2*	5.14E-2	9.03E-2
Best Estimates (chi-squared (2) = 1.21)	3.46E-2	8.48E-2*	1.49E-1
Lower Bounds (chi-squared (2) = 1.21)	5.70E-2	1.40E-1	2.46E-1*

[a]90% confidence limits shown.
*An asterisk indicates potencies used to calculated RRDs.

Table 2-30

RRD ESTIMATES FOR CADMIUM (mg/m^3)[a]

Neoplasm	Estimation Method	Level of Extra Risk 10^{-6} RRD$_l$	MLE	RRD$_u$	0.25 RRD$_l$	MLE	RRD$_u$
Lung Cancer	1	1.12E-6	3.45E-6	1.40E-5	2.97E-1	8.61E-1	3.49
	2	1.36E-6	3.94E-6	1.60E-6	4.20E-1	1.22	4.94

[a]From Thun *et al.* (117) data.

Chlorambucil

Chlorambucil (CAS No. 305-03-3) is a drug used as an immunosuppressive agent in the treatment of certain nonmalignant diseases (rheumatoid arthritis, psoriasis, etc.) and as an antineoplastic agent for combatting hematopoietic system neoplasms and carcinomas of the breast, lung, and genital organs (118). Chlorambucil is an alkylating agent, interacts with DNA in mammalian cells *in vitro*, and is mutagenic in bacteria and fungi (2). It is not surprising then that chlorambucil is highly suspected of being a carcinogen.

Four papers discussing the human carcinogenicity of chlorambucil have been reviewed. Rieche (119) provides an overview of the carcinogenicity of antineoplastic agents in general. He cites a study in which chlorambucil was given for the treatment of non-Hodgkin's lymphoma. An eightfold risk of skin cancer was observed. Other investigators have noted leukemia rather than skin cancer after chlorambucil treatment. In a study of aklylating-agent therapy of ovarian cancer, Reimer *et al.* (120) found a relative risk for acute nonlymphocytic leukemia of 36 (13 cases observed vs 0.36 expected). Chlorambucil was not the only chemotheraputic agent used in this multi-center study and some of the patients received radiation therapy as well. That is also the case in a report of five clinical trials given by Greene *et al.* (121). These authors report that 2 acute non-lymphocytic leukemias were observed, as opposed to 0.009 expected, in patients receiving more than 2000 mg of chlorambucil (6 mg/day for two years initially prescribed). These ovarian cancer patients also received pelvic irradiation, however.

The study described by Berk *et al.* (122) provides the information necessary to estimate RRDs for chlorambucil. In a study of treatment of polycythemia vera, they conducted a ramdomized trial with three treatment arms: phlebotomy alone, phlebotomy plus chlorambucil, and phle-

botomy plus radioactive phosphorus. These authors concluded that chlorambucil significantly increased the risk of acute leukemia.

Table 2-31 displays the information pertinent to calculation of RRDs. This data is based on the phlebotomy-only (untreated) group and that portion of the chlorambucil-treated group with complete dose information. Since the data is obtained from a randomized clinical trial, we opted to use the untreated group to calculate expected numbers of leukemias. This seems appropriate because the authors note that there are reports of an association between polycythemia vera and leukemia irrespective of chlorambucil treatment. Two out of 134 untreated patients developed acute leukemia, so the expected value for the low-dose group, for example, is

$$\frac{2}{134} \cdot 60 = 0.90.$$

To calculate cumulative doses, we had to assume an average daily dose for the two groups ($\leq$4 mg/day and >4 mg/day) and a duration of dosing. The authors state that only one patient received more than 10 mg per day, so we assumed an average of 7 mg per day for the high-dose group. A value of 2 mg/day was used for the low-dose group. The authors do not clearly state the average length of dosing; they do state that chlorambucil treatment was stopped, apparently close to the date the article was written. At that time, the chlorambucil group was followed for an average of 5.4 years. That value was used to calculate cumulative doses, as shown in Table 2-31.

Uncertainty arises in this analysis because of the following features of the published report:

1. The average duration of dosing is not presented. We have had to assume that follow-up time is a good surrogate for duration

of exposure, probably not a terrible assumption given that chlorambucil treatment has been terminated. Nevertheless, $\alpha_1 = \gamma_1 = 0.2$.

2. No averages are provided for the dosage-defined groups, so again these were estimated. Consequently, α_4 and γ_4 have also been given a value of 0.2.
3. The expected numbers of deaths is based on a very small population of 134 phlebotomized, polycythemia vera patients. This undoubtedly leads to substantial potential variability in the leukemia responses seen. That being the case, α_8 and γ_8 are equal to 0.3.

As a result of these considerations, $\alpha = \gamma = 1.7$. The resulting bounds on cumulative dose are displayed in Table 2-31.

Table 2-32 displays the results of fitting the standard models to the dose and response data described above. Table 2-33 provides the corresponding RRD estimates when the calculated potency parameters are applied to the standard exposure scenario.

Table 2-31

DOSE AND ACUTE LEUKEMIA RESPONSE DATA FOR CHLORAMBUCIL[a]

Average Daily Dose (mg)	Number of Patients	Number of Leukemias	Expected Number of Leukemias[b]
0	134	2	---
≤4 (6.4, 10.8, 18.4)[c]	60	5	0.90
>4 (22.2, 37.8, 64.3)	31	7	0.46

[a]From Berk *et al.* (122).
[b]Based on experience of the phlebotomy-only group; see text.
[c]In parentheses are the lower bounds, best estimates, and upper bounds for cumulative dose, expressed in mg-yrs.

Table 2-32

LEUKEMIA POTENCY PARAMETER ESTIMATES FOR CHLORAMBUCIL, BASED ON THE STUDY BY BERK *ET AL.*[a]

Dose Measure	Potencies ((mg-yrs)$^{-1}$) Lower Limit[2]	MLE	Upper Limit[2]
Upper Bounds	1.45E-1*	2.30E-1	3.38E-1
Best Estimates	2.47E-1	3.91E-1*	5.75E-1
Lower Bounds	4.20E-1	6.64E-1	9.76E-1*

[a]Fit of the model to the data is adequate; chi-squared (1) ≤ 0.03.
[b]90% confidence limits are shown.

Table 2-33

RRD ESTIMATES[a] FOR CHLORAMBUCIL (mg/day)

Estimation Method	Level of Extra Risk					
	10^{-6}			0.25		
	RRD_l	MLE	RRD_u	RRD_l	MLE	RRD_u
1	1.93E-6	4.82E-6	1.30E-5	4.83E-1	1.21	3.24
2	2.17E-6	5.43E-6	1.46E-5	7.21E-1	1.80	4.84

[a]Based on the data of Berk *et al.* (122) and the risk of leukemia morbidity.

Chromium

The metal chromium and its compounds are mined and produced in large quantities for use in the metallugical, refractory, and chemical industries: ferrochromium alloys are used as additives in the production of stainless and other special steels, chromite refractory materials are used in iron and steel processing, nonferrous alloy refining, glass-making, and cement processing (123). In addition to the elemental state, two oxidation states (+3 and +6) are commonly found. Trivalent and hexavalent compounds are the only ones known to play a role in biologic systems. Apparently, the hexavalent forms are easily reduced to the trivalent state after exposure to organic matter but the oxidation of trivalent to hexavalent forms is unlikely in a biological context. It is the case that hexavalent compounds are readily absorbed from the lung whereas trivalent compounds dissipate slowly. On the other hand it is believed that the reduction of hexavalent chromium to the trivalent state and the formation of complexes is the mechanism by which hexavalent chromium reacts with nucleic acid (124). Indeed, the hexavalent form has caused DNA damage, mutations, and chromosomal aberrations in species ranging from bacteria to mammals. Trivalent chromium, conversely, shows no evidence of producing these effects (2).

The epidemiologic literature contains many reports of the health effects of chromium exposure. In a report on chromium plating industry employees, Royle (125) found nonmalignant respiratory symptoms to be more prevalent than among industrial workers without chromium exposure. Also found was a risk of skin and intranasal ulceration that increased with duration of chromic acid exposure. As early as 1948, a study of chromate plant workers revealed an increased risk of respiratory cancer (cf. 124, 126-128 for review of many epidemiologic studies). This has been corroborated in numerous occupational studies (129-136). Several of these and other studies have suggested a link between chromium expo-

sure and gastrointestinal cancer and at least one case-control study (137) postulates an effect of chromium on nasal and sinonasal cancer. It is unfortunate that these studies lack the exposure data needed for a quantitative approach to risk assessment.

Three cohorts have been identified that provide information on exposures to chromium. A small Norwegian company producing zinc chromate has been the subject of study by Langard and his associates (138-140). The plant produced only lead chromate from 1948 to 1951, adding zinc chromate production at the latter date. Lead chromate production ceased in 1956. Only 133 men worked in the facilities between 1948 and 1972 and only 24, those exposed for at least 3 years before January, 1973, were analyzed. By the time of the last update (follow-up through 1980), 6 lung cancers were found compared to 0.135 expected from national rates. Expected gastrointestinal cancer is reported only through 1975; 0.47 cases were expected but 3 were observed.

Chromium concentrations were measured in 1972 (Table 2-34). Earlier measurements were not available but the authors state that interviews indicate that concentrations in the past were of the same magnitude as those indicated. Plant C was built in 1972, the end of the cohort-defining period. Consequently, Plant C is not considered in estimation of cumulative exposures. Apparently, the workers rotated from job to job, so an average exposure is calculated for the group as a whole. The arithmetic average of the concentrations in Table 2-34 for plants A and B is 0.45 mg/m^3; this is the assumed average exposure. In addition, the cohort members worked for 4 to 19 years; more than half of them worked for 6 years or less, including six who worked for four years only. This information is used to estimate an average length of exposure of 8 years. Consequently, the average cumulative dose for this cohort is estimated to be

$(0.45\ mg/m^3)\cdot(8\ years) = 3.6\ mg\text{-}yrs/m^3$.

Bounds on that best estimate have been set to 1.85 and 8.82 mg-yrs/m^3 ($\alpha = 1.95$ and $\gamma = 2.45$). These result from the following considerations:

1. No specific average duration of employment is given. The information discussed above has allowed estimation of 8 years as the average, but the uncertainty remaining contributes a value of 0.2 to α_1 and γ_1.
2. No concentration measurements were performed before 1972. Langard and Norseth believe that these are at least indicative of the magnitude of concentrations prevailing at earlier times. Nevertheless, a value of 0.2 is assumed for α_2, and γ_2 is set equal to 0.5.
3. Several exposure estimates are presented, but no estimate of an average, plant-wide exposure is given. By averaging those estimates given, some uncertainty is perpetuated. Consequently, α_4 and γ_4 have been set to 0.2.
4. Some uncertainty relates to the applicability of the reported exposures. In addition to the fact that area samples are reported, some men were exposed for an additional time to levels more like those found in Plant C. This occurred between 1972 and 1980 and presumably would have little or no effect on cancer incidence up to 1980. This latter concern legitimately affects the upper bound, through γ_6, which is set equal to 0.25. The factor α_6 is set to 0.05.
5. Expected numbers in the analysis were derived from national rates, known to differ from the rates prevailing locally. Moreover, the risk of lung cancer is greatly influenced by smoking. Five of the six lung cancer cases were smokers, but the authors did not consider smoking to be an important

confounder. Nevertheless, a value of 0.3 for α_8 and γ_8 is considered appropriate to cover the uncertainty introduced.

Langard *et al.* (141) studied a cohort of ferrosilicon and ferrochromium workers specifically to see if trivalent forms of chromium entailed risks similar to those of hexavalent chromium. Cohort membership was restricted to men employed for at least one year who started before 1960 (and who were alive after January 1, 1953). Follow-up extended from 1953 to 1977. A total of 976 individuals constitute the cohort; they were categorized by the area of the facility in which most of their employment was spent. The dichotomy studied by the authors was ferrochromium workers vs. all others. The former group experienced 23 cancers (7 lung cancers) with 23.49 (3.10 lung cancers) expected; among the other workers 41 cancers (2 lung cancers) were observed and 55.95 (6.35 lung cancers) were expected.

The calculation of average chromate exposure is accomplished as follows. No duration of employment is given for the two groups, ferrochromium workers and others. An assumed average length of employment of 10 years is assumed, since this population is in a "isolated community" with a stable work force: several members of the cohort worked continuously from 1928 to 1977 in the plant. Total chromium concentration measurements from 1975 are presented in Table 2-35. These values are used to derive cumulative chromate exposure. Between 11% and 33% of the detected chromium was water soluble, assumed by the original authors to be chromate. An average of 22% is assumed. Hence the mean chromate concentrations in ferrochromium jobs ranged from 0.0088 to 0.064 mg/mg^3 with an arithmetic average of 0.025 mg/m^3 over the four jobs listed under that department. This value is assumed to characterize the ferrochromium workers exposures which, coupled with the duration of exposure assumed, 10 years, gives a cumulative exposure of

$$(0.025\ mg/m^3)\cdot(10\ years) = 0.25\ mg\text{-}yrs/m^3.$$

On the other hand, the nonferrochromium workers include the maintenance workers, who averaged (following the same procedure as described above for ferrochromium workers) 0.011 mg/m^3 of chromate. The 127 maintenance workers are combined with the remaining 524 workers to provide an estimated average cumulative exposure for nonferrochromium workers of

$$(0.011\ mg/m^3)\cdot(10\ years)\cdot(127/524) = 0.027\ mg\text{-}yrs/m^3.$$

The dose and response data are summarized in Table 2-36.

The uncertainty in this study is considerable. The following features contribute to the derivation of uncertainty bounds.

1. Nothing quantitative is known about duration of exposure. That being the case, α_1 and γ_1 equal 1.5.
2. The only concentration measurements of chromium in the atmosphere are from 1975. Production started in 1928. Apparently, several changes in the production routines entailing different exposures occurred in that interval. Langard *et al.* speculate that chromate exposures must have been high enough to produce perforations of the nasal septum, which may occur at concentrations of 0.1 mg/m^3 or higher. The factor contributing to lower bound estimation, α_2, is set to zero, but the upper bound factor, γ_2, is set equal to 0.8.
3. The measurements of concentration, even when they were performed are not terribly extensive, though they apparently covered the areas and jobs expected to entail chromium exposure. A value of 0.2 is assigned to α_3 and γ_3.
4. No average chromium concentrations for various departments are given. Nor is there information on how many men worked at each

job. Either piece of information would have aided in the calculation of average cumulative exposure. In general, the range of concentration values is not too great, so the uncertainty is not so drastic here, perhaps. A value of 0.1 is assumed for α_4 and γ_4.

5. Some recording bias is introduced by classifying cohort members by the department they worked in for the longest time. Some nominally unexposed persons may have spent some time in the ferrochromium department, and ferrochromium workers may have spent a considerable amount of time in jobs entailing no chromium exposure. The factors α_5 and γ_5 have been set to 0.5.
6. Total chromium concentrations were converted to chromate concentrations. The factor used to accomplish this, 22%, is subject to some variability (the percentages encountered ranged from 11% to 33%) and, moreover, the method may not be precise. Chromate content was based on solubility. The solubility of chromic (trivalent) as well as chromate compounds varies (124). In any case, a factor of 0.7 is assigned to α_7 and γ_7 to account for this uncertainty.
7. Expected numbers of cancers are based on national rates, known to exceed local rates for lung cancer incidence. Again, smoking status may play a role, although the cohort's smoking behavior appears not to differ from the national pattern. A factor of 0.1 is appropriate for α_8 and γ_8.

The resulting uncertainty factors, $\alpha = 4.1$ and $\gamma = 4.9$, have been used to determine bounds on cumulative exposure (Table 2-36).

The final study for which quantitative risk estimates can be derived is that of Axelsson and Rylander (142) and Axelsson *et al.* (143). The cohort under consideration consists of 1876 male workers employed at a ferrochromium plant in Sweden. The cohort members worked at least one

year between 1930 and 1975. Cancer incidence was determined from 1958 to 1975 and compared to incidence rates from the county in which the factory was located. No significant differences with respect to total or respiratory cancers were seen in the factory when compared to expected values derived from those rates.

The workers at this facility were primarily exposed to metallic and trivalent chromium, although exposures to hexavalent chromium did occur. Table 2-37 displays the concentrations at four working sites as estimated by recent measurements and interviews with retired workers and foremen employed in the 1930's. It should be noted that asbestos-containing materials (textiles, plates, asbestos-isolated tubes) were used in the plant. From 1931 to 1940 2100 kg of asbestos per year were used; from 1941-1950 650 kg/yr were used. Workers were classified according to the working site at which they spent the majority of their time. They were also classified by length of employment, but unfortunately no cross-classification by length and working site is provided. Hence, it is necessary to estimate an average duration of employment for the entire cohort as opposed to working site-specific durations. A total of 768 men worked 1 to 5 years (assumed average, 3 years) 538 worked 5 to 15 years (assumed average, 10 years), and 517 worked more than 15 years (assumed average, 25 years). The estimated average duration of exposure is

$$\frac{(768 \cdot 3) + (538 \cdot 10) + (517 \cdot 25)}{1823} = 11.3 \text{ years.}$$

The cumulative exposure estimates based on the hexavalent chromium concentrations displayed in Table 2-37 (using 0.03 mg/m^3 for the transport, metal grinding, and sampling site) and a duration of 11.3 years are shown in Table 2-38. Also shown are the total malignancy and respiratory cancer responses observed and expected. Two of the respiratory cancers among the maintenance workers and one among the arc-furnace

workers were due to pleural mesothelioma and hence may be attributed to asbestos exposure. This observation strengthens the conclusion of the original authors that exposure to chromium was not related to respiratory cancer at this factory.

Also displayed in Table 2-38 are the bounds on cumulative exposure to hexavalent chromium. The uncertainty factors used to derive those bounds are based on the following features of the study:

1. Although length of employment intervals of reasonable size are presented, these had to be used for all four job categories, even though employment histories may well differ for different jobs. Both α_1 and γ_1 have been set equal to 0.3.
2. No hygiene data were available from the period when the observed cancers would have been induced. The original authors state that conditions have improved considerably over the past ten years (since 1970) and they warn against using the exposure data to derive dose-response relationships. We have done so despite their warning, but reflect the uncertainty in this regard by setting α_2 equal to 0.2 and γ_2 equal to 0.8. Since general approximations to exposures were presented, it is possible that they were overestimated (bearing on α_2) but more likely that they were underestimated and, hence, the wider bound above the best estimate relative to that below.
3. The number of measurements forming the basis of the exposure estimates is not documented. In addition, it appears that exposure to hexavalent chromium also occurred in a chromate reduction process not accounted for in the job categories given. No exposure estimates for that process were available. To account for both of these factors, $\alpha_3 = 0.3$ and $\gamma_3 = 0.5$. The factor γ_3 is larger because the lack of exposure estimates for the reduction process, where some employees may have

worked, means that potential exposures are not accounted for.

4. Some recording bias is present in the format of the categorization. Exposure at jobs other than that defining the category is ignored. This could entail either greater or lesser cumulative exposures in the transport and maintenance categories, only lesser cumulative exposure for arc-furnace workers, and only greater cumulative exposure for office and storage area workers. For the latter group, an arbitrary upper bound has been selected to reflect this feature, 0.01 mg-yrs/m^3. For the other categories, this uncertainty is reflected as follows:

Arc-furnace workers:	$\alpha_5 = 0.2$, $\gamma_5 = 0$;
Transport, metal grinder, sampling:	$\alpha_5 = 0.1$, $\gamma_5 = 0.2$;
Maintenance:	$\alpha_5 = 0.2$, $\gamma_5 = 0.1$.

5. The report by Axelsson *et al.* appears to indicate that area samples are the basis of exposure estimates. This uncertainty with respect to the applicability of the estimate is consistent with α_6 and γ_6 equal to 0.2.

6. Although local, county incidence rates were used to calculate expected numbers of cancers, it was not possible to account for other chemical exposures, the most important of which was asbestos exposure, nor for smoking habits. The asbestos exposure is crucial given the observation of 3 mesotheliomas. The extent of the influence of asbestos exposure on the development of lung cancer in the cohort members is not known. In accordance with this uncertainty, and that introduced by unknown smoking behavior of the cohort, α_8 and γ_8 have been assigned a value of 0.5.

In this case, the uncertainty factors α and γ are group dependent. The values entailed by the discussion above are:

Arc-furnaces:	$\alpha = 2.7$, $\gamma = 3.3$;
Transport, metal grinder, sampling:	$\alpha = 2.6$, $\gamma = 3.5$;
Maintenance:	$\alpha = 2.7$, $\gamma = 3.4$.

The potency parameteres calculated from the data in the three studies are displayed in Table 2-39. The parameters pertain to several end-points, ranging from respiratory morbidity to mortality from all malignancies. The morbidity results (143) should be viewed with the greatest skepticism since asbestos exposure may have played an important role in the observed responses and, moreover, the model fails to fit the respiratory cancer data. Nevertheless, the RRD estimates corresponding to the potencies displayed have been calculated and are presented in Table 2-40.

Table 2-34

XPOSURE IN DIFFERENT WORK
LANGARD AND NORSETH (139)

ation	Mean Chromate Concentration (mg/m^3)
.ling	0.43
. raw materials	0.35
an (all departments)	0.19
ack filling	1.35
ixing raw materials	0.33
oreman	0.04
Sack filling	0.08
Mixing raw materials	0.01

Table 2-35

TOTAL CHROMIUM CONCENTRATIONS IN DIFFERENT
DEPARTMENTS; LANGARD ET AL. (141)[a]

nt/Operation	Number of Samples	Mean Chromium Concentration (mg/m^3)
chromium department		
otmen	20	0.04
Cleaner baler	5	0.09
Crane driver	10	0.04
Packing	10	0.29
Maintenance people		
General maintenance	9	0.09
Transport men	9	0.01
Other	--	0

[a]Only personal samples are reported. Departments other than maintenance and ferrochromium are assumed to have no atmospheric chromium, as indicated by the authors.

Table 2-36

DOSE AND RESPONSE DATA FROM CHROMATE-EXPOSED COHORT OF LANGARD *ET AL.* (140)

Exposure Group	All Malignant Neoplasms		Lung Cancers	
	Observed	Expected	Observed	Expected
Nonferrochromium workers (0.0066, 0.027, 0.13)[a]	41	55.95	2	6.35
Ferrochromium workers (0.061, 0.25, 1.22)	23	23.49	7	3.10

[a]In parentheses are the lower bounds, best estimates, and upper bounds, respectively, for average chromate exposure in each group, expressed as mg-yrs/m^3.

Table 2-37

ESTIMATED CONCENTRATIONS OF CHROMIUM BY WORKING SITE; AXELSSON *ET AL.* (143)

Working Site	Concentrations (mg/m^3)	
	Cr^0+Cr^{3+}	Cr^{6+}
Arc-furnaces	2.5	0.25
Transport, metal grinder, sampling	0.5 - 2.5	0.01 - 0.05
Maintenance	2.5	0.05
Office, storage area	0	0

Table 2-38

DOSE AND RESPONSE DATA FOR CHROMIUM-EXPOSED COHORT OF AXELSSON *ET AL.* (143)

Exposure Group	All Malignant Neoplasms		Respiratory Cancer	
	Observed	Expected	Observed	Expected
Arc-furnaces (1.04, 2.82, 9.31)[a]	31	30.8	2	2.1
Transport, metal grinder, sampling (0.13, 0.34, 1.19)	26	30.0	0	2.1
Maintenance (0.21, 0.56, 1.90)	19	15.6	4	1.0
Office, storage area (0, 0, 0.01)	11	9.5	1	0.7

[a]In parentheses are the lower bounds, best estimates, and upper bounds, respectively, for cumulative exposure to hexavalent chromium (mg-yrs/m^3) in each group.

Table 2-39

POTENCY PARAMETER ESTIMATES FOR CHROMIUM

Study	Response	Dose Measure	Potencies ((mg-yrs/m^3)$^{-1}$) Lower Limit[a]	MLE	Upper Limit[a]
Langard and Vigander (140)	Lung Cancer Mortality (0 degrees of freedom)	Upper Bounds	2.73*	4.93	8.04
		Best Estimates	6.68	1.21E+1*	1.97E+1
		Lower Bounds	1.30E+1	2.35E+1	3.83E+1*
	GI Cancer Mortality (0 degrees of freedom)	Upper Bounds	1.98E-1*	6.10E-1	1.29
		Best Estimates	4.85E-1	1.50*	3.15
		Lower Bounds	9.44E-1	2.91	6.13*
Langard *et al.* (141)	Lung Cancer Mortality (chi-squared (1) = 3.7)	Upper Bounds	1.28E-1*	7.82E-1	1.68
		Best Estimates	6.16E-1	3.80*	8.18
		Lower Bounds	2.52	1.56E+1	3.35E+1*
	All Malignancies Mortality (chi-squared (1) = 4.0)	Upper Bounds	-2.58E-1*	0.00	1.62E-1
		Best Estimates	-1.26	0.00*	7.90E-1
		Lower Bounds	-5.17	0.00	3.23*

Table 2-39 (continued)

POTENCY PARAMETER ESTIMATES FOR CHROMIUM

Study	Response	Dose Measure	Potencies ((mg-yrs/m^3)$^{-1}$) Lower Limit[a]	MLE	Upper Limit[a]
Axelsson *et al.* (143)	Respiratory Cancer Morbidity (chi-squared (3) = 11.0)	Upper Bounds	-8.43E-2*	1.35E-2	1.47E-1
		Best Estimates	-2.13E-1	4.46E-2*	1.47E-1
		Lower Bounds	-5.76E-1	1.21E-1	1.31*
	All Malignancies Morbidity (chi-squared (3) = 1.5)	Upper Bounds	-2.15E-2*	1.30E-3	2.76E-2
		Best Estimates	-7.09E-2	4.39E-3*	9.15E-2
		Lower Bounds	-1.92E-2	1.17E-2	2.48E-1*

[a]90% confidence limits shown.
*An asterisk marks the parameters used to derive RRD estimates.

Table 2-40

RRD ESTIMATES FOR CHROMIUM (mg/m^3)

Study	Response	Estimation Method	Level of Extra Risk: 10^{-6} RRD_L	10^{-6} MLE	10^{-6} RRD_u	0.25 RRD_L	0.25 MLE	0.25 RRD_u
Langard and Vigander (142)	All Malignant Neoplasms	1	7.63E-9	2.42E-8	1.07E-7	1.91E-3	6.06E-3	2.68E-2
		2	8.73E-9	2.77E-8	1.23E-7	2.70E-3	8.57E-3	3.79E-2
	GI Cancer Mortality	1	5.95E-8	2.44E-7	1.84E-6	1.49E-2	6.09E-2	4.60E-1
		2	6.71E-8	2.75E-7	2.08E-6	2.19E-2	8.96E-2	6.77E-1
Langard et al. (141)	Lung Cancer Mortality	1	8.73E-9	7.69E-8	2.29E-6	2.18E-3	1.92E-2	5.71E-1
		2	9.99E-9	8.81E-8	2.62E-6	3.09E-3	2.72E-2	8.08E-1
	All Malignancies Mortality	1	2.43E-8	∞	∞	6.09E-3	∞	∞
		2	3.20E-8	∞	∞	1.03E-2	∞	∞
Axelsson et al. (143)	Respiratory Cancer Morbidity	1	1.78E-7	5.20E-6	∞	4.44E-2	1.30	∞
		2	2.08E-7	6.08E-6	∞	6.36E-2	1.86	∞
	All Malignancies Morbidity	1	1.52E-7	8.57E-6	∞	3.80E-2	2.14	∞
		2	2.32E-7	1.31E-5	∞	7.30E-2	4.12	∞

Cigarette Smoke

Cigarette smoke is probably the most widely studied cause of cancer. The smoke is a heterogeneous mixture of many chemicals several of which are carcinogens themselves. The constituents include nitrosamines, hydrocarbons, formaldehyde, acrylonitrile, benzene, naphthylamine, PAH's and various other particulate substances (144). Cigarette smoke is firmly linked to lung cancer and there are very strong indications that it is associated with cancer of the larnyx, oral cavity, kidney, pancreas, and bladder (145).

The epidemiologic literature on cigarette smoke is extensive and will not be reviewed here. The Surgeon General's reports (cf. 144) provide extensive references to the studies that have been conducted. The remainder of this section is devoted to the development of quantitative risk estimates for cigarette smoke.

The estimates are developed in terms of whole cigarette smoke, gas and particulate phases together, with no reference to particular subfractions. The 1979 Surgeon General's report (144) lists the components of cigarette smoke and provides an overall estimate of the weight of those components that are in the mainstream smoke. The total weight of smoke from one cigarette is about 500 mg. Conversions to weight-based measurements of consumption are based on this value.

Doll and Peto (146, 147) have reported on a study involving 34,400 British doctors who responded in 1951 to a questionnarie about their smoking habits. Most of these were subsequently followed for 20 years and causes of death for 10,072 decendents were recorded. Changes in smoking habits were ascertained in follow-up questionnaries collected during the seventh and fifteenth years of the study.

The authors concluded that cancers of the lung, esophagus, and other respiratory sites (lip, tongue, mouth, pharnyx excluding nasopharynx, larynx, and trachea) could be directly attributed to cigarette smoking. Although cancers of the rectum and pancreas occurred at significantly higher rates in smokers, the authors did not consider these to be related to smoking. Also, even though cancer of the bladder was not found to be increased in this study, because cigarettes have been implicated as the cause of bladder cancer in other studies, the authors considered bladder cancer "probably wholly or partly attributable to smoking."

Since cigarette smoking is so pervasive, our standard approach of estimating a potency for a chemical in terms of a relative risk and applying this to standard mortality rates could lead to serious errors; the "background" rates, as given in vital statistics, include smokers and nonsmokers and so do not represent mortality among the unexposed. Consequently, specialized methods must be applied to estimate RRDs for cigarette smoke. Doll and Peto (147) estimated that among smokers who started smoking at ages 16 to 25 and who smoked 40 or less cigarettes per day the annual lung cancer incidence* in the age range 40-79 was

$$0.273\times10^{-12}\cdot(\text{cigarettes/day} + 6)\cdot(\text{age} - 22.5)^{4.5}. \qquad (2\text{-}5)$$

This equation is intended to apply to smokers who, once they begin smoking, smoke a constant amount daily throughout life. Assuming that the period from diagnosis until death for lung cancer is roughly 2 years, this expression for incidence can be converted to one for mortality by replacing the 22.5 by 24.5.

*Age of onset of lung cancer was estimated for the subcohort used in this analysis, thereby allowing the estimation of incidence rates as opposed to mortality rates.

Table 2-41 gives age-dependent death rates for lung cancer for non-smokers and for smokers of 20 cigarettes (one pack) per day derived from the above equation. (Although Doll and Peto caution against using the equation for cancer rates in non-smokers, it is considered accurate enough for our purposes because lung cancer risk in non-smokers is only a small fraction of that in smokers anyway.) Table 2-41 also contains *age-dependent death rates for all causes for both smokers and non-smokers* obtained from Table XIII of Doll and Peto (146).

Applying a life table analysis (for example, Crump and Allen, 148, page 444) to the nonsmoker data in Table 2-41, the lifetime risk of lung cancer is estimated to be 0.0086. Applying this method of analysis to the data for smokers yields a lifetime risk of lung cancer of 0.0933. The extra risk of lung cancer in smokers who smoke 20 cigarettes per day is therefore estimated to be (0.0933 - 0.0086)/(1-.0086) = 0.085.

Doll and Peto (146, Table IV) estimated that the increased annual death rate (standardized for age) from cancer of the esophagus and other respiratory sites is 11 + 12 = 23, versus a corresponding increase of 130 for lung cancer. Therefore, the extra risk of total cancer is estimated by multiplying the extra risk of 0.085 for lung cancer by the ratio (130 + 23)/130 = 1.18. This results in an estimated extra risk of all cancer from 20 cigarettes per day of (0.085)(1.18) = 0.10.

The best estimate of the RRD corresponding to an extra risk of 0.25 for lung cancer is therefore

(20 cigarettes/day/0.085)(0.25) = 59 cigerettes per day.

The corresponding value for total cancer is 50 cigarettes per day. Since the temporal dose pattern to which equation (2-5) applies (lifetime constant exposure beginning at age 16 - 25) closely approxi-

mates the default pattern to which all risk estimates are adjusted (45 years beginning at age 20), no adjustments to the estimates are required; they represent our best estimates of RRDs.

Uncertainty considerations are based on the discussion in the methods portion of this section, as described below:

1. As with other studies relying on questionnaries and recall of habits, uncertainty arises with respect to length of exposure and exposure in the less recent past. With cigarette smoking, this may not be as significant a problem, but $\alpha_1 = \gamma_1 = 0.3$ and $\alpha_2 = \gamma_2 = 0.2$.
2. Some recording bias is introduced by not adjusting smoking habit categorization based on data obtained in later questionnaires. This should not be a serious confounder, though, so α_5 and γ_5 have been assigned a value of 0.1.
3. In converting from number of cigarettes to weight of cigarette smoke, some uncertainty is introduced. The conversion factor, 500 mg smoke per cigarette, is based on standard cigarettes smoked to standard butt lengths. Actual smoking habits undoubtedly vary, so the factors α_7 and γ_7 have been set equal to 0.2.
4. In the place of expected numbers of deaths, we have estimated annual mortality rates for nonsmokers. This is based on the equation that Doll and Peto explicitly warn against using for nonsmokers. Consequently, α_8 and γ_8 have been set equal to 0.5.

Another uncertainty not fitting into the standard categories discussed above involves the indirect estimation of increased risk for all malignant neoplasms. A factor of 0.2 is added to the total of the uncertainty subfactors mentioned above. Hence, α and γ equal 2.3 for lung cancer; they equal 2.5 for all malignant neoplasms.

The RRD estimates and their bounds derived from the Doll and Peto study are given in Table 2-42.

Table 2-41

ANNUAL DEATH RATES PER 100,000 AMONG BRITISH PHYSICIANS

Age	Nonsmokers		Smokers	
	Total[a]	Lung Cancer[b]	Total[c]	Lung Cancer[d]
	I	II	III	IV
35-39	132	0.101	196	1.90
40-44	151	0.438	326	8.22
45-49	221	1.32	574	24.8
50-54	540	3.20	1090	60.0
55-59	844	6.70	1679	125.7
60-64	1431	12.6	2767	237.2
65-69	2081	22.0	4573	413.7
70-74	4236	36.1	6642	678.7
75-79	7529	56.5	9636	1060.0
80-84	9071	84.7	14261	1590.5

[a]From Doll and Peto (146), Table 13.
[b]From Doll and Peto (147), using 24.5 in their equation for incidence rather than 22.5 in order to convert from incidence to mortality (assuming an average delay of 2 years between diagnosis of lung cancer and death) and assuming no cigarettes smoked.
[c]From Doll and Peto (145), Table 13.
[d]From Doll and Peto (146), using 24.5 in their equation for incidence rather than 22.5 in order to convert from incidence to mortality (assuming an average delay of 2 years between diagnosis of lung cancer and death) and assuming an average of 20 cigarettes smoked per day.

Table 2-42

RRD ESTIMATES[a] FOR CIGARETTE SMOKE (mg/day)

	Level of Extra Risk					
	10^{-6}			0.25		
Response	RRD_l	MLE	RRD_u	RRD_l	MLE	RRD_u
Lung Cancer Mortality	5.12E-2	1.18E-1	2.71E-1	1.28E+4	2.95E+4	6.78E+4
All Malignancies Mortality	4.00E-2	1.00E-1	2.50E-1	1.00E+4	2.50E+4	6.25E+4

[a]Based on the data in Doll and Peto (146).

DES

The synthetic estrogen diethylstilbestrol (DES) is one of several estrogens that were commonly prescribed, in the period 1940 to 1960, to women who were threatening to abort, had a history of prior pregnancy loss, or had other complications (149). In fact, in the mid-1940's, it was suggested that increasing amounts of DES be administered to all women during pregnancy to decrease hazards of late complications for both mothers and babies. As early as 1953, however, some indications that DES may not, in fact, have therapeutic value were published (150). More recently, of course, reports of the health hazards of intrauterine DES exposure have proliferated.

Short-term tests are negative or equivocal. DES did not elicit unscheduled DNA synthesis in mammalian cells, nor did it induce mutations in bacterial systems; the results of chromosomal anomaly tests are equivocal for a variety of test species; but cell transformations and sperm abnormalities have been noted (2).

Several nonneoplastic abnormalities of the genito-urinary tract in humans are reportedly linked to intrauterine DES exposure (151). In females these include vaginal adenosis, cervical erosions, and ridges (152). Intraepithelial glandular abnormalities are also documented (153). Male offspring of DES-treated mothers have increased incidences of anotomical and functional abnormalities, including hypotrophic testes, epididymal cysts, and pathologic semen (154, 155).

The cancer hazard of DES is more widely known. Some reports have indicated a risk to those treated with DES themselves, both male (156) and female (157), although these are not unambiguously linked to the DES exposure (158, 159). By far the clearest evidence of a carcinogenic effect of DES is provided by studies of genital cancer in female off-

spring of DES-treated mothers. Greenwald (160) and Greenwald and Nasca (161) report seven cases of vaginal adenocarcinoma from the New York State Cancer Registry; mothers of six (and possibly all seven) of the cases were treated with DES whereas no mother of any of the 12 controls was so treated. Among 830 young women in the Philadelphia area who were exposed to DES in utero, 8 adenocarcinomas were discovered (162).

Even among females exposed transplacentally to DES, for whom an excess risk is not seriously questioned, the risk is apparently small. Lanier *et al.* (149) estimated the incidence of cervical or vaginal adenocarcinoma associated with in utero DES exposure to be no more than 4 per 1000 and Herbst *et al.* (163), using the Registry of Clear Cell Adenocarcinoma of the Genital Tract in Young Females (RCCAGTYF), suggest that the cumulative risk of that type of cancer in DES-exposed females is between 0.14 and 1.4 per thousand.

The previously cited reports have not been able to quantify doses of DES administered to the mothers. We have attempted to do so, and to derive RRD estimates on the basis of a series of articles by Herbst and his associates (164-166). The original case-control study identified 8 cases of vaginal adenocarcinoma and 32 individually-matched controls. A control was selected from the same hospital as her corresponding case; the controls were born within five days of their respective cases and on the same type of service. Seven of the 8 cases were exposed in utero to DES; none of the controls were exposed to DES.

Unfortunately, dosage information is not presented in the case-control study. Dosage is estimated from the other two reports. The study of adenocarcinoma cases identified in the RCCAGTYF published in 1972 provides information on dose and duration of DES exposure for 46 cases whose mothers were treated with DES (Table 2-43). Using the 32 cases with known duration of therapy, we estimate average length of exposure

to be

$$\frac{(0.5x2) + (1.5x3) + (3.5x3) + (8x24)}{32} = 6.5 \text{ months},$$

where the numbers in parentheses are the products of the midpoints of the duration categories and the number of cases in each category. We have assumed an average "throughout pregnancy" value of 8 months. Average daily dose can be similarly estimated if the "increasing" dosage is known. Herbst *et al.* (166) describe a standard, increasing treatment pattern used at the time of pregnancy of the cases' mothers in the area in which the cases were born:

> "During or before the sixth week 2.5 mg daily was given, increasing to 5 mg in the seventh week. An additional 5 mg/week administered every two weeks until the fifteenth week, when 25 mg per day was prescribed. The daily dosage was then increased by 25 mg each month reaching a maximum of 150 mg...[T]he drug was discontinued at the end of the 35th week."

This "increasing" dose pattern yields an average daily dose of

$$[(2.5x2) + (5x2) + (10x2) + (15x2) + (20x2) + (25.4) + (50x4) + (75x4) + (100x4) + (125x4) + (150x1)] / 31 = 57 \text{ mg}.$$

Here we assumed that treatment began in the 4th week of pregnancy, on average. Consequently, the average daily dose for the RCCAGTYF cases is estimated to be

$$[(5x4) + (30x11) + (100x6) + (57x9)]/30 = 49 \text{ mg}$$

where the values in parentheses are the products of the midpoints of the dosage categories (Table 2-43, assuming a value of 100 mg/day for the

">50 mg daily" group) and the number of cases in those groups. A cumulative dose estimate to be used in the case-control study is

$$(6.5 \text{ months}) \times (49 \text{ mg/day}) = 318.5 \text{ mg-months} = 26.5 \text{ mg-years}.$$

The dose and response data are combined in Table 2-44.

The bounds on dose displayed in Table 2-44 are based on the following considerations:

1. Length of exposure is very roughly estimated from groups presented without average values. Consequently, α_1 and γ_1 are set equal to 0.2.
2. Similarly, dose groups are presented without averages and they too had to be combined. Hence, α_4 and γ_4 are assumed to be 0.3.
3. Some recording bias is introduced by categorizing dose and duration separately rather than a cross-classification, for example. In this case, α_5 and γ_5 have been assigned a value of 0.2
4. Neither dose nor duration estimates came from the exposed individuals in the case-control study. Instead, other exposed females, largely from the same geographical area and exposed at the same time, were used to estimate these parameters. The question of the applicability of these values leads to estimates of α_6 and γ_6 of 0.3.

The resulting uncertainty factors are $\alpha = \gamma = 2.0$.

The potency parameter estimates shown in Table 2-45 display a great deal of variability. This is due to the small size of the study and to the fact that no control individuals were exposed to DES. Even greater

variability is displayed in the RRD estimates (Table 2-46). It should be noted that the RRD estimate pertains to 45 years of DES use, much longer than the actual period of exposure, nine months or less.

Table 2-43

DOSAGE AND DURATION OF STILBESTROL THERAPY; HERBST *ET AL.* (165)

Dosage	Number of Cases	Duration	Number of Cases
≤ 10 mg daily	4	< 1 month	2
10 - 50 mg daily	11	1 - 2 months	3
> 50 mg daily	6	2.1 - 5 months	3
"increasing"	9	"throughout pregnancy"	24
unknown	16	unknown	14

Table 2-44

DOSE AND RESPONSE DATA FOR CASE-CONTROL STUDY OF HERBST *ET AL.* (164)

Cumulative Exposure (mg-years)	Cases[a]	Controls
0	1	32
26.5 (13.3, 53.0)[b]	7	0

[a]The cases are adenocarcinomas of the vagina.
[b]In parentheses are the lower bound and upper bound for dose estimated for the DES-exposed individuals.

Table 2-45

VAGINAL CANCER POTENCY PARAMETER ESTIMATES FOR DES, FROM DATA IN HERBST *ET AL.* (164)

Dose Measure	Potencies ((mg-yrs)$^{-1}$) Lower Limit[a]	MLE	Upper Limit[a]
Upper Bounds	4.34*	6.79E+1	1.09E+16
Best Estimates	8.68	1.36E+2*	2.17E+16
Lower Bounds	1.73E+1	2.71E+2	4.33E+16*

[a]90% confidence limits are shown.
*An asterisk marks the parameters used to derive RRD estimates.

Table 2-46

RRD ESTIMATES[a] FOR DES (mg/day)

Estimation Method	Level of Extra Risk 10^{-6} RRD_l	MLE	RRD_u	0.25 RRD_l	MLE	RRD_u
1	6.28E-22	2.00E-7	6.23E-6	1.57E-16	5.01E-2	1.57
2	6.99E-22	2.22E-7	6.98E-6	2.13E-16	6.79E-2	2.12

[a]Based on the risk of vaginal cancer and the data in Herbst *et al.* (164).

Epichlorohydrin

The alkylating agent epichlorohydrin (CAS No. 106-89-8) is used in the manufacture of glycerine and epoxide resins and in several other manufacturing settings. Acute reactions to epichlorohydrin in humans have included skin burns, eye and throat irritation, and EEG changes (167). Short-term testing, as with many alkylating agents, revealed positive results with respect to DNA damage, mutagenicity, and chromosomal anomalies in bacteria, plants, insects, and mammalian species. Indications of chromosomal abnormalities in epichlorohydrin-exposed workers have been noted (2).

The epidemiologic data are scanty and are ambiguous with respect to the carcinogenicity of epichlorohydrin in humans. Studies of three occupational cohorts are available. The first set of studies investiaged workers at Shell Oil (cf. 168, 169). There seems to be some increase in lung cancer risk in the cohort, but it appears to be among those exposed to isopropyl alcohol in addition to epichlorohydrin. In any case, no estimates of atmospheric concentrations of either chemical were available.

Shellenberger *et al.* (170) evaluated the mortality experience of epichlorohydrin-exposed workers for Dow Chemical. Members of this cohort, which included 553 individuals, could have been exposed to epichlorohydrin as early as 1957, when production began. Each member had at least one month of exposure at some time between 1957 and 1976, at which time follow-up ceased. Two cancer deaths -- an adenocarcinoma of the stomach and a metastatic malignant melanoma -- are reported.

Exposure measurements for epichlorohydrin were available only since the early 1970's. Other sources, however, have allowed Shellenberger *et al.* to estimate exposures for the glycerine and epoxy resin departments.

deaths, four neoplasms.

Exposure estimates, once again, were available only late in the exposure period, 1977-1978. The personal exposure measurement obtained at that time averaged less than 1 ppm. It is known, however, that conditions were worse during the earlier time periods, with epichlorohydrin concentrations reaching peaks of 10-25 ppm. Nevertheless, we have selected 1 ppm as an assumed average exposure level. It should be noted that many cohort members were exposed to a number of other chemicals, particularly allyl chloride.

Duration of exposure is documented in Table 2-49. Length of exposure for the entire cohort averaged 9.3 years. Combining categories to get the "10 or fewer years of exposure" and "more than 10 years of exposure" groups (the groups for which we have observed and expected cancer mortality) yields average duration estimates of

$$\frac{(2.5 \times 190) + (7.5 \times 142)}{332} = 4.6 \text{ years}$$

and

$$\frac{(12.5 \times 141) + (17.5 \times 110) + (25 \times 23)}{274} = 15.6 \text{ years,}$$

respectively. These estimates use the midpoints of each duration category (assuming a maximum of 30 for the last duration group) and yield an average for the entire cohort of 9.6, fairly good agreement with the stated value of 9.3.

The cumulative exposure groups defined by the assumed average concentration of epichlorohydrin (1 ppm) and durations of exposure are displayed in Table 2-50 along with the numbers of observed and expected responses.

The bounds on dose (cf. Table 2-50) are derived on the basis of these considerations:

1. Although duration of exposure is categorized without averages for the categories, the overall average of 9.3 years gives us guidance on the accuracy of our approximations. Since the latter yield an average duration of 9.6 years, the factor for the lower bound ought to be somewhat larger than that for the upper bound. Hence, $\alpha_1 = 0.2$ and $\gamma_1 = 0.1$.
2. The most serious uncertainty involves exposures early in the exposure period. Since those were undoubtedly larger than the assumed 1 ppm average, $\gamma_2 = 0.8$ but $\alpha_2 = 0$.
3. The exposure estimates presented came from a survey of European facilities, not limited to the four plants included in the present study. Hence, $\alpha_3 = \gamma_3 = 0.3$ to cover uncertainty with respect to completeness of measurements and $\alpha_6 = \gamma_6 = 0.3$ to account for uncertainty pertinent to questions of applicability of those values to these four plants.
4. Some small amount of uncertainty is associated with the expected values presented. Not only are national rates used for control purposes, but other exposures (e.g. allyl chloride, a suspected carcinogen) affect the probability of carcinogenic response. Consequently, α_8 and γ_8 have been set equal to 0.1.

The uncertainty factors based on the foregoing discussion are $\alpha = 1.9$ and $\gamma = 2.6$.

The potency parameters from these studies are displayed in Table 2-51. Neither study supports the notion that epichlorohydrin is carcinogenic in humans, so the MLE estimates of potency are zero. In other words, the best estimate of RRD is infinite although finite lower limits are obtained (Table 2-52).

Table 2-47

DURATION OF EXPOSURE TO EPICHLOROHYDRIN FOR THE COHORT STUDIES BY SHELLENBERGER *ET AL.*

Months Exposed	Percent of Employees
1 - 6	30.7
7 - 12	13.2
13 - 18	8.6
19 - 24	6.2
25 - 36	8.7
37 - 48	9.6
49 - 60	4.3
61 - 120	12.0
121 - 180	4.3
181+	2.4

Table 2-48

DOSE AND RESPONSE DATA FOR EPICHLOROHYDRIN-EXPOSED COHORT OF SHELLENBERGER *ET AL.*

Cumulative Exposure (ppm-yrs)	All Malignant Neoplasms	
	Observed	Expected
0.66 (0.34, 1.35)[a]	2	1.10
3.93 (2.02, 8.06)	0	1.33
14.9 (7.64, 30.5)	0	1.07

[a]In parentheses are the lower bound and upper bound on dose for each dose group.

Table 2-49

DURATION OF EXPOSURE TO EPICHLOROHYDRIN FOR THE COHORT STUDIES BY TASSIGNON *ET AL.*

Years Exposed	Number and Percent of Employees
≤ 5	190 (31%)
5 - 10	142 (24%)
10 - 15	141 (23%)
15 - 20	110 (18%)
20+	23 (4%)

Table 2-50

DOSE AND RESPONSE DATA FOR EPICHLOROHYDRIN EXPOSED COHORT OF TASSIGNON *ET AL.*

Cumulative Exposure (ppm-yrs)	All Malignant Neoplasms	
	Observed	Expected
4.6 (2.42, 12.0)[a]	1	2.2
15.6 (8.21, 40.6)	3	2.8

[a]In parentheses are the lower bounds and upper bounds on dose for each group.

Table 2-51

EPICHLOROHYDRIN POTENCY PARAMETER ESTIMATES[a]

Study	Dose Measure	Potencies ((mg-yrs/m^3)$^{-1}$) Lower Limit[b]	MLE	Upper Limit[b]
Shellenberger *et al.* (170) (chi-squared (2) = 3.14)	Upper Bounds	-6.49E-1*	0.00	1.95E-2
	Best Estimates	-1.33	0.00*	3.99E-2
	Lower Bounds	-2.58	0.00	7.77E-2*
Tassignon *et al.* (171) (chi-squared (1) = 0.67)	Upper Bounds	-1.45E-2*	0.00	2.03E-2
	Best Estimates	-3.77E-2	0.00*	5.28E-2
	Lower Bounds	-7.16E-2	0.00	1.00E-1*

[a]Based on all malignant neoplasms.
[b]90% confidence limits are shown.
*An asterisk marks the parameters used to derive RRD estimates.

Table 2-52

RRD ESTIMATES[a] FOR EPICHLOROHYDRIN (ppm)

Study	Estimation Method	Level of Extra Risk 10^{-6} RRD$_l$	MLE	RRD$_u$	0.25 RRD$_l$	MLE	RRD$_u$
Shellenberger *et al.* (170)	1	1.01E-6	∞	∞	2.53E-1	∞	∞
	2	1.33E-6	∞	∞	4.27E-1	∞	∞
Tassignon *et al.* (171)	1	7.84E-7	∞	∞	1.96E-1	∞	∞
	2	1.03E-6	∞	∞	3.30E-1	∞	∞

[a]Based on the risk of all malignant neoplasms.

Estrogens

Various forms of estrogenic substances have been used in humans to treat reproductive disorders and as palliative therapy for disseminated carcinoma (172). Conjugated, or natural, estrogens have been used recently to treat menopausal symptoms. The conjugated estrogens have been reported to be nonmutagenic in bacteria and did not induce chromosomal aberrations in mammalian cells *in vitro* (2). It is suspected that exogenous estrogens act by enhancing the effect or altering the balance of endogenous hormones. There have been suggestions that exogenous estrogens are linked to breast, endometrial, and cervical cancer and possibly to malignant melanoma (172). The studies used to calculate RRDs for estrogens have examined breast and endometrial cancer endpoints.

Hoover *et al.* (173) reviewed the records of 1891 white women who were treated with conjugated estrogens and who were seen at one private practice since 1939. Their vital status was ascertained through 1972. Forty-nine breast cancer cases were observed; 39.1 were expected. Unfortunately, the published report does not make available data necessary for calculation of cumulative dose.

A case-control study of menopausal estrogen therapy and breast cancer was conducted by Ross *et al.* (174). The cases (and the matched controls) were from two retirement communities and were 50 to 74 years of age at diagnosis. Estrogen-usage histories were obtained from interviews, medical charts, and pharmacy records. The total accumulated doses of conjugated estrogens for the cases and controls are displayed in Table 2-53. A significant trend for risk ratio with total dose is evident for women with ovaries intact but not for women whose ovaries have been removed.

Horwitz and Stewart (175) present an interesting case-control investigation of estrogen and breast cancer. These authors conclude that breast cancer risk is not increased by exogenous estrogen use. No exposure measures are given however. Moreover, this study investigates the dependence of the risk ratios on the methods employed to select cases and controls. It is the contention of these authors that heterogeneity of the patient subgroups and "inattention to recording bias" in exposure classification have led to inappropriate conclusions concerning the association of estrogens and breast cancer. These concerns may not be pertinent to the study conducted by Ross *et al.* (174) since community rather than hospital controls were used and interviews formed at least part of the basis for exposure classification. The uncertainties that do affect the Ross *et al.* study entail uncertainty factors, α and γ, equal to 1.65, as discussed below:

1. Recall difficulties contribute to uncertainty about the length of estrogen use and about the dosage taken early in the period of use. These factors are mitigated by the use of medical charts and pharmacy records, so α_1, γ_1, α_2, and γ_2 have been set equal to 0.05.
2. No average doses are given for the dose groups. Since we had to approximate these by the midpoints of the group-defining intervals, α_4 and γ_4 are assigned the value 0.3.
3. Some of the estrogenic substances used by the study participants were not conjugated estrogens. Consequently, there is some question about the applicability of the reported doses and α_6 and γ_6 are assumed to be 0.2.
4. The control series appears to be well matched to the cases, so a small value, 0.05, is assigned to α_8 and γ_8.

The possible link between exogenous estrogen use and endometrial cancer has been extensively studied. Smith *et al.* (176) first suggested a

causal association; they conclude that risk of endometrial cancer was "on the order of 5" times greater among users of exogenous estrogens. Dosages, durations of use, and types of estrogen were not considered and the risk varied with other factors, notably obesity and hypertension.

Mack *et al.* (177) performed a case-control study of a Los Angeles retirement community. Sixty-three endometrial cancer cases and 252 matched controls were included. An overall risk ratio of 5.6 (95% confidence interval 2.8 to 11.1) was associated with conjugated estrogen use. Moreover, a trend was observed of increasing relative risk with increasing duration or dose of estrogen (Table 2-54). The dose recorded is mean "size of pill" not mean daily dose. Data presented in Table 2-55 allows us to modify these pill sizes to estimate daily dose. For example, in the group with mean pill size of less than 0.625 mg (assumed average 0.3 mg) 32% of the women had 0-1 drug-free days per month (cases and controls combined), 43% had 2-3 drug-free days, and 25% had four or more. If we use midpoints of the drug-free intervals as estimates of average drugless days (using 10 days for the "4+" category), the average daily dose is computed by

$$0.3[0.32(29.5/30) + 0.43(27.5/30) + 0.25(20/30)] = 0.26 \text{ mg}.$$

Cross-referencing this with duration of use allows calculation of total dose. All the values of total dose are displayed in Table 2-56. [The durations of use are assumed to be the midpoints of the given intervals and 144 months in the longest use group.]

The uncertainty factors determining the bounds on dose displayed in Table 2-56 are derived as follows:

1. Medical charts and pharmacy records were used to document estrogen use. However, the duration used was the minimum

determined from the various sources. Also, duration was grouped, without average values. A value of 0.2 is assigned to α_1 and 0.3 to γ_1.

2. Recall of early estrogen use is augmented by the medical and pharmacy records. Since some use may be ignored (see 1. above) it is somewhat more likely that early estrogen exposure is underestimated. We assume a value of 0.05 for α_2 and a value of 0.1 for γ_2.
3. No average values are given for the "pill size" categories. Hence α_4 and γ_4 are given a value of 0.2.
4. It has been necessary to use the information on drug-free intervals to convert to daily dose. The uncertainty introduced is consistent with a value of 0.2 for α_7 and γ_7.
5. Once again, well-matched controls introduce little uncertainty with respect to "expected numbers." Both α_8 and γ_8 are assumed to be 0.05.

The sum of these considerations entails the uncertainty factors $\alpha = 1.7$ and $\gamma = 1.85$.

Another case-control study is described by McDonald *et al.* (178). Cases were selected from residents of Olmsted County, Minnesota who had pathologically-confirmed diagnoses of endometrial carcinoma between 1945 and 1974. A total of 145 such cases were found. Four controls were age-matched to each case. The controls were also residents of Olmsted County, had intact uteri at the time of diagnosis of the case, and had duration of medical care approximating that of the case. Sixteen cases and sixteen controls had a history of exposure to conjugated estrogens for 6 months or more (cf. Table 2-57). Note that duration of exposure did not differ substantially among the cases and controls who used the medication for longer than six months. For those 32 individuals, an estimate of average length of use is 3.55 years (using the midpoints of

the intervals in Table 2-57 and 6 years for the "3+" group). Assuming that this estimate can be applied to each daily dose group, estimates of total dose can be calculated (Table 2-58). We have not included those who used conjugated estrogens for less than 6 months. Note also that the "daily dose" given may in fact be "pill size" (see discussion of the Mack *et al.* report) (177), though this is not certain. We have not been able to correct for this explicitly since the definitions of "intermittent" and "cyclic" are not given. The control group, however, contained more individuals on less than continuous regimens, so the effective doses in that group may have been smaller than indicated.

The uncertainty considerations are as follows:

1. Length of estrogen use and the dose pattern were determined from records of the Mayo Clinic. Some patients did not have complete records at that institution. In addition, duration categories are presented without average values. Consequently, $\alpha_1 = 0.2$, $\gamma_1 = 0.3$, $\alpha_2 = 0$ and $\gamma_2 = 0.2$. The subfactors contributing to the upper bound are larger because of the possible underestimation of duration and early dosing for patients with incomplete records.
2. A possible recording bias is present since duration and dose are not cross-classified. Hence both α_5 and γ_5 have been assigned a value of 0.2.
3. Since it is not certain whether the dosages listed are pill size or daily doses, α_6 and γ_6, pertaining to the applicability of the reported values, have been set equal to 0.3.
4. A well-matched control series entails little uncertainty; both α_8 and γ_8 equal 0.05.

The resulting uncertainty factors are $\alpha = 1.75$ and $\gamma = 1.95$.

Quantitative estimation can be based on the description of a case-control study conducted by Gray *et al.* (179). The 205 endometrial carcinoma cases diagnosed at one private practice between 1947 and 1976 were matched to the same number of controls who had hysterectomy based on age, year of diagnosis (operation), parity, and weight. Estrogen use was recorded ignoring use "just prior to diagnosis to control abnormal bleeding." The distribution of cases and controls by duration of use and strength of tablet usually taken is given in Table 2-59. In this case calculation of total dose and definition of dose groups is more problematical. Durations of use are not similar among users in the case and control groups and, moreover, the data presented describes strength of estrogen usually taken. Nevertheless, if we assume an average duration of 7.6 years of daily use for all users, then dose groups can be defined as in Table 2-60. Again, it is likely that the number of controls has been artificially elevated in the higher dose groups.

Uncertainty is slightly greater in this study than in the previously discussed studies. In this case, $\alpha = 1.95$ and $\gamma = 2.15$; these factors are derived by consideration of the following features:

1. Since the records of only one private practice were accessed, it is possible that early use of estrogen is missed. Duration of use groups are again presented without average values. We assign a value of 0.2 to α_1 and a value of 0.3 to γ_1.
2. It is also possible that early estrogen use is underestimated since records from only one practice form the base of exposure data. In this case $\alpha_2 = 0$ but $\gamma_2 = 0.1$.
3. Recording biases occur in two instances. First, duration of use and dosage are not cross-classified. Moreover, the pattern of use is not the same for the cases and the controls, although they have been grouped to calculate an average duration of use. A value of 0.4 is assumed for α_5 and γ_5 to cover these possible

biases.

4. Estrogen use categories are based on the dose usually taken. The degree to which this makes the recorded values inapplicable is not known; α_6 and γ_6 are set equal to 0.3.
5. Little uncertainty is introduced by the well-matched control series. Both α_8 and γ_8 are assumed to be 0.05.

Yet another case-control study is that reported by Antunes *et al.* (180). The endometrial cancer cases were drawn from all patients with primary cancer of the uterine body admitted to six Baltimore-area hospitals between 1973 and February 28, 1977. The controls were female patients matched to the cases on hospital, race, age, and date of admission and who were not in the gynecology, obstetrics, or psychiatry departments. The distribution of cases and controls from this study is given in Table 2-61. Note how different the estrogen histories are for the two groups. In fact, they differ to such an extent that it is not possible to accurately define dose groups and no quantitative risk estimation is based on this study. Had cases and controls been simultaneously cross-classified, by dose and duration of estrogen use, the appropriate data would have been available.

Hammond *et al.* (181) provide a follow-up study of hypoestrogenic women who were either given exogenous estrogen or not. Cumulative dose of estrogen, in mg-months, is categorized for those 301 women prescribed estrogens (Table 2-62). These women were treated for at least 5 years. If a woman received the lowest daily dose reported, 0.625 mg, the minimum dose would be 37.5 mg-months. The average cumulative dose for the treated women is

$$\frac{52.6 \times 96 + 106.3 \times 86 + 300 \times 105}{287} = 159.2 \text{ mg-months}$$

where 52.6, 106.3, and 300 mg-months are the assumed average doses for

the three treated groups shown in Table 2-62. Combination of the groups is necessary because expected values are given only for the no-estrogen and estrogen-treated women as a whole. Table 2-63 displays the resultant dose and response data.

The bounds on dose in the treated group shown in that table result from the uncertainty factors, α and γ, both of which equal 1.45. This value stems from the following considerations:

1. Average values for the cumulative-dose groups are not provided. Both α_4 and γ_4 are equal to 0.3.
2. Some small amount of the estrogen taken by these women, and counted in the cumulative dose estimates, was not conjugated. A small value, 0.05, is assumed for α_6 and γ_6 to account for this uncertainty.
3. The expected number of endometrial cancers was derived from incidence data collected in the southeast region for the Third National Cancer Survey. Some uncertainty with respect to use of that data to compute expected values entails a value of 0.1 for α_8 and γ_8.

Hulka *et al.* (182) undertook a case-control study in North Carolina that utilized two control series, one drawn from hospital gynecology services and one from the community. A total of 256 invasive endometrial cancer cases were identified from 1970 through 1976. Controls, 224 from the hospital and 321 from the community, were selected to give age distributions (and year of admission distribution for hospital controls) comparable to the cases. Estrogen history was determined from interviews and physicians' records. Few nonwhite women had a history of estrogen use, whether cases or controls, and even fewer had been treated with estrogens for more than six months. Analysis was therefore restricted to white women. Among these women, relative risk of endometrial cancer was

elevated to 4.2 or 3.7 (compared to hospital or community controls, respectively) for those using conjugated estrogens for more than 3 1/2 years. Unfortunately, the data presented in this report does not allow calculation of cumulative or total doses for conjugated estrogens alone; nonconjugated estrogens were considered simultaneously when dose and duration were investigated. Hence, no quantitative estimates were computed for use in our investigation.

Shapiro *et al.* (183) conducted a case-control study of exogenous estrogen and endometrial cancer specifically designed to avoid a particular bias thought to be present in some other case-control studies. That is, if estrogens cause symptoms, mainly postmenopausal bleeding, leading to closer examination and hence diagnosis of uterine cancer that might otherwise have been overlooked, than selection of cases would be to some degree conditional on use of estrogens. Shapiro and his colleagues found that, even in women who had not been taking estrogens for a year, the risk of endometrial cancer was elevated compared to never-users when use lasted at least one year. Overall, use of conjugated estrogen entailed a significant relative risk of 3.9. No dosage information was available.

Another case-control study specifically designed to examine potential biases is that described by Spengler *et al.* (184). These authors found that the risk of endometrial cancer was increased among estrogen users and that the risk increased with duration of use and daily dose. The potential sources of bias (comparability of cases and controls, selection of controls, postmenopausal bleeding, medical surveillance, recall of estrogen use, extent of disease, and influence of prior hysterectomy in the controls) were found not to unduly influence the risk estimates. Quantitative risk estimation was not possible, again because daily dose and duration of use were not cross-classified, and the two groups showed substantial difference in the distribution of these factors (cf.

discussion of Antunes *et al.* (180)).

The literature reviewed reveals a consistent pattern of increased risk of endometrial cancer among estrogen users. The data for breast cancer is not as conclusive. Five studies present data sufficient for potency estimation. The potency parameters so estimated are given in Table 2-64. When these parameters are applied in our standard exposure scenario (45 years of use starting at age 20, an unrealistic scenario for conjugated estrogen use) the resulting RRD estimates are shown in Table 2-65.

Table 2-53

NUMBERS OF BREAST CANCER CASES AND CONTROLS BY TOTAL ACCUMULATED DOSE OF CONJUGATED ESTROGEN AND OVARIAN STATUS[a]

Ovarian Status	Dose (mg)	Cases	Controls
Ovaries Intact	0	50	103
	1 - 1499	21	56
	1500+	28	23
Ovaries Removed	0	13	29
	1 - 1499	6	15
	1500+	7	21
All[b]	0	64	134
	1 - 1499	28	73
	(1.24, 2.05, 3.38)[c]		
	1500+	37	48
	(3.73, 6.16, 10.2)[c]		

[a]From Ross *et al.* (174).
[b]Includes persons with ovary status unknown.
[c]In parentheses are the lower bounds, best estimates, and upper bounds, respectively, for cumulative dose (in mg-yrs) in each group.

Table 2-54

RISK RATIOS BY DOSE AND DURATION OF ADMINISTRATION OF CONJUGATED ESTROGEN FOR ENDOMETRIAL CARCINOMA CASES AND CONTROLS[a]

Duration of Use (months)	Mean Dose ≤ 0.625 mg Cases/Controls	RR[c]	> 0.625 mg Cases/Controls	RR[c]	Total[b] Cases/Controls	RR[c]
1 - 11	5/9	6.6	0/8	0.0	6/26	2.8
12 - 59	8/28	3.4	5/2	29.8	15/40	4.5
60 - 95	3/6	6.0	2/2	11.9	7/9	9.3
96+	4/10	4.8	8/5	19.1	17/23	8.8
Total[b]	23/55	5.0	15/19	9.4	59/109	5.6

[a]From Mack *et al.* (177).
[b]Including those for which dose or duration (or both) was not known.
[c]Based on 12 cases and 143 controls who were nonusers of conjugated estrogens.

Table 2-55

NUMBERS OF ENDOMETRIAL CARCINOMA CASES AND CONTROLS BY DRUG-FREE DAYS IN CYCLE AND MEAN PILL SIZE[a]

Drug-Free Interval[b] (Days)	Pill Size ≤ 0.625 mg Cases	Pill Size ≤ 0.625 mg Controls	Pill Size > 0.625 mg Cases	Pill Size > 0.625 mg Controls
0 - 1	5	14	2	5
2 - 3	7	19	6	5
4+	2	13	3	5

[a]From Mack *et al.* (177).
[b]A cycle is assumed to last for 30 days, hence these are the number of drug-free days per month.

Table 2-56

NUMBERS OF ENDOMETRIAL CARCINOMA CASES AND CONTROLS BY TOTAL DOSE[a]

Total Dose (mg-yrs)	Number of Cases	Number of Controls
0	12	143
0.140 (8.22E-2, 0.258)[b]	5	9
0.458 (0.269, 0.846)	0	8
0.778 (0.458, 1.44)	8	28
1.68 (0.992, 3.12)	3	6
2.54 (1.49, 4.69)	5	2
3.11 (1.83, 5.76)	4	10
5.49 (3.23, 10.2)	2	2
10.1 (5.97, 18.8)	8	5

[a]Derived from data in Mack *et al.* (177).
[b]In parentheses are the lower and upper bounds on cumulative dose for each group.

Table 2-57

DISTRIBUTION OF CASES AND CONTROLS BY DURATION, DOSE, AND TYPE OF ADMINISTRATION OF CONJUGATED ESTROGENS[a]

Exposure	Number of Cases	Number of Controls
Duration:		
None	124	533
<6 mo.	5	31
6 mo. - 1 yr.	4	5
1 - 2 yrs.	0	3
2 - 3 yrs.	3	2
3+ yrs	9	6
Daily Dose:[b]		
0.625 mg	2	8
1.25	10	8
2.5	4	0
Type of Administration:		
Intermittent	1	4
Cyclic	4	6
Continuous	11	6

[a]Derived from data in McDonald *et al.* (178).
[b]Data presented only for those using conjugated estrogens for at least 6 months.

Table 2-58

NUMBERS OF ENDOMETRIAL CARCINOMA
CASES AND CONTROLS IN OLMSTED COUNTY BY TOTAL DOSE[a]

Total Dose (mg-yrs)	Number of Cases	Number of Controls
0	124	533
2.22 (1.27, 4.33)[b]	2	8
4.44 (2.54, 8.66)	10	8
8.89 (5.08, 17.3)	4	0

[a]Based on data in McDonald *et al.* (178).
[b]In parentheses are the lower and upper bounds, respectively, for cumulative dose in each group.

Table 2-59

DISTRIBUTION OF ENDOMETRIAL CARCINOMA CASES AND CONTROLS BY DURATION OF USE AND PILL STRENGTH OF CONJUGATED ESTROGEN[a,b]

Exposure	Number of Cases	Number of Controls
Duration (yrs):		
0 - 4	8	8
5 - 9	7	2
10+	10	1
Pill Strength (mg):[c]		
0.3	7	2
0.625	14	9
1.25	11	1

[a]From Gray *et al.* (179).
[b]Unknowns excluded in both cases. 150 cases and 174 controls received no hormones.
[c]Strength of pill usually used.

Table 2-60

NUMBERS OF ENDOMETRIAL CARCINOMA CASES AND CONTROLS IN A LOUISVILLE, KENTUCKY PRIVATE PRACTICE BY TOTAL DOSE[a]

Total Dose (mg-yrs)	Number of Cases	Number of Controls
0	150	174
2.28 (1.17, 4.90)[b]	7	2
4.75 (2.44, 10.2)	14	9
9.50 (4.87, 20.4)	11	1

[a]Based on data presented in Gray *et al.* (179).
[b]In parentheses are the lower and upper bounds, respectively, for cumulative dose in each group.

Table 2-61

NUMBER OF ENDOMETRIAL CANCER CASES AND CONTROLS IN BALTIMORE-AREA HOSPITALS BY DAILY DOSE AND DURATION OF USE OF CONJUGATED ESTROGENS[a]

Exposure	Number of Cases	Number of Controls
Duration of use (yr):		
None	274	390
<1	11	7
1 - 5	17	8
5+	36	3
Daily Dose (mg):		
None	274	390
<1	23	9
1 - 2	27	5
2+	6	2

[a]From Antunes *et al.* (180).

Table 2-62

DISTRIBUTION OF HYPOESTROGENIC PATIENTS BY TOTAL DOSE OF ESTROGEN[a]

Estrogen Equivalents (mg-months)	Number of Patients	Number of Endometrial Cancers
0	309	3
≤67.6	96	6
67.6 - 145	86	3
> 145	105	2
Unknown	14	0

[a]From Hammond *et al.* (181).

Table 2-63

DOSE AND RESPONSE DATA FOR HYPOESTROGENIC PATIENTS[a]

Dose (mg-yrs)	Endometrial Cancers	
	Observed	Expected
0	3	2.45
13.3 (9.17, 19.3)[b]	11	1.20

[a]From Hammond *et al.* (181).
[b]In parentheses are the lower and upper bounds, respectively, for cumulative dose in the treated group.

Table 2-64

POTENCY PARAMETER ESTIMATES FOR ESTROGENS

Response	Study	Dose Measure	Potencies ((mg-yrs)$^{-1}$) Lower Limit[a]	MLE	Upper Limit[a]
Breast Cancer Morbidity	Ross *et al.* (174) (chi-squared (1) = 2.5)	Upper Bounds	1.06E-2*	5.27E-2	1.09E-1
		Best Estimates	1.74E-2	8.70E-2*	1.80E-1
		Lower Bounds	2.88E-2	1.44E-1	2.98E-1*
Endometrial Cancer Morbidity	Mack *et al.* (177) (chi-squared (7) = 14.8)	Upper Bounds	5.94E-1*	1.07	1.78
		Best Estimates	1.10	1.98*	3.30
		Lower Bounds	1.87	3.35	5.60*
	McDonald *et al.* (178) (chi-squared (2) = 3.8)	Upper Bounds	2.46E-1*	4.65E-1	8.16E-1
		Best Estimates	4.80E-1	9.06E-1*	1.59
		Lower Bounds	8.40E-1	1.58	2.78*
	Gray *et al.* (179) (chi-squared (2) = 3.2)	Upper Bounds	8.92E-2*	1.93E-1	3.71E-1
		Best Estimates	1.92E-1	4.14E-1*	7.96E-1
		Lower Bounds	3.73E-1	8.06E-1	1.55*

Table 2-64 (continued)

POTENCY PARAMETER ESTIMATES FOR ESTROGENS

Response	Study	Dose Measure	Potencies ((mg-yrs)$^{-1}$) Lower Limit[a]	MLE	Upper Limit[a]
Endometrial Cancer Morbidity	Hammond *et al.* (181) (chi-squared (1) = 0.12)	Upper Bounds	2.62E-1*	4.23E-1	6.31E-1
		Best Estimates	3.81E-1	6.14E-1*	9.16E-1
		Lower Bounds	5.52E-1	8.91E-1	1.33*

[a]90% confidence limits shown.
*An asterisk marks the parameters used to derive RRD estimates.

Table 2-65

RRD ESTIMATES FOR ESTROGENS (mg/day)

Study	Response	Estimation Method	Level of Extra Risk: 10^{-6} RRD_L	10^{-6} MLE	10^{-6} RRD_u	0.25 RRD_L	0.25 MLE	0.25 RRD_u
Breast Cancer Morbidity	Ross et al. (174)	1	6.46E-7	2.21E-6	1.82E-5	1.62E-1	5.53E-1	4.55
		2	8.13E-7	2.78E-6	2.29E-5	2.39E-1	8.17E-1	6.73
Endometrial Cancer Morbidity	Mack et al. (177)	1	1.12E-7	3.16E-7	1.05E-6	2.79E-2	7.90E-2	2.63E-1
		2	1.32E-7	3.74E-7	1.25E-6	3.82E-2	1.08E-1	3.60E-1
	McDonald et al. (178)	1	2.25E-7	6.90E-7	2.54E-6	5.62E-2	1.73E-1	6.35E-1
		2	2.66E-7	8.17E-7	3.00E-6	7.69E-2	2.36E-1	8.68E-1
	Gray et al. (179)	1	4.03E-7	1.51E-6	7.01E-6	1.01E-1	3.78E-1	1.75
		2	4.77E-7	1.79E-6	8.30E-6	1.38E-1	5.17E-1	2.40
	Hammond et al. (181)	1	4.71E-7	1.02E-6	2.38E-6	1.18E-1	2.55E-1	5.96E-1
		2	5.57E-7	1.21E-6	2.82E-6	1.61E-1	3.48E-1	8.15E-1

Ethylene Oxide

The oxirane ethylene oxide (CAS No. 75-00-2) is used in the manufacture of many other chemicals and as a fumigant and sterilizing gas, especially in the hospital industry (185). As an alkylating agent, it is highly suspect with respect to carcinogenicity. Indeed, it demonstrates mutagenic activity in short-term tests on cells of bacteria, plants, insects, and mammals. DNA damage and chromosomal anomalies have been noted in several species, including humans (2).

NIOSH has conducted industrial hygiene studies in a number of hospitals. Time-weighted average exposures for the relevant personnel (those who work with or around sterilization equipment) ranged from nondetectable to about 10 ppm. Korpela *et al.* (186) measured only small amounts of ethylene oxide dispersed from gas sterilizers. Nevertheless, the epidemiologic literature contains studies of hospital workers (and health instrument manufacturing employees) with observable cytogenetic effects presumably due to ethylene oxide (187-189).

Landrigan *et al.* (189) state that OSHA believes that ethylene oxide exposure may increase the risk of malignancies, particularly leukemia. This view is based, at least in part, on the results of three occupational studies. In a study of ethylene oxide producers, Morgan *et al.* (185) observed cancers of several sites in exposed workers. No leukemias were observed and the total number of malignancies did not differ significantly from that expected on the basis of U.S. vital statistics. The authors claim that small sample size reduced the power to detect an effect of ethylene oxide, especially with respect to leukemia.

On the other hand, Hogstedt and his colleagues have found significant increases in leukemia in two small cohorts. Hogstedt *et al.* (190)

found three leukemias among workers at a technical factory that sterilized hospital equipment with 50% ethylene oxide and 50% methyl formate. A total of 230 individuals worked in or around the area entailing exposure. National cancer rates predicted 0.2 cases of leukemia among these workers. They worked between 1968 and 1977 for 4 to 10 years (assumed average, 7 years). Seventy of the employees were exposed to TWA concentrations of 20 ppm. The other 160 individuals were only occasionally in this high exposure area. It is assumed that their TWA exposures averaged 10 ppm. As a whole, the estimate of average exposure for this cohort is

$$\frac{(70 \times 20) + (160 \times 10)}{230} = 13 \text{ ppm.}$$

This average exposure combined with the assumed average exposure period yields a cumulative dose estimate of

$$(13 \text{ ppm}) \cdot (7 \text{ yrs}) = 91 \text{ ppm-yrs.}$$

Uncertainty factors α and γ have been estimated to be 1.8 upon consideration of the following features of the study:

1. Length of exposure varied from 4 to 10 years, but no average length of exposure is given. Uncertainty attendant with estimation of average duration is reflected in the choice of 0.2 for α_1 and γ_1.
2. The only measurements of ethylene oxide concentrations occurred in 1977. Exposure may have begun as early as 1968 for some individuals. It does not appear that concentrations would have changed much over those 10 years, however, because the process does not seem to have changed over that period. A factor of 0.1 is assigned to both α_2 and γ_2.

3. It is not known how complete the measurements taken in 1977 were. Certainly, they were detailed enough to ascertain the breathing zone concentrations for individuals who worked in the storage hall. Time-weighted average concentrations are not given for the majority of employees who only occasionally ventured into the hall. Uncertainty is associated with the approximation of 10 ppm TWA for those workers and is mirrored in the selection of a value of 0.4 for α_3 and γ_3.
4. Finally, the use of national mortality rates does not, perhaps, give the best estimate of expected values. These workers were exposed to methyl formate as much as to ethylene oxide. A fairly minimal value of 0.1 is assigned to α_8 and γ_8.

The lower bound, best estimate, and upper bound for dose, 51, 91, and 164 ppm-years, respectively, have been used to derive estimates of β_U, β, and β_L.

The other study by Hogstedt *et al.* (191) utilized employment data from a company that has produced ethylene oxide since the beginning of the 1940's. Included in the follow-up study were men who had hematological investigations performed in 1960-61 and who were employed for more than 1 year. Follow-up started in January, 1961 and ended in December 1977; however, accumulation of person-years at risk for each individual did not begin until 10 years after the beginning of exposure. The men in this cohort were exposed to other chemicals besides ethylene oxide, including ethylene dichloride, ethylene chlorohydrin, and ethylene itself.

Estimation of exposure in this cohort is difficult. Subcohorts of full-time exposed, intermittently exposed, and unexposed individuals were identified, but the level of exposure or duration of exposure is never fully documented. During the mid-1940's (1941-1947) it is believed that

ethylene oxide TWA exposures were somewhat less than 25 mg/m^3. From 1950 through 1963, increased ethylene oxide production entailed exposures between 10 and 50 mg/m^3. Production of ethylene oxide terminated in 1963. It continued to be used in manufacture; the concentrations associated with this operation ranged from 1 to 10 mg/m^3 in the 1970's. Since the cohort members must have been employed in 1960-61, the values of ethylene oxide concentration from 1950 to 1963 (10-50 mg/m^3) are most important in determining exposure. Periods before and after were associated with less exposure. Consequently, a value of 20 mg/m^3 is assumed for an average TWA exposure among the full-time exposed; half that value, 10 mg/m^3, is assumed for the intermittently exposed group.

Hogstedt *et al.* (191) state that the majority of exposed persons were employed before 1950. Evidently, most had more than ten years of employment. Nothing more is known about duration of exposure to ethylene oxide. An average length of employment of 10 years is assumed. The resulting best estimate of cumulative exposure is

$$(20\ \text{mg/m}^3) \times (10\ \text{years}) = 200\ \text{mg-yrs/m}^3$$

for the full-time exposed group and 100 mg-yrs/m^3 for the intermittently exposed group. The dose and response data are displayed in Table 2-66.

The bounds on dose indicated in that table are based on α and γ values derived with reference to the following considerations:

1. The average length of employment is not known, nor is a range of durations presented. The value assumed, ten years, is based solely on the fact that most of the workers were employed before 1950 and must have worked until 1960-61 to be members of the cohort. That being the case, the lower bound ought to be relatively closer to the best estimate, based on this feature

at least, than the upper bound, but both should be fairly wide. The value for α_1 is 0.5 and for γ_1 is 0.8.

2. The measurements of exposure are rather incomplete. This has made it difficult to estimate exposures appropriate to the full-time exposed group. It is not entirely clear when cohort members were exposed. Both α_3 and γ_3 have been set equal to 0.5, the maximum value allowed to reflect incompleteness of measurements.
3. For both exposed groups there is uncertainty with respect to the applicability of the reported levels of atmospheric ethylene oxide because the exact timing of exposure is not known and because area samples may not be the best method to determine effective, personal exposures. In the intermittently exposed group there is an additional uncertainty: it is not known to what extent intermittently-exposed individuals are exposed. Merely halving the full-time exposed estimate may not be accurate or appropriate. For the full-time exposed group, α_6 and γ_6 equal 0.1 whereas α_6 and γ_6 are 0.3 for the intermittently exposed group.
4. This cohort was exposed to several other chemicals besides ethylene oxide. Ideally, expected numbers of deaths would reflect these exposures. This uncertainty is in addition to that corresponding to use of national mortality rates. Overall, α_8 and γ_8 have been set equal to 0.2.

The uncertainty factors resulting from these considerations depend on the dose group. For the full-time exposed group, $\alpha = 2.3$ and $\gamma = 2.6$. For the intermittently-exposed group, $\alpha = 2.5$ and $\gamma = 2.8$.

The potency parameter estimates from this cohort are presented in Table 2-67, along with those from the first study discussed. The RRD estimates derived from those potencies are displayed in Table 2-68.

Table 2-66

DOSE AND RESPONSE DATA FOR ETHYLENE OXIDE-EXPOSED EMPLOYEES; HOGSTEDT *ET AL.* (191)

Dose Group	All Malignant Neoplasms		Leukemia	
	Observed	Expected	Observed	Expected
Unexposed (0, 0, 0)[a]	1	2.0	0	0
Intermittently Exposed (40, 100, 280)	3	3.4	1	0.13
Full-time Exposed (87, 200, 520)	9	3.4	2	0.14

[a]In parentheses are the lower bounds, best estimates, and upper bounds, respectively, for exposure (mg-yrs/m^3) in the dose groups. These have been estimated; see text.

Table 2-67

ETHYLENE OXIDE LEUKEMIA POTENCY PARAMETER ESTIMATES

Study	Dose Measure	Potencies ((mg-yrs/m^3)$^{-1}$) Lower Limit[a]	MLE	Upper Limit[a]
Hogstedt *et al.* (190) (one dose group)	Upper Bound	1.84E-2*	4.73E-2	9.45E-2
	Best Estimate	3.32E-2	8.52E-2*	1.70E-1
	Lower Bound	5.927E-2	1.52E-1	3.04E-1*
Hogstedt *et al.* (191) (Chi-squared (2)$\leq 4\times10^{-3}$)	Upper Bounds	9.38E-3*	2.50E-2	5.06E-2
	Best Estimates	2.49E-2	6.66E-2*	1.35E-1
	Lower Bounds	5.86E-2	1.57E-1	3.18E-1*

[a]90% confidence limits are shown.
*An asterisk marks the parameters (i.e. β_L, β, and β_U) used to derive RRDs for each study.

Table 2-68

RRD ESTIMATES FOR ETHYLENE OXIDE (mg/m^3)[a]

Study	Estimation Method	Level of Extra Risk 10^{-6} RRD_l	MLE	RRD_u	0.25 RRD_l	MLE	RRD_u
Hogstedt *et al.* (190)	1	9.07E-6	3.24E-5	1.50E-4	2.27	8.09	3.74E+1
	2	1.03E-5	3.66E-5	1.69E-4	3.43	1.22E+1	5.67E+1
Hogstedt *et al.* (191)	1	8.68E-6	4.14E-5	2.94E-4	2.17	1.04E+1	7.35E+1
	2	9.81E-6	4.68E-5	3.32E-4	3.28	1.57E+1	1.11E+2

[a]Based on the risk of leukemia.

Isoniazid

Isonicotinic acid hydrazide or isoniazid (INH; CAS No. 54-85-3) was introduced in 1952 as a chemotherapeutic agent to combat tuberculosis (192). It is now the most widely used antituberculosis drug, given alone in preventive therapy and in combination with other drugs for treatment of the active disease (193).

Isoniazid has not been clearly linked to cancer in humans. INH has induced DNA repair in bacteria. In mice treated early in embryogenesis, isoniazid caused specific-locus mutations and in host-mediated assays in rodents, it caused bacterial mutation, due partly to the formation of hydrazine (2). Apparently, human metabolism of INH does not produce hydrazine, an agent strongly suspected of being a carcinogen (194). There was no evidence of DNA damage in lymphocytes of patients receiving isoniazid (2).

Nevertheless, several investigations of a possible relationship between isoniazid and cancer have been reported. Hammond *et al.* (195) considered this question a mere 14 years after isoniazid's introduction. Of particular interest is their report on 311 tuberculosis patients treated with isoniazid for various lengths of time [55 for less than 1 year; 97 for 1 to 2 years; 87 for 2 to 3 years; 29 for 3 to 4 years; 11 for 4 to 5 years; 9 for 5 to 6 years; 20 for 6 years or longer; 3 uncertain]. Using midpoints of those intervals (assuming 10 years average treatment in the six-years-or-longer group), average duration of INH therapy was 2.57 years. The standard daily dose was 4 mg INH per kg body weight. The average total dose for these patients is estimated to be 3752.2 mg/kg, equivalent to a cumulative dose of 10.3 mg-yrs/kg.

Possibly as many as 10 cancer cases were seen in these patients. Five (and a probable sixth) were cancers of the respiratory tract, and there

was one each of bladder cancer, chronic myelogenous leukemia, liver cancer, and a death with a "hilar density suggesting tumour". Even accepting the 10 as true cancer cases, the observed number is not significantly greater than the 6.3 expected from local rates. Nevertheless, these values can contribute to the estimation of the quantitative relationship between isoniazid use and cancer development, assuming one exists.

Uncertainty associated with this study, leading to factors α and γ both equal to 1.3, is caused by two factors:

1. Length of exposure is categorized by one-year groups, but those groups are presented without average values. A small factor, 0.1, is assigned to α_1 and γ_1.
2. It has been suggested (192) that there may exist an association between tuberculosis itself and lung cancer. Hammond *et al.* failed to detect such a link in the tuberculosis patients included in their prospective study. Nevertheless, this adds some uncertainty to the expected number of deaths that Hammond *et al.* present, so α_8 and γ_8 are set equal to 0.2.

Consequently, the 10 observed and 6.3 expected cancer deaths are associated with an average dose estimated to be 10.3 mg-yrs/kg, but possibly as low as 7.9 mg-yrs/kg or as high as 13.4 mg-yrs/kg.

Stott et al. (196) reviewed the mortality experience of tuberculosis patients admitted to two British sanatoria from 1950 to 1957, *i.e.*, the period just before and just after the introduction of isoniazid. Their follow-up period extended for nearly 20 years, through 1973, yet no evidence of carcinogenicity for isoniazid was found. There was, in fact, no dose-response trend for all cancer or for cancers of the respiratory system (Table 2-69). Once again, these values can be used to

derive quantitative estimates and bounds on risk, even though the evidence for carcinogenicity is negative. Arithmetic averages are assumed to represent the average dose of each group (cf. Table 2-69) and these values can be used in the dose-response analysis. The uncertainty in the dose values stems from two sources.

1. The dosage groups are presented without average values. The factors α_4 and γ_4 have been given a value of 0.2.
2. General population rates of disease were used to determine expected numbers of deaths. As mentioned above, this may be inappropriate for tuberculosis patients, and so α_8 and γ_8 have the value of 0.2.

The uncertainty factors, $\alpha = \gamma = 1.4$, have been used to define the bounds on dose presented in Table 2-69.

Glassroth *et al.* (197) reviewed two Public Health Service trials of isoniazid prophylaxis among household members of tuberculosis patients and among mental institution patients with tuberculosis infections. Participants were randomized into treated and control groups and given the appropriate drug for one year. Those receiving isoniazid averaged 5 mg/kg/day, for a total of 1825 mg/kg (5 mg-yr/kg). No particular increase in all cancer or cancers of specific sites was noted among the INH-treatment groups when follow-up was continued for 11 to 14 years (Tables 2-70 and 2-71). Since the age and sex distributinos of the placebo and isoniazid groups in the household members trial were similar, one can use Table 2-70 to derive an expected number of cancer deaths to accompany the 108 observed cancer deaths. For each year of observation, the expected number is based on the number of INH patients at risk times the rate in the placebo population. The first year, for example, yields an expected number of

$(1/12595) \times 12439 = 0.99.$

Altogether, 107.6 cancer deaths are expected during the fourteen years for which results are available.

Uncertainty leads us to estimate bounds on cumulative dose of 3.8 and 6.25 mg-yrs/kg, based on the factors $\alpha = 1.3$ and $\gamma = 1.25$, respectively derived as follows:

1. Medication was taken for at most 1 year. Some participants stopped taking their medication, but we have no indication of the average duration of INH exposure. A factor of 0.05 is assigned to α_1, but since the maximum duration is known, $\gamma_1 = 0$.
2. It is stated that the daily dose of INH was between 4 and 7 mg/kg, with most patients receiving 5 mg/kg. The average may differ somewhat from 5 mg/kg, so α_4 and γ_4 have been set equal to 0.05.
3. The expected numbers of deaths are based on a fairly small population, the placebo group. One might expect substantial variability in death rates based on small numbers, so α_8 and γ_8 are both assigned a value of 0.2.

Other studies have examined isoniazid carcinogenicity but lack the quantitative meaures to support risk estimation. Ferebee (192) found no link between INH and cancer mortality in any of the Public Health Service clinical trials. In a case-control study, there were suggestions that isoniazid use may be a risk factor for bladder cancer in females. No such suggestion pertained to males (198). On the other hand Sanders and Drapper (199) found no evidence to suggest that isoniazid taken during pregnancy affects cancer development in the offspring. Clemmesen and Hjalgrim-Jensen (200) studied tubercular patients followed for up to 24 years. They concluded that isoniazid was

not linked to cancer but that tuberculosis was associated with lung cancer, both of which are associated with cigarette smoking. Additional negative evidence on the carcinogenicity of INH is provided by Howe et al. (201). These authors found no difference in cancer incidence or mortality for a large group of Canadian tuberculosis patients. A year later, Boice and Fraumeni (202) again could discern no link between isoniazid therapy and cancer. Finally, Costello and Snider (193), reviewing a Public Health Service preventive therapy trial, could find no evidence of an etiologic role of isoniazid in cancer development. The Puerto Rican participants in the household contact trial (cf. Table 2-70) were followed for an average of 18 years.

Overall, the evidence does not support a conclusion that isoniazid is carcinogenic in humans. The studies with quantitative data all provide potency parameter estimaets that are positive (although the lower limits for the Glassroth *et al.* study are negative), indicating some carcinogenic potential for INH (Table 2-72). The RRD estimates derived from those parameters, and assuming 45 years of exposure to isoniazid starting at age 20, are displayed in Table 2-73.

Table 2-69

DOSE AND RESPONSE DATA FOR TUBERCULOSIS PATIENTS TREATED WITH ISONIAZID[a]

Total Dose of Isoniazid(g)	All Malignant Neoplasms		Malignant Neoplasms of Respiratory Tract	
	Observed	Expected	Observed	Expected
<50 (17.9, 25, 35)[b]	31	20.9	11	6.9
50 - 99 (53.8, 75, 105)	24	16.0	10	5.2
100 - 199 (107, 150, 210)	24	24.9	8	8.7
200+ (357, 500, 700)	19	14.3	8	5.1

[a]From Stott *et al.* (196).
[b]In parentheses are the lower bounds, best estimates, and upper bounds for dose in each group.

Table 2-70

CANCER DEATHS AMONG HOUSEHOLD MEMBERS OF TUBERCULAR PATIENTS BY TREATMENT GROUP AND YEAR OF OBSERVATION[a]

Year of Observation	Placebo		Isoniazid	
	Population at Risk	Number of Cancer Deaths	Population at Risk	Number of Cancer Deaths
1	12594	1	12439	3
2	12568	10	12401	8
3	12518	4	12365	10
4	12484	10	12329	10
5	12438	10	12287	9
6	12390	9	12248	11
7	12344	13	12196	8
8	12284	8	12150	5
9	12241	10	12097	11
10	12175	10	12056	11
11	12110	11	11992	10
12	11982	7	11866	5
13	8229	2	8011	4
14	2394	4	2379	3
TOTAL		109		108

[a]From Glassroth et al. (197).

Table 2-71

CANCER DEATHS AMONG MENTAL INSTITUTION TUBERCULAR PATIENTS BY TREATMENT GROUP AND YEAR OF OBSERVATION[a]

Year of Observation	Placebo		Isoniazid	
	Population at Risk	Number of Cancer Deaths	Population at Risk	Number of Cancer Deaths
1	12326	31	12884	38
2	11779	39	12189	31
3	11300	33	12174	34
4	10848	37	11324	30
5	10430	32	10924	34
6	10068	30	10523	32
7	9661	27	10111	39
8	9299	24	9762	30
9	9002	13	9432	13
10	6120	10	6427	14
11	3742	2	3875	1
TOTAL		278		296

[a]From Glassroth et al. (197).

Table 2-72

POTENCY PARAMETER ESTIMATES FOR ISONIAZID

Study	Response	Dose Measure	Potencies (mg-yrs/kg)$^{-1}$ Lower Limit[a]	MLE	Upper Limit[a]
Hammond *et al.* (195)	All Malignant Neoplasms (0 degrees of freedom)	Upper Bounds	2.08E-3*	4.38E-2	9.85E-3
		Best Estimates	2.70E-3	5.70E-2*	1.28E-1
		Lower Bounds	3.52E-3	7.43E-2	1.67E-1*
Stott *et al.* (196)	All Malignant Neoplasms (chi-squared (3) = 7.9)	Upper Bounds	1.42E-3*	1.37E-2	2.80E-2
		Best Estimates	1.96E-3	1.92E-2*	3.92E-2
		Lower Bounds	2.79E-3	2.69E-2	5.50E-2*
	Respiratory Cancer (chi-squared (3) = 5.9)	Upper Bounds	1.61E-3*	2.30E-2	5.00E-2
		Best Estimates	2.22E-3	3.21E-2*	7.00E-2
		Lower Bounds	3.18E-3	4.50E-2	9.82E-2*
Glass-roth *et al.* (197)	All Malignant Neoplasms (0 degrees of freedom)	Upper Bounds	-1.84E-2*	5.95E-4	2.12E-2
		Best Estimates	-2.30E-2	7.43E-4*	2.65E-2
		Lower Bounds	-3.03E-2	9.78E-4	3.49E-2*

[a]90% confidence limits are shown.
*An asterisk marks the parameters used to derive RRD estimates.

Table 2-73

RRD ESTIMATES FOR ISONIAZID (mg/kg/day)

Study	Response	Estimation Method	Level of Extra Risk 10^{-6} RRD_L	MLE	RRD_u	0.25 RRD_L	MLE	RRD_u
Hammond et al. (195)	All malignant neoplasms	1	4.71E-7	1.38E-6	3.79E-5	1.18E-1	3.45E-1	9.48
		2	6.20E-7	1.82E-6	4.99E-5	1.98E-1	5.82E-1	1.60E+1
Stott et al. (196)	All malignant neoplasms	1	1.43E-6	4.11E-6	5.55E-5	3.58E-1	1.03	1.39E+1
		2	1.88E-6	5.41E-6	7.31E-5	6.03E-1	1.73	2.34E+1
	Respiratory cancer	1	2.77E-6	8.48E-6	1.69E-4	6.93E-1	2.12	4.22E+1
		2	3.20E-6	9.78E-6	1.95E-4	9.85E-1	3.01	6.00E+1
Glass-roth et al. (197)	All malignant neoplasms	1	2.26E-6	1.06E-4	∞	5.64E-1	2.65E+1	∞
		2	2.97E-6	1.39E-4	∞	9.50E-1	4.46E+1	∞

Melphalan

Melphalan (CAS No. 148-82-3) is a chemical used to treat various malignant diseases, especially multiple myeloma, malignant melanoma, and adenocarcinomas of the ovary (203). It is an alkylating agent and hence highly suspect as a carcinogen. Melphalan is mutagenic in bacterial tests, has induced chromosomal aberrations and sister chromatid exchanges in mammalian cells, and has produced chromosome damage in the lymphocytes of human patients treated therapeutically (2).

Numerous case reports have documented second malignancies in patients whose first malignancy has been treated with melphalan. Gori *et al.* (204) describe a case of acute myeloblastic leukemia following treatment of breast cancer with 300 mg of melphalan given over 72 weeks (12 courses of 5 mg/day for 5 days every 6 weeks). A cytogenetic study of this patient revealed chromosomal damage including the same translocation in 6 out of 8 karyotype analyses.

Law and Blom (205) noted 7 patients out of 57 with multiple myeloma who had second neoplasms (4 with acute leukemia, 3 with solid-organ tumors). All were treated with melphalan, although these authors speculate that multiple myeloma itself may be a risk factor for other neoplasms.

Einhorn (206) described four cases of acute leukemia among 474 ovarian cancer patients treated with melphalan. Other chemotherapy or radiotherapy accompanied melphalan treatment in some cases.

Greene *et al.* (121) review five clinical trials testing alkylating agent therapy (with or without irradiation) of ovarian cancer. A total of 1399 women were included in these trials which tested 5-fluorouracil, acinomycin-D, cyclophosphamide, and chlorambucil in addition to melphalan. Eight different treatment regimens included melphalan

therapy, sometimes with irradiation or other alkylating agents. Among the 773 women in those treatment regimens, 10 acute nonlymphocytic leukemias were observed whereas only 0.08 were expected.

Greene *et al.* report the leukemia pattern by total dose for two of the trials that used melphalan alone (Table 2-74). We have selected the groups that have not received any radiation therapy to investigate the dose-response behavior of melphalan and we have converted total dose to cumulative dose by dividing by 365 (Table 2-75).

Average doses assumed for the groups displayed in Table 2-75 are the midpoint of the low dose group and an arbitrarily obtained value of 3.30 mg-years (1200 mg) for the high dose group. Some uncertainty is associated with those estimates, as discussed below:

1. The dose groups presented are fairly wide and are presented without averages. To account for this α_4 and γ_4 for the low dose group are set equal to 0.2, whereas α_4 and γ_4 for the high dose group are 0.3.
2. In this morbidity study, expected numbers of cases were determined from the Connecticut Tumor Registry. Some uncertainty as to use of these numbers (as opposed to numbers based on leukemia seen among those with ovarian cancer, for example) leads us to select a value of 0.1 for α_8 and γ_8.

The group-specific uncertainty factors ($\alpha = \gamma = 1.3$ for the low dose group, $\alpha = \gamma = 1.4$ for the high dose group) determine the bounds on dose given in Table 2-75. These are used to determine sensitivity of the analysis to uncertainty in the quantitative estimates.

Table 2-76 presents the potency parameters estimated from the acute nonlymphocytic leukemia response data in the melphalan-treated groups.

The corresponding RRD estimates, based on the exposure scenario of a white male being exposed for 45 years starting at age 20, are given in Table 2-77.

Table 2-74

OBSERVED AND EXPECTED CASES OF ACUTE NONLYMPHOCYTIC LEUKEMIA BY TRIAL AND INITIAL CHEMOTHERAPY DOSE[a]

Trial and Treatment Regimen[b]	Number of Patients	Observed	Expected
M.D. Anderson Hospital:			
Pelvic/abdominal irradiation	89	1[c]	0.019
< 700 mg melphalan	41	0	0.015
≥ 700 mg melphalan	42	4	0.011
Gynecologic Oncology Group			
Trial 1:			
Observation after surgery	68	0	0.011[d]
Pelvic irradiation	55	0	0.008[d]
< 700 mg melphalan	43	0	0.007
≥ 700 mg melphalan	29	1	0.007

[a]From Greene *et al.* (121).
[b]The treatment regimens with melphalan are specified as follows: for the M.D. Anderson Hospital trial, 1 mg/kg every 4 weeks for 12 cycles; for the Gynecologic Oncology Group 1 trial, 1 mg/kg every 4 weeks for 18 cycles.
[c]This patient was subsequently treated extensively with melphalan.
[d]These expected values are approximated: the authors had combined the expected values for the two non-melphalan regimens in this trial.

Table 2-75

DOSE AND RESPONSE DATA FOR MELPHALAN-TREATED AND CONTROL PATIENTS[a]

Cumulative Dose (mg-yrs)	Observed Leukemia Cases	Expected Leukemia Cases
0	0	0.011
< 1.92 (0.74, 0.96, 1.25)[b]	0	0.022
≥ 1.92 (2.36, 3.30, 4.62)	5	0.018

[a]From Greene et al. (121).
[b]In parentheses are the reasonable lower bounds, best estimates, and reasonable upper bounds for average dose in each group.

Table 2-76

LEUKEMIA POTENCY PARAMETER ESTIMATES FOR MELPHALAN, BASED ON THE STUDY OF GREENE *ET AL.*[a]

Dose Measure	Potencies ((mg-yrs)$^{-1}$) Lower Limit[b]	MLE	Upper Limit[b]
Upper Bounds	2.23E+1*	3.47E+1	7.93E+1
Best Estimates	3.09E+1	4.85E+1*	1.08E+2
Lower Bounds	4.27E+1	6.79E+1	1.48E+2*

[a]The fit of the model to the data is adequate; chi-squared (2) ≤ 2.65.
[b]90% confidence limits are shown.
*An asterisk marks the parameters used to derive RRD estimates.

Table 2-77

RRD ESTIMATES FOR MELPHALAN (mg/day)[a]

Estimation Method	Level of Extra Risk					
	10^{-6}			0.25		
	RRD_l	MLE	RRD_u	RRD_l	MLE	RRD_u
1	1.28E-8	3.88E-8	8.46E-8	3.19E-3	9.71E-3	2.11E-2
2	1.44E-8	4.37E-8	9.52E-8	4.76E-3	1.45E-2	3.16E-2

[a]Based on the risk of leukemia morbidity estimated from Greene *et al.* (121).

Methylene Chloride

The halogenated hydrocarbon methylene chloride (dichloromethane, DCM) is a nonflammable solvent used in a number of industrial capacities including degreasing; paint stripping; manufacture of photographic film, textiles and plastics; and food additive extracting. Infrequent reports of adverse effects in humans have appeared since 1936. Those effects include headaches, incoordination, and irritability among others, but no systematic investigation of toxic reactions is available (207). Pharmacokinetic analyses of DCM are available, however, including a report by Riley *et al.* (208) that postulates the involvement of only two tissues (water and fat) in methylene chloride metabolism. More recently, it has been found that two metabolic pathways exist, one involving production of carboxyhemoglobin (209). DCM is mutagenic in prokaryote and insect cells, but apparently not in mammalian cells (2).

Two recent occupational cohort studies provide information on the carcinogenicity of DCM. Both report negative findings: no increased risk of cancer appears to be associated with methylene chloride exposure. Nevertheless, risk estimates can be derived from these reports.

Friedlander *et al.* (207) describe a cohort of 751 hourly, male employees of one department in a facility using DCM as the primary solvent since the 1940's. Cohort members were those employed in 1964 and were followed through 1980. An internal control group composed of hourly, male employees at the same facility who were not exposed to methylene chloride was used to calculate expected numbers of deaths. A total of 24 malignant neoplasms were observed in the cohort versus 28.64 expected (210).

The authors of this study believe that the members of the cohort were all exposed to similar levels of DCM. The fact that the employees in

the DCM department all had similar tasks, that deployment in the department was flexible, that methylene chloride is highly volatile, and that the process did not change substantially for the 30 years prior to 1976 contribute to this belief. Area and personal DCM concentration measurement, along with carboxyhemoglobin determinations, support estimated time-weighted average exposures of between 30 and 125 ppm. An average of 78 ppm is assumed for the following calculations. The members of this cohort averaged about 26.5 years of exposure (Hearne, personal communication). Consequently, the estimated average cumulative exposure for the cohort is

$$(78 \text{ ppm}) \times (26.5 \text{ years}) = 2067 \text{ ppm-years}.$$

The uncertainty associated with this estimate leads to uncertainty factors, α and γ, equal to 1.6 and 1.85, respectively, based on the following considerations:

1. Although the process has remained relatively stable for many years, some changes in the ventilation system did occur. The authors suggest that exposures prior to 1959 may have been somewhat higher than those used to derive our average exposure estimate. Consequently, $\gamma_2 = 0.2$ and $\alpha_2 = 0$.
2. The measurements of exposure since 1959 are fairly spotty, occurring in 1959, 1966, 1973 and 1974 for a total of 307 samples. The exposures measured varied from 0 to 350 ppm, indicating that the variability might have been better documented with more extensive measurement. A factor of 0.3 is assumed for α_3 and γ_3.
3. The average exposure is not given, merely a range of 30 to 125 ppm as a reasonable interval for exposure. Since we had to estimate an average, a factor of 0.2 is assigned to α_4 and γ_4.

4. Most of the measurements that determined the range of possible exposures were area rather than personal samples. A nominal value of 0.05 is assumed for α_6 and γ_6 to account for this feature. Similarly, some of the measurements were based on carboxyhemoglobin determinations which were converted to estimates of DCM exposure on the basis of experimental studies. In this case α_7 and γ_7 are equated to 0.1 to cover the uncertainty in that conversion.

The reasonable bounds on dose obtained from these considerations are 1253 and 3824 ppm-years. These are used to test the sensitivity of the analysis to unknown features of this cohort.

The second occupational study of methylene chloride's health effects is reported by Ott *et al.* (209, 211). These authors identified a plant using DCM as a solvent since 1954 in the production of cellulose triacetate fibers and a second plant that had similar production characteristics but did not use DCM. The cohort studied consisted of employees who worked at least three months in the preparation or extrussion areas of either plant between 1954 and 1977. A total of 1271 DCM-exposed and 948 control workers were identified. Follow-up extended through June 1977. Among the white male or female employees, 7 malignant neoplasms were observed in the exposed group (11.5 expected on the basis of U.S. national rates) and 7 in the control group (12.3 expected). Both exposed and unexposed workers came into contact with acetone and had other minor exposures.

Jobs were categorized by exposure to methylene chloride into three groups: low (averaging 140 ppm, TWA), moderate (280 ppm), and high (475 ppm). Unfortunately, all we know about the distribution of the cohort in these categories is that 25% of the workforce was assigned to the high-exposure area and that most encountered only low DCM concentra-

tions. If we assume that 60% had low exposures and 15% moderate exposure, then the average exposure is

$$(.25 \times 475) + (.15 \times 280) + (.60 \times 140) = 245 \text{ ppm.}$$

Duration of exposure was similarly categorized, as follows:

less than 1 year (assumed average 0.5 yrs):	218 employees;
1 to 4 years (average 3 years):	496 employees;
5 to 9 years (average 7.5 years):	207 employees;
more than 10 years (average 17 years):	352 employees.

These numbers lead to an estimate of average length of exposure of

$$\frac{(218 \times 0.5) + (496 \times 3) + (207 \times 7.5) + (352 \times 17)}{1271} = 7.2 \text{ years.}$$

The average cumulative exposure estimate associated with this cohort is

$$245 \text{ ppm} \times 7.2 \text{ years} = 1764 \text{ ppm-years.}$$

The uncertainty associated with this estimate is reflected in the factors $\alpha = 2.05$ and $\gamma = 2.45$, which lead to reasonable bounds on dose of 860 and 4322 ppm-years. The following features of the study contributed to the uncertainty of the estimate:

1. Length of exposure was estimated for the entire cohort combined, based on a categorization presented without average values for the categories. Consequently, both α_1 and γ_1 are assumed to be 0.3.
2. Methylene chloride concentrations were measured extensively, but only in 1977 and 1978. Nothing is recorded about concentrations that might have prevailed earlier in the employment

history of the cohort. Nor is there any information about process changes that might have affected exposures. To account for this uncertainty, $\alpha_2 = 0.4$ and γ_2 is assigned a value of 0.8.

3. The distribution of the cohort over three exposure classes is not completely known, making the calculation of average exposure for the entire cohort difficult. As a result, α_4 and γ_4 are equal to 0.3.
4. Expected numbers are based on national rates. Some small amount of uncertainty associated with this feature entails a value of 0.05 for α_8 and γ_8.

These studies do not indicate a carcinogenic hazard associated with methylene chloride exposure. This is reflected in the maximum likelihood estimates of potency equal to zero (Table 2-78). Of course, this implies infinite RRD estimates (Table 2-79), *i.e.* the safety of any amount of DCM, but lower limits on the RRD estimates suggest that a one in a million risk from exposure to about 10^{-3} ppm for 45 years is consistent with the data.

Table 2-78

POTENCY PARAMETER ESTIMATES FOR METHYLENE CHLORIDE[a]

Study	Dose Measure	Potencies ((ppm-yrs)$^{-1}$) Lower Limit[b]	MLE	Upper Limit[b]
Friedlander *et al.* (207) (0 degrees of freedom)	Upper Bounds	-1.05E-4*	0.00	3.53E-5
	Best Estimates	-1.94E-4	0.00*	6.53E-5
	Lower Bounds	-3.19E-4	0.00	1.08E-4*
Ott *et al.* (209, 211) (chi-squared (1) = 4.04)	Upper Bounds	-1.70E-4*	0.00	3.79E-5
	Best Estimates	-4.16E-4	0.00*	9.28E-5
	Lower Bounds	-8.53E-4	0.00	1.90E-4*

[a]Based on the risk of all malignant neoplasms.
[b]90% confidence limits shown.
*An asterisk marks the parameters used to derive RRD estimates.

Table 2-79

RRD ESTIMATES[a] FOR METHYLENE CHLORIDE (ppm)

Study	Estimation Method	Level of Extra Risk 10^{-6} RRD$_L$	MLE	RRD$_U$	0.25 RRD$_L$	MLE	RRD$_U$
Friedlander *et al.* (207)	1	7.31E-4	∞	∞	1.83E+2	∞	∞
	2	9.62E-4	∞	∞	3.08E+2	∞	∞
Ott *et al.* (209, (211)	1	4.14E-4	∞	∞	1.03E+2	∞	∞
	2	5.44E-4	∞	∞	1.74E+2	∞	∞

[a]Based on the risk of all malignant neoplasms.

Nickel

Nickel is a silvery metal found in nature as the ores *milerite* (sulfide) and *garnierite* (silicate), the latter being the most important commercially (212). Nickel is liberated via conversion to the subsulfide, Ni_3S_2, which is air-roasted to give nickel oxide, NiO, followed by carbon reduction to the metal. Nickel is used chiefly in the production of alloys, including stainless steels. It is also used in electroplating, catalysts, coinage and pigments. Nickel alloys have been used in jewelry, and in dental and surgical prostheses (213).

Various nickel compounds have been examined in short-term tests. Nickel carbonyl has been found to inhibit DNA-dependent RNA polymerase activity, probably by binding to chromatin or DNA (214). *In vitro* tests using mammalian cells have shown nickel compounds to inhibit cellular uptake of thymidine-^{3}H and to induce chromosomal aberrations, somatic mutations, and morphological transformation. Bacterial mutagenicity tests have been uniformly negative however (215).

Most of the epidemiological data on the carcinogenicity of nickel has resulted from studies of occupationally exposed individuals, primarily nickel refinery workers. Although a number of studies have shown an increased risk of respiratory cancer to be associated with work in nickel refineries, there is no clear consensus as to which of the nickel compounds is implicated. Increased risk of lung and nasal sinus cancer was first noted among nickel refinery workers in Clydach, South Wales (216-218). Initially, the increased risk was thought to be associated with nickel carbonyl. However, the risk of respiratory cancer dropped dramatically after precautions were taken against exposure to dust in the refining process, although exposure to nickel carbonyl gas continued. Norseth (219) claims that the slightly soluble nickel salts are the important occupational carcinogens.

Studies of refinery workers at the Port Colborne and Copper Cliff sintering plants in Canada demonstrated increased risks of respiratory cancer, particularly of the lung and nasal sinuses (220-222). The sintering operation produced dust containing nickel sulfides and oxides.

Pedersen *et al.* (223) found an increased risk of respiratory cancer, including lung, nasal sinus and larynx, among workers at the Falconbridge refinery in Norway. The highest risk was associated with workers involved in roasting, smelting and electrolysis. A later study by Kreyberg (224) confirmed that exposure to nickel dust and fumes was associated with increased risk of lung cancer. Further confirmation was supplied by Magnus *et al.* (225), who also controlled for smoking habits of workers. They concluded that the interaction of smoking and nickel exposure with respect to lung cancer is closer to additive than to multiplicative.

Lessard *et al.* (226) noted an increased risk of lung cancer for workers in a nickel smelter in New Caledonia in the South Pacific, where the refining of nickel has been conducted for more than a century. They concluded that cigarette smoking, for which their analysis controlled, was an important factor to consider, but that previous studies linking nickel exposure to lung cancer had rarely done so.

Several studies of occupational exposure to nickel other than in refining operations have been carried out with mixed results. Silverstein *et al.* (227) found a significant excess of lung cancer among workers involved in die-casting and electroplating. However, Bernacki *et al.* (228) found no apparent increase in risk of lung cancer mortality among workers in an aircraft engine factory, and Godbold and Tompkins found no evidence of increased risk of mortality due to respiratory cancer among nickel-exposed workers in a gaseous diffusion plant.

A case-control study (230) implicated nickel exposure as a cause of laryngeal cancer. In studying the mortality of men employed in a plant manufacturing nickel alloys in England, Cox *et al.* (231) found no evidence of an occupational hazard in men exposed regularly to atmospheres containing on average between 0.04 and 0.84 mg/m^3 nickel and nickel oxide. Although the study by Cox *et al.* included limited information on exposure, this data could not be incorporated into a quantitative analysis.

Norseth (219) noted the general lack of dose estimates for nickel exposure both in the refining industry and in other industries where exposure to nickel compounds occurs. He expressed the need for careful dose registration before a quantitative cancer risk analysis can be performed. In the present literature review, only two cohort studies were found for which estimates of exposure to nickel could be derived. The investigation of Polednak (232) involved welders at Oak Ridge nuclear facilities who were employed between 1943 and 1973. Follow-up ended on January 1, 1974. A total of 1059 white, male welders were included, but our interest is focussed on 536 welders working at the Gaseous Diffusion Plant who have some data on nickel oxide exposure intensity and duration. Table 2-80 displays the TWA concentrations of nickel associated with the welding operations conducted at the plant. The operation specifically mentioned as a major part of the work at the plant is welding of nickel-lined pipe. Consequently, we will assume the average TWA exposure for the workers to be the level associated with that procedure, 0.13 mg/m^3, which is also the median of the values displayed.

Length of exposure has been used to define two subgroups: those exposed for less than 50 weeks and those exposed for 50 or more weeks. Polednak states that those exposed for longer periods were employed for 104 to 378 weeks. We have assumed average durations of 25 and 241 weeks for

the two groups. Coupled with the nickel concentration estimates discussed above, these figures yield cumulative exposure groups as displayed in Table 2-81.

Several uncertainties contribute to the factors $\alpha=2.0$ and $\gamma=2.8$ that determine the bounds on dose seen in Table 2-81. These are discussed below:

1. Length of exposure is grouped very crudely and presented without average values. Both α_1 and γ_1 are assigned the value 0.3.
2. All the nickel concentration measurements were performed after 1975. Polednak states that these "provide a lower limit for estimation of levels in earlier years". As a consequence $\alpha_2 = 0$, but $\gamma_2 = 0.8$.
3. It is not known how many personal samples were used to determine the exposure estimates. That being the case, α_3 and γ_3 both equal 0.3.
4. The range of possible exposures was 0.04 to 0.57 mg/m^3. No average value was presented. To cover the uncertainty of estimating an average value, α_4 and γ_4 have been set equal to 0.3.
5. Respiratory cancer is the endpoint of interest. Hence, smoking behavior undoubtedly influences calculation of actual expected values. Polednak presents data suggesting that the proportion of heavy smokers in the subcohort analyzed here was much the same from 1950 to 1969 as that found in all U.S. white males, the background population used to estimate expected values. To account for other smoking differences and for use of national rather than local rates of death, α_8 and γ_8 are given values of 0.1.

Enterline and Marsh (233) conducted a study of workers in a nickel refinery in Huntington, West Virginia. A cohort of 185 men employed between 1922 and 1947 was studied. Of these, 266 had worked in either the calcining or melting and casting departments for at least a year, while 1589 had worked in the refinery operation for less than a year or had worked in an associated nickel alloy production plant. A second cohort of 1354 male employees hired after 1946 (after the calcining operation was terminated) was also studied.

Exposure estimates were derived by the use of limited sample data along with more plentiful recent samples. Whenever possible, the modern data were adjusted on the basis of knowledge of process changes and environmental controls that were implemented over the years. The authors stated that the historical exposures estimated from modern data can be assumed to be no larger than the true exposures. Using these exposure data, an estimate of each worker's cumulative and average nickel exposure was calculated, based on departmental assignments as shown in personnel records.

Expected numbers of deaths were calculated based on a six-county area surrounding Huntington, West Virginia, since it was noted that this area had a mortality experience that differed somewhat from that of the entire United States. Observed and expected deaths for all malignant neoplasms and for respiratory cancers are given in Table 2-82, where only those cohort members who lived 20 years or more after first exposure are included. The authors stated that none of the differences between observed and expected numbers in Table 2-82 was statistically significant.

Table 2-83 displays the relationship between cumulative to nickel during the first twenty years of employment and the respiratory cancer mortality pattern after 20 years from first exposure. Enterline and Marsh

state that none of the groups displayed significantly increased respiratory cancer mortality rates. The average exposures for the groups were presented by Enterline and Marsh, but the bounds are based on the following considerations:

1. Measurements of exposure early in the exposure period are limited. Extrapolations backward from the plentiful, recent measurements took into consideration changes in the process and environmental controls. Nevertheless, some uncertainty persists and is reflected in our choice of $\alpha_2 = 0.1$ and $\gamma_2 = 0.3$.
2. Area samples, as opposed to personal samples, formed the basis of the departmental exposure estimates. A fairly small value of 0.1 is assigned to α_6 and γ_6 to account for possible differences between area and personal exposure.
3. Once again, smoking status could not be used to calculate expected numbers of respiratory cancer deaths. Local rates of death were used in those calculations, however. Both α_8 and γ_8 have been assigned a value of 0.05.

The resulting uncertainty factors are $\alpha = 1.25$ and $\gamma = 1.45$.

Table 2-84 displays the potency parameter estimates obtained from the Polednak (232) and Enterline and Marsh (233) studies. The best estimates of and reasonable bounds on the potencies have been used to estimate RRDs. Note that the negative lower bound on potency from the Polednak study entails an infinite upper bound on the RRD estimate, *i.e.* this study is consistent with the hypothesis that nickel is not carcinogenic in humans.

Table 2-80

CONCENTRATIONS OF NICKEL FROM PERSONAL AIR SAMPLERS WORN BY WELDERS AT THE OAK RIDGE GASEOUS DIFFUSION PLANT, POLEDNAK (232)[a]

Welding Procedure	TWA Average Air Concentrations(mg/m^3)
MIG welding on Ni-plated steel	0.57
TIG welding on Ni-plated steel	0.04
SMA welding on Ni-lined pipe	0.13
MIG welding on carbon steel	0.25
TIG welding on stainless steel	0.08

[a]Measurements are from 1975-1977.

Table 2-81

DOSE AND RESPONSE DATA FOR NICKEL-EXPOSED WORKERS STUDIED BY POLEDNAK (232)

Cumulative Exposure ($mg\text{-}yrs/m^3$)	Respiratory Cancer Deaths	
	Observed	Expected
0.0625 (0.0312, 0.175)[a]	2	3.23
0.602 (0.301, 1.69)	5	2.86

[a]In parentheses are the lower bounds and upper bounds for cumulative exposure in each dose group.

Table 2-82

OBSERVED AND EXPECTED DEATHS FOR 3 GROUPS OF MALE NICKEL WORKERS, 20 YEARS OR MORE AFTER FIRST EXPOSURE[a]

	Hired before 1947				Hired after 1946	
	Refinery		Nonrefinery			
Cancer Type	O	E	O	E	O	E
All Malignant Neoplasms	27	19.22	133	131.24	9	12.80
Respiratory Neoplasms	10	7.55	49	46.62	4	6.26

[a]From Enterline and Marsh (233).

Table 2-83

DOSE AND RESPONSE DATA FOR NICKEL-EXPOSED COHORT STUDIED BY ENTERLINE AND MARSH (233)[a]

Cumulative Exposure ($mg\text{-}yrs/m^3$)	Respiratory Cancer Deaths	
	Observed	Expected
< 0.83 (0.28, 0.35, 0.51)[b]	11	15.96
0.83 - 4.17 (1.83, 2.29, 3.32)	28	27.87
4.17 - 16.7 (6.63, 8.29, 12.0)	20	14.14
≥16.7 (37.6, 47.0, 68.2)	4	2.48

[a]Cumulative exposure is calculated for the first twenty years of employment and mortality is for the period starting at 20 years from first employment.

[b]In parentheses are the lower bounds, best estimates, and upper bounds for exposure in each dose group.

Table 2-84

NICKEL RESPIRATORY CANCER POTENCY PARAMETER ESTIMATES

Study	Dose Measure	Potencies ((mg-yrs/m^3)$^{-1}$) Lower Limit[a]	MLE	Upper Limit[a]
Polednak (232)	Upper Bounds	-6.71E-2*	3.94E-1	1.07
(Chi-squared (1) = 0.62)	Best Estimates	-1.89E-1	1.11*	2.99
	Lower Bounds	-3.77E-1	2.21	5.99*
Enterline & Marsh (233)	Upper Bounds	1.01E-3*	1.40E-2	3.10E-2
(Chi-squared (3) = 2.53)	Best Estimates	1.48E-3	2.03E-2*	4.49E-2
	Lower Bounds	1.85E-3	2.54E-2	5.62E-2*

[a]90% confidence limits are shown.
*An asterisk marks the parameters (i.e. the β_L, β, and β_u estimates) used to derive RRDs for each study.

Table 2-85

RRD ESTIMATES[a] FOR NICKEL (mg/m^3)

Study	Estimation Method	Level of Extra Risk: 10^{-6} RRD$_l$	10^{-6} MLE	10^{-6} RRD$_u$	0.25 RRD$_l$	0.25 MLE	0.25 RRD$_u$
Polednak (232)	1	4.54E-8	2.46E-7	∞	1.14E-2	6.15E-2	∞
	2	5.25E-8	2.84E-7	∞	1.61E-2	8.74E-2	∞
Enterline and Marsh (233)	1	4.84E-6	1.34E-5	2.69E-4	1.21	3.35	6.71E+1
	2	5.59E-6	1.55E-5	3.10E-4	1.71	4.76	9.54E+1

[a]Based on respiratory cancer risk.

PCB

Commercial preparations of polychlorinated biphenyls (PCBs) such as Aroclors and Kanechlors are mixtures containing the biphenyl molecule with a variable number of chlorines substituted at various locations on the double biphenyl ring. These mixtures are thermally stable and possess excellent dielectric properties. They were consequently used extensively for heat transfer, as in electric transformers, and in capacitors. PCBs have also been used in plasticizers, inks, and for carbonless duplicating paper (234). Production and use of PCBs in the U. S. has been severely limited, compared to earlier, large-scale use, since 1979. Older transformers and capacitors still contain PCBs so those maintaining them can be exposed (235). The stability of PCBs also ensures their presence in the environment for extended periods.

Although PCBs have been shown to be carcinogenic to rodents when administered orally, the short-term tests have been largely negative. Only two of many PCB mixtures tested have been shown to be mutagenic in the *Salmonella* test (2).

Acute effects of PCB poisoning have been observed in two incidents of accidental contamination of cooking oil. The long-term effects, such as cancer, of low-level, chronic exposure to PCBs are not well documented. This is so despite the fact that most individuals contain measurable quantities of PCB in their tissues (236) due mostly to consumption of contaminated food (237). By far the largest fraction of PCB that is absorbed is stored in the fat (238), and the half-life for PCB in the body is quite long.

Marino *et al*. (239, 240) have carried out an extensive occupational hygiene and acute health effect study of capacitor workers. PCB blood levels were determined for both current and past employees. The authors

state that blood concentrations of trichlorobiphenyls may reflect the current PCB exposure level more closely than that of pentachlorobiphenyls. Cancer follow-up was not available for this cohort.

Bahn *et al.* (241), in a preliminary report, document 2 malignant melanomas in a group of men thought to be heavily exposed to PCBs. Since standard rates would suggest that only 0.04 melanomas would be expected, these authors suggest that close attention be given to investigating any possible relationship. Melanomic response ties in with the other dermatological aspects of PCB exposure, chloracne and the contention of Maroni *et al.* (242, 243) that dermal exposure is the primary route of absorption. No further information is available on the cohort experiencing the increased rate of melanoma.

Two cohorts have been followed for cancer mortality and also have some data on PCB exposure. Bertazzi *et al.* (244, 245) discuss a cohort of workers employed at a capacitor manufacturing plant. The cohort members are men and women employed for at least one week between 1946 and 1978. Mortality was monitored through 1982.

Measurement of atmospheric PCB concentrations was rare. Three determinations in 1954 averaged 6100 $\mu g/m^3$. The next reported samples were done in 1977, by which time the concentrations were between 48 and 275 $\mu g/m^3$. The only other information relevant to estimation of exposure pertains to the types of PCBs used: before 1964 the most commonly used mixtures contained 54% chlorine, from 1965 to 1970 more 42% chlorine mixtures were used, and after 1970 only mixtures containing 42% chlorine were used (until 1980, when PCB use ceased). For cumulative exposure estimation, we assume an average concentration of 3000 $\mu g/m^3$.

The reports by Bertazzi *et al.* are limited in several other respects. The average duration of exposure is not given. We use the default value

of 7 years. Moreover, mortality experience is broken down by sex, but the same causes of death are not reported for each sex. The analyses for this cohort are therefore limited to those cancers documented in both males and females, *i.e.* all malignant neoplasms and hematologic neoplasms (Table 2-86). No malanomas were observed, but digestive system neoplasms were overrepresented in males.

The cumulative dose determined for this cohort is

$$(3000\ \mu g/m^3)\cdot(7\ \text{years}) = 21000\ \mu g\text{-yrs}/m^3.$$

The uncertainty associated with this estimate is considerable. The uncertainty factors, α and γ, are both equal to 3.3, leading to bounds on dose of 6364 and 69300 $\mu g\text{-yrs}/m^3$. The following summarizes the features influencing uncertainty calculations:

1. Length of exposure is completely unknown. Consequently, α_1 and γ_1 equal 1.5.
2. The plant was in operation, using PCBs, since 1946. The first PCB measurements were performed in 1954. This is a rather short time of undocumented exposure. In this case, α_2 and γ_2 are set equal to 0.3.
3. PCB concentration measurements are very incomplete. The average exposure we estimate is based on practically no information. Both α_3 and γ_3 have been set equal to 0.5.
4. A large uncertainty relates to the applicability of the atmospheric PCB concentrations. It is strongly suspected that skin absorption may be the route yielding the bulk of the PCB dose. In this special circumstance, a value of 1.0 is assigned to α_6 and γ_6.

Brown and Jones (235) identified a cohort of 2,567 employees engaged in the manufacture of electrical capacitors at two plants. Both plants had been using PCBs for more than 30 years. I[illegible]rial hygiene measurements (from 1977) at both plants revealed PCB levels, from personal air samples, of between 24 and 393 $\mu g/m^3$ in one plant and between 170 and 1260 $\mu g/m^3$ in the other. The authors state that the first plant had recently initiated new production techniques so that the lower atmospheric concentrations of PCBs were probably not representative of the exposures experienced by the workers for the majority of their employment. We assumed that the values reported at the second plant (Table 2-87) are more representative and have used those values for workers at both plants. The average exposure that is used in the subsequent calculations is 631 $\mu g/m^3$.

The distribution of the cohort members according to duration of employment in PCB-exposed jobs is given in Table 2-88. The data in that table suggest an average length of exposure of about 4 years.

The carcinogenic response seen in this cohort is presented in Table 2-89. None of the observed causes of death differed significantly from the expected values for the cohort as a whole. All malignant neoplasms and cancer of the rectum and liver have been broken down by length of employment (Table 2-90). No trend with increasing duration of employment is evident, but analysis by cumulative exposure is facilitated by such a presentation.

Since Bertazzi *et al.* present evidence of an increased risk of digestive system malignancies, that response, as well as lymphatic and hematopoietic system malignancies, liver cancer, and all malignant neoplasms, are used to calculate potencies. The latter two of the endpoints are analyzed using the duration groups shown in Table 2-90; dose and response data are presented in Table 2-91. Digestive and hematologic

cancers are not divided by duration of exposure. They are associated with an overall estimate of cumulative exposure, namely

$$(631\ \mu g/m^3)\cdot(4\ \text{years}) = 2524\ \mu g\text{-yrs}/m^3.$$

Uncertainty in this cohort study is described below:

1. Length of exposure is well documented, although the duration catagories are presented without average values. A value of 0.2 is assigned to α_1 and γ_1 for all end points.
2. The only measurements of PCB concentrations were done in 1977, so many years of exposure are undocumented. No attempt was made to estimate earlier levels, which were probably higher than those measured in 1977. Consequently, $\alpha_2 = 0$ but $\gamma_2 = 0.8$.
3. Given the large variability seen among the various job titles, relatively few measurements are available, even in 1977. To reflect this uncertainty, α_3 and γ_3 have been set equal to 0.3.
4. The same concern about the applicability of atmospheric PCB concentrations as was present in the Bertazzi study is present here. Again, α_6 and γ_6 are set equal to 1.0.
5. National mortality rates were used to calculate expected numbers of deaths. Some small amount of uncertainty is associated with this choice; α_8 and γ_8 are set equal to 0.05.

The uncertainty factors are $\alpha = 2.55$ and $\gamma = 3.35$.

The potency parameters shown in Table 2-92 and the corresponding RRD estimates (Table 2-93) reveal a substantial difference between the two studies. The Brown and Jones study is essentially negative; the Bertazzi *et al.* cohort did experience some increased mortality. The latter cohort is estimated to have encountered higher concentrations

the results are difficult to reconcile.

Table 2-86

MORTALITY EXPERIENCE OF A PCB-EXPOSED COHORT OF WORKERS[a]

Cause of Death	Observed Deaths	Expected Deaths
All neoplasms	26	12.9
Hematologic Neoplasms	7	2.2

[a]From Bertazzi *et al.* (245).

Table 2-87

CONCENTRATIONS OF PCB AT PLANT 2[a]

Job Title	Number of Samples	Total Sampling Time (min)	TWA ($\mu g/m^3$)
Degreaser	1	381	1260
Solder	3	884	1060
Tanker	9	2120	850
Moveman (soldering area)	3	752	720
Heat soak operator	3	872	630
Tester	3	917	290
Pump mechanic	1	377	280
Floorman (pre-assembly)	6	1683	170

[a]From Brown and Jones (235); personal air samples are reported.

Table 2-88

DURATION OF EMPLOYMENT AMONG COHORT MEMBERS IN PCB EXPOSURE JOBS[a]

Duration	Plant 1	Plant 2	Total
3 - 6 mo.	216	418	634
6 mo. - 1 yr.	147	288	435
1 - 2 yr.	185	293	478
2 - 3 yr.	94	146	240
3 - 10 yr.	247	311	558
10+ yr.	79	143	222
TOTAL	968	1599	2567

[a]From Brown and Jones (235).

Table 2-89

CANCER RESPONSE AMONG CAPACITOR MANUFACTURERS[a]

Neoplasm	Observed Deaths	Expected Deaths
All maglignant neoplasms	39	43.79
Digestive organs and peritoneum	13	9.85
Respiratory system	7	7.98
Lymphatic and hematopoietic	2	4.34
Other	17	21.62

[a]From Brown and Jones (235).

Table 2-90

OBSERVED AND EXPECTED CANCER DEATHS BY
LENGTH OF EXPOSURE AMONG CAPACITOR MANUFACTURERS[a]

Neoplasm	Length of Employment (yrs)	Deaths Observed	Deaths Expected
All malignant neoplasms	0.25 - 5	31	30.99
	5 - 9	3	7.05
	10 - 14	3	3.28
	15 - 19	2	1.73
	20 +	0	0.74
Rectum	0.25 - 5	2	0.83
	5 - 9	0	0.20
	10 - 14	2	0.09
	15 - 19	0	0.05
	20 +	0	0.02
Liver	0.25 - 5	3	0.74
	5 - 9	0	0.19
	10 - 14	0	0.08
	15 - 19	0	0.04
	20 +	0	0.02

[a]From Brown and Jones (235).

Table 2-91

DOSE AND RESPONSE DATA FOR BROWN AND JONES COHORT OF PCB-EXPOSED WORKERS

Cumulative Dose (μg-yrs/m^3)	All Malignant Neoplasms		Liver Cancers	
	Observed	Expected	Observed	Expected
1578 (619, 5286)[a]	31	30.99	3	0.74
4732 (1856, 15852)	3	7.05	0	0.19
7888 (3039, 26424)	3	3.28	0	0.08
11042 (4330, 36991)	2	1.73	0	0.04
15775 (6186, 52846)	0	0.74	0	0.02

	Digestive Organ Cancers		Lymphatic and Hematopoietic Cancers	
	Observed	Expected	Observed	Expected
2524 (990, 8455)	13	9.85	2	4.34

[a]In parentheses are the lower bounds and upper bounds, respectively, for cumulative dose in each group.

Table 2-92

POTENCY PARAMETER ESTIMATES FOR PCBs

Study	Response	Dose Measure	Potencies ((μg-yrs/m³)⁻¹) Lower Limit[a]	MLE	Upper Limit[a]
Bertazzi *et al.* (244, 245)	All Malignant Neoplasms (0 degrees of freedom)	Upper Bounds	7.94E-6*	1.47E-5	2.26E-5
		Best Estimates	2.62E-5	4.84E-5*	7.45E-5
		Lower Bounds	8.65E-5	1.60E-4	2.64E-4*
	Hematologic Neoplasms (0 degrees of freedom)	Upper Bounds	1.27E-5*	3.15E-5	5.75E-5
		Best Estimates	4.18E-5	1.04E-4*	1.90E-4
		Lower Bounds	1.38E-4	3.43E-4	6.26E-4*
Brown & Jones (235)	All Malignant Neoplasms (chi-squared (4) = 3.13)	Upper Bounds	-2.16E-5*	0.00	6.82E-6
		Best Estimates	-7.25E-5	0.00*	2.29E-5
		Lower Bounds	-1.85E-4	0.00	5.85E-5*
	Liver Cancer (chi-squared (4) ≤ 4.8)	Upper Bounds	-6.54E-5*	7.00E-5	3.12E-4
		Best Estimates	-2.19E-4	2.35E-4*	1.04E-3
		Lower Bounds	-5.57E-4	6.06E-4	2.68E-3*

Table 2-92 (continued)

POTENCY PARAMETER ESTIMATES FOR PCBs

Study	Response	Dose Measure	Potencies ($(\mu g\text{-}yrs/m^3)^{-1}$) Lower Limit[a]	MLE	Upper Limit[a]
Brown & Jones (235)	Digestive System Neoplasms (0 degrees of freedom)	Upper Bounds	-1.13E-5*	3.78E-5	1.00E-4
		Best Estimates	-3.78E-5	1.27E-4*	3.35E-4
		Lower Bounds	-9.64E-5	3.23E-4	8.55E-4*
	Hematologic Neoplasms (0 degrees of freedom)	Upper Bounds	-1.07E-4*	0.00	3.73E-5
		Best Estimates	-3.60E-4	0.00*	1.25E-4
		Lower Bounds	-9.17E-4	0.00	3.19E-4*

[a]90% confidence limits are shown.
*An asterisk marks the parameters used to derive RRD estimates.

Table 2-93

RRD ESTIMATES FOR PCBs ($\mu g/m^3$)

Study	Response	Estimation Method	Level of Extra Risk: 10^{-6} RRD_L	10^{-6} MLE	10^{-6} RRD_u	0.25 RRD_L	0.25 MLE	0.25 RRD_u
Bertazzi et al. (244, 245)	All Malignant Neoplasms	1	3.20E-4	1.63E-3	9.91E-3	8.00E+1	4.07E+2	2.48E+3
		2	4.21E-4	2.14E-3	1.30E-2	1.35E+2	6.86E+2	4.17E+3
	Hematologic Neoplasms	1	8.49E-4	5.11E-3	4.19E-2	2.12E+2	1.28E+3	1.05E+4
		2	9.79E-4	5.90E-3	4.83E-2	3.25E+2	1.96E+3	1.60E+4
Brown & Jones (235)	All Malignant Neoplasms	1	1.35E-3	∞	∞	3.37E+2	∞	∞
		2	1.77E-3	∞	∞	5.67E+2	∞	∞
	Liver Cancer	1	5.25E-3	5.99E-2	∞	1.31E+3	1.50E+4	∞
		2	5.70E-3	6.51E-2	∞	1.79E+3	2.04E+4	∞
	Digestive System Neoplasms	1	4.26E-4	2.88E-3	∞	1.07E+2	7.19E+2	∞
		2	4.81E-4	3.25E-3	∞	1.57E+2	1.06E+3	∞
	Hematologic Neoplasms	1	1.67E-3	∞	∞	4.17E+2	∞	∞
		2	1.92E-3	∞	∞	6.37E+2	∞	∞

Phenacetin

Phenacetin (CAS No. 62-44-2) is an aniline derivative that has been used extensively in analgesic mixtures, usually in combination with phenazone and caffeine. It has been produced in the U.S. for over 50 years (246). Abuse of these analgesic mixtures has been associated with nephropathic changes, notably renal papillary necrosis. Suggestions of carcinogenicity have come from animal studies and numerous human case reports (see below). Short-term tests have been equivocal. Phenacetin was mutagenic in the *Salmonella* test in the presence of hamster liver microsome preparations, but not in the presence of rat or mouse preparations. A minor human metabolite of phenacetin was mutagenic. Some chromosome aberrations due to phenacetin have been reported, but recessive lethal mutations and micronuclei were absent in some test systems (2).

Case reports of renal pelvis carcinoma in association with renal papillary necrosis have proliferated since the first report of such effects by Hultengren *et al.* (247). In that report, 5 of the 6 necrosis-carcinoma cases were in abusers of phenacetin-containing analgesics (abuse was defined as intake of 1 g of phenacetin per day for at least one year or a total consumption exceeding 1 kg). Case descriptions that followed came from Australia (248), the United States (249), and particularly Sweden, where Bengtsson, Angervall, and their associates have described a number of studies of urinary tract disorders. In one early study (250) 242 patients with chronic non-obstructive pyelonephritis were classified according to analgesic abuse. Eight of the 104 abusers developed transitional cell tumors of the renal pelvis; none of the nonabusers developed those tumors. The period of observation averaged slightly over 5 years in the 79% of the patients who were followed up. Angervall *et al.* (251) retrospectively studied the 15 cases of renal pelvis tumors seen in one hospital between 1960 and 1968. Ten could with certainty be classified as abusers; two others may also

have ingested large amounts of phenacetin. Further evidence of a link between phenacetin-containing analgesic and renal pelvis cancer was presented by Johansson *et al.* (252). Of 62 patients with such cancer, 38 had definite history of abuse. For the remaining patients "it could only be stated that there had been heavy abuse ... over several years." By 1978 (253) these authors were able to identify more than 100 cases of uroepothelial renal pelvis tumors associated with abuse of phenacetin-containing analgesics, mostly from Sweden.

Other aspects of the carcinogenicity of phenacetin have been noted. Burnett *et al.* (249) describe a case of renal pelvis cancer that developed in the remarkably short period of 4 months. Transitional-cell carcinomas of the bladder have been linked to long-term use of analgesics containing phenacetin (254). By 1975, Rathert *et al.* (255) could identify from the literature 119 cases of renal pelvis carcinoma (at least 3 with coincident bladder cancer) and 5 patients with bladder tumors all of whom had ingested large quantities of analgesics. The only common ingredient in the analgesic mixtures was phenacetin. These authors suggest however that phenazone and caffeine, commonly mixed with phenacetin, enhance the excretion of the potentially carcinogenic metabolites of phenacetin.

Epidemiologic studies, as opposed to case reports, have further implicated analgesic abuse as a cancer risk factor. Gonwa *et al.* (256) conducted both prospective and retrospective studies. In the retrospective mode, 115 patients with transitional-cell carcinoma of the renal pelvis, ureter, bladder, or urethra were seen in one hospital between January, 1974 and April, 1979. Of these, 6 had analgesic-associated nephropathy (they consumed 9 to 36 g of phenacetin during 20 to 40 years of analgesic ingestion). Compared to the 109 cases without analgesic abuse, these 6 cases had significantly more renal pelvis tumors (compared to numbers of ureter, bladder, or urethra cancers) and a

significantly greater mortality rate. The prospective study identified 98 patients with interstitial nephritis not associated with analgesic abuse and 48 patients with interstitial nephritis associated with analgesic abuse. These individuals were followed up for 3 to 5 years. Four of the 48 and none of the 98 patients developed transitional-cell carcinoma of the urinary tract, a significant difference.

A case-control study in the Netherlands investigating phenacetin use and bladder cancer was reported by Fokkens (257). A total of 1084 bladder cancer patients and 1094 control patients were interviewed about their consumption of analgesic drugs. Eighteen cases and 16 controls admitted to more than incidental intake of phenacetin-containing analgesics. The majority of the preparations contained 250 mg phenacetin, 250 mg acetosal, and 50 mg of caffeine. This information has been used to convert consumption to grams of phenacetin-containing analgesics, so as to be compatible with other studies (see below). That is, 1 g of phenacetin is assumed to be equivalent to 2.2 g of phenacetin-containing analgesic. The distribution of consumption in these units is displayed in Table 2-94.

Uncertainty in this study stems from a variety of sources which combine to yield uncertainty factors α and γ both equal to 1.55. Specific items are discussed below:

1. As in most case-control studies, the subjects were required to recall both duration and dosage of analgesic use. This feature has prompted us to assign a value of 0.1 to α_1 and γ_1 (for uncertainty in duration) and to α_6 and γ_6 (for uncertainty in daily dose).
2. We converted from measurements of phenacetin to measurements of analgesics. To the extent that consumption deviated from the 250 mg of phenacetin per 550 mg analgesic (45% phenacetin),

uncertainty is introduced. Fokkens merely states that the majority of the analgesics were of that mixture; other authors have reported mixtures containing 43% phenacetin (255) and IARC (246) lists mixtures that have as little as 32% and as much as 86% phenacetin. In any case, this factor is not believed to contribute greatly to uncertainty, so α_7 and γ_7 have been set equal to 0.05.

3. Finally, in lieu of expected numbers of cancers, the study design calls for selection of an appropriate control series. Since the controls were not individually matched to the cases in this study, the value 0.3 has been chosen for α_8 and γ_8.

The bounds on dose resulting from these uncertainty considerations are displayed in Table 2-94.

McCredie *et al.* (258) conducted a case-control study carried out in New South Wales, Australia that investigated renal pelvis cancer rather than bladder cancer. Forty women and 27 men were histologically confirmed to have renal pelvis cancer. Two control series were selected. The first (49 women and 35 men) were friends or relatives of cancer or renal disease patients. The second (61 women and 35 men) were selected from among individuals attending a walk-in clinic. Interviewers elicited information on analgesic consumption and smoking.

The authors present results relating to phenacetin-containing for women only, since so few men consumed analgesics. Ignoring analgesics consumed less than 5 years before the diagnosis or interview, the distribution of cases and controls by total phenacetin-containing analgesic consumption is shown in Table 2-95. The average consumption values shown in that table have been estimated; the value of 25 g in the lowest consumption group is due to the fact that those with absolutely no consumption have been merged with those who consumed some, but less

than 100 g, of phenacetin-containing analgesics.

Uncertainty considerations in this study are in many ways similar to those pertaining to the Fokkens study, as discussed as follows:

1. Recall uncertainty contributes the same value of 0.1 to α_1, γ_1, α_6 and γ_6.
2. Total consumption groups are presented without average values. The intervals are wide, so the maximum value, 0.3, is assigned to α_4 and γ_4.
3. Once again, nonmatched controls entail a value of 0.3 for α_8 and γ_8.

The uncertainty factors, $\alpha = \gamma = 1.8$, result in the bounds on dose shown in Table 2-95.

McCredie and her associates conducted another case-control study among females in Australia, this time examining both bladder and renal pelvis cancer cases and nonmatched controls drawn from the electoral rolls of New South Wales (259). Mailed questionnaires elicited information on analgesic consumption, smoking history, as well as demographic data. One hundred fifty-four (154) bladder cancer cases and 31 renal pelvis cancer cases, along with 440 controls, were enrolled. Significantly fewer controls were smokers than either case series. Phenacetin-containing analgesic consumption was also more prevalent among the cases; for both bladder and renal pelvis cancer a dose-response trend with respect to phenacetin consumption was evident, even after controlling for tobacco use. Table 2-96 displays the distribution of cases and controls according to phenacetin analgesic intake. The table also lists the estimated average total intake values for the groups defined, i.e. 25, 550, and 2000 g of phenacetin-containing analgesics, and the bounds on total dose.

Those bounds come from the following features of the study, the same ones affecting the earlier McCredie *et al.* study:

1. Recall uncertainty contributes a value of 0.1 to α_1, γ_1, α_6, and γ_6, as in the previous two studies.
2. Again, no average values for the groups are presented. Both α_4 and γ_4 equal 0.3
3. Nonmatched controls entail a value of 0.3 for α_8 and γ_8. Overall uncertainty is reflected in the factors $\alpha = \gamma = 1.8$.

All three of the case-control studies described above have been used to derive potency estimates (Table 2-97). The RRD estimates obtained by application of those potency parameters in the standard exposure scenario are also available (Table 2-98).

Table 2-94

NUMBER OF BLADDER CANCER CASES AND CONTROLS FROM FOKKENS (257), BY TOTAL PHENACETIN-CONTAINING ANALGESIC CONSUMPTION

Total Phenacetin-Containing Analgesic Consumption (g)	Cases	Controls
0	1003	1017
<4400 (1296, 2009, 3114)[a]	6	13
4400 - 12100 (4684, 7260, 11253)	9	3
>12100 (17268, 26765, 41486)	3	0

[a]In parentheses are the lower bounds, best estimates, and upper bounds, respectively, for total dose in each group.

Table 2-95

NUMBER OF FEMALE RENAL PELVIS CANCER CASES AND CONTROLS FROM MCCREDIE *ET AL.* (258), BY CONSUMPTION OF PHENACETIN-CONTAINING ANALGESICS

Phenacetin-Containing Analgesic Consumption (g)[a]	Cases	Controls[b]
< 100 (13.9, 25, 45)[c]	15	87
100 - 5000 (1417, 2550, 4590)	7	17
> 5000 (4167, 7500, 13500)	18	6

[a]Ignoring consumption less than 5 years prior to diagnosis of cancer or interview.
[b]Both control series have been combined.
[c]In parentheses are the lower bounds, best estimates, and upper bounds, respectively, for total dose in each group.

Table 2-96

NUMBER OF BLADDER CANCER AND RENAL PELVIS CANCER CASES AND CONTROLS FROM MCCREDIE *ET AL.* (259) BY CONSUMPTION OF PHENACETIN-CONTAINING ANALGESICS[a]

Phenacetin-Containing Analgesic Consumption (g)	Bladder Cancer Cases	Renal Pelvis Cancer Cases	Controls
< 100 (14, 25, 45)[b]	113	17	384
100 - 1000 (305, 550, 990)	6	0	9
> 1000 (1111, 2000, 3600)	35	14	47

[a]The numbers are estimated from percentages given in the original article.

[b]In parentheses are the lower bounds, best estimates, and upper bounds, respectively, for total dose in each group.

Table 2-97

PHENACETIN POTENCY PARAMETER ESTIMATES

Study	Response	Dose Measure	Potencies ((g-yrs)$^{-1}$) Lower Limit[a]	MLE	Upper Limit[a]
Fokkens (257)	Bladder cancer (chi-squared (2) = 5.5)	Upper Bounds	7.34E-3*	3.16E-2	7.63E-2
		Best Estimates	1.14E-2	4.90E-2*	1.18E-1
		Lower Bounds	1.76E-2	7.59E-2	1.83E-1*
McCredie *et al.* (258)	Renal pelvis cancer (chi-squared (1) = 2.8)	Upper Bounds	1.56E-1*	2.76E-1	4.67E-1
		Best Estimates	2.80E-1	4.97E-1*	8.38E-1
		Lower Bounds	5.04E-1	8.96E-1	1.51*
McCredie *et al.* (259)	Bladder cancer (chi-squared (1) = 0.8)	Upper Bounds	9.31E-2*	1.68E-1	2.69E-1
		Best Estimates	1.68E-1	3.03E-1*	4.85E-1
		Lower Bounds	3.03E-1	5.46E-1	8.76E-1*
	Renal pelvis cancer (chi-squared (1) = 1.0)	Upper Bounds	3.30E-1*	6.01E-1	1.00
		Best Estimates	5.59E-1	1.09*	1.82
		Lower Bounds	1.07	1.96	3.29*

[a]90% confidence limits are shown.

*An asterisk marks the parameters (μ_L, μ, μ_U) used to derive RRDs for each study and response.

Table 2-98

RRD ESTIMATES FOR PHENACETIN (g/day)

Study	Response	Estimation Method	Level of Extra Risk 10^{-6} RRD_L	MLE	RRD_u	0.25 RRD_L	MLE	RRD_u
Fokkens (257)	Bladder Cancer	1	4.25E-6	1.59E-5	1.06E-4	1.06	3.98	2.65E+1
		2	4.69E-6	1.75E-5	1.17E-4	1.52	5.68	3.79E+1
McCredie et al. (258)	Renal Pelvis Cancer	1	1.60E-6	4.86E-6	1.55E-5	3.99E-1	1.22	3.88
		2	1.83E-6	5.57E-6	1.78E-5	5.62E-1	1.71	5.46
McCredie et al. (259)	Bladder Cancer	1	8.89E-7	2.58E-6	8.37E-6	2.22E-1	6.44E-1	2.09
		2	9.81E-7	2.84E-6	9.23E-6	3.18E-1	9.20E-1	2.99
	Renal Pelvis Cancer	1	7.35E-7	2.23E-6	7.32E-6	1.84E-1	5.56E-1	1.83
		2	8.42E-7	2.55E-6	8.39E-6	2.58E-1	7.83E-1	2.58

Reserpine

Reserpine, a medicinal drug extracted from the roots of the plant *Rauwolfia serpentina*, is used to treat hypertension and has been used in the past as a sedative (260). It has been suggested (261) that reserpine may act as a "promoter" of breast cancer, that it affects cancer incidence only while it is being used. Short-term tests for mutations, chromosomal aberrations, or DNA synthesis have been uniformly negative (2). In fact, the epidemiologic literature presents a mixed picture of reserpine as a carcinogen. A portion of that literature is reviewed below.

The carcinogenic response suggested by some studies to be associated with reserpine use is breast cancer. Ross *et al.* (262) compared prolactin levels in long-term reserpine users to those in non-users. It is suspected that prolactin may play a role in breast carcinogenesis. Although the mean prolactin level was 50% higher among the reserpine users, Ross *et al.* suggest that that increased level would most likely cause only a small increase in breast cancer incidence.

Two case-control studies published in 1975 (263, 264) failed to find a purported association between reserpine use and breast cancer. A further study (265) found that a link between reserpine use and breast cancer disappeared after correcting for other variables (in this case, duration of hypertension, the condition treated by reserpine). Kewitz *et al.* (266) corroborate the lack of a strong etiologic contribution from reserpine. In one of two prospective studies, Labarthe and O'Fallon (267) did not discern an effect due to reserpine use; among users 11 cases were observed with 10.8 expected. On the other hand, Danielson *et al.* (261) followed up women in a group health organization and found a relative risk of 1.7 for recent users of reserpine with respect to breast cancer. This result was not significant however; the

90% confidence limit on the relative risk included 1.

One case-control study and one clinical trial report provide information necessary for a quantitative estimation of reserpine risk. The case-control study (268) selected 273 breast cancer patients from 5 Baltimore-area hospitals and two individually-matched control series, one from the hospitals and one from the neighborhoods of the cases. Overall, reserpine use was not associated with breast cancer, no matter which control group was used. For analysis of response by total dose, a significant portion of the cases and controls could not be used; they had incomplete data on reserpine use. The portions of the groups that do have adequate data used reserpine as shown in Table 2-99. Displayed in that table are the cases matched to the neighborhood controls and the neighborhood controls themselves; this case-control pairing provided the highest proportion of cases with adequate data.

The dose data presented in Table 2-99 results from the following considerations. The best estimates are arithmetic averages of the group-defining ranges. Uncertainty considerations are as follows:

1. Dose determination depends on recall of past behavior. In this case, the cases and controls were asked who had treated them for hypertension. Then, at that point, doctors' or hospitals' records were checked for dosage and duration. That being the case, uncertainty related to recall affects only the upper bound: dose will not be smaller than determined by this method, but if periods of treatment are not recalled, dose could be larger. The factor related to upper bound calculation and completeness of measurement, γ_3, is set equal to 0.2; $\alpha_3 = 0$.
2. The dose groups were presented without average values. The limits of the groups are fairly small. A nominal value of 0.1 is assigned to α_4 and γ_4.

3. The neighborhood controls were matched to the cases on the basis of age (± 5 years), race, and neighborhood of residence. Other health and demographic characteristics did not differ either (except for number of nulliparous or primiparous women: 42% of the cases as opposed to 27% of the controls). On the other hand, a large fraction of the cases and controls did not have dose information. It is not known if this has influenced the comparability of the two groups. A value of 0.1 is assumed for α_8 and γ_8.

The resulting factors, $\alpha = 1.2$ and $\gamma = 1.4$, determine the bounds on dose. These bounds and the best estimates are used in the estimation of β, β_L, and β_u (Table 2-100).

The Hypertension Detection and Follow-Up Program provides data on more than 2500 women treated for hypertension. Curb *et al.* (269) have used this program to investigate the reserpine-breast cancer association. A total of 1036 women received reserpine at one time or another, for an average of 1.97 years. The dosage of reserpine prescribed was between 0.1 and 0.25 mg/day (assumed average 0.175 mg/day). The resulting cumulative dose for those taking reserpine is estimated to be

$$(1.97 \text{ years})\cdot(0.175 \text{ mg/day}) = 0.345 \text{ mg-yrs.}$$

Seven breast cancers were observed among the reserpine users. Based on the experience of the 1493 women who never took reserpine during the study, the relative risk for breast cancer among the reserpine users is estimated to be 1.28, adjusting for age, race, and whether or not hypertension treatment had begun before the study began. This corresponds to an expected value of 5.47 breast cancers. The observed and expected responses (7 vs. 5.47) are used with the dose data to determine the potency parameter estimates shown in Table 2-100. The best estimate of

dose is presented above, 0.345 mg-yrs, and the bounds, 0.265 and 0.586 mg-yrs, are consequences of the uncertainty factors α and γ, 1.3 and 1.7, respectively, which are determined as follows:

1. The medications prescribed prior to the study for those with hypertension are not documented. Over a quarter of the women in the study had had hypertension for 10 years or longer. A substantial portion of time, with potential reserpine use, is not factored into the dose calculations. Once again, this affects only the upper bound on average dose. The factor γ_2 is set equal to 0.4 to account for this, whereas α_2 is set to zero.
2. The range of dosage (0.1 to 0.25 mg/day) is presented but no average dosage is presented. This fairly narrow range is consistent with α_4 und γ_4 equal to 0.1.
3. The expected number of breast cancers is based on specially-treated hypertensives who never received reserpine and is adjusted for age, race, and prior antihypertension medication use. Some variability in that calculation is presented by Curb *et al*. Consequently, α_8 and γ_8 have been assigned a value of 0.2 to account for that variability and the uncertainty with regard to selection of the model used to estimate relutive risk.

RRD estimates derived from these two sources, the case-control study of Lilienfeld *et al*. and the prospective study by Curb *et al*. are based on the potency parameters shown in Table 2-100. The RRDs are displayed in Table 2-101. The prospective study (269) is not inconsistent with a hypothesis of no carcinogenic effect of reserpine.

Table 2-99

BREAST CANCER CASES AND MATCHED NEIGHBORHOOD CONTROLS WITH RESPECT TO CUMULATIVE DOSE OF RESERPINE; DATA FROM LILIENFELD *ET AL.*

Cumulative Dose (mg-yrs)[a]	Cases	Controls
0	121	119
0 - 0.068 (0.028, 0.034, 0.048)[b]	3	4
0.071 - 0.137 (0.086, 0.103, 0.144)	2	5
0.140 - 0.822 (0.399, 0.479, 0.671)	5	3
0.822+ (1.028, 1.233, 1.726)	3	0

[a]Lilienfeld *et al.* present total doses in mg. Cumulative doses were derived by dividing by 365. 1 mg-yr is equivalent to taking 1 mg of reserpine per day for a year.

[b]In parentheses are the lower bounds, best estimates, and upper bounds, respectively, for average dose in each group. These were not presented by the original authors.

Table 2-100

BREAST CANCER POTENCY PARAMETER ESTIMATES FOR RESERPINE

Study	Dose Measure	Potencies ((mg-yrs)$^{-1}$) Lower Limit[a]	MLE	Upper Limit[a]
Lilienfeld et al. (268) (chi-squared (3) = 3.05)	Upper Bounds	1.51E-1*	1.44	4.36
	Best Estimates	2.11E-1	2.02*	6.10
	Lower Bounds	2.54E-1	2.42	7.32*
Curb et al. (269) (0 degrees of freedom)	Upper Bounds	-4.83E-1*	5.53E-1	1.98
	Best Estimates	-7.08E-1	8.11E-1*	2.91
	Lower Bounds	-9.22E-1	1.06	3.79*

[a]90% confidence limits are shown.
*An asterisk marks the parameters used to derive RRD estimates.

Table 2-101

RRD ESTIMATES[a] FOR RESERPINE (mg/day)

Study	Estimation Method	Level of Extra Risk: 10^{-6} RRD$_l$	10^{-6} MLE	10^{-6} RRD$_u$	0.25 RRD$_l$	0.25 MLE	0.25 RRD$_u$
Lilienfeld *et al.* (268)	1	2.63E-8	9.53E-8	1.28E-6	6.58E-3	2.38E-2	3.19E-1
	2	3.31E-8	1.20E-7	1.61E-6	9.72E-3	3.52E-2	4.71E-1
Curb *et al.* (269)	1	5.08E-8	2.37E-7	∞	1.27E-2	5.94E-2	∞
	2	6.40E-8	2.99E-7	∞	1.88E-2	8.76E-2	∞

[a]Based on the risk of breast cancer.

Saccharin

The artificial sweetener saccharin (CAS No. 128-44-9) was discovered accidentally in 1879 and has been the subject of debate with respect to its safety for human consumption since about 1890. Not only is saccharin a sweetener, it is used as a brightener in automobile bumpers, as an intermediary in fungicide production, and previously as an antiseptic and food preservative. The primary exposure for humans is from low-sugar food and beverages and sugar substitutes (270).

Short-term testing of saccharin has produced mixed results. It is mutagenic in cells of some animal and plant species but not in others or in bacteria. In mammalian cells, there are conflicting reports about induction of chromosomal anomalies *in vitro*, about production of dominant lethal mutations, and about specific-locus somatic mutation test results. No data on humans are available (2).

A pharmacokinetic study in women who use saccharin daily showed that saccharin is rapidly absorbed into the blood and is retained with a half-life of about 7.5 hours (271). The data from this study also indicate that one or more high-retention areas may exist. Animal species tested stored saccharin in high concentration in the kidney and urinary bladder. The lower urinary tract is the area of greatest concern for human saccharin carcinogenesis.

In fact, several investigations have examined the relationship between saccharin consumption and cancer of the bladder. In 1974, Morgan and Jain (272) conducted a case-control study that could find no association between artificial sweetener use and bladder cancer, although the risk was increased among smokers and, especially, male smokers who drank cola or alcohol. On the other hand, Howe *et al.* (273) claim that a significantly increased relative risk of 1.6 exists in males who ever used

saccharin as opposed to those who never used saccharin. These authors also claim a dose-response relationship was seen for both duration and frequency of use.

Further investigations have failed to confirm this finding. Morrison and Buring (274), in a case-control study of lower urinary tract cancer, found no consistent pattern of relative risk with respect to frequency or duration. Hoover and Strasser (275) performed a large, population-based case-control investigation. Again, no overall relationship between saccharin consumption and bladder cancer was noted, although non-smoking women and heavy-smoking men who also consumed artificial sweeteners, those groups suggested to be at greater risk on the basis of animal studies, did have increased risk. Wynder and Stellman (276) also conducted a case-control study, of bladder cancer in this case, and found no dose-response relationship with respect to saccharin consumed, measured by quantity, duration, or the combination of the two. These authors detected no evidence that artificial sweeteners promote the carcinogenic effect of tobacco smoke. Finally, a study from Denmark (277) failed to detect any increased risk among regular artificial sweetener users.

One other study has addressed this question and also provides quantitative estimates of exposure. Armstrong *et al.* (278) report the results of a prospective study of cancer mortality among members of the British Diabetic Association (BDA). The study included 5971 members, 3003 men and 2968 women, most of whom registered between 1965 and 1968. Deaths were monitored until July 1, 1973. A total of 16,247 person-years of observation were contributed by the males, 15,932 by the females. Four bladder cancer deaths were recorded whereas 5.8 were expected.

Saccharin consumption was determined from a survey of a sample of all BDA members polled in 1973. The males averaged 0.99 mg/kg body weight/

day of saccharin and the females 0.65 mg/kg/day, based on the reported average number of saccharin tablets per day and assumed average body weights like those of other diabetics. The duration of diabetes among those surveyed is distributed as in Table 2-102. If we use the mid-points of the intervals shown in that table (and use 35 years for the longest duration group) we can calculate an average duration of diabetes of

$$[(2.5 \times 539) + (7.5 \times 353) + (15 \times 384) + (25 \times 172) + (35 \times 99)] / 1547 = 11.3 \text{ years}$$

in the men and 11.4 years among the women. We assume that these values approximate the duration of saccharin use. The cumulative dose for the males is then

$$(0.99 \text{ mg/kg/day}) \times (11.3 \text{ yrs}) = 11.2 \text{ mg-yrs/kg}$$

and for females is 7.41 mg-yrs/kg. If these two values are averaged, with weights equal to the person-years of observation of each sex, a best estimate of cumulative exposure for members of this cohort is 9.32 mg-yrs/kg.

Uncertainties associated with that estimate, and with the study as a whole, combine to yield uncertainty factors α and γ both equal to 2.3. These have been derived as follows:

1. Length of saccharin use is greatly in question. Not only may duration of diabetes be a poor substitute for duration of consumption, but the duration categories are presented without average values. Both α_1 and γ_1 equal 0.3.
2. The surveys eliciting saccharin consumption patterns asked about current use. Different patterns that may have prevailed at earlier times are missed, contributing a value of 0.2 to α_2

and γ_2.

3. Substantial uncertainty is involved in the mere use of the numbers derived from the BDA survey. The subset included in the mortality study may have consumed saccharin at a rate different than the general membership. Consequently, we assign a value of 0.3 to α_6 and γ_6.
4. The authors converted consumptions measured in tablets of saccharin per day to mg/kg/day. That conversion relied on an average weight that was assumed to apply to the study participants, even though weights were not available for the participants themselves. The uncertainty in that conversion is probably not too great, so α_7 and γ_7 have been assumed to be 0.1.
5. Expected numbers of deaths were determined from a 10% random sample of deaths which occurred in England or Wales in 1972. It seems that this may introduce more uncertainty than using the entire population as the reference. We might also consider that bladder cancer is related to smoking, a factor not controlled for in the calculation of expected values. As a result, we assume that α_8 and γ_8 equal 0.4.

The bounds on cumulative dose resulting from these considerations are 4.05 and 21.44 mg-yrs/kg.

The potency parameters associated with the dose-response data from Armstrong *et al.* are displayed in Table 2-103. As expected, the RRD estimates derived from those parameters applied to the standard exposure scenario (45 years of exposure starting at age 20) indicate the lack of a strong relationship between saccharin and bladder cancer (Table 2-104). The finite lower bound on RRD reflects the degree of association that is possible given the statistical and other uncertainties associated with this single usable study.

and γ_2.

3. Substantial uncertainty is involved in the mere use of the numbers derived from the BDA survey. The subset included in the mortality study may have consumed saccharin at a rate different than the general membership. Consequently, we assign a value of 0.3 to α_6 and γ_6.
4. The authors converted consumptions measured in tablets of saccharin per day to mg/kg/day. That conversion relied on an average weight that was assumed to apply to the study participants, even though weights were not available for the participants themselves. The uncertainty in that conversion is probably not too great, so α_7 and γ_7 have been assumed to be 0.1.
5. Expected numbers of deaths were determined from a 10% random sample of deaths which occurred in England or Wales in 1972. It seems that this may introduce more uncertainty than using the entire population as the reference. We might also consider that bladder cancer is related to smoking, a factor not controlled for in the calculation of expected values. As a result, we assume that α_8 and γ_8 equal 0.4.

The bounds on cumulative dose resulting from these considerations are 4.05 and 21.44 mg-yrs/kg.

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Table 2-102

DURATION OF DIABETES AMONG BDA MEMBERS,
FROM DATA IN ARMSTRONG *ET AL.* (278)

Duration of Diabetes (yrs)	Number of Subjects Men	Women
0 - 4	539	475
5 - 9	353	306
10 - 19	384	408
20 - 29	172	156
30+	99	77

Table 2-103

BLADDER CANCER POTENCY PARAMETERS FOR SACCHARIN,
FROM DATA IN ARMSTRONG *ET AL.*[a]

Dose Measure	Potencies ((mg-yrs/kg)$^{-1}$) Lower Limit[b]	MLE	Upper Limit[b]
Upper Bounds	-3.30E-2*	0.00	1.62E-2
Best Estimates	-7.60E-2	0.00*	3.72E-2
Lower Bounds	-1.75E-1	0.00	8.57E-2*

[a]No degrees of freedom allow evaluation of the fit of the model.
[b]90% confidence limits are shown.
*An asterisk marks the parameters used to derive RRD estimates.

Table 2-104

RRD ESTIMATES[a] FOR SACCHARIN (mg/kg/day)

Estimation Method	Level of Extra Risk					
	10^{-6}			0.25		
	RRD_l	MLE	RRD_u	RRD_l	MLE	RRD_u
1	3.37E-5			8.42		
2	3.51E-5			1.25E+1		

[a]Based on the risk of bladder cancer and the data in Armstrong *et al.* (278).

Trichloroethylene

Trichloroethylene (CAS No. 79-01-6; abbreviated here TCI) is an asymmetrical ethylene similar in structure to vinyl chloride. Trichloroethylene is used primarily as a metal degreaser; it has been used as a solvent in the textile industry and for adhesives. In addition, trichloroethylene has served as a general anesthetic and for many years was used as an extraction solvent (for decaffeinating coffee, for example) (279).

Trichloroethylene is considered to be weakly mutagenic (and only when activated by an enzyme system) and weakly active in cell transformation (2, 280). In fact, it is believed that the short-lived, epoxide intermediate formed during trichloroethylene metabolism is the ultimate carcinogen which binds to cellular macromolecules.

Many articles have described human trichloroethylene pharmacokinetics and metabolism (281-287). Several of these describe the time course of trichloroethylene metabolites in blood, urine, and expired air under experimental conditions. One of them (282) presents data from an experiment in which volunteers were exposed to 200 ppm of trichloroethylene for 7 hours each of 5 consecutive days. If equilibrium between exposure to trichloroethylene and trichloracetic acid (TCA) excretion in urine occurs by the end of a working week (287), then the amount of TCA in urine corresponding to an occupational exposure to 200 ppm is roughly 400 mg/24 hr. If we assume that 1.2 to 2.4 liters of urine are voided in a 24-hour period (284), then the corresponding concentration of TCA is 167 to 333 mg/ℓ.

Occupational investigations of this relationship are also represented in the literature (284, 287). In a preliminary study, Smith (287 found that the ratio of time-weighted, atmospheric trichloroethylene (in ppm)

to urinary TCA concentration (in mg/ℓ) was roughly 1:2. He does not report the atmospheric concentrations studied. A more detailed study (284) presents TCA concentrations for trichloroethylene exposures ranging from 0 to 175 ppm. A nonlinear relationship was found; progressively larger atmospheric levels produce smaller increases in TCA excretion. That relationship is consistent with the data reported by Stewart *et al.* (282).

Several mortality studies have been reported (288-292). Only the studies by Axelson *et al.* and Tola *et al.* provide estimates of exposure, both of them in terms of TCA concentrations in urine. None of these mortality studies establish an association of trichloroethylene with a particular type of cancer. The study by Blair (290) of metal polishers and platers included workers exposed to TCI in degreasing operations. Increased proportional mortality was noted for liver and esophageal cancer but unfortunately no levels of TCI were recorded and exposure to other putative carcinogens including nickel and chromium compounds was also common. The brief report by Paddle (292) is intended merely to document the lack of liver cancers among TCI manufacturers, and the proportional mortality study by Blair *et al.* (290) of dry cleaning employees records no trichloroethylene exposures, which would in any case have been confounded by extensive contact with tetrachloroethylene and carbon tetrachloride. Due to limitations in the other studies, quantitative risk estimates will be derived from Tola *et al.* (291) and Axelson *et al.* (288) only.

The cohort of workers identified by Tola *et al.* is known from files of a Finnish laboratory that measured urine TCA concentrations of trichloroethylene-exposed workers. The total cohort contains 2084 men and women who contributed some 13933 person-years of follow-up. No single cancer type predominated; cancers of the gall bladder, lung, breast, uterus, and testis and multiple myeloma have been diagnosed.

Table 2-105 presents the distribution of cancer deaths found by Tola *et al.*--11 in all--by urine TCA concentrations. This table, and analysis of this cohort, will be limited to the authors' original list of workers who had their TCA levels measured (i.e. excluding the poisoning cases). No expected values are presented in this format and, unfortunately, the presentation of expected numbers in other places in the paper includes the poisoning cases. Bearing this in mind, two options are used to provide mortality data in the form needed:

1. Assume that the age distribution for each group in Table 2-105 is roughly the same and distribute the 14.3 expected cancer deaths over the groups according to the total number of workers in each group (Table 2-106). Tola *et al.* state that the expected number of cancers in their highest 3 categories (highest 2 in Table 2-106) is about 2 as opposed to our estimated 2.6, so our calculations could be considered to underestimate the relative risk in the higher groups.
2. Combine the groups from Table 2-105 into an aggregated group with one exposure estimate, 10 observed cancer deaths, and 13.8 expected cancer deaths.[a]

Both of these options require estimates of mean TCA concentrations, either for the groups as defined in Table 2-106 or for the cohort as a whole. For estimation of cumulative doses, this poses some problem because, in the first place, the values recorded are highest TCA measured with no accounting for lower levels and, secondly, no average duration of exposure is provided for members of this cohort. The second of these issues is dealt with by assuming a default value of 7 years average length of employment.

[a]The 13.8 expected deaths is based on inclusion of 2004 people in the analysis out of a total of 2084, the number on which the authors based the calculation of expected numbers.

Urine TCA concentrations were converted to atmospheric TCI levels by using data from Ikeda *et al.* (284) (Table 2-107). We determined that a simple linear regression of $\log_e(TCA)$ on $\log_e(TCI)$ provided an adequate description of the data. The resulting equation,

$$\log_e(TCA) = 1.57 + 0.82 \cdot \log_e(TCI) ,$$

was inverted to obtain estimates of TCI dependent on our estimated average TCA concentrations. The best estimates for each dose group, expressed in ppm-years, derived from the equation above, an assumed seven-year average exposure, and using midpoints of the intervals shown in Table 2-106 (300 in the last group) are given in Table 2-108.

Table 2-108 also presents reasonable upper and lower bound on those dose estimates. The group-dependent factors α and γ that determine the bounds are derived on the basis of the following considerations:

1. Length of exposure is completely unknown. Hence α_1 and γ_1 are set equal to 1.5.
2. The number of urine TCA concentration measurements for each individual varied and it is not known how frequently the measurements were taken. It appears that there is great uncertainty with respect to the completeness of the exposure profile of each individual, and so we set α_3 and γ_3 equal to 0.5.
3. The groups displayed in Table 2-106 are given without average values. As these had to be estimated, α_4 and γ_4 equal 0.2.
4. A serious recording bias exists due to the fact that the exposed individuals were classified according to their maximum TCA concentrations, as opposed to their average concentrations. We have no way to determine the averages, so α_5 has been set equal to 0.8 for all but the lowest group, for which $\alpha_5 = 0.4$.

In all cases $\gamma_5 = 0$.

5. Some uncertainty about the applicability of the reported TCA values for use in estimating TCI exposures is raised by Tola *et al.* when they state "it is possible that some of the workers with low urinary trichloracetic acid values were not actually exposed to trichloroethylene at all but to some other degreaser such as perchloroethylene." To reflect this $\alpha_6 = 0.2$ in the lowest group, $\alpha_6 = 0$ in the other groups, and $\gamma_6 = 0$ in all groups.
6. Another important uncertainty concerns the conversion from urine TCA concentrations to atmospheric TCI concentrations. We judge that α_7 and γ_7 should be equal to 1 to adequately cover all the variability inherent in that conversion.
7. Expected values were determined from national mortality rates, which is probably not too bad for a small country like Finland. However, we had to estimate the expected numbers of cancer deaths that were appropriate for each dose group. This adds uncertainty, reflected in the choice of 0.2 for α_8 and γ_8.

The overall uncertainty factors are $\alpha = 5.0$ in the lowest dose group, $\alpha = 5.2$ in all other dose groups, and $\gamma = 4.4$.

Axelson *et al.* (288) have identified a cohort of workers employed at a TCI producer in Sweden. Follow-up was successful for 518 men exposed to TCI with known duration of exposure, although that duration is not reported. Those men with a latency period of a least 10 years contributed 3843 person-years with 9 cancers observed. Again, no single type of cancer predominated - one each of stomach, colon, pancreas, pulmonary, prostate, kidney, and brain cancer and of melanoma and leukemia are represented. Men with at least 10 years latency were divided into high and low exposure groups based on average reported urine TCA concentrations, with 100 mg/ℓ as the cut point. This subcohort is the subject

of our analyses (Table 2-109).

The high exposure group corresponds in exposure to the highest group in the Tola *et al.* cohort. Consequently, we assumed the average TCA concentration for that group to be 300 mg/ℓ. A value of 50 mg/ℓ was used for the low exposure group. The corresponding atmospheric trichloroethylene concentrations, using the Ikeda *et al.* (284) data, are 154.7 and 17.4 ppm, re pectively. Since duration of exposure was not reported, the default value of 7 years was used so that the best estimates of dose are 121.8 and 1082.9 ppm-years for the low and high exposure groups, respectively.

Uncertainty considerations are very similar for the Axelson *et al.* data and the Tola *et al.* data. The uncertainty factors corresponding to the Axelson cohort have been derived as follows:

1. Length of exposure is, again, completely unknown so that α_1 and γ_1 are set equal to 1.5.

2. The laboratory that determined TCA concentrations discarded most records prior to 1967. Consequently the categorization is based only on more recent determinations. We have assigned a value of 0.2 to α_2 and a value of 0.4 to γ_2 to try to account for this uncertainty.

3. Once more, the completeness of the measurements is not documented, so that α_3 and γ_3 have been given a value of 0.5

4. No average values are provided for either exposure group. The value 0.2 is assigned to α_4 and γ_4.

5. The same uncertainties with respect to the applicability and conversion of urine TCA values are present here as were present in the Tola *et al.* study. Consequently $\alpha_6 = 0.2$ in the low dose group, $\alpha_6 = 0$ in the high dose group, $\gamma_6 = 0$ in both group, and $\alpha_7 = \gamma_7 = 1.0$ in both groups.

The resulting uncertainty factors are dose group dependent: for the low dose group $\alpha = 4.6$ and $\gamma = 4.6$; for the high dose group $\alpha = 4.4$ and $\gamma = 4.6$. The bounds on dose are displayed in Table 2-110.

The potency parameter estimates from these two studies are presented in Table 2-111 and the corresponding RRD estimates in Table 2-112. The data are consistent with a hypothesis of no carcinogenic activity for trichloroethylene (i.e. the upper bounds on RRD from both studies are infinite).

Table 2-105

DISTRIBUTION OF 2004 WORKERS EXPOSED TO TRICHLOROETHYLENE WITH REGARD TO THE HIGHEST MEASURED VALUE OF URINARY TRICHLORACETIC ACID (TCA)[a]

TCA in Urine (mg/ℓ)	Cancer Deaths	Others	Total
<10.0	4	883	887
10.0-49.9	2	736	738
50.0-99.9	2	192	194
100.0-499.9	2	164	166
≥500.0	0	19	19

[a]From Tola *et al.* (291)

Table 2-106

OBSERVED AND EXPECTED NUMBERS OF CANCER DEATHS BY HIGHEST MEASURED VALUE OF URINARY TRICHLOROACETIC ACID, TOLA *ET AL.* TRICHLOROETHYLENE-EXPOSED COHORT

TCA in Urine (mg/ℓ)	Total Number	Observed Cancer Deaths	Expected Cancer Deaths[a]
<10.0	887	4	6.1
10.0-49.9	738	2	5.1
50.0-99.9	194	2	1.3
≥100.0	185	2	1.3

[a]Expected values calculated by distributing the 14.3 deaths expected for the 2084 people by the number in each group.

Table 2-107

TCA CONCENTRATIONS IN URINE SAMPLES FROM WORKERS EXPOSED TO TRICHLOROETHYLENE AT VARIOUS CONCENTRATIONS[a]

Trichloroethylene Concentrations in the Air (ppm)	No. of Measurements	TCA Concentration[b] (mg/ℓ)
3	9	12.7 (8.8-18.2)
5	5	20.2 (10.0-40.8)
10	6	17.6 (10.3-30.0)
25	4	77.2 (51.6-115.6)
40	4	90.6 (50.2-163.8)
45	5	138.4 (83.2-216.5)
50	5	146.6 (76.3-281.7)
60	5	155.4 (104.3-231.4)
120	4	230.1 (199.0-267.4)
175	4	235.8 (187.2-296.9)

[a]From Ikeda *et al.* (284).
[b]Geometric means together with SD ranges in parentheses.

Table 2-108

DOSE AND RESPONSE DATA DERIVED FROM TOLA *ET AL.* TRICHLOROETHYLENE-EXPOSED COHORT

Group	Dose (ppm-years) Lower Bound	Best Estimate	Upper Bound	Observed Cancer Deaths	Expected Cancer Deaths
1	1.47	7.34	32.3	4	5.1
2	12.6	65.3	287.3	2	5.1
3	38.4	199.6	878.2	2	1.3
4	208.2	1082.6	4763.4	2	1.3
Entire Cohort	22.4	116.5	512.6	10	13.8

Table 2-109

DESCRIPTION OF THE AXELSON *ET AL.* SUBCOHORT OF TRICHLOROETHYLENE-EXPOSED MEN WITH AT LEAST 10 YEARS LATENCY[a]

Group	Person-years of Observation	Observed Number of Cancer Deaths	Expected Number of Cancer Deaths
1:Low Exposure (≤100 mg/ℓ TCA)	3095	6	7.7
2:High Exposure (>100 mg/ℓ TCA)	548	3	1.8

[a]From Axelson *et al.* (288).

Table 2-110

DOSE AND RESPONSE DATA DERIVED FROM THE
AXELSON *ET AL.* COHORT OF TRICHLOROETHYLENE-EXPOSED WORKERS

Group	Dose (ppm-years) Lower Bound	Best Estimate	Upper Bound	Observed Cancer Deaths	Expected Cancer Deaths
1	26.5	121.8	560.3	6	7.7
2	246.1	1082.9	4981.3	3	1.8

Table 2-111

POTENCY PARAMETER ESTIMATES FOR TRICHLOROETHYLENE[a]

Study	Dose Measure	Potencies ((ppm-yrs)$^{-1}$) Lower Limit[b]	MLE	Upper Limit[b]
Tola *et al.* (291) (chi-squared (3) = 3.00)	Upper Bounds	-1.04E-4*	8.95E-5	4.28E-4
	Best Estimates	-4.59E-4	3.94E-4*	1.88E-3
	Lower Bounds	-2.39E-3	2.04E-3	9.78E-3*
Axelson *et al.* (288) (chi-squared (1) = 5.9)	Upper Bounds	-7.09E-5*	9.65E-5	3.62E-4
	Best Estimates	-3.26E-4	4.44E-4*	1.67E-3
	Lower Bounds	-1.43E-3	1.99E-3	7.41E-3*

[a]Based on the risk of all malignant neoplasms.
[b]90% confidence limits are shown.
*An asterisk marks the parameters used to derive RRD estimates.

Table 2-112

RRD ESTIMATES[a] FOR TRICHLOROETHYLENE (ppm)

Study	Estimation Method	Level of Extra Risk 10^{-6} RRD_L	MLE	RRD_U	0.25 RRD_L	MLE	RRD_U
Tola *et al.* (291)	1	8.05E-6	2.00E-4	∞	2.01	5.00E+1	∞
	2	1.06E-5	2.63E-4	∞	3.39	8.42E+1	∞
Axelson *et al.* (288)	1	1.06E-5	1.77E-4	∞	2.66	4.43E+1	∞
	2	1.40E-5	2.33E-4	∞	4.48	7.47E+1	∞

[a]Based on the risk of all malignant neoplasms.

Vinyl Chloride

The halogenated hydrocarbon vinyl chloride (CAS No. 74-01-4) is used primarily in the plastics industry. At one time it was used as a refrigerant and as an extraction solvent (293). Vinyl chloride has been found to be mutagenic in a number of test systems, even in the absence of metabolic activation, and it induces chromosomal aberrations and sister chromatid exchanges *in vivo* in mammalian species. In addition, vinyl chloride was noted to have alkylated liver DNA of rats treated *in vivo* (2). It has been suggested (294) that the carcinogenic moiety of vinyl chloride may be the epoxide formed during metabolism.

The epidemiologic literature includes several articles describing the toxic and carcinogenic effects associated with vinyl chloride exposure. (295-302).

Although there are suggestions that vinyl chloride is linked to nervous system and hematopoietic and lymphatic system tumors, it is most firmly associated with angiosarcoma of the liver, a cancer rarely seen outside of vinyl chloride-exposed populations, and in occupational settings with respiratory cancer. In accordance with the guidelines outlined earlier in this section, risk estimates have been developed for liver cancer (since vital statistics on angiosarcoma specifically are absent), for respiratory cancer, and for all malignant neoplasms.

The studies by Barnes (303), Jones (304), and Aryanpur (305) describe the industrial processes involving work with vinyl chloride and the associated atmospheric concentrations of that chemical. The reports by Nicholson, Henneberger, and Seidman (294) and Nicholson, Henneberger, and Tarr (306) describe, in general, the hazards associated with employment in the VC-PVC industry and the trends in cancer mortality that may be expected due to past exposures. Kuzmack and McGaughy (307) analyze

exposures that may be encountered by populations living near vinyl chloride monomer or polymerization facilities.

Several studies describe the cancer mortality experience of occupational cohorts (308-316). Angiosarcomas of the liver were found in many of these cohorts.

Unfortunately, the data on exposure to vinyl chloride necessary for a quantitative assessment of risk are available only for those cohorts described by Ott *et al.*, Fox and Collier, Buffler *et al.*, and Heldaas *et al.* The study by Fox and Collier alone presents data on expected numbers of liver cancers. This study forms the basis of the liver cancer risk estimates. Ott *et al.* do not provide respiratory cancer data, so the other three studies are used for estimation of respiratory cancer risk. All four studies have been used for calculation of risk of any malignant neoplasm. The cohorts and the derivations of the risk estimates are described below.

Ott *et al.* (314) studied the mortality experience of 594 employees with potential exposure to vinyl chloride between 1942 and 1960. Follow-up was through 1974. Although there were no deaths due to any liver malignancy, the observed number of total malignancy deaths exceeded the expected number in the high exposure category.

Some of the workers studied by Ott *et al.* were also exposed to arsenic, which is a known human carcinogen. In order to avoid a possible confounding effect of arsenic exposure, only analyses by Ott *et al.* which omitted workers exposed to arsenic were utilized.

Based upon industrial hygiene data, each job was assigned an exposure level of low (<25 ppm), intermediate (25-200 ppm) or high (>200 ppm). This classification was based primarily upon measurements of time-

weighted average concentrations for an 8-hour day. Ott *et al.* attempted to take into account in the classification frequent short term exposures to several thousand ppm encountered in some jobs. For risk assessment, estimates of average exposures for each of these exposure categories are needed. Except for the job classification of "coagulator" (which had estimated 8-hour TWA's of 135-825 ppm), none of the job classifications had estimated exposures in excess of 385 ppm; however, several categories had 120-385 or 95-350 ppm as an estimated range of concentrations. Based on these and similar observations, it appears reasonable to assign an average concentration of 300 ppm to Ott's high exposure range (>200 ppm). For the intermediate exposure range (25-200 ppm) an average of $[(25)(200)]^{1/2} = 70$ ppm was assumed and an average exposure of 25/2 = 12.5 ppm was assumed for the low exposure range (<25 ppm).

Ott *et al.* assigned individuals to exposure groupings based on the highest exposure experienced for one or more months. Numbers of workers in these groupings by years of exposure are shown in Table 2-113. In this table years of cumulative exposure are calculated in two ways: by considering all years of exposure and by ignoring years of exposure at lower levels. By this latter method, an individual exposed at high levels for six months, and at lower levels for ten years, would be classified in the high category with less than one year of exposure.

Table 2-114 shows the observed and expected deaths for all malignant neoplasms by exposure level and according to whether exposure was less than or greater than one year. Only data on all malignant neoplasms are recorded in this way and consequently risk estimates were developed only for this disease category. In these mortality analyses, duration of exposure was separated into two categories: less-than-one-year and one-year-or-longer. Exposures at lower levels were not considered in assigning individuals to less-than-one-year or one-year-or-longer categories (i.e., results in this table correspond to the rows in Table

2-113 labeled "High levels only", "Intermediate levels only", and "Low levels only").

In order to use the mortality results in Table 2-114 for making quantitative estimates of risk, we need to estimate average exposures for each category in ppm-years. This can be done, but is made more complicated by the fact that Ott *et al.* placed workers in exposure groups by the highest exposure in any one- month period. Certain assumptions about length of exposures are based on the pattern of employment outlined in Table 2-113. First, average lengths of exposure for the four duration of exposure categories are assumed to be 0.5, 5, 15 and 27 years. A low-intermediate exposure is calculated as the average of the low and intermediate levels estimates discussed above, i.e. 41 ppm. The 417 men classified by exposure level are considered to have the following exposure pattern:

High exposure group, 163 men:

- 20+ years of low-to-high exposure; 27 men:
  - 19 with high exposure for 15 years and low-intermediate exposure for 12 years,
  - 8 with high exposure for 5 years and low-intermediate exposure for 22 years.
- 10-19 years of low-to-high exposure, 39 men:
  - 39 with high exposure for 5 years and low-intermediate exposure for 10 years.
- 1-9 years of low-to-high exposure, 64 men:
  - 24 with high exposure for 5 years,
  - 40 with high exposure for 1/2 year and low-intermediate exposure for 4.5 years.
- <1 year of low-to-high exposure, 33 men:
  - 33 with 1/2 year of high exposure.

Intermediate exposure group, 73 men:

10-19 years of low-to-intermediate exposure, 6 men:

5 with 15 years of intermediate exposure,

1 with 5 years of intermediate exposure and 10 years of low exposure.

1-9 years of low-to-intermediate exposure, 38 men:

35 with 5 years of intermediate exposure,

3 with 1/2 year of intermediate exposure and 4.5 years of low exposure.

<1 year of low-to-intermediate exposure, 29 men:

29 with 1/2 year of intermediate exposure.

Low exposure group, 181 men:

1 with 27 years of low exposure,

3 with 15 years of low exposure,

50 with 5 years of low exposure,

127 with 1/2 year of low exposure.

These assumptions allow calculation of cumulative dose to accompany the observed and expected numbers of cancer deaths given in Table 2-114. For example, the dose in the group exposed for >1 year to high exposures is estimated as

$$[19\cdot(15\cdot300+12\cdot41) + 8\cdot(5\cdot300+22\cdot41) + 39\cdot(5\cdot300+10\cdot41) + 24\cdot(5\cdot300)]/[19+8+39+24] = 2495 \text{ ppm-years.}$$

The group exposed for less than a year to high levels has an average dose of

$$[40(0.5\cdot300+4.5\cdot41) + 33(0.5\cdot300)]/[40+33] = 251 \text{ ppm-years.}$$

The remaining dose estimates are similarly derived (Table 2-115). Table 2-115 also presents the bounds on the dose estimates. The factors that

contribute to the uncertainty in the dose estimates for this cohort are given below, along with the corresponding numerical contribution to α and γ:

1. Length of exposure is broken down into groups of width up to ten years. No averages are given for the groups, hence $\alpha_1 = \gamma_1 = 0.2$.
2. Although exposure to vinyl chloride began as early as 1942, occupational hygiene measurements began only in 1950. It is likely that vinyl chloride concentrations may have been somewhat higher prior to 1950 than after, so a portion of the cohort may have experienced doses higher that those calculated. Since it is a period of only 8 years and no drastic process changes are documented, a relatively small value for γ_2, namely 0.2, is selected. The factor α_2 is set equal to zero.
3. A continuous concentration analyzer has been in operation at least one of the units since 1959. Measurements since 1950 have been fairly complete for the plant as a whole and, apparently for the various job classifications, although this is not clearly documented. Accordingly, α_3 and γ_3 are set equal to 0.2.
4. The categories of exposure, "high", "medium", and "low", have been broadly defined and no average values for the groups have been given. Consequently, $\alpha_4 = \gamma_4 = 0.3$.
5. A serious recording bias results from classification by the highest exposure experienced. An attempt at partial correction is reflected in the assumptions about distribution of individuals across exposure groups based on Table 2-113. The uncertainty associated with this bias is still substantial, however, and α_5 has been assigned a value of 0.6. Since the assumptions may possibly over correct the bias, γ_5 is 0.2.

6. Since area, not personal, samples are used to estimate exposures, both α_6 and γ_6 have been given values of 0.05.
7. Some small amount of uncertainty is associated with the choice of U.S. national mortality rates to represent the expected mortality experience of the cohort. Both α_8 and γ_8 have been set equal to 0.05 to account for this effect.

The resulting values of α and γ are 2.4 and 2.2, respectively, with the resulting bounds on dose as represented in Table 2-115.

Fox and Collier (313) studied the mortality experience of over 7000 British workers exposed to vinyl chloride. The study covered persons who may have been exposed through industrial employment in Great Britain between the years 1940 and 1974. Two factories employing 25% of the cohort started production in 1969 and 1970; thus, follow-up was quite short for a sizable fraction of the cohort. Two cases of liver angiosarcoma were found. Mortality from all malignant neoplasms was less than expected, when compared to national rates. Dose response analyses were presented by Fox and Collier for all malignant neoplasms, liver cancer, lung cancer, and brain cancer.

Workers were classified into low, medium, and high exposure categories, depending upon whether the time weighted average exposures in the job in which they received their maximum exposure was less that 25 ppm, between 25 and 200 ppm, or greater than 200 ppm. Workers were also classified as to whether their exposures were constant (most of the time) or intermittent (occasional). No measurements of air concentrations made before the mid-1960s were available.

This study involved workers from a number of different companies, and each company classified exposures of its own employees No mention is made of the time required in the job with the maximum exposure level in

order for that job to be the basis for a worker's exposure classification. These shortcomings make estimates of average exposures problematical. Since the exposure ranges are the same as were used by Ott *et al.*, and there is no evidence that the average exposures in the various categories differed between the two studies, the same average exposures are assumed for the Fox and Collier cohort as were assumed earlier for the Ott *et al.* cohort--namely, averages of 12.5 ppm, 70 ppm, and 300 ppm for 0-25 ppm, 25-200 ppm, and 200+ ppm constant exposures, respectively. The corresponding concentrations for the intermittent exposures are assumed to be 7 ppm, 30 ppm, and 150 ppm.

Table 2-116 displays the cohort, broken down by exposure intensity and duration. Assumed average lengths of exposure are 5, 15, and 27 years in the duration groups. Average exposures are estimated for the high, medium, and low exposure categories, combining constant and intermittent groups and the duration classes. As an example, the average cumulative exposure for the high exposure group is estimated as

$$\frac{[(605)(5)+(142)(15)+(34)(27)](300)+[(60)(5)+(35)(15)+(11)(27)](150)}{605 + 142 + 34 + 60 + 35 + 11}$$

$$= 2244 \text{ ppm-years.}$$

Table 2-117 also contains the response data for all malignant neoplasms, liver cancer, and lung cancer as well as the bounds on dose estimates. The exposure estimation for the Fox and Collier cohort was even less certain than for the group described by Ott *et al.* Specific issues are discussed below:

1. Length of exposure is grouped, much the same as Ott *et al.* grouped exposure duration, again without averages for the groups. Moreover, "constant" and "intermittent" exposures are not well-defined. The value for α_1 and γ_1 assigned in this case is 0.3.

2. Although the follow-up period began in 1940, exposure estimates were available only since the mid-1960's. The possibility for underestimation of early exposures is great, so $\gamma_2 = 0.7$ ($\alpha_2 = 0$).
3. No documentation is provided on the completeness of the concentration measurements done since the mid-1960's that form the basis of the exposure estimates. A value of 0.3 is selected for α_3 and γ_3.
4. Once again, no averages for the exposure categories are given. The same definitions were used as in the Ott *et al.* study, so α_4 and γ_4 are the same also, namely 0.3.
5. Exposure classification is based on maximum exposure and no data is provided that allows for factoring-in time spent at other, lower-exposure jobs. Although the upper bound need not be modified in this case ($\gamma_5 = 0$), the lower bound is affected to a much greater extent than in the Ott *et al.* uncertainty estimation. Consequently, α_5 has been set equal to 0.9.
6. Substantial uncertainty exists with respect to the applicability of the reported exposures. Several different facilities were studied and each classified its own exposures, possibly affecting consistency over the whole cohort. It is not known if area samples were used to define exposures, although one would suspect that they or "best guesses" were employed. The problem of the definition of "constant" and "intermittent" exposure also influences uncertainty here. The value of α_6 and γ_6 is 0.3.
7. National rates were used to calculate expected numbers of deaths. Fairly wide time intervals for the early part of follow-up (1940-55, 1956-65) were compared to death rates of single years (1951 and 1961 respectively). The factors α_8 and γ_8 are set to 0.1.

The uncertainty factors α and γ have the values 3.2 and 3.0. The bounds on dose obtained by applying these factors (Table 2-117) are used to investigate the sensitivity of the analysis to possible misestimation, particularly of the exposures.

Buffler *et al.* (310) studied individuals employed in a vinyl chloride monomer production plant that began operations in 1948. A total of 481 males employed for at least two consecutive months between 1948 and 1975 were included in their cohort. Dr. Buffler and her colleagues were kind enough to supply a copy of the cohort history which allowed inclusion of all white males (504) in the following analyses.

Cumulative exposures were calculable for each individual once concentrations of vinyl chloride were assigned to each job code. The original Buffler *et al.* publication provided estimated time-weighted average levels for the jobs entailing exposure to vinyl chloride, but only for the time period 1971-1975. The authors state that from 1948 to 1960 exposure to concentrations of 200-500 ppm were not uncommon. Through 1960, the threshold limit value was 500 ppm. In 1961, the company reduced its standard for exposure to 50 ppm (TWA). It was the authors' opinion that levels before 1971, though higher, would have been such that the ratio of levels for any two jobs would be roughly the same as the ratio after 1971. Using this information, time-dependent concentration estimates have been derived and are shown in Table 2-118.

The resulting dose and response data for all malignant neoplasms and lung cancer are presented in Table 2-119.

Uncertainty with respect primarily to exposure estimates in this analysis are as follows, discussed in terms of the factors α_i and γ_i.

The uncertainty factors α and γ have the values 3.2 and 3.0. The bounds on dose obtained by applying these factors (Table 2-117) are used to investigate the sensitivity of the analysis to possible misestimation, particularly of the exposures.

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The resulting dose and response data for all malignant neoplasms and lung cancer are presented in Table 2-119.

Uncertainty with respect primarily to exposure estimates in this analysis are as follows, discussed in terms of the factors α_i and γ_i.

1. No measurements of vinyl chloride concentrations were available before 1971. Extrapolation to those periods between 1948 and 1970 has been accomplished with reference to certain assumptions about the conditions prevailing at that time, but this is highly uncertain. The uncertainty affects both upper and lower bounds on dose estimates, since the extrapolation may indeed overestimate early exposure. Consequently, α_2 and γ_2 have both been assigned a value of 0.8.
2. The completeness of the measurements of vinyl chloride concentration is not documented. A few of the specific job titles lacked estimates of associated exposure, and the original authors had to rely in part on the judgement of plant supervisors and others with experience at the facility to derive estimates. A value of 0.3 is assumed for α_3 and γ_3.
3. A minor amount of uncertainty is attributable to the question of the applicability of the reported exposures. The value 0.05 is given to α_6 and γ_6 to reflect the use of area samples and "classification groups" instead of personal samples.
4. Since one of the endpoints considered with this cohort is respiratory cancer, it would be most appropriate to use expected numbers of deaths derived by reference to smoking-specific death rates. This was not possible, but it is not known if the smoking behavior of the cohort differed from national patterns. Both α_8 and γ_8 are assigned a value of 0.1.

All other factors (such as recording bias, grouping without average values, length of exposure uncertainty) do not apply. The resulting value for α and γ, 2.25, is used to derive reasonable bounds for the dose variable (Table 2-119).

Heldaas *et al.* (316) described a cohort of workers employed by a Norwegian producer of vinyl chloride monomer and polyvinyl chloride.

The manufacture of these products began in 1950. Of 1233 workers who started work before 1975 and who worked more than one month, the authors selected for study 454 males who were employed for at least one year and who began before 1970. The follow-up period for which cancer incidence was determined (the studies previously described used cancer mortality as their endpoint), extended from 1953 to 1979. Norwegian national rates were used for comparison purposes.

According to the report, the plant design and process operation must have entailed high concentrations of vinyl chloride, but no industrial hygiene surveys were performed before 1974. Based on sporadic measurements carried out with an "explosion-meter", interviews with workers, and an odor threshold of about 500 ppm, the following vinyl chloride monomer concentration history was assumed:

1950 to 1954:	2000 ppm
1955 to 1959:	1000 ppm
1960 to 1967:	500 ppm
1968 to 1974:	100 ppm

These concentrations, coupled with work histories of the cohort members, allowed the authors to calculate cumulative exposures and classify each member according to his cumulative exposure by the end of follow-up. Table 2-120 displays the classification presented by Heldaas *et al*. That table also presents the observed and expected incidence of all

The bounds on the doses have been derived by assuming a value for α and γ of 2.8. That value is itself derived by consideration of the following contributions to uncertainty.

1. Formal measurement of vinyl chloride concentrations began only in 1974. The need to extrapolate back to 1950 introduces great uncertainty. Since some guess was ventured as to the high

values that might have been prevalent, uncertainty above and below the best estimates is present. Both α_2 and γ_2 are given a value of 0.8.

2. The exposure groups defined by the authors are extremely wide and are presented without averages. Arithmetic averages have been assumed for the groups (cf. Table 2-120) but, of course, there is no way to know how accurate these may be. A value of 0.3 is assigned to α_4 and γ_4.
3. Some uncertainty is associated with the presumed applicability of the exposures reported. The authors presented information indicating that certain jobs entailed greater vinyl chloride exposure that others. Yet, their extrapolation was, for the most part, based on time but not job classification. Whether this would entail over- or under-estimation, in general, is not known. Consequently, the value of 0.3 is assigned tc α_6 and γ_6.
4. The definition of the dose groups in Table 2-120 is based on one measure for each cohort member, i.e. his total cumulative exposure. In reality, as each member continues to work at the plant, his cumulative exposure variable increases and passes through one or more of the groups defined. It would be better to attribute person-years, as opposed to individuals, to the groups and calculate expected values on that basis. Moreover, the authors indicate that cancer incidence in the local area surrounding the facility differ from the national rates. Consequently, the factors accounting for uncertainty of the expected response rate, α_8 and γ_8, are given a value of 0.4 to reflect these uncertainties and that relating to use of non-smoking-specific rates for comparison.

The dose-response model has been fit to the data from the four studies of Ott *et al.*, Fox and Collier, Buffler *et al.*, and Heldaas *et al.* The

resulting potency parameters are given in Table 2-121.

The potency parameters have been used, in turn, to estimate RRDs. A mixed bag of RRD estimates result (Table 2-122). Three of the four studies, including the morbidity study, cannot rule out the hypothesis that vinyl chloride has no effect on overall carcinogenesis. The same mixed results are apparent for respiratory cancer. Only one study contained data relevant to liver cancer risk (313) and that data appears to indicate a definite risk associated with vinyl chloride exposure.

Table 2-113

DURATION OF EXPOSURE BY LEVEL OF EXPOSURE FOR EACH EXPOSURE GROUPING (ARSENIC WORKERS EXCLUDED), VINYL CHLORIDE-EXPOSED COHORT[a]

Exposure Group and Level of Exposure	Number of Employees With Cumulative Exposure of: <1 yr	1-9 yr	10-19 yr	20+ yr
High-exposure group				
Low-to-high levels	33	64	39	27
High levels only	73	71	19	0
Intermediate exposure group				
Low-to-intermediate levels	29	38	6	0
Intermediate levels only	32	36	5	0
Low-exposure group				
Low levels only	127	50	3	1
Unmeasured exposure group				
Unmeasured or low levels	39	44	16	6

[a]Ott *et al.* (314).

Table 2-114

OBSERVED AND EXPECTED DEATHS BY EXPOSURE INTENSITY AND DURATION OF EXPOSURE, 1942-1973, OTT *ET AL.* (314) VINYL CHLORIDE-EXPOSED COHORT (ARSENIC WORKERS EXCLUDED)

Exposure Intensity and Duration	Deaths Due to Malignant Neoplasms	
	Observed	Expected
High Exposure		
< 1 yr	3	2.2
> 1 yr	6	2.9
Intermediate Exposure		
< 1 yr	0	1.4
> 1 yr	2	1.5
Low Exposure		
< 1 yr	0	2.4
> 1 yr	1	1.7

Table 2-115

DOSE AND RESPONSE INFORMATION FOR THE VINYL CHLORIDE-EXPOSED COHORT OF OTT *ET AL.* (314)
(ARSENIC WORKERS EXCLUDED)

Exposure Intensity and Duration	Cumulative Exposure (ppm-years) Lower Bound	Best Estimate	Upper Bound	Deaths Due to Malignant Neoplasms Observed	Expected
High Exposure					
< 1 yr	105	251	552	3	2.2
> 1 yr	1040	2495	5489	6	2.9
Intermediate Exposure					
< 1 yr	16.7	40	88	0	1.4
> 1 yr	182	438	964	2	1.5
Low Exposure					
< 1 yr	2.58	6.2	13.6	0	2.4
> 1 yr	31.2	75	165	1	1.7

Table 2-116

LEVELS OF EXPOSURE AND LENGTHS OF EXPOSURE FOR MEN IN THE FOX AND COLLIER (313) VINYL CHLORIDE-EXPOSED COHORT

Length of Exposure (years)	Levels of Exposure: Constant High	Constant Medium	Constant Low	Intermittent High	Intermittent Medium	Intermittent Low	Total No. (%)
0-9	605	1202	890	60	1857	1094	5708 (77.0%)
10-19	142	117	263	35	210	351	1118 (15.1%)
20+	34	92	114	11	130	202	583 (7.9%)
Total (%)	781 (10.5%)	1412 (19.0%)	1266 (17.1%)	106 (1.4%)	2197 (29.7%)	1647 (22.2%)	7409 (100%)

Constant = Most of the time.
Intermittent = Occasionally.
High = greater than 200 ppm.
Medium = between 25 and 200 ppm.
Low = less than 25 ppm.

Table 2-117

DOSE AND RESPONSE INFORMATION FOR THE FOX AND COLLIER (313) COHORT OF VINYL CHLORIDE-EXPOSED WORKERS

Cumulative Exposure (ppm-years)			All Malignant Neoplasms		Liver Cancer		Respiratory Cancer	
Lower Bound	Best Estimate	Upper Bound	Observed	Expected	Observed	Expected	Observed	Expected
27.5	88	264	53	57.5	1	0.75	21	23.2
103	331	993	53	59.7	1	0.77	23	24.4
70[illegible]	2244	6732	9	9.6	2	0.13	2	3.7

Table 2-118

ESTIMATED VINYL CHLORIDE CONCENTRATIONS FOR
BUFFLER *ET AL.* COHORT, BY TIME AND JOB CLASSIFICATION

Job Classification	Concentration (ppm) 1948-1960	1961-1970	1971-1975
Control Lab Personnel	446	44.6	22.3
Development Lab Personnel	82	8.2	4.1
Production Personnel			
Control A	154	15.4	7.7
Control B	56	5.6	2.8
Control C	88	8.8	4.4
Class 3 Operators	114	11.4	5.7
Loaders and Plant Men			
Class 1,2 Operators	142	14.2	7.1
Head Packaging Operator	246	24.6	12.3
Material Handling Operator	4	0.4	0.2
Packaging Operator, Service Technician	148	14.8	7.4
Certain Supervisory Positions			
Production Superintendent, Assistant Production Superintendent, Production Engineer, R & D Engineer, Engineer, Safety Engineer, Sr. Production Engineer	38	3.8	1.9
Parts Technician, Sr.	4	0.4	0.2
Manager	6	0.6	0.3
Other	36	3.6	1.8
Maintenance Personnel			
Boilermaker, Apprentice	28	2.8	1.4
Welder, Apprentice	4	0.4	0.2
Machinist, Apprentice, Helper, Crew Leader	22	2.2	1.1
Pipefitter, Apprentice, Helper	34	3.4	1.7
Utility Man	4	0.4	0.2
Instrument Technician	64	6.4	3.2
Production Foreman, Shift Foreman	86	8.6	4.3
Maintenance Foreman	8	0.8	0.4
Utility Crew Leader, Rotating Shift Foreman, Foreman, Other	50	5.0	2.5
Other Personnel	76	7.6	3.8

Table 2-119

DOSE AND RESPONSE DATA FOR THE VINYL CHLORIDE-EXPOSED COHORT OF BUFFLER *ET AL.* (310)

Cumulative Exposure (ppm-yrs)	All Malignant Neoplasms		Respiratory Cancers	
	Observed	Expected	Observed	Expected
0 - 75 (1.7, 3.9, 8.8)[a]	2	3.36	1	1.10
75 - 150 (47, 106, 238)[a]	2	0.56	0	0.22
150 - 300 (91, 204, 459)[a]	2	0.69	2	0.27
300+ (378, 859, 1912)[a]	2	1.62	2	0.64

[a]In parentheses are the lower bound, best estimate, and upper bound on dose, respectively.

Table 2-120

DOSE AND RESPONSE DATA FOR THE VINYL CHLORIDE-EXPOSED COHORT OF HELDAAS *ET AL.* (316)[a]

Cumulative Exposure (ppm-yrs)	All Malignant Neoplasms		Respiratory Cancers	
	Observed	Expected	Observed	Expected
0 - 500 (89, 250, 700)[b]	6	7.06	2	1.01
500 - 2500 (536, 1500, 4200)[b]	3	3.10	0	0.40
2500+ (1339, 3750, 10500)[b]	14	9.95	3	1.44

[a]Incidence, not mortality, is presented for observed and expected responses.

[b]In parentheses are the lower bound, best estimate, and upper bound on dose, respectively, derived for the exposure groups. These values were not provided by the authors.

Table 2-121

POTENCY PARAMETER ESTIMATES FOR VINYL CHLORIDE

Study	Response	Dose Measure	Potencies ((ppm-yrs)$^{-1}$) Lower Limit[a]	MLE	Upper Limit[a]
Ott *et al.* (314)	All Malignant Mortality (chi-squared (5) = 4.3)	Upper Bounds	3.52E-5*	1.99E-4	4.26E-4
		Best Estimates	7.74E-5	4.38E-4*	9.38E-4
		Lower Bounds	1.86E-4	1.05E-3	2.25E-3*
Fox & Collier (313)	All Malignant Mortality (chi-squared (2) = 1.14)	Upper Bounds	-7.03E-5*	0.00	4.09E-5
		Best Estimates	-2.11E-4	0.00*	1.23E-4
		Lower Bounds	-6.75E-4	0.00	3.93E-4*
	Liver Cancer Mortality (chi-squared (2) = 0.67)	Upper Bounds	4.67E-4*	1.46E-3	3.09E-3
		Best Estimates	1.40E-3	4.38E-3*	9.28E-3
		Lower Bounds	4.49E-3	1.41E-2	2.98E-2*
	Respiratory Cancer Mortality (chi-squared (2) = 1.07)	Upper Bounds	-1.29E-4*	0.00	5.16E-5
		Best Estimates	-3.87E-4	0.00*	1.55E-4
		Lower Bounds	-1.24E-3	0.00	4.95E-4*

Table 2-121 (continued)

POTENCY PARAMETER ESTIMATES FOR VINYL CHLORIDE

Study	Response	Dose Measure	Potencies ((ppm-yrs)$^{-1}$) Lower Limit[a]	MLE	Upper Limit[a]
Buffler *et al.* (310)	All Malignant Mortality (chi-squared (3) = 5.8)	Upper Bounds	-2.10E-4*	3.38E-4	1.25E-3
		Best Estimates	-4.70E-4	7.47E-4*	2.78E-3
		Lower Bounds	-1.06E-3	1.71E-3	6.34E-3*
	Respiratory Cancer Mortality (chi-squared (3) = 5.3)	Upper Bounds	3.58E-4*	1.73E-3	3.92E-3
		Best Estimates	7.91E-4	3.84E-3*	8.73E-3
		Lower Bounds	1.81E-3	8.74E-3	1.98E-2*
Heldaas *et al.* (316)	All Malignant Morbidity (chi-squared (2) = 0.31)	Upper Bounds	-3.78E-6*	3.52E-5	8.35E-5
		Best Estimates	-1.06E-5	9.85E-5*	2.34E-4
		Lower Bounds	-2.96E-5	2.76E-4	6.55E-4*
	Respiratory Cancer Morbidity (chi-squared (2) ≤ 1.4)	Upper Bounds	-1.53E-5*	9.01E-5	2.61E-4
		Best Estimates	-4.28E-5	2.52E-4*	7.32E-4
		Lower Bounds	-1.20E-4	7.06E-4	2.05E-3*

[a]90% confidence limits are shown.
*An asterisk marks the parameters used to derive RRD estimates.

Table 2-122

RRD ESTIMATES FOR VINYL CHLORIDE (ppm)

Study	Response	Estimation Method	Level of Extra Risk 10^{-6} RRD_L	MLE	RRD_u	0.25 RRD_L	MLE	RRD_u
Ott et al. (314)	All Malignant Mortality	1	3.50E-5	1.80E-4	2.24E-3	8.75	4.50E+1	5.60E+2
		2	4.60E-5	2.37E-4	2.95E-3	1.47E+1	7.58E+1	9.43E+2
Fox & Collier (313)	All Malignant Mortality	1	2.00E-4	∞	∞	5.00E+1	∞	∞
		2	2.63E-4	∞	∞	8.43E+1	∞	∞
	Liver Cancer Mortality	1	4.72E-4	3.20E-3	3.01E-2	1.18E+2	8.01E+2	7.52E+3
		2	5.13E-4	3.48E-3	3.27E-2	1.61E+2	1.09E+3	1.03E+4
	Respiratory Cancer Mortality	1	5.49E-4	∞	∞	1.37E+2	∞	∞
		2	6.34E-4	∞	∞	1.95E+2	∞	∞
Buffler et al. (310)	All Malignant Mortality	1	1.24E-5	1.05E-4	∞	3.10	2.64E+1	∞
		2	1.63E-5	1.39E-4	∞	5.23	4.44E+1	∞
	Respiratory Cancer Mortality	1	1.37E-5	7.09E-5	7.61E-4	3.43	1.77E+1	1.90E+2
		2	1.58E-5	8.18E-5	8.78E-4	4.87	2.52E+1	2.70E+2

Table 2-122 (continued)

RRD ESTIMATES FOR VINYL CHLORIDE (ppm)

Study	Response	Estimation Method	Level of Extra Risk 10^{-6} RRD_L	MLE	RRD_u	0.25 RRD_L	MLE	RRD_u
Heldaas et al. (316)	All Malignant Morbidity	1	5.74E-5	3.82E-4	∞	1.44E+1	9.55E+1	∞
		2	8.78E-5	5.84E-4	∞	2.76E+1	1.84E+2	∞
	Respiratory Cancer Morbidity	1	1.13E-4	9.19E-4	∞	2.83E+1	2.30E+2	∞
		2	1.32E-4	1.07E-3	∞	4.04E+1	3.29E+2	∞

Summary of Results

Of the two basic methods described above, Method 2 more appropriately considers the timing of exposure in the calculation of RRD estimates. Note that the Method 2 RRD estimates are uniformly larger than the corresponding Method 1 RRD estimates, though by only a small factor. This is a result of the life-table aspect of Method 2; the probability of getting cancer in the older age groups is discounted by the likelihood of dying at earlier ages of other causes. Method 1 lacks this feature. Consequently, this summary of results is framed in terms of the Method 2 RRD estimates.

The summary also includes only the estimates corresponding to an extra risk of 0.25. By emphasizing these estimates, we hope to avoid difficulties associated with extrapolation of results to low levels of risk. In most cases, the RRDs corresponding to an extra risk of 0.25 are not far from the range of doses reported in the epidemiological studies supplying the necessary quantitative data.

The Method 2 estimates of doses corresponding to an extra risk of 0.25 determined for all the responses observed in the selected studies are displayed in Figure 2-1. The RRD estimates have been converted to the units of mg/kg/day and correspond to the specific scenario chosen, 45 years of exposure (240 days per year) starting at age 20. Figure 2-1 indicates the particular responses chosen to represent the RRD estimates for each chemical; Table 2-123 summarizes the selected values. These are the values that define the human intervals and point estimates to which the bioassay results are compared.

DISCUSSION

For the most part, prospective cohort studies and case-control reports have supplied the data necessary for the quantitative approach adopted here. Both forms of study have limitations that influence our ability to derive risk estimates. Case-control studies concentrate on a single carcinogenic response, and look at differences in exposure between the cases and the controls. It is possible that other carcinogenic effects of the same exposure are missed with this format, perhaps biasing the risk estimates. Since we opted to examine only single responses (or all malignant neoplasms when a specific response was not suggested) this may not be a particular problem in the current analysis. However, case-control studies present some difficulties with respect to sequencing of events; it is not easy to determine in some cases which exposures preceded the disease or which exposures may have occurred or been modified because of the disease (cf. the discussion of estrogens). Moreover, when reliance on patients recall of timing and intensity of exposure has been necessary, uncertainty is compounded.

Prospective studies suffer from many of the same problems. Exposure in the less recent past is often highly uncertain. Observed responses may have nothing to do with exposure to the suspected carcinogen, a fact that one attempts to reflect in the calculation of expected (without exposure) numbers of cancers. But, once again, uncertainty is associated with those estimates of expected numbers. Finally, incomplete follow-up means incomplete information on the carcinogenic potential of the chemical in question.

Many of these uncertainties, particularly those related to exposure and dose calculations, are included in the estimation of reasonable bounds on the RRDs. The subfactors used to calculate the uncertainty factors, α and γ, have been selected so as to reflect the degree to which the

uncertainty represented by a subfactor might affect the estimation of the "true" dose or exposure. So, for example, the subfactors relating to categorization of exposure (α_4 and γ_4) are selected from the interval [0, 0.3] whereas those relating to recording biases (α_5 and γ_5) are chosen from [0, 1.0]. The possible effect on dose estimation related to the latter factor (which could result from classification of workers by their maximal exposure) is deemed to be greater than the possible effect on dose estimation related to the former factor (which is primarily the estimation of an average value for a range of exposures). On the other hand, specific cases exist in which the uncertainty associated with α_4 and γ_4 is greater than that associated with α_5 and γ_5, because, under the the guidelines for selecting the subfactors, we are at liberty to select them so that $\alpha_5 < \alpha_4 \leq 0.3$ and $\gamma_5 < \gamma_4 \leq 0.3$.

If, for example, the only uncertainty is associated with the categorization of exposure (α_4 and γ_4), in that averages had to be estimated for a range of exposures, and if the values of $\alpha_4 = \gamma_4 = 0.3$ were selected, then this implies that the "true" average cumulative exposure may be as much as a factor of 1.3 larger or smaller than the estimated average. Obviously, any such selections are themselves estimates, and, moreover, somewhat arbitrary estimates.

Thus, in this analysis, specific ranges have been defined and, for subfactors representing specific elements of uncertainty, values have been selected from those ranges. A specific value is selected somewhat arbitrarily and subjectively as providing a "reasonable" multiplicative factor for reflecting that uncertainty in the dose estimates. It has not been possible to investigate the effect on the analyses (comparisons with the bioassay-based results) of choosing other reasonable ranges or particular values for the uncertainty subfactors. A simulation study of that issue might be informative.

In the meantime, it is appropriate to view the uncertainty bounds for cumulative exposure in two ways. First, within the epidemiological analysis, one can see the bounds as providing information on the sensitivity of the analysis to reasonable changes in the exposure data. Second, in the context of comparisons of the bioassay-based estimates to the epidemiologically derived estimates (cf. Volume 3 of this report), the intervals defined by the combination of statistical and exposure uncertainty (those shown in Table 2-123) are important in determining the degree of similarity (the fit) of the animal estimates and the human estimates. Hence, as long as the uncertainty estimates are consistent from study to study and chemical to chemical, even if they are somewhat arbitrary, then the intervals defined in part by those uncertainty factors provide a consistent measure of the weight that should be attached to any given chemical when the comparison is made. Chemicals with wider intervals (more uncertainty) should not influence the evaluation of how well the animal-based results predict the human-based results as much as a chemical with a shorter interval. It is in this sense that the uncertainty factors and the intervals defined by reference to the range of reasonable doses contribute most heavily to the present analysis.

In closing, one further feature of the epidemiological analysis requires comment. For comparison with the bioassay-based results, a single triple of RHD estimates has been selected (Table 2-123). That triple is selected from among all the responses and studies analyzed, but it is not the result of combining responses or studies. That procedure is followed for several reasons. First, it is not clearly appropriate to combine studies that may differ in their definition of cohort membership, latency period, cumulative exposure classes, control series, or even endpoint. The methodology for combining case-control study results is unknown and even for prospective studies the appropriate method is not clear (317). Second, the studies for which quantitative data appro-

priate for the approach adopted here are usually a small subset of the whole set of epidemiological information. While we wanted to derive quantitative estimates, we also wished to have the flexibility to select as our final answers numbers that were as reflective of the consensus from the epidemiological literature as possible. This entails selecting a particular carcinogenic response that is generally agreed to be associated with exposure to the chemical of interest and selecting a study yielding results consistent with the consensus, at least in terms of having high potency, low potency, or (perhaps) no carcinogenic effect in humans. To avoid bias when comparing results in animals and humans, all such selections were made independently of the animal results.

In general, the RRD estimates selected are reflective of the whole of the epidemiological data. In some instances, very similar estimates were obtained from each study analyzed (cf. Figure 2-1, ethylene oxide or methylene chloride). We have chosen estimates from particular studies, but some other selection may also be appropriate. We have not investigated the effect such choices may have on the comparisons with the bioassay-based estimates, although we expect it to be small.

Table 2-123

RRD ESTIMATES[a] SELECTED FROM THE EPIDEMIOLOGIC DATA

Chemical	$RRD_{H,L}$	RRD_{H}	$RRD_{H,U}$
Aflatoxin	4.30E-4	1.64E-3	1.08E-2
Arsenic	2.05E-2	5.84E-2	1.57E-1
Asbestos	1.20E-2	7.00E-2	4.10E-1
Benzene	1.20E+1	2.53E+1	7.61E+1
Benzidine	1.20E-4	6.43E-4	2.56E-3
Cadmium	6.00E-2	1.74E-1	7.05E-1
Chlorambucil	1.57E-2	3.91E-2	1.05E-1
Chromium	4.41E-4	3.89E-3	1.15E-1
Cigarette smoke	2.79E+2	6.41E+2	1.47E+3
DES	4.63E-18	1.47E-3	4.61E-2
Epichlorohydrin	1.79E-1	∞	∞
Estrogens	1.67E-3	5.13E-3	1.89E-2
Ethylene oxide	4.69E-1	2.24	1.59E+1
Isoniazid	1.45	6.78E+1	∞
Melphalan	1.04E-4	3.15E-4	6.86E-4
Methylene chloride	8.63E+1	∞	∞
Nickel	2.46E-1	6.80E-1	1.36E+1
PCB's	2.24E-2	1.51E-1	∞
Phenacetin	6.91	2.00E+1	6.50E+1
Reserpine	4.08E-4	1.91E-3	∞
Saccharin	1.90E+1	∞	∞
Trichloroethylene	2.61	6.48E+1	∞
Vinyl chloride	5.90E+1	4.00E+2	3.76E+3

[a]The estiamtes correspond to an extra risk of 0.25 and to the exposure scenario selected, exposure 240 days per year for 45 years starting at age 20. The estimates are expressed in terms of mg/kg/day.

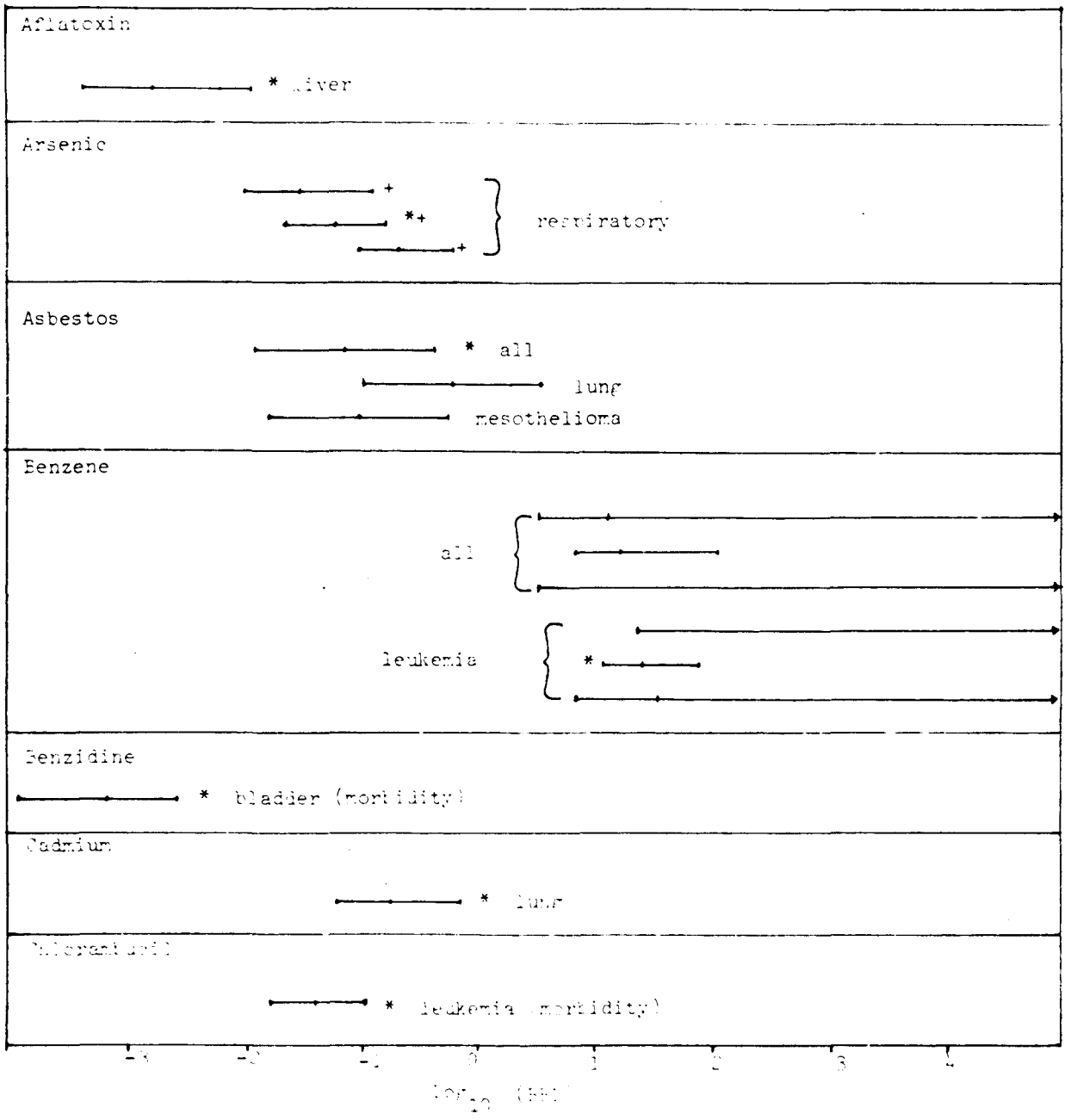

Figure 2-1

Representation of RR Estimates Obtained for All Chemicals and Each Putative Site of Action

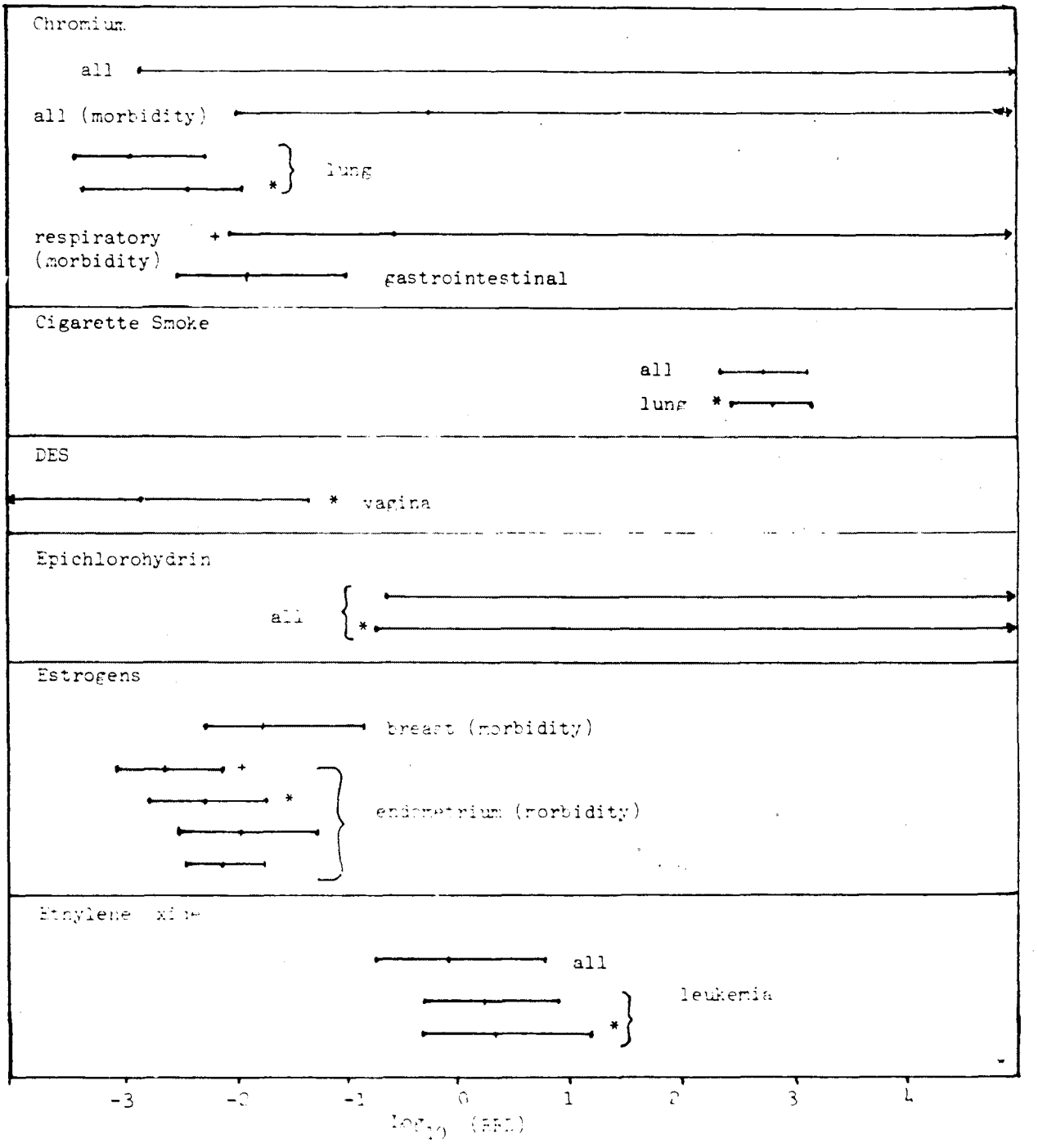

Figure 2-1 (continued)

Representation of ERR Estimates Obtained for All Chemicals and Each Putative Site of Action

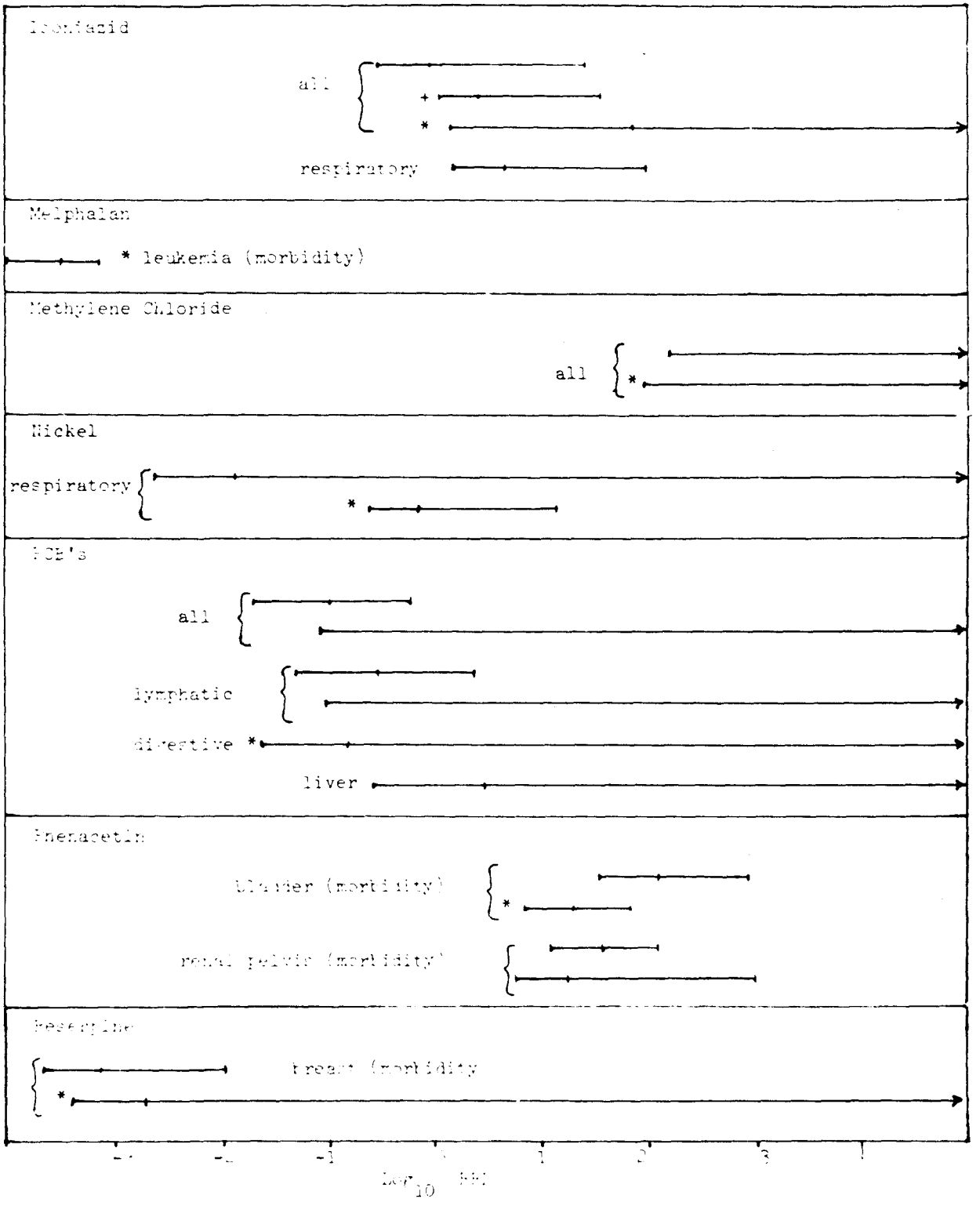

Figure 2-1 (continued)

Representation of RRI Estimates Studied for All Nonlinear and Each Putative Site of Action

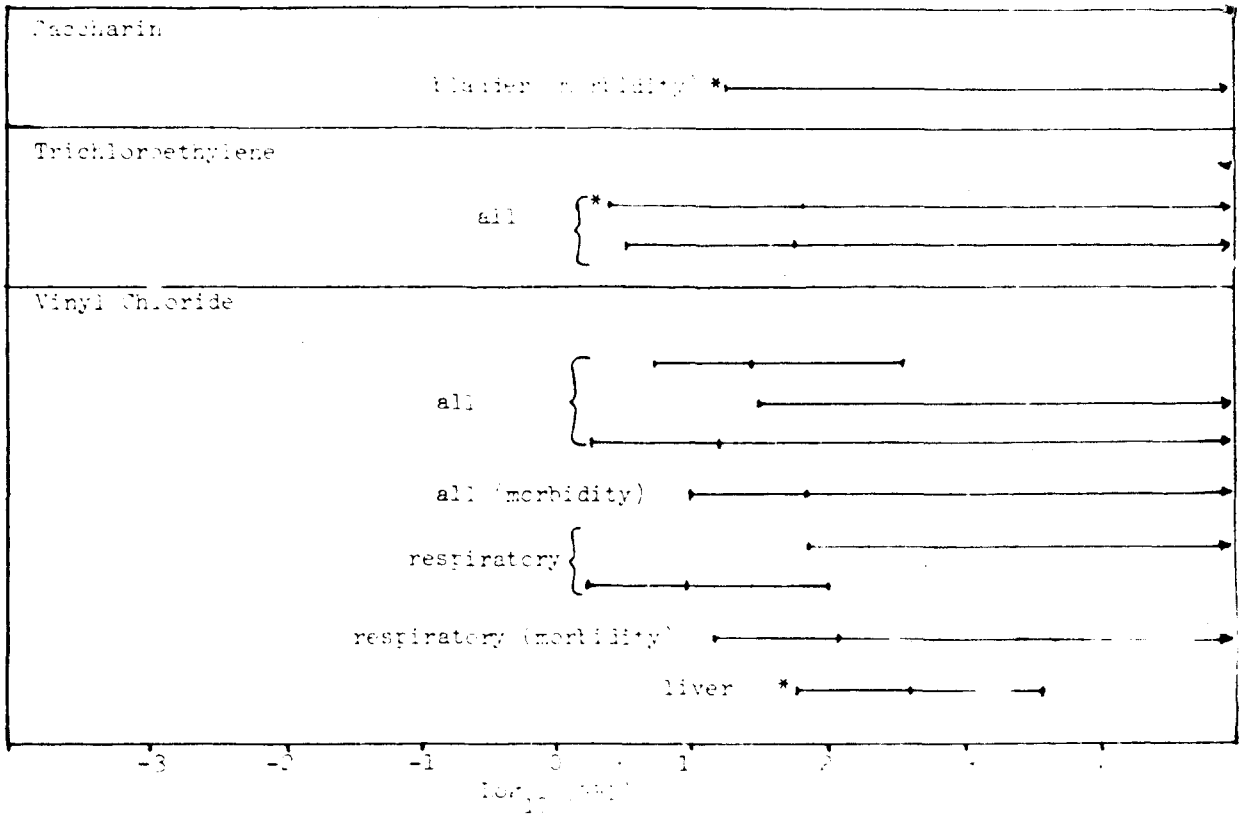

Figure 2-1 (continued)

Representation of BMD estimates (table 1) for All Chemicals and Each Statistical Distribution

*An asterisk marks the data selected to represent the chemical when [illegible] with tissue-based estimates are [illegible].

+A "low sig" marks [illegible] the statistical [illegible] of a lower-bound [illegible].

REFERENCES

1. Breslow, N. and Day, N. (1980). Statistical Methods in Cancer Research Volume 1. The Analysis of Case-Control Studies. International Agency for Research on Cancer. Lyon.

2. International Agency for Research on Cancer (1982). Chemicals, industrial processes and industries associated with cancer in humans. IARC Monographs on the Carcinogenic Risk of Chemicals to Humans Supplement 4.

3. Sankale, M., Gendron, Y., and Courbil, L. J. (1983). Le Cancer primitif du foie en miliuu tropical. Medecine Tropicale 43(3):239-252.

4. Wang, Y., Lan, L., Ye, B., Xu, Y., Liu, Y. and Li, W. (1983). Relation between geographical distribution of liver cancer and climiate-aflatoxin B_1 in China. Scientia Sinica 26(11):1166-1175.

5. Stora, C., Dvorackova, I., and Ayraud, N. (1981). Characterization of aflatoxin B_1 (AFB) in human liver cancer. Research Communications in Chemical Pathology and Pharmacology 31(1):77-84.

6. Stoloff, L. (1983). Aflatoxin as a cause of primary liver-cell cancer in the United States: A probability study. Nutrition and Cancer 5(3-4):165-186.

7. Van Rensburg, S. J., Kirsipuu, A., Coutinho, L. P., and Van Der Watt, J. J. (1975). Circumstances associated with the contamination of food by aflatoxin in a high primary liver cancer area. South African Medical Journal 49:877-883.

8. Keen, P. and Martin, P. (1971a). Is aflatoxin carcinogenic in man? The evidence in Swaziland. Tropical and Geographical Medicine 23:44-53.

9. Nizami, H. M. and Zuberi, S. J. (1977). Aflatoxin and liver cancer in Karachi, a preliminary survey. Journal of the Pakistan Medical Association June 351-352.

Keen, P. and Martin, P. (1971b). The toxicity and fungal infestation of foodstuffs in Swaziland in relation to harvesting and storage. Tropical and Geographical Medicine 23:35-43.

Hayes, R. B., Van Nieuwenhuize, J. P., Raatgever, J. W., and Ten Kate, F. J. W. (1984). Aflatoxin exposures in the industrial setting: An epidemiological study of mortality. Food and Chemical Toxicology 22(1):39-43.

12. Bulatao-Jayme, J., Almero, E. M., Castro, M. C. A., Jardeleza, M. T. R. and Salamat, L. A. (1982). A case-control dietary study of primary liver cancer risk from aflatoxin exposure. International Journal of Epidemiology 11(2):112-119.

13. Linsell, C. A. and Peers, F. G. (1977). Aflatoxin and liver cell cancer. Transactions of the Royal Society of Tropical Medicine and Hygiene 71(6):471-473.

14. Carlborg, F. W. (1979). Cancer, mathemathical models and aflatoxin. Food and Chemical Toxicology 17:159-166.

15. Keyfitz, F. (1968). World Population - An Analysis of Vital Data. University of Chicago Press, Chicago.

16. Shank, R. C., Bhamarapravati, N., Gordon, J. E., and Wogan, G. N. (1972). Dietary aflatoxin and human liver cancer. IV. Incidence of primary liver cancer in two municipal populations of Thailand. Food and Chemical Toxicology 10:171-179.

17. Peers, F. G. and Linsell, C. A. (1977). Dietary aflatoxins and human primary liver cancer. Annals of Nutrition and Metabolism 31:1005-1018.

18. Peers, F. G., Gilman, G. A., and Linsell, C. A. (1976). Dietary aflatoxin and human liver cancer. A study in Swaziland. International Journal of Cancer 17:167-176.

19. Department of Health and Human Services (1982). Vital Statistics of the United States, 1978. Volume II - Mortality, Part A. National Center for Health Statistics, Hyattsville, Maryland.

20. International Agency for Research on Cancer (1980). Some metals and metallic compounds. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans 23:39-141.

21. Neubauer, O. (1947). Arsenical cancer: A review. British Journal of Cancer 1:192-251.

22. Lander, J. J., Stanley, R. J., Sumner, H. W., Boswell, D. C., and Aach, R. D. (1975). Angiosarcoma of the liver associated with Fowler's solution (potassium arsenite). Gastroenterology 68: 1582-1586.

23. Roat, J. W., Wald, A., Mendelow, H., and Pataki, K. I. (1982). Hepatic angiosarcoma associated with short-term arsenic ingestion. The American Journal of Medicine 73:933-936.

24. Tseng, W. (1977). Effects and dose-response relationships of skin cancer and blackfoot disease with arsenic. Environmental Health Perspectives 19:109-119.

25. Tseng, W., Chu, H., How, S., Fong, J., Lin, C. and Yeh, S. (1968). Prevalence of skin cancer in an endemic area of chronic arsenicism in Taiwan. Journal National Cancer Institute 40:453-462.

26. Paton, G. R. and Allison, A. C. (1972). Chromosome damage in human cell cultures induced by metal salts. Mutation Research 16:332-336.

27. Petres, J., Baron, D., and Hagedorn, M. (1977). Effects of arsenic cell metabolism and cell proliferation: Cytogenetic and biochemical studies. Environmental Health Perspectives 19: 223-227.

28. Bencko, V. (1977). Carcinogenic, teratogenic, and mutagenic effects of arsenic. Environmental Health Perspectives 19:179-182.

29. Environmental Protection Agency (1984). Health Assessment Document for Inorganic Arsenic. EPA-600/8-83-021F.

30. Hill, A. B. and Faning, E. L. (1948). Studies in the incidence of cancer in a factory handling inorganic compounds of arsenic. British Journal of Industrial Medicine 5:1-6.

31. Kuratsune, M., Tokudome, S., Shirakusa, T., Yoshida, M., Tokumitsu, Y., Hayano, T., and Seita, M. (1974). Occupational lung cancer among copper smelters. International Journal of Cancer 13:552-558.

32. Tokudome, S. and Kuratsune, M. (1976). A cohort study on mortality from cancer and other causes among workers at a metal refinery. International Journal of Cancer 17:310-317.

33. Ott, M. G., Holder, B. B., and Gordon, H. L. (1974). Respiratory cancer and occupational exposure to arsenicals. Archives of Environmental Health 29:250-255.

34. Enterline, P. E. and Marsh, G. M. (1981). Mortality Among Workers Exposed to Arsenic and Other Substances in a Copper Smelter. Presented at the Arsenic Symposium, November 4-6, 1981.

35. Pinto, S. and Bennett, B. (1963). Effect of arsenic trioxide exposure on mortality. Archives of Environmental Health 7: 583-591.

36. Pinto, S. S., Enterline, P. E., Henderson, V., and Varner, M. O. (1977). Mortality experience in relation to a measured arsenic trioxide exposure. Environmental Health Perspectives 19:127-130.

37. Enterline, P. E. and Marsh, G. M. (1980). Mortality studies of smelter workers. American Journal of Industrial Medicine 1:251-259.

38. Lee, A. M. and Fraumeni, J. F. (1969). Arsenic and respiratory cancer in man: An occupational study. Journal of the National Cancer Institute 42(6):1045-1052.

39. Lubin, J. H., Pottern, L. M., Blot, W. J., Tokudome, S., Stone, B. J., and Fraumeni, J. F. (1981). Respiratory cancer among copper smelter workers: Recent mortality statistics. Journal of Occupational Medicine 23(11):779-784.

40. Higgins, I., Welch, K., Oh, M., Bond, G., and Hurwitz, P. (1981). Influence of arsenic exposure and smoking on lung cancer among smelter workers: A pilot study. American Journal of Industrial Medicine 2:33-41.

41. Welch, K., Higgins, I., Oh, M., and Burchfiel, C. (1982). Arsenic exposure, smoking, and respiratory cancer in copper smelter workers. Archives of Environmental Health 37(6):325-335.

42. Lee-Feldstein, A. (1983). Arsenic and respiratory cancer in humans: Follow-up of copper smelter employees in montana. Journal of the National Cancer Institute 70(4):601-610.

43. Crump, K. S. and Ng, T-H. (1983). Quantitative Risk Assessment for Environmental Exposure to Inorganic Arsenic. Unpublished report.

44. Consumer Product Safety Commission (1983). Chronic Hazard Advisory Panel on Asbestos. U.S. Consumer Product Safety Commission, Directorate for Health Sciences, Washington, D.C

45. Occupational Safety and Health Administration (1983). Quantitative Risk Assessment for Asbestos Related Cancers. Office of Carcinogen Standards. OSHA Contract J-9-F-2-0074.

46. Environmental Protection Agency (1985). Asbestos Health Effects Update. Office of Health and Environmental Assessment, Washington, D.C.

47. Ontario Royal Commission (1984). Report of The Royal Commission on Matters of Health and Safety Arising from the Use of Asbestos in Ontario. Ontario Ministry of the Attorney General.

48. National Academy of Science (1984). Asbestiform Fibers: Nonoccupational Health Risks.

49. Doll, R. and Peto, J. (1985). Effects on Health of Exposure to Asbestos. Prepared for Health and Safety Commission. London.

50. McDonald, J. C. and McDonald, A. D. (1977). Epidomiology of mesothelioma from estimated incidence. Preventive Medicine 6:426-446.

51. Hammond, E.C., Selikoff, I.J., and Seidman, H. (1979). Asbestos Exposure, Cigarette Smoking, and Death Rates. In: Health Hazards of Asbestos Exposure. Selikoff, I.J. and Hammond E.C. (eds.). New York Academy of Sciences. New York.

52. McDonald, J. C., Liddel, F. D. K., Gibbs, G. W., Eyssen, G. E., and McDonald, A. D. (1980). Dust exposure and mortality in chrysotile mining, 1910-75. British Journal of Industrial Medicine 37:11-24.

53. Nicholson, W. J., Selikoff, I. J., Seidman, H., Lilis, R., and Formby, P. (1979). Long-term mortality experience of chrysotile miners and millers in Thetford mines, Quebec. Annals New York Academy of Sciences 330:11-21.

54. Rubino, G., ,Piolatto, G., Newhouse, M., Scansetti, G., Aresini, G., amd Murray, R. (1979). Mortality of chrysotile asbestos workers at the Balangero Mine, Northern Italy. British Journal of Industrial Medicine 36:187-194.

55. Crump, K. S. (1984). Expert Testimony on Environmental Protection Agency Regional Hearings on Asbestos. Boston. June 1984.

56. Henderson, V. L. and Enterline, P. E. (1979). Asbestos exposure: factors associated with excess cancer and respiratory disease mortality. Annals New York Academy of Sciences 330:117-126.

57. Weill, H., Hughes, J., and Waggenspack, C. (1979). Influence of dose and fiber type of respiratory malignancy risk in asbestos cement manufacturing. American Review of Respiratory Disease 120:345-354.

58. Dement, J. M., Harris, R. L., Symons, J. M., and Shy, C. (1982). Estimates of dose-response for respiratory cancer among chrysotile asbestos textile workers. In: Inhaled Particles, Walton, W.H. (ed.). Volume V. Oxford. Pergamon. pp. 869-887.

59. Berry, G. and Newhouse, M.L. (1983). Mortality of workers manufacturing friction materials using asbestos. British Journal of Industrial Medicine 40:1-7.

60. Peto, J. (1980). Lung Cancer Mortality In Relation to Measured Dust Levels in an Asbestos Textile Factory. In: Biological Effects of Mineral Fibres. Volume 2. Wagner, J. (ed.). International Agency for Research on Cancer. IARC Scientific Publications No. 30.

61. Finkelstein, M. M. (1983). Mortality in Asbestos Cement Factory Workers. (In publication).

62. Finkelstein, M. M. (1983). Mortality among long-term employees of an Ontario asbestos cement factory. British Journal of Industrial Medicine 40:138-144.

63. Seidman, H., Lilis, R. and Selikoff, I. (1979). Short-term asbestos work exposure and long-term observation. Annals New York Academy of Sciences 330:61.

64. Selikoff, I., Hammond, E. and Seidman, H. (1979). Mortality experience of insulation workers in the United States and Canada. Annals New York Academy of Sciences 300:91.

65. International Agency for Research on Cancer (1979). Benzene. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans 7:203-221.

66. Hunter, C. G. (1968). Solvents with reference to studies on the pharmacodynamics of benzene. Proceeding of the Royal Society Medicine 61:913-915.

67. Hunter, C. G. and Blair, D. (1972). Benzene: Pharmacokinetic studies in man. Annals of Occupational Hygiene 15:193-199.

68. Docter, H. J. and Zielhuis, R. L. (1967). Phenol excretion as a measure of benzene exposure. Annals of Occupational Hygiene 10:317-326.

69. Berlin, M. (1984). Low Level Benzene Exposure in Sweden: Effect on Blood Elements and Body Burden of Benzene. Institute of Environmental Health, University of Lund. MARC, Chelsea College, London.

70. McMichael, A. J., Spirtas, R., Kupper, L. L. and Gamble, J. F. (1975). Solvent exposure and leukemia among rubber workers: An epidemiologic study. Journal of Occupational Medicine 17(4): 234-239.

71. Arp, E. W., Wolf, P. H., and Checkoway, H. (1983). Lymphocytic leukemia and exposure to benzene and other solvents in the rubber industry. Journal of Occupational Medicine 25(8):598-602.

72. Checkoway, H., Wilcosky, T., Wolf, P., and Tyroler, H. (1984). An evaluation of the associations of leukemia and rubber industry solvent exposures. American Journal of Industrial Health 5:239-249.

73. Infante, P. and White, M. (1983). Benzene: Epidemiologic observations of leukemia by cell type and adverse health effects associated with low-level exposure. Environmental Health Perspectives 52:75-82.

74. Vigiani, E. C. and Saita, G. (1964). Benzene and leukemia. The New England Journal of Medicine 271(17):872-876.

75. Vigliani, E. C. (1976). Leukemia associated with benzene exposure. Annals of the New York Academy of Sciences 143-151.

76. Aksoy, M., Erdem, S., and DinCol, G. (1974). Leukemia in shoeworkers exposed chronically to benzene. Blood 44(6):837 841.

77. Aksoy, M., Erdem, S., DinCol, K., Hepyuksel, T., and Dincol, G. (1974). Chronic exposure to benzene as a possible contributary etiologic factor in Hodgkin's disease. Blut 28:293-298.

78. Aksoy, M., Erdem, S., Erdogan, G., and Dincol, G. (1974). Acute leukaemia in two generations following chronic exposure to benzene. Human Herdeity 24:70-74.

79. Aksoy, M., Erdem, S., Erdogan, G., and Dincol, G. (1976). Combination of genetc factors and chronic exposure to benzene in the aetiology of leukaemia. Human Heredity 26:149-153.

80. Aksoy, M. (1980). Different types of malignancies due to occupational exposure to benzene: A review of recent observations in Turkey. Environmental Research 23:181-190.

81. Aksoy, M. (1981). Problems with benzene in Turkey. Regulatory Toxicology and Pharmacology 1:147-155.

82. Aksoy, M. (1983). Malignancies Due to Occupational Exposure to Benzene. Unpublished report.

83. Aksoy, M., Erdem, S., DinCol, G., Kutlar, A., Bakioglu, I., Hepyuksel, T. (1984). Clinical observations showing the role of some factors in the etiology of multiple myeloma. Acta Haematol 71:116-120.

84. Runion, H. E. and Scott, L. M. (1983). Benzene Exposure in the United States. International Conference on Benzene. New York City, November 3-4, 1983.

85. Holmerg, B. and Lundberg, P. (1984). Benzene: Standards, Occurrence and Exposure. Unit of Occupational Toxicology, Research Department, National Board of Occupational safety and Health. S-17184 SOLNA, Sweden.

86. Ott, M. G., Townsend, J. C., Fishbeck, W. A., and Langner, R. A. (1978). Mortality among individuals occupationally exposed to benzene. Archives of Environmental Health 33:3-10.

87. Rinsky, R. A., Young, R. J., and Smith, A. B. (1981). Leukemia in benzene workers. American Journal of Industrial Medicine 2: 217-245.

88. Wong, O. (1983). An Industry-Wide Mortality Study of Chemical Workers Occupationally Exposed to Benzene. Chemical Manufacturers Association. Environmental Health Associates, Inc. Berkley, CA.

89. Crump, K. and Allen, B. (1984). Quantitative Estimates of Risk of Leukemia From Occupational Exposure to Benzene. Prepared for U.S. Occupational Safety and Health Administration.

90. Tsuchiya, K., Okubo, T., and Ishizu, S. (1975). An epidemiological study of occupational bladder tumours in the dye industry of Japan. British Journal of Industrial Medicine 32:203-209.

91. Mancuso, T. F. and El-Attar, A. A. (1967). Cohort Study of Workers Exposed to Betanaphthylamine and Benzidine. Journal of Occupational Medicine 9(6):277-285.

92. Morinaga, K., Oshima, A., and Hara, I. (1982). Multiple Primary Cancers Following Exposure to Benzidine and Beta Naphthylamine. American Journal of Industrial Medicine 3:243-246.

93. Goldwater, L. J., Rosso, A. J., and Kleinfeld, M. (1965). Bladder tumors in a coal tar dye plant. Archives of Environmental Health 11:814-817.

94. Case, R. A. M., Hosker, M. E., McDonald, D. B., and Pearson, J. T. (1954). Tumours of the Urinary Bladder in Workmen Engaged in the Manufacture and Use of Certain Dyestuff Intermediates in the British Chemical Industry. British Journal of Industrial Medicine 11:75-104.

95. Rubino, G. F., Scansetti, G., Piolatto, G., and Pira, E. (1982). The carcinogenic effect of aromatic amines: An epidemiological study on the role of o-toluidine and 4,4' methylene bis (2-methylaniline) in inducing bladder cancer in man. Environmental Research 27:241-254.

96. Walker, B., Jr., and Gerber, A. (1981). Occupational exposure to aromatic amines: Benzidene and benzidene-based dyes. National Cancer Institute Monographs 58:11-13.

97. Horton, A. W. and Bingham, E. L. (1977). Risk of bladder tumors among benzidene workers and their serum properdin levels. Journal of the National Cancer Institute 58:1225-1228.

98. Lower, G. M., Jr., Nilsson, T., Nelson, C. E., Wolf, H., Gamsky, T. E., and Bryan, G. T. (1979). N-Acetyltransferase phenotype and risk in urinary bladder cancer: Approaches in molecular epidemiology. Preliminary results in Sweden and Denmark. Environmental Health Perspectives 29:71-79.

99. Zavon, M. R., Hoegg, U., and Bingham, E. (1973). Benzidene exposure as a cause of bladder tumors. Archives of Environmental Health 27:1-7.

100. National Institutes of Health (1981). Surveillance, Epidemiology, and End Results: Incidence and Mortality Data, 1973-77. National Cancer Institute Monographs 57.

101. Rinde, E., and Troll, W. (1975). Metabolic Reduction of Benzidine Azo Dyes to Benzidine in the Rhesus Monkey. Journal of the National Cancer Institute 55:181-187.

102. National Academy of Sciences Executive Committee (1975). Contemporary Pest Control Practices and Prospects. Pest Control: An Assessment of Present and Alternative Technologies, Vol. 1.

103. International Agency for Research on Cancer (1975). Cadmium and cadmium compounds. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man 11:39-41.

104. Piscator, M. (1981). Role of cadmium in carcinogenesis with special reference to cancer of the prostate. Environmental Health Perspectives 40:107-120.

105. Welinder, H., Skerfving, S., and Henriksen, O. (1977). Cadmium metabolism in man. British Journal of Industrial Medicine 34: 221-228.

106. Flanagan, P. R., McLellan, J. S., Haist, J., Cherian, M. G., Chamberlain, M. J., and Valberg, L. S. (1978). Increased dietary cadmium absorption in mice and human subjects with iron deficiency. Gastroenterology 74:841-846.

107. Kolonel, L. N. (1976). Association of cadium with renal cancer. Cancer 37:1782-1787.

108. Bako, G., Smith, E. S. O., Hanson, J., and Dewar, R. (1982). The geographical distribution of high cadmium concentrations in the environment and prostate cancer in Alberta. Canadian Journal of Public Health 73:92-94.

109. Berg, J. W. and Burbank, F. (1972). Correlations between carcinogenic trace metals in water supplies and cancer mortality. Annals of the New York Academy of Sciences 199:249-261.

110. Potts, C. L. (1965). Cadmium proteinuria: The health of battery workers exposed to cadmium oxide dust. Annals of Occupational Hygiene 8:55-61.

111. Kipling, M. D. and Waterhouse, J. A. H. (1967). Cadmium and prostatic carcinoma. The Lancet April 1:730-731.

112. Lemen, R. A., Lee, J. S., Wagoner, J. K., and Blejer, H. P. (1976). Cancer mortality among cadmium production workers. Annals of the New York Academy of Sciences 271:273-279.

113. Kjellstrom, T., Friberg, L., and Rahnster, B. (1979). Mortality and cancer morbidity among cadmium-exposed workers. Environmental Health Perspectives 28:199-204.

114. Elinder, C-G., Kjellstrom, T., Hogstedt, C., Andersson, K. and Spang, G. (1985). Cancer mortality of cadmium workers. British Journal of Industrial Medicine 42:651-655.

115. Armstrong, B. G. and Kazantzis, G. (1983). The mortality of cadmium workers. The Lancet June 25:1425-1427.

116. Sorchan, T. and Waterhouse, J. A. H. (1983). Mortality study of nickel-cadmium battery workers by method of regression models in life tables. British Journal of Industrial Medicine 40:293-300

117. Thun, M. J., Schnorr, T. M., Smith, A. B., Halperin, W. E., and Lemen, R. A. (1985). Mortality among a cohort of U. S. cadmium production workers--an update. Journal of the National Cancer Institute 74(2):325-333.

118. International Agency for Research on Cancer (1981). Chlorambucil. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man 26:115-136.

119. Rieche, K. (1984). Carcinogenicity of antineoplastic agents in man. Cancer Treatment Reviews 11:39-67.

120. Reimer, R. R., Hoover, R., Fraumeni, J. F., and Young, R. C. (1977). Acute leukemia after alkylating-agent therapy of ovarian cancer. The New England Journal of Medicine 297(4):177-181.

121. Greene, M. H., Boice, J. D., Greer, B. E., Blessing, J. A., and Dembo, A. J. (1982). Acute nonlymphocytic leukemia after therapy with alkylating agents for ovarian cancer. The New England Journal of Medicine 307(23):1416-1421.

122. Berk, P. D., Goldberg, J. D., Silverstein, M. N., Weinfeld, A., Donovan, P. B., Ellis, J. T., Landaw, S. A., Laszlo, J., Najean, Y., Pisciotta, A. V. and Wasserman, L. R. (1981). Increased incidence of acute leukemia in polycythemia vera associated with chlorambucil therapy. The New England Journal of Medicine 304(8):441-447.

123. International Agency for Research on Cancer (1980). Chromium and chromium compounds. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans 23:205-323.

124. Hayes, R. B. (1979). Cancer and Occupational Exposure to Chromium Chemicals. In: Reviews in Cancer Epidemiology, Vol. 1. Lilienfeld, A. M. (ed.). Elsevier/North-Holland Publisher. New York, New York.

125. Royle, H. (1975). Toxicity of chromic acid in the chromium plating industry (1). Environmental Research 10:39-53.

126. Baetjer, A. M. (1950). Pulmonary carcinoma in chromate workers. I. A review of the literature and report of cases. Archives of Industrial Hygiene and Occupational Medicine 2(5):487-504.

127. Enterline, P. E. (1974). Respiratory cancer among chromate workers. Journal of Occupational Medicine 16(8):523-526.

128. Stern, R. M. (1983). Assessment of risk of lung cancer for welders. Archives of Environmental Health 38(3):148-155.

129. Taylor, F. H. (1966). The relationship of mortality and duration of employment as reflected by a cohort of chromate workers. American Journal of Public Health 56(2):218-229.

130. Royle, H. (1975b). Toxicity of chromic acid in the chromium plating industry (2). Environmental Research 10:141-163.

131. Ohsaki, Y., Abe, S., Kimura, K., Tsuneta, Y., Mikami, H., and Murao, M. (1978). Lung cancer in Japanese chromate workers. Thorax 33:372-374.

132. Hayes, R. B., Lilienfeld, A. M., and Snell, L. M. (1979). Mortality in chromium chemical production workers: a prospective study. International Journal of Epidemiology 8(4):365-374.

133. Dalager, N. A., Mason, T. J., Fraumeni, J. F., Hoover, R., and Payne, W. W. (1980). Cancer mortality among workers exposed to zinc chromate paints. Journal of Occupational Medicine 22(1):25-29.

134. Alderson, M. R., Rattan, N. S., and Bidstrup, L. (1981). Health of workmen in the chromate-producing industry in Britain. British Journal of Industrial Medicine 38:117-124.

135. Sheffet, A., Thind, I., Miller, A. M., and Louria, D. B. (1982). Cancer mortality in a pigment plant utilizing lead and zinc chromates. Archives of Environmental Health 37(1):44-52.

136. Davies, J. M. (1984). Lung cancer mortality among workers making lead chromate and zinc chromate pigments at three English factories. British Journal of Industrial Medicine 41:158-169.

137. Hernberg, S., Westerholm, P., Schultz-Larsen, K., Degerth, R., Kuosma, E., Englund, A., Engzell, U., Hansen, H. S., and Mutanen, P. (1983). Nasal and sinonasal cancer. Connection with occupational exposure in Denmark, Finland and Sweden. Scandinavian Journal of Work Environment and Health 9:315-326.

138. Langard, S. and Norseth, S. (1979). Cancer in the gastrointestinal tract in chromate pigment workers. Arhiv Za Higijenu Rada I Toksikologiju 30(Suppl):301-304.

139. Langard, S. and Norseth, T. (1975). A cohort study of bronchial carcinomas in workers producing chromate pigments. British Journal of Industrial Medicine 32:62-65.

140. Langard, S. and Vigander, T. (1983). Occurrence of lung cancer in workers producing chromium pigments. British Journal of Industrial Medicine 40:71-74.

141. Langard, S., Andersen, A., and Gylseth, B. (1980). Incidence of cancer among ferrochromium and ferrosilicon workers. British Journal of Industrial Medicine 37:114-120.

142. Axelsson, G. and Rylander, R. (1979). Cancer mortality among ferrochromium workers. Arhiv Za Higijenu Rada I Toksikologiju 30(Suppl):305-310.

143. Axelsson, G., Rylander, R., and Schmidt, A. (1980). Mortality and incidence of tumours among ferrochromium workers. British Journal of Industrial Medicine 37:121-127.

144. Department of Health, Education, and Welfare (1979). Smoking and Health. A Report to the Surgeon General. No. (PHS) 79-50066.

145. Loeb, L. A., Ernster, V. L., Warner, K. E., Abbotts, J. and Laszio, J. (1984). Smoking and lung cancer: an overview. Cancer Research 44:5940-5958.

146. Doll, R. and Peto, R. (1976). Mortality in relation to smoking: 20 years' observations on male British doctors. British Medical Journal 2:1515-1536.

147. Doll, R. and Peto, R. (1978). Cigarette smoking and bronchial carcinoma: dose and time relationships among regular and lifelong non-smokers. Journal of Epidemiology and Community Health 32:303-313.

148. Crump, K. S., and Allen, B. C. (1985). Methods for quantitative risk assessment using occupational studies. The American Statistician 4(4):442-450.

149. Lanier, A. P, Noller, K. L., Decker, D. G., Elveback, L. R., and Kurland, L. T. (1973). Cancer and stilbestrol: A follow-up of 1,719 persons exposed to estrogens in utero and born 1943-1959. Mayo Clinic Proceedings 48:793-799.

150. Dieckmann, W. J., Davis, M. E., Rynkiewicz, L. M., and Pottinger, R. E. (1953). Does the administration of diethylstilbestrol during pregnancy have therapeutic value. American Journal of Obstetrics and Gynecology 66:1062-1081.

151. Robboy, S. J., Scully, R. E., Welch, W. R., and Herbst, A. L. (1977). Intrauterine diethylstilbestrol exposure and its consequences. Archives of Pathology and Laboratory Medicine 101:1.

152. Ulfelder, H. (1976). DES - transplacental teratogen - and possibly also carcinogen. Teratology 13:101-104.

153. Fu, Y. S., Reagan, J. W., Richart, R. M., and Townsend, D. E. (1979). Nuclear DNA and histologic studies of genital lesions in diethylstilbestrol-exposed progeny. American Journal of Clinical Pathology 72(4):515-520.

154. Gill, W. B., Schumacher, G. F. B., and Bibbo, M. (1976). Structural and functional abnormalities in the sex organs of male offspring of mothers treated with diethylstilbestrol. The Journal of Reproductive Medicine 16(4):147-153.

155. Gill, W. B., Schumacher, G. F. B., and Bibbo, M. (1977). Pathological semen and anatomical abnormalities of the genital tract in human male subjects exposed to diethylstilbestrol in utero. The Journal of Urology 117:477-480.

156. Bellet, R. E. and Squitieri, A. P. (1974). Estrogen-induced hypernephroma. The Journal of Urology **112**:160-161.

157. Greenberg, E. R., Barnes, A. B., Resseguie, L., Barrett, J. A., Burnside, S., Lanza, L. L., Neff, R. K., Stevens, M., Young, R. H., and Colton, T. (1984). Breast cancer in mothers given diethylstilbestrol in pregnancy. The New England Journal of Medicine **311**:1393-1398.

158. Bibbo, M., Haenszel, W. M., Wied, G. L., Hubby, M., and Herbst, A. L. (1978). A twenty-five-year follow-up study of women exposed to diethylstilbestrol during pregnancy. The New England Journal of Medicine **298**(14):763-767.

159. Hadjimichael, O. C., Meigs, J. W., Falcier, F. W., Thompson, W. D., and Flannery, J. T. (1984). Cancer risk among women exposed to exogenous estrogens during pregnancy. Journal of the National Cancer Institute **73**(4):831-834.

160. Greenwald, P., Barlow, J. J., Nasca, P. C., and Burnett, W. S. (1971). Vaginal cancer after maternal treatment with synthetic estrogens. The New England Journal of Medicine **285**(7):390-392.

161. Greenwald, P. and Nasca, P. C. (1973). Transplacental induction of vaginal cancer by synthetic estrogens. Progress in Clinical Cancer **5**:13-19.

162. Mangan, C. E., Giuntoli, R. L., Sedlacek, T. V., Rocereto, T., Rubin, E., Burtnett, M., and Mikuta, J. J. (1979). Six years' experience with screening of a diethylstilbestrol exposed population. American Journal of Obstetrics and Gynecology **134**:860-865.

163. Herbst, A. L., Cole, P. C., Colton, T., Robboy, S. J., and Scully, R. E. (1977). Age-incidence and risk of diethylstilbestrol-related clear cell adenocarcinoma of the vagina and cervix. American Journal of Obstetrics and Gynecology **128**(1):43-50.

164. Herbst, A. L., Ulfelder, H., and Poskanzer, D. C. (1971) Andenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. The New England Journal of Medicine **284**(16):878-881.

165. Herbst, A. L., Kurman, R. J., Scully, R. E., and Poskanzer, D. C. (1972). Clear-cell adenocarcinoma of the genital tract in young females. The New England Journal of Medicine **287**(25):1259-1264.

, D. C., Robboy, S. J., Friedlander, L.,
). Prenatal exposure to stilbestrol. A
f exposed female offspring with unexposed
ournal of Medicine 292(7):334-339.

on Chemical Safety (1984). Epichloro-
health criteria 33. World Health
:1-51.

nsky, R. A. (1979). Reanalysis of the Shell
tudy. U. S. Department of Health, Education and
ion of Surveillance, Hazard Evaluations and Field

E. (1982). Importance of sequential exposure in the
f epichlorohydrin and isopropanol. The Annals of the
emy of Sciences 381:344-349.

r, R. J., McClimans, C. D., Ott, M. G., Flake, R. E.,
R. L. (1979). An Evalution of the Mortality
of Employees with Potential for Exposure to
hydrin. Midland, Michigan, Dow Chemical Toxicology
Laboratory.

n, J. P., Bos, G. D., Craigen, A. A., Jacquet, B., Kueng,
anouziere-Simon, C., and Pierre, C. (1983). Mortality in
pean cohort occupationally exposed to epichlorohydrin.
ational Archives of Occupational and Environmental Health
25-336.

Beral, V. (1980). Hormones and Cancer. In: Reviews of Cancer Epidemiology. Lilienfeld, A. (ed.). Elsevier Press. New York.

3. Hoover, R., Gray, L. A., Cole, P., and MacMahon, B. (1976). The New England Journal of Medicine 295:401-405.

174. Ross, R. K., Paganini-Hill, A., Gerkins, V. B., Mack, T. M., Pfeffer, R., Arthur, M., and Henderson, B. E. (1980). A case control stud of menopausal estrogen therapy and breast cancer. Journal of the American Medical Association 243:1635-1639.

175. Horwitz, R. I. and Stewart, K. R. (1984). Effect of clinical features on the association of estrogens and breast cancer. The American Journal of Medicine 76:192-198.

176. Smith, D. C., Prentice, R., Thompson, D. J., and Herrman, W. L. (1975). Association of exogenous estrogen and endometrial carcinoma. The New England Journal of Medicine 293:1164-1167.

177. Mack, T. M., Pike, M. C., Henderson, B. E., Pfeffer, R. I., Gerkins, V. R., Arthur, M., and Brown, S. E. (1976). Estrogens and endometrial cancer in a retirement community. The New England Journal of Medicine 294:1262-1267.

178. McDonald, T. W., Annegers, J. F., O'Fallon, W. M., Dockerty, M. B., Malkasian, G. D., and Kurland, L. T. (1977). Exogenous estrogen and endometrial carcinoma: Case-control and incidence study. The American Journal of Obstetrics and Gynecology 127:572-579.

179. Gray, L. A., Christopherson, W. M., and Hoover, R. N. (1977). Estrogens and Endometrial Carcinoma. Obstetrics and Gynecology 49:385-389.

180. Antunes, C. M. F., Stolley, P. D., Rosenshein, N. B., Davies, J. L., Tonascia, J. A., Brown, C., Burnett, L., Rutledge, A., Pokempner, M., and Garcia, R. (1979). Endometrial cancer and estrogen use. The New England Journal of Medicine 300:9-13.

181. Hammond, C. B., Jelovsek, F. R., Lee, K. L., Creasman, W. T., and Parker, R. T. (1979). Effects of long-term estrogen replacement therapy II. Neoplasia. The American Journal of Obstetrics and Gynecology 133:537-547.

182. Hulka, B. S., Fowler, W. C., Kaufman, D. G., Grimson, R. C., Greenberg, B. G., Hogue, C. J. R., Berger, G. S., and Pulliam, C. C. (1980). Estrogen and endometrial cancer: Cases and two control groups from North Carolina. The American Journal of Obstetrics and Gynecology 137:92-101.

183. Shapiro, S., Kaufman, D. W., Slone, D., Rosenberg, L., Miettinen, O. S., Stolley, P. D., Rosenshein, N. B., Watring, W. G., Leavitt, T., and Knapp, R. C. (1980). Recent and past use of conjugated estrogens in relation to adenocarcinoma of the endometrium. The New England Journal of Medicine 303:485-489.

184. Spengler, R. F., Clarke, E. A., Woolever, C. A., Newman, A. M., and Osborn, R. W. (1981). Exogenous estrogens and endometrial cancer: a case-control study and assessment of potential biases. American Journal of Epidemiology 114:497-506.

185. Morgan, R. W., Claxton, K. W., Divine, B. J., Kaplan, S. D., and Harris, V. B. (1981). Mortality among ethylene oxide workers. Journal of Occupational Medicine 23(11):767-770.

186. Korpela, D. B., McJilton, C. E., and Hawkinson, T. E. (1983). Ethylene oxide dispersion from gas sterilizers. American Industrial Hygiene Association Journal 44(8):589-591.

187. Garry, V. F., Hozier, J., Jacobs, D., Wade, R. L., and Gray, D. G. (1979). Ethylene Oxide: Evidence of human chromosomal effects. Environmental Mutagenesis 1:375-382.

188. Vainio, H. (1982). Inhalation anesthetics, anticancer drugs and sterilants as chemical hazards in hospitals. Scandanavian Journal of Work, Environmental, and Health 8:94-107.

189. Landrigan, P. J., Meinhardt, T. J., Gordon, J., Lipscomb, J. A., Burg, J. R., Mazzuckelli, L. F., Lewis, T. R., and Lemen, R. A. (1984). Ethylene oxide: An overview of toxicologic and epidemiologic research. American Journal of Industrial Medicine 6: 103-115.

190. Hogstedt, C., Malmqvist, N., and Wadman, B. (1979). Leukemia in workers exposed to ethylene oxide. Journal of the American Medical Association 241(11):1132-1133.

191. Hogstedt, C., Rohlen, O., Berndtsson, B. S., Axelson, O., and Ehrenberg, L. (1979). A cohort study of mortality and cancer incidence in ethylene oxide production workers. British Journal Industrial Medicine 36:276-280.

192. Ferebee, S. H. (1970). Controlled chemoprophylaxis trials in tuberculosis. A general review. Advances in Tuberculosis Research 17:28-106.

193. Costello, H. D. and Snider, D. E. (1980). The incidence of cancer among participants in a controlled, randomized isoniazid preventive therapy trial. American Journal of Epidemiology 3(1):67-74.

194. International Agency for Research on Cancer (1974). Isonicotinic acid hydrazide. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man 4:159-172.

195. Hammond, E. C., Selikoff, I. J., and Robitzek, E. H. (1967). Isoniazid therapy in relation to later occurrence of cancer in adults and in infants. British Medical Journal 2:792-795.

196. Stott, H., Peto, J., Stephens, R., Fox, W., Sutherland, I., Foster-Carter, A. F., Teare, H. D., and Fenning J. (1976). An assessment of the carcinogenicity of isoniazid in patients with pulmonary tuberculosis. Tubercle 57:1-15.

197. Glassroth, J. L., White, M. C., and Snider, D. E. (1977). An assessment of the possible association of isoniazid with human cancer deaths. American Review of Respiratory Disease 116:1065-1074.

198. Miller, C. T., Neutel, C. I., Nair, R. C., Marrett, L. D., Last, J. M., and Collins, W. E. (1978). Relative importance of risk factors in bladder carcinogenesis. Journal of Chronic Diseases 31:51-56.

199. Sanders, B. M, and Draper, G. J. (1979). Childhood cancer and drugs in pregnancy. British Medical Journal 1:718-719.

200. Clemmesen, J. and Hjalgrim-Jensen, S. (1979). Is isonicotinic acid hydrazide (INH) carcinogenic to man? A 24-year follow up of 3371 tuberculosis cases. Ecotoxicology and Environmental Safety 3:439-450.

201. Howe, G. R., Lindsay, J., Coppock, E., and Miller, A. B. (1979). Isoniazid exposure in relation to cancer incidence and mortality in a cohort of tuberculosis patients. International Journal of Epidemiology 8(4):305-312.

202. Boice, J. D. and Fraumeni, J. F. (1980). Late effects following isoniazid therapy. American Journal of Public Health 70(9): 987-989.

203. International Agency for Research on Cancer (1975). Melphalan, Medphalan and Merphalan. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man 9:167-180.

204. Gori, S., Donti, E., Venti, G., Mecucci, C., Crino, L., and Tonato, M. (1983). Acute myeloblastic leukemia after adjuvant chemotherapy with melphalan in breast cancer case report with cytogenetic analysis. Tumori 69:117-122.

205. Law, I. P. and Blom, J. (1977). Second malignancies in patients with multiple myeloma. Oncology 34:20-24.

206. Einhorn, N. (1978). Acute leukemia after chemotherapy (Melphalan). Cancer 41:444-447.

207. Friedlander, B. R., Hearne, T., and Hall, S. (1978). Epidemiologic investigation of employees chronically exposed to methylene chloride. Journal of Occupational Medicine 20(10):657-666.

208. Riley, E. C., Fassett, D. W., and Sutton, W. L. (1966). Methylene chloride vapor in expired air of human subjects. American Industrial Hygiene Journal 27:341-348.

209. Ott, M. G., Skory, L. K., Holder, B. B., Bronson, J. M., and Williams, P. R. (1983). Health evaluation of employees occupationally exposed to methylene chloride. General study design and environmental considerations. Scandinavian Journal of Work, Environment and Health 9(Suppl 1):1-7.

210. Hearne, F. T. and Friedlander, B. R. (1981). Follow-up of methylene chloride study. Journal of Occupational Medicine 23:660.

211. Ott, M. G., Skory, L. K., Holder, B. B., Bronson, J. M., and Williams, P. R. (1983). Health evaluation of employees occupationally exposed to methylene chloride. Mortality. Scandinavian Journal of Work, Environment and Health 9(Suppl 1):8-16.

212. Environmental Protection Agency (1983). Health Assessment Document for Nickel. EPA-600/8-83-012.

213. NIOSH. (1977). Criteria for a Recommended Standard. Occupational Exposure to Inorganic Nickel. U.S. Government Printing Office, Washington D.C.

214. Sunderman, F. W. (1968). Nickel carcinogenesis. Diseases of the Chest 54(6):41-48.

215. Sunderman, F. W. (1981). Recent research on nickel carcinogenesis. Environmental Health Perspectives 40:131-141.

216. Doll, R. (1958). Cancer of the lung and nose in nickel workers. British Journal of Industrial Medicine 15:217-223.

217. Doll, R., Mathews, J. D., and Morgan, L. G. (1977). Cancer of the lung and nasal sinuses in nickel workers: a reassessment of the period of risk. British Journal of Industrial Medicine 34:102-105.

218. Morgan, J. G. (1958). Some observations on the incidence of respiratory cancer in nickel workers. British Journal of Industrial Medicine 15:224-234.

219. Norseth, T. (1980). Cancer hazards caused by nickel and chromium exposure. Journal of Toxicology and Environmental Health 6:1219-1227.

220. Sutherland, R. B. (1959). Respiratory Cancer Mortality in Workers Employed in an Ontario Nickel Refinery (1930-1957). Division of Industrial Hygiene. Department of Health for Ontario.

221. Sutherland, R. B. (1969). Mortality Among Sinter Workers. International Nickel Company of Canada, Limited. Cooper Cliff Smelter. Environmental Health Services Branch. Ontario Department of Health.

222. Chovil, A., Sutherland, R. B., and Halliday, M. (1981). Respiratory cancer in a cohort of nickel sinter plant workers. British Journal of Industrial Medicine 38:327-333.

223. Pedersen, E., Hogetveit, A. C., and Andersen, A. (1973). Cancer of respiratory organs among workers at a nickel refinery in Norway. International Journal of Cancer 12:32-41.

224. Kreyberg, L. (1978). Lung cancer in workers in a nickel refinery. British Journal of Industrial Medicine 35:109-116.

225. Magnus, K., Andersen, A., and Hogetveit, A. C. (1982). Cancer of respiratory organs among workers at a nickel refinery in Norway. International Journal of Cancer 30:681-685.

226. Lessard, R., Reed, D., Maheux, B., and Lambert, J. (1978). Lung cancer in New Caledonia, a nickel smelting island. Journal of Occupational Medicine 20(12):815-229.

227. Silverstein, M., Mirer, F., Kotelchuck, D., Silverstein, B., and Bennett, M. (1981). Mortality among workers in a die-casting and electroplating plant. Scandinavian Journal of Work, Environment and Health 7(Suppl 4):156-165.

228. Bernacki, E. J., Parsons, G. E., and Sunderman, F. W. (1978). Investigation of exposure to nickel and lung cancer mortality. Annals of Clinical and Laboratory Science 8(3):190-194.

229. Godbold, J. H. and Tompkins, E. A. (1979). A long-term mortality study of workers occupationally exposed to metallic nickel at the Oak Ridge gaseous diffusion plant. Journal of Occupational Medicine 21(12):799-806.

230. Olsen, J. and Sabroe, S. (1984). Occupational causes of laryngeal cancer. Journal of Epidemiology and Community Health 38:117-121.

231. Cox, J. E., Doll, R., Scott, W. A., and Smith, S. (1981). Mortality of nickel workers: Experience of men working with metallic nickel. British Journal of Industrial Medicine 38:235-239.

232. Poledrak, A. P. (1981). Mortality among welders, including a group exposed to nickel oxides. Archives of Environmental Health 36(5):235-242.

233. Enterline, P. E. and Marsh, G. M. (1982). Mortality among workers in a nickel refinery and alloy manufacturing plant in West Virginia. Journal of the National Cancer Institute 68(6):925-933.

234. International Agency for Research on Cancer (1978). Polychlorinated Biphenyls. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man 18:43-103.

235. Brown, D. P. and Jones, M. (1981). Mortality and industrial hygiene study of workers exposed to polychlorinated biphenyls. Archives of Environmental Health 36(3):120-129.

236. Safe, S. (1984). Polychlorinate biphenyls (PCBs) and polybrominated biphenyls (PBBs): Biochemistry, toxicology, and mechanism. Criticals Reviews in Toxicology 13(4):319-396.

237. Cordle, F., Corneliussen, P., Jelinek, C., Hackley, B., Lehman, R., McLaughlin, J., Rhoden, R., and Shapiro, R. (1978). Human exposure to polychlorinated biphenyls and polybrominated biphenyls. Environmental Health Perspectives 24:157-172.

238. Unger, M. O. and Nordberg, G. F. (1979). Distribution of PCB and DDT among human tissues. Arhiv Za Higijenu Rada I Toksikologiju 30:537-543.

239. Maroni, M., Colombi, A., Cantoni, S., Ferioli, and Foa, V. (1981). Occupational exposure to polychlorinated biphenyls in electrical workers. I. Environmental and blood polychlorinated biphenyls concentrations. British Journal of Industrial Medicine 38:49-54.

240. Maroni, M., Colombi, A., Cantoni, S., Ferioli, and Foa, V. (1981). Occupational exposure to polychlorinated biphenyls in electrical workers. II. Health effects. British Journal of Industrial Medicine 38:55-60.

241. Bahn, A. K., Rodenwaike, I., Herrmann, N., Grover, P., Stellman, J., and O'Leary, K. (1976). Melanoma after exposure to PCBs. The New England Journal of Medicine 295:450.

242. Maroni, M., Colombi, A., Arbosti, G., Cantoni, S., and Foa, V. (1981). Occupational exposure to polychlorinated biphenyls in electrical workers. II. Health effects. British Journal of Industrial Medicine 38:55-60.

243. Maroni, N., Colombi, A., Cantoni, S., Ferioli, E., and Foa, V. (1981). Occupational exposure to polychlorinated biphenyls in electrical workers. I. Environmental and blood polychlorinated biphenyls concentrations. British Journal of Industrial Medicine 38:49-54.

244. Bertazzi, P. A., Zocchetti, C., Guercilena, S., Foglia, M. D., Pesatori, A., and Riboldi, L. (1981). Mortality study of male and female workers exposed to PCB's. Prevention of Occupational Cancer - International Symposium pp. 242-248. Helsinke, Finland.

245. Bertazzi, P., Riboldi, L., Pesatori, A., Radice, L., and Zocchetti, C. (1985). Cancer Mortality of Electrochemical Workers Exposed to PCB. Unpublished report.

246. International Agency for Research on Cancer (1980). Phenacetin. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man 24:135-161.

247. Hultengren, N., Lagergren, C., and Ljungqvist, A. (1965). Carcinoma of the renal pelvis in renal papillary necrosis. Acta Chirurgica Scandinavica 130:314-320.

248. Adam, W. R., Dawborn, J. K., Price, C. G., Riddell, J., and Story, H. (1970). Anaplastic transitional-cell carcinoma of the renal pelvis in association with analgesic abuse. The Medical Journal of Australia May 30:1108-1109.

249. Burnett, K. R., Miller, J. B., and Greenbaum, E. I. (1980). Transitional cell carcinoma: Rapid development in phenacetin abuse. AJR 134:1259-1261.

250. Bengtsson, U., Angervall, L., Ekman, H., and Lehmann, L. (1968). Transitional cell tumors of the renal pelvis in analgesic abusers. Scandinavian Journal of Urology and Nephrology 2:145-150.

251. Angervall, L., Bengtsson, U., Zetterlund, C. G., and Zsigmond, M. (1969). Renal pelvic carcinoma in a swedish district with abuse of a phenacetin-containing drug. British Journal of Urology 41:401-409.

252. Johansson, S., Angervall, L., Bengtsson, U., and Wahlqvist, L. (1974). Uroepithelial tumors of the renal pelvis associated with abuse of phenacetin-containing analgesics. Cancer 33:743-753.

253. Bengtsson, U., Johansson, S., and Angervall, L. (1978). Malignancies of the urinary tract and their relation to analgesic abuse. Kidney International 13:107-113.

254. Begley, M., Chadwick, J. M., and Jepson, R. P. (1970). A possible case of analgesic abuse associated with transitional cell carcinoma of the bladder. The Medical Journal of Australia 12: 1133-1134.

255. Rathert, P., Melchior, H., and Lutzeyer, W. (1975). Phenacetin: A carcinogen for the urinary tract. Journal of Urology 113: 653-657.

256. Gonwa, T. A., Corbett, W. T., Schey, H. M., and Buckalew, V. M. (1980). Analgesic-associated nephropathy and transitional cell carcinoma of the urinary tract. Annals of Internal Medicine 93(2):249-252.

257. Fokkens, W. (1979). Phenacetin abuse related to bladder cancer. Environmental Research 20:192-198.

258. McCredie, M., Ford, J. M., Taylor, J. S., and Stewart, J. H. (1982). Analgesics and cancer of the renal pelvis in New South Wales. Cancer 49(12):2617-2625.

259. McCredie, M., Stewart, J. H., Ford, J. M., and MacLennan, R. A. (1983). Phenacetin-containing analgesics and cancer of the bladder or renal pelvis in women. British Journal of Urology 55:220-224.

260. International Agency for Research on Cancer (1980). Reserpine. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man 24:211-241.

261. Danielson, D. A., Jick, H., Hunter, J. R., Stergachis, A., and Madsen, S. (1982). Nonestrogenic drugs and breast cancer. American Journal of Epidemiology 116(2):329-332.

262. Ross, R. K., Paganini-Hill, A., Krailo, M. D., Gerkins, V. R., Henderson, B. E., and Pike, M. C. (1984). Effects of reserpine on prolactin levels and incidence of breast cancer in postmenopausal women. Cancer Research 44:3106-3108.

263. O'Fallon, W. M., Labarthe, D. R., and Kurland, L. T. (1975). Rauwolfia derivatives and breast cancer. The Lancet Aug. 16: 292-296.

264. Laska, E. M., Siegel, C., Meisner, M., Fischer, S., and Wanderling, J. (1975). Matched-pairs study of reserpine use and breast cancer. The Lancet Aug. 16:296-300.

265. Kodlin, D. and McCarthy, N. (1978). Reserpine and breast cancer. Cancer 41(2):761-768.

266. Kewitz, H., Jesdinsky, H. J., Kreutz, G., and Schulz, R. (1980). Reserpine and breast cancer. Archives Internationales de Pharmacodynamie et de Therapie 246:22-24.

267. Labarthe, D. R. and O'Fallon, W. M. (1980). Reserpine and breast cancer: A community-based longitudinal study of 2,000 hypertensive women. Journal of the American Medical Association 243(22):2304-2310.

268. Lilienfeld, A. M., Chang, L., Thomas, D. B., and Levin, M. L. (1976). Rauwolfia derivatives and breast cancer. The John Hopkins Medical Journal 139(2):41-50.

269. Curb, J. D., Hardy, R. J., Labarthe, D. R., Borhani, N. O., and Taylor, J. O. (1982). Reserpine and breast cancer in the hypertension detection and follow-up program. Hypertension 4:307-311.

270. Arnold, D. L., Moodie, C. A., Grice, H. C., Charbonneau, S. M., Stavric, B., Collins, B. T., McGuire, P. F., Zawidzka, Z. Z., and Munro, I. C. (1980). Long-term toxicity of *ortho toluenesulfonamide* and sodium saccharin in the rat. Toxicology and Applied Pharmacology 52:113-152.

271. Colburn, W. A., Bekersky, I., and Blumenthal, H. P. (1981). Dietary saccharin kinetics. Clinical Pharmacology and Therapeutics 30(4):558-563.

272. Morgan, A. and Jain, M. (1974). Bladder cancer: smoking, beverages and artificial sweeteners. Canadian Medical Association Journal 111:1067-1070.

273. Howe, G. R., Burch, J. D., Miller, A. B., Morrison, B., Gordon, P., Weldon, L., Chambers, L. W., Fodor, G., and Winsor, G. M. (1977). Artificial sweetners and human bladder cancer. The Lancet 17:578-581.

274. Morrison, A. S. and Buring, J. E. (1980). Artificial sweeteners and cancer of the lower urinary tract. The New England Journal of Medicine 302(10):537-541.

275. Hoover, R. and Strasser, P. H. (1980). Artificial sweeteners and human bladder cancer: Preliminary results. The Lancet 19:837-840.

276. Wynder, E. L. and Stellman, S. D. (1980). Artificial sweetener use and bladder cancer: A case-control study. Science 207: 1214-1216.

277. Moller-Jensen, O., Knudsen, J. B., Sorensen, B. L., and Clemmesen, J. (1983). Artificial sweeteners and absence of bladder cancer risk in Copenhagen. International Journal of Cancer 32:577-582.

278. Armstrong, B., Lea, A. J., Adelstein, A. M., Donovan, J. W., White, G. C. and Ruttle, S. (1976). Cancer mortality and saccharin consumption in diabetics. British Journal of Preventive and Social Medicine 30:151-157.

279. International Agency for Research on Cancer (1979). Trichloroethylene. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man **20**:545-572.

280. Page, N. (1979). Assessment of trichloroethylene as an occupational carcinogen. IARC Scientific Publication **25**:75-79.

281. Stewart, R. D. and Dodd, H. C. (1964). Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride, and 1, 1, 1-trichloroethane through the human skin. American Industrial Hygiene Association Journal **25**:439-446.

282. Stewart, R. D., Dodd, H. C., Gay, H. H., and Erley, D. S. (1970). Experimental human exposure to trichloroethylene. Archives of Environmental Health **20**:64-71.

283. Stewart, R. D., Gay, H. H., Erley, D. S., Hake, C. L., and Peterson, J. E. (1962). Observations on the concentrations of trichloroethylene in blood and expired air following exposure of humans. American Industrial Hygiene Association Journal **23**: 167-170.

284. Ikeda, M., Ohtsuji, H., Imamura, T., and Komoike, Y. (1972). Urinary excretion of total trichloro-compounds, trichloroethanol, and trichloroacetic acid as a measure of exposure to trichloroethylene and tetrachloroethylene. British Journal of Industrial Medicine **29**:328-333.

285. Kimmerle, G. and Eben, A. (1973). Metabolism, excretion and toxicology of trichloroethylene after inhalation. 2. Experimental human exposure. Archives of Toxicology **30**:127-138.

286. Sato, A., Nakajima, T., Fujiwara, Y., and Murayama, N. (1977). A pharmacokinetic model to study the excretion of trichloroethylene and its metabolites after an inhalation exposure. British Journal of Industrial Medicine **34**:56-63.

287. Smith, G. F. (1978). Trichlorethylene - relationship of metabolite levels to atmospheric concentrations: preliminary communication. Journal of the Royal Society of Medicine **71**:591-595.

288. Axelson, O., Andersson, K., Hogstedt, C., Holmberg, B., Molina, G., and de Verdier, A. (1978). A cohort study on trichloroethylene exposure and cancer mortality. Journal of Occupational Medicine **20**(3):194-196.

289. Blair, A. (1980). Mortality among workers in the metal polishing and plating industry, 1951-1969. Journal of Occupational Medicine **22**(3):158-162.

290. Blair, A., Decoufle, P., and Grauman, D. (1979). Causes of death among laundry and dry cleaning workers. American Journal of Public Health 69(5):508-511.

291. Tola, S., Vilhunen, R., Jarvinen, E., and Korkala, M. L. (1980). A cohort study on workers exposed to trichloroethylene. Journal of Occupational Medicine 22(11):737-740.

292. Paddle, G. M. (1983). Incidence of liver cancer and trichloroethylene manufacture: joint study by industry and a cancer registry. British Medical Journal 286(846):836.

293. International Agency for Research on Cancer (1979). Vinyl chloride, polyvinyl chloride and vinyl chloride-vinyl acetate copolymers. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man 19:377-438.

294. Nicholson, W. J., Henneberger, P. K., and Seidman, H. (1984). Occupational hazards in the VC-PVC industry. Progress in Clinical and Biological Research 141:155-175.

295. Suciu, I., Prodan, L., Ilea, E., Paduraru, A., and Pascu, L. (1975). Clinical manifestations in vinyl chloride poisoning. Annals of the New York Academy of Sciences 246:53-69.

296. Brady, J., Liberatore, F., Harper, P., Greenwald, P., Burnett, W., Davies, J. N. P., Bishop, M., Polan, A., and Vianna, N. (1977). Angiosarcoma of the liver: An epidemiologic survey. Journal of the National Cancer Institute 59(5):1383-1385.

297. Delorme, F. and Theriault, G. (1978). Ten cases of angiosarcoma of the liver in Shawinigan, Quebec. Journal of Occupational Medicine 20(5):338-340.

298. Popper, H., Thomas, L. B., Telles, N. C., Falk, H., and Selikoff, I. J. (1978). Development of hepatic angiosarcoma in man induced by vinyl chloride, thorotrast, and arsenic. American Journal of Pathology 92(2):349-376.

299. Spirtas, R. and Kaminski, R. (1978). Angiosarcoma of the liver in vinyl chloride/polyvinyl chloride workers. Journal of Occupational Medicine 20(6):427-429.

300. Wagoner, J. K. (1978). Vinyl chloride and pulmonary cancer. Journal of Environmental Pathology and Toxicology 1:361-362.

301. Infante, P. F. (1981). Observations of the site-specific carcinogenicity of vinyl chloride to humans. Environmental Health Perspectives 41:89-91.

302. Maltoni, C., Lefemine, G., Ciliberti, A., Cotti, G., and Carretti, D. (1984). Experimental research on vinyl chloride carcinogenesis. In: Archives of Research on Industrial Carcinogenesis 2:27-35. Maltoni, C. and Mehlman, M. A. (eds.) Princeton Scientific Publishers, Inc., Princeton, New Jersey.

303. Barnes, A. W. (1976). Vinyl chloride and the production of PVC. Proceeding of the Royal Society of Medicine 69:277-281.

304. Jones, J. H. (1981). Worker exposure to vinyl chloride and poly(vinyl chloride). Environmental Health Perspectives 41: 129-136.

305. Aryanpur, J. (1977). Vinyl chloride: Its impact on occupational medicine practice. Journal of Occupational Medicine 19(10): 689-692.

306. Nicholson, W. J., Henneberger, P. K., and Tarr, D. (1984). Trends in cancer mortality among workers in the synthetic polymers industry. Progress in Clinical and Biological Research 141:65-78.

307. Kuzmack, A. M. and McGaughy, R. E. (1975). Quantitative Risk Assessment for Community Exposure to Vinyl Chloride. Office of Health and Ecological Effects. U. S. Environmental Protection Agency.

308 Nicholson, W. J., Hammond, E. C., Seidman, H., and Selikoff, I. J. (1975). Mortality experience of a cohort of vinyl chloride poly-vinyl chloride workers. Annals of the New York Academy of Sciences 246:225-230.

309. Tabershaw, I. R. and Gaffey, W. R. (1974). Mortality study of workers in the manufacture of vinyl chloride and its polymers. Journal of Occupational Medicine 16(8):509-518.

310. Buffler, P. A., Wood, S., Eifler, C., Suarez, L., and Kilian D. J. (1979). Mortality experience of workers in a vinyl chloride monomer production plant. Journal of Occupational Medicine 21(3):195-203.

311. Waxweiler, R. J., Stringer, W., Wagoner, J. K., Jones, J., Falk, H. and Carter, C. (1976). Neoplastic risk among workers exposed to vinyl chloride. Annals of the New York Academy of Sciences 271:40-48.

312. Byren, D., Engholm, G., Englund, A., and Westerholm, P. (1976). Mortality and cancer morbidity in a group Swedish VCM and PCV production workers. Environmental Health Perspectives 17:167-170.

313. Fox, A. J. and Collier, P. F. (1977). Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain. British Journal of Industrial Medicine 34:1-10.

314. Ott, M. G., Langner, R. R., and Holder, B. B. (1975). Vinyl chloride exposure in a controlled industrial environment. Archives of Environmental Health 30:333-339.

315. Duck, B. W., Carter, J. T., Coombes, E. J. (1975). Mortality study of workers in a polyvinyl-chloride production plant. The Lancet Dec. 13:1197-1199.

316. Heldaas, S. S., Langard, S. L., Andersen, A. (1984). Incidence of cancer among vinyl chloride and polyvinyl chloride workers. British Journal of Industrial Medicine 41:25-30.

317. Goldsmith, J. and Beeser, S. (1984). Strategies for pooling data in occupational epidemiological studies. Annals Academy of Medicine 13(2)(suppl):297-310.