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LAND DISPOSAL BAN VARIANCE PETITIONER'S GUIDANCE MANUAL

DRAFT

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SPECIAL NOTE

This draft guidance manual is based on a proposed rule, the approach and content of the final version of the guidance, when issued, will be dependent on the approach promulgated in the final Land Disposal Restrictions Rule. Promulgation of the first phase of final land disposal restrictions is scheduled for November 1986.

Land Disposal Ban Variance
Petitioners Guidance Manual

CONTENT

I. Introduction

This guidance manual provides a basic description of the requirements for petitioning the Agency for removal of restrictions placed on the land disposal of any hazardous waste under Section 3004 (d), (e), or (g) of the Resource Conservation and Recovery Act (RCRA). To obtain approval for a petition, it must be demonstrated that land disposal is a management practice that will be protective of human health and the environment. To be protective, Section 3004 of RCRA requires that the petitioner demonstrate "... to a reasonable degree of certainty, that there will be no migration of hazardous constituents from the disposal unit or injection zone for as long as the wastes remain hazardous." This manual will describe the process by which such petitions will be prepared and submitted to the Agency for review and approval.

The November 8, 1984 amendments to RCRA provide the Agency a basis on which to restrict hazardous wastes from land disposal. The restriction decision is not based on an absolute prohibition of land disposal of hazardous waste but takes into account the relationship between concentrations of Appendix VIII constituents in waste leachate and the risk they may present to a potentially exposed population. The Agency has developed a decision mechanism for land disposal restrictions that accounts for the toxicity of a waste, and the fate and transport of waste leachate as it may affect human or environmental exposure. A general description of

this mechanism will be outlined below such that the petitioner may understand the basis of the restriction decision and also become aware of the possible avenues available for pursuing a petition demonstration.

The performance standard of no migration for as long as the wastes remain hazardous is operationalized by allowing migration of waste constituents at or below concentration levels in all media (surface water, ground water, and air) that are protective of human health and the environment. The establishment of concentration levels in each media that are protective of human health and the environment is based on toxicological data, in conjunction with established Agency protocol for analyzing toxicological data. The reader may refer to Appendix III for a general description of Agency protocol used to evaluate toxicolgical data. A concentration level that is found by the Agency to be protective of human health is referred to as the Reference dose (RfD) for noncarcinogens (threshold toxicants) and as the risk-specific dose (RSD) for carcinogens (non-threshold toxicants). The RFD corresponds to a dose that is reasonably protective of human health when exposure is chronic. The RSD corresponds to a dose that presents a specific probabiity of cancer over and above the normal background probability of cancer for an individual over a lifetime, within a range of 10^{-4} to 10^{-7}.

The RfD and RSD underpin the restriction decision process. They are used to calculate Screening Levels (SL) that determine whether a waste having a specific leachate concentration

is restricted from land disposal or not. The Agency does not use the concentration of the constituents in the waste itself to compare with the SLs. Instead the Agency uses the concentration of the constituents in the waste leachate to compare with the SL(s). The reader should refer to "Test Methods for the Evaluation of Solid Waste, Physical/Chemical Methods", SW-846 for a discussion of waste leachates and the extraction and measuring techniques used to determine concentration levels of Appendix VIII constituents. A waste is restricted from land disposal whenever its leachate contains any one or more Appendix VIII constituents in concentrations that exceed that calculated SL for that respective constituent.

The SL(s) are determined by "backcalculating" from concentrations that are protective of human health, at the point of exposure to a point or zone that is located immediately beneath or adjacent to the disposal unit. Backcalculating involves reversing the normal direction of fate and transport models that usually start with the source concentration and calculate the fate and transport of a substance to determine its concentration at a point of exposure. Thus the end result of backcalculation is a maximum waste or leachate concentration for each Appendix VIII constituent. The backcalculation is performed for each Appendix VIII constituent for each media. Thus for a given Appendix VIII constituent, there will be two SL(s), one for air and one for water. Whichever SL for a given constituent is lowest will be used as the maximum allowable concentration in the waste (for air) or in the leachate (for water) for land

disposal. Owner/operators and/or generators whose waste leachate has concentrations of Appendix VIII constituents at or below the lowest SL need only certify that this is so. Details for certification will be discussed below. Those owner/operators who exceed any SL for any constituents in their waste leachate must either comply with applicable treatment standards, petition for a variance, or stop land disposal of the waste altogether.

The fate and transport models that are used to backcalculate SL(s) from RfD($) and RSD(s) are generic by design. The models incorporate a universal facility type that is representative of the various types of facilities defined as land disposal units. In addition the model incorporates a Monte Carlo approach for simulating the range of anticipated disposal scenarios. This approach accommodates variation in environmental settings, the uncertainties in specific chemical properties, and the range of engineered system releases from land disposal units. Rather than specifying a single value for each input parameter to the model to represent a reasonable worst case, the Monte Carlo simulation method involves a large number of computer runs with values for each input parameter drawn from data sets representative of the range and distribution of possible values for each parameter. Moreover, where parameters are dependent (correlated), the relationships are accounted for in the simulation. The SL's thus derived are intended to be protective of human health and the evnironment at all disposal unit sites.

The Agency is aware that the generic model approach will not always account for the multitude of variations that may

exist among actual existing or future land disposal units and the environmental settings they may be operating in. The generic screening levels computed by the model are based on the level corresponding to the 90th percentile of the range of hydrogeologic scenarios arranged from favorable to least favorable cases. Thus, the generic value may be more conservative than necessary for sites that fall below the 90th percentile. Thus, the petition process allows the petitioner to demonstrate that the subject facility will safely contain the waste of interest despite the results of the generic model. The petitioner may challenge the results of the generic model on the basis of unique site-specific factors and values not accounted for in the model.

The petitioner may not, however, challenge through the petition process either the RfD or the estimates of carcinogenic potency used by the Agency to calculate the RSD. (See Appendix III). Any challange to the established RfD(s) or carcinogenic potency estimates must be presented to the appropriate office of the Agency for review. The Agency will assess the merits of any challenges to either an RfD or carcinogenic potency estimates and any resulting revisions will apply across the board to all Agency applications of the RfD and the RSD.

Essentially there are two approaches whereby a petitioner may successfully obtain petition approval. They are:

(1) The leachate concentration of any Appendix VIII constituent will never exceed the lowest back calculated SL, based on an analysis of site

specific data, and thus any migration that does occur will not endanger human health.

(2) The leachate concentration of any one or more Appendix VIII constituent will exceed the lowest applicable SLs, yet because of unique site specific factors, will not endanger human health.

The first approach would be based on unique natural physical or biologic phenomena not completely accounted for in the generic Screening Level models. In addition to natural phenomena, engineered systems may be considered for their efficacy in controlling constituent migration to the extent that they are effective over the time the waste remains hazardous. In summary, the petitioner must demonstrate that as a result of natural chemical and physical processes at the site, hazardous constituents are immobilized, diluted, or degraded by the time they reach points of potential exposure such that human health is protected.

The second approach may also be supported by evidence mentioned in the first approach as it may modify exposure to existing or potential populations in proximity of the site. In addition, the petitioner may present information concerning the nature and size of the potentially exposed population, and toxicological data relevant to potential exposure scenarios to demonstrate that human health is protected. Under this approach, the petitioner would be responsible for demonstrating that an exposure scenario whereby the leachate constituent concentrations of the waste would result in concentrations at the potential point or points of exposure exceeding the

established RfD or RSD would still be protective of human health. This approach requires that a site-specific risk management decision be made regarding the degree to which the RfD or RSD could be exceeded for a particular site and waste stream. For the RSD, the Agency is willing to consider departures from the 10^{-6} level of individual risk to a maximum of 10^{-4} based on considerations of the size and nature of the existing or future exposed population. For the RfD, the Agency will consider situations in which site specific exceedances may be reasonable given the size and nature of the existing or potential population, the severity of the disease outcome, and the reversibility of any toxic effects.

The guidance manual describes a number of avenues open to the petitioner for demonstrating to the Agency that a particular waste should be approved for site specific land disposal. Recognizing that such a demonstration can be extremely complex, depending upon the characteristics of the waste and the disposal unit site, the Agency has developed a flexible process that identifies those situations that require a relatively simple demonstration relying on data readily available to the petitioner, and also identifies those more complex situations that require a more detailed analysis and potentially extensive site-specific data collection to obtain petition approval. The petitioner will be able to readily determine whether he or she qualifies for a simple analysis or

must perform a more detailed site analysis. Using this guidance manual, the petitioner will also be able to determine the likelihood for approval of a petition, or whether the combined waste and site characteristics indicate that approval is highly unlikely. The petitioner should be able to quickly determine the amount of effort required to obtain petition approval, and decide whether another waste management alternative is preferable.

This guidance manual will describe criteria that the Agency will use to evaluate petitions and determine whether an approval is justified. The decision will be based on the Agency's evaluation of the performance of the disposal unit combined with its location in meeting the standard of performance stated in Section 3004 (d), (e), and (g) of RCRA. The criteria have been developed to do the following:

1. Approve or reject a petition based on data and analyses already available to the Agency;
2. Determine eligibiity for a petition based on minimum data requirements;
3. Determine eligibility for a simplified site analysis;
4. Approve or reject a petition based on the results of a simplified site analysis;
5. Approve or reject a petition based on the results of a detailed site analysis.

The evaluation criteria will consist of screening factors, minimum requirements for data quality and quantity, use of simulation models, and the use of health and environmental-based screening levels. These criteria will be applied in a tiered fashion, in which a petitioner can initially determine the

depth of analysis required. If the petitioner is rejected in the first tier (screening step), or in the second tier (simplified site analysis), he still has the option of proceeding to a third tier analysis (detailed site or health effects analysis). At each step in the process, the petitioner can re-evaluate the decision to pursue the petition.

The following sections of this guidance manual describe the components of each of the three tiers, and the decision criteria to be used in evaluating petitions. Section II discusses the waste testing and analysis requirements. Section III outlines the screening factors that constitute the 1st Tier analysis. Section IV describes the approach to be used in the 2nd Tier, the simplified site analysis. Section V describes the objectives of the Exposure and Population Analysis, which is optional to a petitioner performing a 2nd Tier analysis, and may be required as an optional component of all 3rd Tier analyses. Section VI briefly describes the components and scope of a 3rd Tier, detailed site analysis. Additionally, a series of appendices are included to provide perspective on the Agency's risk assessment and risk management policies.

II. Waste Analysis

The petitioner must perform a waste analysis to determine the presence and concentration of all Appendix VIII constituents. Wastes containing any of these constituents are restricted from land disposal in concentrations in excess of the applicable

Screening/Treatment Levels. The petitioner must identify all of the Appendix VIII constituents present in the restricted wastes that exceed these levels.

The petitioner should perform the waste analysis by using sampling and analyical methods described in "Test Methods for the Evaluation of Solid Waste, Physical/Chemical Methods", SW-846, insuring that representative samples are taken.
The petitioner may use other equivalent test methods that have been approved by the Agency. The use of the Toxicity Characteristic Leaching Procedure (TCLP) is required as a standard method for characterizing waste leachate. Exhibit II-1 displays the process for applying the TCLP. The petitioner may also provide additional data on the physical and chemical characteristics of the waste, if such data is relevant to the type of demonstration being performed.

Exhibit II-2 lists some of the data that the petitioner may be required to provide, if he is performing a 3rd Tier analysis. Exhibit II-2 also indicates the specific types of data that should be necessary for a 2nd Tier analysis. Exhibit

II-3 is a suggested format for reporting the results of the waste leachate analysis and the identification of chemical constituents and their concentrations. The petitioner should assure that the information included on this exhibit describes the subject waste leachate accurately and completely. If the petition is approved, it will be approved for a waste that exhibits precisely the characteristics described on

EXHIBIT II-1. TCLP FLOWCHART

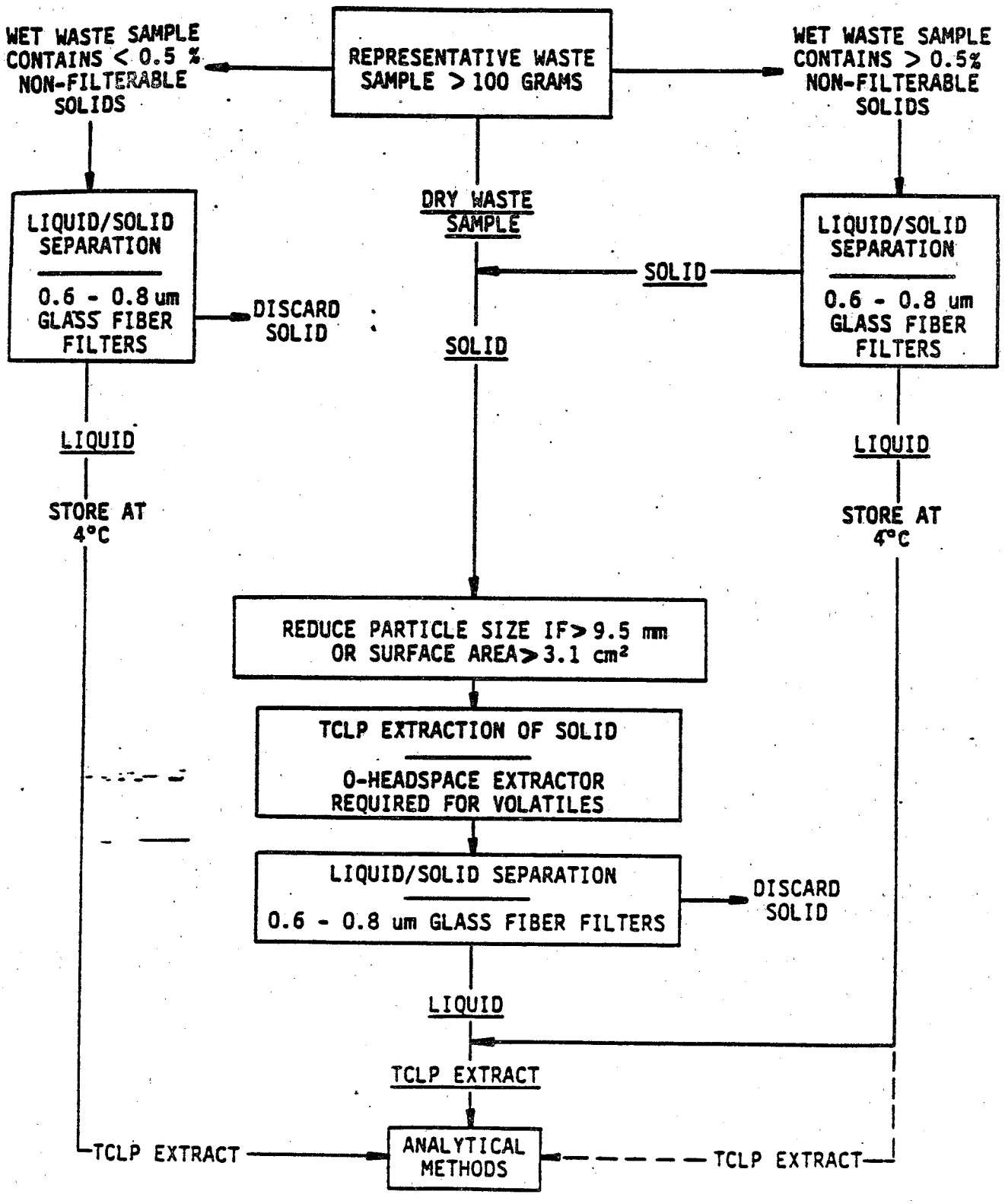

EXHIBIT II-2. WASTE INFORMATION REQUIREMENTS

(to be provided for each petitioned waste)

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1 Waste Name:

2 List all applicable EPA Hazardous Waste Codes (including F, K, U, and P code designations as outlined in 40 CFR.31, 32, and 33):

3 List originating industry and provide 3 digit SIC code:

4 List all manufacturing process(es) that produce the waste:

5 List constituents of the waste (use commonly accepted compound names):

6 Complete the following sections pertaining to hazardous properties for each waste and its constituent members:

- Is the waste considered ignitable using criteria outline in 261.21? (Y/N)
- Is the waste considered corrosive using criteria outlined in 261.22? (Y/N)
- Is the waste considered reactive using criteria outline in 261.23? (Y/N)
- Is the waste considered to exhibit the characteristics of EP toxicity as outlined in 261.24? (Y/N)

7 List the quantity of banned waste as a percentage of the total waste present in the disposal facility (weight basis):

8 List the respective length of time of disposal of each waste including banned and non-banned in the facility (attach sheet separately):

9 List the frequency of each waste (weight/unit time) received in the facility on a daily, monthly, and yearly basis:

10 Estimate the maximum quantity of waste to be received by the facility (if there is no basis for estimation, list the design capacity of the facility).

11 List and discuss all pretreatment processes and their respective end effects on the waste:

12 List and discuss all processes for handling and storage of the waste and the important design specifications for each unit operation:

13 If applicable, list the complete time of processing of the waste:

EXHIBIT II-2 (Continued) REQUIRMENTS FOR PHYSICAL/CHEMICAL/ BIOLOGICAL CHARACTERISTICS OF THE WASTE AND EACH OF ITS CHEMICAL CONSTITUENTS

(information to be provided seperately for each waste and for each component of wastes that are mixtures)

Molecular Structure (attach diagram separately):

Molecular weight:

Density:

Phase (at STP):

Viscosity:

Boiling Point:

Freezing Point:

Solubility in polar solvent (water):

Solubility non-polar solvent:

Plot solubilities (both solvent types) as a function of pH (range 2-12) (attach graph separately):

Dissociation constant:

Octanol/water partition coefficient:

Henry's Law constant:

Critical volume, temperature, anmd pressure:

Vapor pressure:

Diffusivity (kinematic viscosity):

Thermal conductivity:

Biodegradation rate:

Oxidation rate:

Photolysis rate:

Bioacculation (bioconcentration) potential:

PEL (Permissible Exposure Limit):

IDLH (Immediately Dangerous to Life and Health):

THV (Threshold Limit Value):

Exhibit II-3 Generator Name _____
Waste Description _____

Appendix VIII Constituents	Concentration (mg/liter)			Standard Deviation	Number of Analyses
	Average	Maximum	Minimum		

this exhibit. If the waste that is being generated and managed in a land disposal unit as a result of petition approval does not exhibit the characteristics described on this exhibit, the petition approval will be revoked. The waste will no longer be eligible for land disposal, until a revised petition is submitted and approved. Continued land disposal of a waste that no longer qualifies for petition approval is considered to be grounds for enforcement action by the Agency.

Once the petitioner has completed the waste analysis and has determined the presence of various Appendix VIII constituents and their concentrations, he or she should determine which of these constituents exceed the Screening/Treatment Levels. (See Appendix II). These levels are published in various Federal Register notices, corresponding to the proposed schedule for restricting wastes from land disposal published in the Federal Register on May 31, 1985. The petition must address all Appendix VIII constituents that exceed these levels. In some cases, there may be present in the waste an Appendix VIII constituent for which no Screening/Treatment Level exists, due to the timing of the development of these levels. When this case arises, the petitioner may choose to include these additional constituents in the demonstration, if he has reason to believe that eventually the screening level that will be established would be less than the concentration in the subject waste leachate. If the additional constituents are included and the petition was approved, the waste could be land

disposed, and no future petition would be necessary. The petitioner may also choose to exclude these additional constituents, if he estimates that the screening level eventually established would not be exceeded by the level in the subject waste. If the petition was approved, there is the possibility that the waste may be banned at some future time, due to the establishment of different screening levels.

As an alternative to performing a full Appendix VIII analysis of the subject waste, the petitioner may submit information to the Agency that certain Appendix VIII constituents are not present in the waste, due to their absence from the raw materials used in the process that produces the waste, and due to the manufacturing process itself. The Agency reserves the right to require additional analyses for specific chemicals that may be suspected to be present, based on information already available to the Agency or similar manufacturing processes and similar raw materials. If, upon subsequent testing of the waste, it is determined that additional constituents are present that were certified as not being present, the approved petition will be revoked until such time as a revised petition demonstration, that includes the additional constituents, is completed and approved. Continued land disposal of a waste with constituent concentrations that exceed applicable SL's constitutes a violation of the operating permit and may result in enforcement action.

For those wastes that contain a substantial number of Appendix VIII constituents, the petitioner may choose to group similar chemicals according to properties related to the rate of

mobility and persistence in the environment. If such a grouping can be made, the petitioner may include in the analysis only one chemical from any group that represents, in a reasonable fashion, the mobility and persistence of all of the group members. In selecting an indicator chemical constituent, the petitioner should consider the relative amounts in the waste of the various group members. A chemical that is similar to the other group members, but not present in a concentration as high as other chemicals may not be a suitable indicator for that group. Additionally, the petitioner should consider the unique characteristics of the various environmental media (air, ground water, surface water, and soil) at the disposal unit site, in selecting a specific chemical as an indicator for a group of like chemicals.

To use an indicator chemical approach based on chemical and physical properties that relate to the wastes' mobility and persistence, the petitioner must present reasonable evidence to demonstrate that the grouping is justified. In many cases, chemicals that belong to a generic group (i.e., solvents, polycyclic aromatics, metals, etc.) may have similar chemical structure and may be expected to be transported in air, soil, surface water, or ground water at nearly the same velocities. The petitioner will be required to present reasonable evidence that minor variations in chemical structure do not represent major variations in mobility and persistence.

The petitioner should also consider possible synergistic effects when using an indicator chemical to simulate the mobility and persistence of a group of chemicals. The Agency will review for reasonableness the petitioner's grouping and selection of an indicator chemical. The Agency will refer to the qualitative structure activity relationship between the group members, various estimators of mobility and persistence (e.g., Henrys' law constant, octanol water partition coefficient, etc.), and any other field monitoring or research data that may establish a basis for grouping of chemical constituents. The petitioner must be cautioned that the use of indicator chemicals for performing the exposure analysis does not allow the same type of grouping for performing the health effects analysis described in Section V, should such an analysis be performed. The health effects analysis must include the effects on the exposed individuals of each chemical constituent subject to the petition, not merely the indicator of mobility and persistence which is used to estimate potential exposure levels.

The petitioner should include in the petition a concise summary of the waste analysis and any grouping or selection of indicators. This summary should identify specific chemicals and their expected ranges of concentrations that will form the basis for the 2nd Tier analysis. For the 3rd Tier analysis

additional data may be required, depending upon the nature of the demonstration to be performed. At a minimum, some estimation of the annual volume of the subject waste should be made. This estimation may be based on historical production rates projected into the future, or on the design capacity of the disposal unit.

III. 1st Tier Analysis - Screening Factors

This section describes a series of screening factors that the petitioner must consider prior to preparing a petition demonstration under either the 2nd Tier or 3rd Tier analyses. These screening factors are designed to indicate to the petitioner the likelihood of obtaining petition approval and the type and level of analyses required. Also, the screening factors identify certain decision points for the petitioner in the demonstration, and identify decision criteria that the Agency will use in evaluating petitions.

There are several purposes to be served by the use of screening factors in the petition process. The Agency believes that the statutory performance standard requires a positive demonstration of safety before petition approval is justified. Therefore, the petition process must be capable of identifying any site-specific features that would clearly be unfavorable to petition approval. This early identification of unfavorable features provides warning to the petitioner that ultimate approval may not be likely, and that the petition may be ineligible for a 2nd Tier analysis. The screening factors also will provide

basic pre-requisites to a 2nd Tier or 3rd Tier analysis, in describing minimum data and administrative requirements. Additionally, the screening factors provide an objective and systematic method for reviewing petitions received from generators and disposal units across the country.

The screening factors that the Agency will use may be briefly described as follows:

A. Approval Criteria

These criteria will allow the Agency to grant approval to a petition immediately, with no further data or analyses required by the petitioner. The petitioner will certify to the Agency that the approval criteria are met, based on unique waste or site conditions or based on the results of previous studies. The petitioner will be given written notice of the approval following Agency review of appropriate information already available to the Agency to corroborate the certification of the petitioner.

B. Rejection Criteria

These criteria will identify situations that render a prospective petitioner ineligible for a petition demonstration. If the petitioner cannot meet these criteria, the Agency will not commence review of the petition.

C. Eligibility for a 2nd Tier Simplified Analysis

These criteria will identify those petitions that are eligible for a simplified site analysis, as described in Section IV. Since a 2nd Tier analysis generally involves use of site-specific data of reasonable quality that are already available

to the petitioner or easily obtainable, and an analysis that involves the Screening/Treatment Level models, these criteria will identify those sites that contain features that cannot be analyzed with these models. Such sites may involve the use of additional conservative assumptions as a means of justifying the 2nd Tier analysis, or may require that a 3rd Tier analysis be performed.

The screening factors and the criteria associated with each are contained in Appendix I of this document.

IV. 2nd Tier Analysis - Simplified Site Analysis

A. Objectives

This section describes the requirements for completing a simplified site analysis. The objectives of a simplified site analysis are to determine on a site-specific basis, a level or concentration in a waste that will not threaten human health and the environment when that waste is placed in a land disposal unit, and to make this determination in a comprehensive way without requiring extensive data collection and complex analyses. The simplified site analysis must rely on site-specific input data already available to the petitioner or to the Agency, or on data that should be readily attainable by the petitioner from independent sources. Where adequate data is unattainable without an extensive or time-consuming site analysis, the use of estimates and assumptions is acceptable, as long as the estimates

and assumptions are reasonably conservative. The simplified site analysis must rely on an analytical tool that is appropriate for simulating the site's environmental conditions. The use of the unmodified versions of the Screening/Treatment Level models should constitute the most simplified analysis that would be acceptable for a petition demonstration.

B. Screening/Treatment Level Models

The models that the Agency has developed for determining the Screening/Treatment Levels may be used for a simplified site analysis. The models have been constructed so as to simulate a generic disposal unit, and have built-in assumptions that specify the generic site conditions relative to the hydrogeology, topography, and climate. The petitioner may use either of the models (air, ground water, and surface water) if he or she so chooses. The models require certain specific input values for hydrogeologic, topographic, and climatic factors. The models calculate an acceptable leachate concentration for each constituent based on the appropriate human health criteria at the point of human exposure. Using site-specific data, the petitioner may run the models and establish site-specific screening levels for each Appendix VIII constituent that is of concern to the petition demonstration. Using the same back calculation approach that established the nationally applicable Screening/Treatment Levels, the petitioner may determine that

approval is justified by comparing the actual waste constituent concentrations to the site-specific levels.

As an alternative, the petitioner may use other simplified models to simulate the behavior of the subject waste, using actual waste constituent concentrations, and predict the likely levels of each contaminant in the air, ground water, surface water, and soil at any points of potential exposure. The use of any other models requires adequate validation for the intended application. This predicted exposure level would be compared to the appropriate RfD's and RSD's to determine whether petition approval was justified.

C. Data Requirements

Regardless of the type of modeling approach employed by the petitioner, the data requirements for a 2nd Tier analysis should be similar. The simplified analysis should make maximum use of site-specific data that is reasonably accurate, and that is already available to or easily attainable by the petitioner. Much of the data that is required for a RCRA Part B permit, especially the data required for establishing a Subpart F ground-water monitoring program, is directly relevant to a petition demonstration. In some cases, the models chosen may require some additional data, or may require that the data be re-formatted. The Agency will accept reasonably accurate data or estimates to satisfy these additional requirements.

In reviewing the input data supplied by the petitioner for the 2nd Tier analysis, the Agency will apply a "reasonableness" test. Using published sources of hydrogeologic, topographic, and climatic data, in addition to any actual site data collected by the Agency or State, the petition reviewer will determine if the petitioner's data is reasonably accurate. If any doubt exists as to the reasonable accuracy of the petitioner's data, the Agency will perform an appropriate sensitivity analysis of the model results. If, in the opinion of the petition reviewer, the results of the sensitivity analysis indicate that substantially different results may be obtained by varying the input data, the petitioner may be asked for documentation to support the original data, the Agency may require that a 3rd Tier analysis be performed that includes additional on-site sampling and analyses and thorough quality control, or the Agency may reject the petition due to an unreasonable degree of uncertainty in the analysis.

The objective of a "reasonableness" test is to determine, on a site-by-site basis, whether the petitioner's data is within the range of typical values of measured parameters for specific geologic, hydrologic, and climatic regions. The Agency will review the petitioner's data to assure that it is consistent with ranges of values in various published reference sources, and that each factor is internally consistent with other factors where a dependency relationship is expected to exist. Examples of reference sources that the Agency may use are the following:

1. Parameters and Variables Appearing in Repository Siting Models, NUREG/CR-3066; by J.W. Mercer, S.D. Thomas, B. Ross 1982, U.S. Nuclear Regulatory Commission.
2. Mercer, J.W., P.S.C. Rao, S.D. Thomas, and B. Ross. "Description of Parameters and Data (and Typical Ranges of Values) Useful for Evaluation of Migration at Hazardous Waste Management Facilities, letter report to U.S. EPA under Contract No. 68-01-6464, 1982.
3. Lyman, W.J., W.F. Reehl and D.H. Rosenblatt. Handbook of Chemical Property Estimation Methods - Environmental Behavior of Organic Compounds. McGraw-Hill, Inc. 1982.

D. Point of Exposure

It is necessary for the petitioner to establish a point or points of potential human exposure in each environmental media where migration could occur. For the purpose of a petition demonstration, the potential exposure points are at the boundaries of the disposal unit, unless the petitioner can establish effective long-term controls over an area beyond the boundaries of the disposal unit. Any legally enforceable restrictions on the use of any on-site water resources within the property boundary where the disposal unit is located would justify a point or points of exposure at the property boundary. An act of the state legislature that places permanent restrictions on the use of any water resources within a carefully defined area beyond the property boundary would allow the petitioner to

establish a point or points of exposure at the limits of this expanded area of effective control. Wherever the point or points of exposure are ultimately established, the petitioner must use the actual linear distance from the center of the disposal unit to the closest point of potential exposure in the simplified modeling analysis.

In considering air migration, the point of potential exposure for direct inhalation during the operating and closure periods of the disposal unit would be at the surface of the impoundment, landfill cell, waste pile, or land treatment unit, unless access to the disposal unit by any unauthorized persons is prevented by an adequate security system, and all authorized personnel are adequately protected from air emissions. If security and on-site safety precautions are adequate, the point of potential human exposure for direct inhalation may be established at the limits of the area controlled by the security system. The actual linear distance from the center of the disposal unit to the closest point of potential air exposure should be used by the petitioner in performing the simplified site analysis under the 2nd Tier approach.

In performing a 2nd Tier analysis involving the Screening/ Treatment Level models, the distance to the point of potential exposure is assumed to be 500 feet. In applying these models to a site specific petition demonstration, the distance assumption cannot be increased without adequately validating all other model assumptions. The balance of assumptions that is

attained in each of the Screening/Treatment Level models would be distorted by varying any one assumption, so that model results may not be consistent with other model applications. The petitioner may wish to demonstrate that actual site conditions deviate from some of the assumed conditions of the Screening/Treatment Level models. This is permissable as long as all model assumptions are adequately validated for the site-specific application.

If an existing source of drinking water, either a ground water or surface water source, is within 500 feet of the disposal unit, the petitioner should modify the Screening/Treatment Level model to include the actual distance rather than the assumed distance of 500 feet. Such a modification should not require any validation, as long as the other assumptions of the model are not changed.

E. Analysis and Decision Criteria

In performing the 2nd Tier analysis, the petitioner should consider the possibility of human exposure to any of the subject waste constituents in the air, ground water, and surface water. Using the Screening/Treatment Level (S/TL) models, the petitioner can determine a site-specific screening levels in the air, in the ground water, and in the surface water for each constituent. Comparison of the site-specific levels to the actual concentration in the waste leachate allows a determination of whether or not there are any threats to human health associated with land disposal of the waste. If an indicator chemical approach was

used for the fate and transport analysis, the petitioner must consider the potential human health effects associated with each chemical, not just the indicator. If no constituent concentration in the waste exceeds the applicable site-specific level, the petition should be approved relative to potential human health effects.

If the petitioner chooses not to use the screening level models, other simplified models that simulate site conditions can be used to determine the maximum concentration that may occur at any points of potential exposure. This maximum concentration can be compared to the human health criteria used in setting Screening/ Treatment Levels. If no constituent concentration in the waste exceeds the applicable site-specific level, the petition should be satisfactory.

If the actual waste constituent concentrations exceed the site-specific levels or result in predicted exposure in excess of the RfD or risk-related dose for a carcinogen, the petition should be rejected. If rejection is likely, the petitioner may choose one of three possible alternatives. One alternative is to accept the results that lead to rejection and withdraw the petition. Another alternative is to perform a site-specific health effects analysis. The third alternative is to perform a detailed site analysis, which also includes an exposure and population analysis. The next section describes the objectives and elements of an exposure and population analysis.

V. Exposure and Population Analysis

The petitioner has the option of performing an exposure and population analysis to support a petition demonstration. The exposure analysis may allow for a reconsideration of a number of exposure-related assumptions that are incorporated into the screening level models that may not be applicable at a specific site. An exposure and population analysis also allows some consideration of the degree of uncertainty involved in the petition demonstration and allows for a more flexible risk based management decision for petition approval.

The petitioner may not directly challenge any of the established RfDs or the established estimate of carcinogenic potency through a petition demonstration. If the petitioner has toxicological data suggesting that an RfD or the estimate of carcinogenic potency be revised, the supporting evidence may be submitted for review and possible incorporation into Agency-wide health criteria.

The Agency is considering the idea of taking the severity of health effects into account in the petition process. However, the Agency presently is unaware of any practical measure that would allow the severity of health effects to be readily used as a factor in a risk management decision. The Agency might consider situations where the health effect is minor, completely reversible, and the exposure causing such a health effect is infrequent.

The Agency is also considering the idea of taking population size into account in the petition process for non-threshold constituents. Exactly how the Agency will incorporate population size to determine a level of risk that is reasonable for a given

site and non-threshold constituent has not been fully developed. In general, the Agency will consider allowing higher levels of individual risk in smaller populations than in larger ones, as long as the incidence of adverse effects is the insignificant.

A. Exposure Assessment

Before any assessment of human health risk can be incorporated into the petition demonstration, it is essential for the petitioner to thoroughly establish:

1) The relevant toxicologic properties of the waste;
2) The amount of waste to be disposed;
3) The concentration of the waste constituents in the leachate;
4) The long term site specific fate and transport of the waste constituents.

This information is requisite to establishing possible exposure pathways and the rate and magnitude of exposure. Only after the exposure pathways have been established and the likely degree of exposure is determined can the final steps of risk assessment be undertaken or can risk management decisions be made.

The petitioner will be responsible for identifying all potential pathways of exposure over the time the waste remains hazardous. In addition the petitioner will be responsible for estimating potential rates of exposure for each pathway for the length of time the waste remains hazardous. It is important to understand that exposure scenarios, (i.e., pathways and rates of exposure) are likely to change over time with major differences occurring when the unit is operating compared to the post closure period or beyond. Thus, it is incumbent upon

the petitioner to anticipate all likely exposure scenarios that may occur during the time the waste remains hazardous, to insure that the demonstration is inclusive of all relevant exposures through time.

The exposure assessment must be based, at a minimum, on the following types of exposure pathways:

1. Drinking water exposure from either a ground water or a surface water source;
2. Ingestion of contaminated food (e.g., aquatic organisms or agricultural products);
3. Dermal contact (e.g. recreational use of surface waters, or bathing);
4. Inhalation of volatile organics, or particulates;
5. Any combination of the above pathways.

For direct pathways of exposure the point of exposure will be assumed to be at the limits of the area of effective control which may be the facility waste management boundary unless use restrictions discussed in Section IV have or will be implemented. For indirect pathways of exposure, the rate of exposure for each intermediate point must be estimated. For example, ingestion of fish by humans will require estimations of constituent concentrations in the surface water, and account for possible bioconcentration of the constituent in the food chain such that a realistic estimate of exposure can be determined for humans consuming the fish. Taking into account bioconcentration phenomena in the food chain is especially important

as it may result in indirect exposures several orders of magnitude greater than direct exposure pathways. For indirect exposure pathways that include foodstuffs as the final exposure medium for humans, the petitioner should determine the frequency and magnitude of consumption of the foodstuff(s) in the potentially exposed population. If the petitioner can show that consumption of any contaminated foodstuff is infrequent enough such that the magnitude of exposure is minimal, a detailed analysis of the intermediate points for an indirect exposure may be omitted.

The screening level models include an assumption that half of the RFD will be accounted for from background levels. The petitioner who challenges the validity of this assumption for his or her site and waste will be required to determine background levels of the constituents(s) at all potential points of exposure. If a petitioner can demonstrate that there is no existing background level of the subject constituent, he or she may use up to 100 percent of the RfD to determine a site specific screening level. Background exposure measurements will be subject to strict quality assurance and quality control procedures that must be approved by the Agency in advance of the petition submission. Background exposure measurements will require that both ambient and occupational exposures are taken into account.

The 50% apportionment assumption used in the screening level models does not apply to carcinogens. Thus the full RSD corresponding to a 10^{-6} individual lifetime risk is applied in the model calculations. In situations where the petitioner wishes to obtain a variance for land disposal of a waste with a leachate concentration in excess of the screening level corresponding to a 10^{-6} lifetime risk, the Agency may require that the petitioner determine background levels of the constituent and take into consideration the prevalance and concentration of other carcinogens in the potentially exposed population when exposure is ambient and/or there is a significant occupational exposure in the population.

In situations where a waste stream contains more than one carcinogen, an additive approach to the risk assessment estimation will be taken. The Agency is unaware of any practical methodology for accurately taking into account synergistic or antagonistic combinations of constituents. The petitioner should refer to the EPA publication Proposed Guidelines for the Health Risk Assessment of Chemical Mixtures and Request for Comments; Notice /Part III, Vol 50 No. 9 Pages 1169-1176/ for a further discussion of Agency policy regarding estimating risk from chemical mixtures.

B. Population Characterization:

The Agency will require a characterization of the current or future population likely to be exposed to constituents leaking from a land disposal unit. The extent of population characterization will depend on the number of Appendix VIII constituents in a waste and their toxicological effects, leachate concentrations, exposure pathways and the relative

contribution of each constituent to overall exposure. At a minimum, the following population characteristics should be determined for existing potentially exposed populations:

1) Sex and age distributions
2) Historical growth rates
3) Sensitive subgroups
4) Major occupational categories of existing populations and type and extent of local industry.

Most of this information can be obtained through the Bureau of Census, U.S. Department of Commerce. However, the petitioner should seek consultation with public health professionals who are experienced with environmental health matters for developing adequate population characterization data.

The presence of sensitive groups such as (but not limited to) pregnant women, children, or chronically ill individuals within a potentially exposed population will affect how the Agency will make a risk management decision for a given site- and waste-specific scenario. The petitioner will be required to identify the size of the most sensitive subgroups within the potentially exposed population. This subgroup should form the basis for determining a site-specific risk level and should be considered in situations where the generic RfD may be exceeded. If the petitioner can show an absence of sensitive subgroups for as long as the waste remains hazardous, the Agency may allow a relaxation of the uncertainty factor (concerning population sensitivity only) for the RfD of a threshold constituent by allowing a commensurate exceedance of the RfD.

The U.S. Department of Health and Human Services, National Center for Health Statistics may be a good source of information on sensitive individuals in the region. All of this information should be presented in tabular form to facilitate easy reference.

The presence or absence of sensitive subgroups over the time a non-threshold constituent remains hazardous will influence the level of risk that will be acceptable. For example, a constituent that is a teratogen will influence the Agency's risk management decision depending on the prevalence of pregnant women in the potentially exposed population.

Certain assumptions are usually made when estimating exposures from chemical wastes. Although dose rates are the ideal measure of exposure, the types of data necessary (absorption and excretion data) for calculating doses for individual constituents are relatively rare and are usually intake route specific. The next best estimation of exposure is to calculate rates of intake for each constituent in each media. Standard assumptions used to calculate intake rates are shown in Exhibit V-1.

Intake rates are a function of the estimated concentration of a constituent in a medium (air, water, food) at the point of exposure, the volume or mass of the contaminated medium taken in by an individual, and the weight of the individual. Human exposure is expressed in terms of intake, which is the amount of a substance taken into the body per unit of body weight per unit time. Intakes are calculated separately for each exposure medium. In addition, intakes have to be summed for each medium across all media specific exposure pathways.

EXHIBIT V-1

STANDARD VALUES USED IN DAILY INTAKE CALCULATIONS

Parameter	Standard Value	Reference
Average body weight, adult	70 kg	EPA, 1980
Average body weight, child	10 kg	ICRP, 1975
Amount of water ingested daily, adult	2 liters	NAS, 1977
Amount of water ingested daily, child	1 liter	NAS, 1977
Amount of air breathed daily, adult	20 m^3	EPA, 1980
Amount of air breathed daily, child	5 m^3	FDA, 1970
Amount of fish consumed daily, adult	6.5 g	EPA, 1980

Example 1: how to apply the standard assumptions.

If contaminant concentration is 3 mg/liter in drinking water:

3 mg/liter x 2 liters/day water consumption - 70 kg body weight
= 0.086 mg/kg/day intake

Example 2: how to apply adjusted assumptions.

If site data indicated that the exposed population has a water consumption rate of 1.2 liters/day and an average weight of 60 kg, and the contaminant concentration is 3 mg/liter in drinking water:

3 mg/liter x 1.2 liters/day water consumption - 60 kg body weight
= 0.06 mg/kg/day intake

The final result should indicate the total oral and inhalation exposure to a constituent. Dermal exposures may also be important depending on the waste and characteristics of the site. The Agency will require that the petitioner either document that dermal exposure is inconsequential to human health or estimate the rate of exposure based on the site and waste-specific scenario.

The standard values used in daily intake calculations shown in Exhibit V-1 are average values and may not be entirely appropriate for a specific site and potentially exposed population. There are many characteristics about a population that may cause sharp deviations from these average values. This is especially true when exposure occurs via ingestion of foodstuffs and liquids. Dietary preferences, methods of preparation, and age of the individual are examples of factors that can strongly influence actual intake rates.

The Agency will supply the petitioner with what it considers to be reasonable assumptions, and/or actual data specific to a constituent, such that exposure estimates can be made. The petitioner may wish to develop data concerning human intake routes instead of using assumptions. The acceptability of any data of this type developed by a petitioner will require strict adherance to a QA/QC plan approved by the Agency. The application of this data for exposure estimates most be carried out by a qualified toxicologist or similar health professionals.

A major emphasis of the petition demonstration rests on the estimation of long term (chronic) exposures to relatively low concentrations of constituents. This type of exposure estimation leads to calculation of a chronic daily intake (CDI) to characterize the risk from non-catastrophic failure of a land disposal unit. However, there may be site and waste specific scenarios where there is a significant probability of catastrophic failure. In situations where catastrophic failure has a significant probability, the Agency may require that a petitioner estimate a subchronic daily intake (SDI) to assess the risk in such a scenario. The major difference in determining an SDI versus a CDI will be in the prediction of the fate and transport of a constituent under the specific catastrophic conditions.

C. Risk Management Factors

The greater the degree of certainty in the quantification of potential exposure for a population the greater the level of confidence there will be in the entire risk assessment process. Greater certainty will allow a higher level of confidence in making risk management decisions for a specific site and waste scenario.

The Agency will place considerable weight on the sources of uncertainty in the petition demonstration. The major sources of uncertainty come from the:

1) fate and transport analysis
2) toxicological data
3) risk estimating procedures.

For non-threshold toxicants, risk management decisions are an inherent part of the process to establish a level that is protective of human health. The petitioner should refer to the November, 1984, EPA Proposed Guidelines for Carcinogenic Risk Assessment (FR46294) to gain insight into Agency protocol for estimating human health risk due to nonthreshold toxicants. The Agency believes that the establishment of a single across-the-board risk level for carcinogens is not appropriate since no dose level is "safe" under all circumstances and since carcinogens differ in the weight of evidence supporting the hazard assessment. The cited guidelines explain how the Agency will handle differences in the weight of evidence that a compound is carcinogenic. Where the weight of evidence suggests that a compound is a known or probable human carcinogen, the protective dose would be calculated for the 10^{-6} level. The 10^{-6} level is viewed by the Agency as a point of departure for making risk management decisions. Choice of 10^{-6} as the initial risk level of concern is made on the basis of past Agency decisions. In general the Agency has made decisions to allow

concentrations of non-threshold toxicants where the individual risk values have been within the range of 10^{-4} to 10^{-7}. The range of allowable risk will be integrated with the weight of evidence approach and the nature and size of existing or future potentially exposed populations. In other words the Agency will tend to favor conservative risk levels where the weight of positive evidence is strong, and there is a large potentially exposed population, and be less conservative where the weight of positive evidence is less and the potentially exposed population is small. The weight of evidence approach, however, requires that there is adequate data to evaluate a compound for carcinogenic potential. A lack of data will cause the Agency to take a conservative approach to the risk management process, since the Agency will not be able to assure that the compound is non-carcinogenic.

For threshold toxicants, out of necessity, risk management decisions have a narrower scope. The RfDs for threshold toxicants are determined primarily from animal toxicological studies which are designed to make point estimates of health effect levels. A priori, the level of risk is set in the same way regardless of the constituent. That is, the RfD is set at a level where no observable adverse effects occur. Because the RfD is based on chronic lifetime exposure to a specific daily amount of a substance, it may not always provide a reasonable guide to evaluating the risks of possible exposure scenarios. This will be especially true of episodic exposures

at relatively high doses. If the petition demonstration can establish such a scenario, it must also be supported by toxicological data that realistically reflects the exposure conditions.

Another scenario that may allow approval of a petition would be when the petitioner is able to demonstrate with great certainty that the maximum rate of exposure will only slightly exceed the RfD. In this case, a qualified toxicologist might judge the amount exceeded to be negligible compared to the statistical error of the toxicological data.

VI. 3rd Tier Analysis - Elements of a Detailed Site Analysis

A. Objectives

For those petitioners that either choose to perform a detailed site analysis, or are ineligible for a 2nd Tier Analysis, the following is a brief description of the components that may be necessary, and an explanation of the quality and quantity of the appropriate data and analyses. Any petitioner performing a 3rd Tier analysis enhances the chances for approval by providing the most accurate and precise information possible. Accuracy and precision are evaluated by the degree to which quality control procedures are followed. The preparation of a thorough, comprehensive quality control plan is, therefore,

an integral part of any 3rd Tier analysis. Quality control procedures apply to any data collection and data analysis, including the use of computer simulation models for analyzing potential migration in the air, soil, surface water, and ground water.

B. Petitioner Conference

It is recommended strongly that the petitioner request a conference with the Agency petition reviewer prior to embarking on extensive petition preparation. The petitioner should be prepared to discuss in qualitative terms the unique features of the disposal unit that may justify granting a petition, and the type and degree of analysis that the petitioner feels is necessary to make an adequate demonstration. It will probably not be necessary to include extensive analyses in all of the cases discussed below to satisfy the requirements of a 3rd Tier analysis. If the petitioner has performed a 2nd Tier analysis, it may be obvious that a certain physical site feature (e.g., the unsaturated zone, the topography, etc.) requires the most in-depth site analysis. The purpose of the conference will be to agree upon the nature and extent of the analysis required, and to discuss, in general, the criteria that the Agency will use to evaluate the data, analyses, and quality control procedures of the petitioner.

The following example illustrates the type of situation in which a petitioner conference would be useful and the type of discussion that would be appropriate. The petitioner is ineligible for a 2nd Tier Analysis since the disposal unit is located in close proximity to an active fault (Screening Factor II-1). The petitioner believes that any seismic activity that is likely to occur would have little or no affect on the integrity of the disposal unit during its operating period or following closure. To demonstrate this, the following considerations would be required:

1. The magnitude of likely ground motion at the disposal unit site;
2. The magnitude and type of likely surface displacement within 1 km of the site;
3. The potential for seismically induced ground failure;
4. The potential for damage due to tsunamis in areas of the country known to be vulnerable.

Ground motion at a site is partly a function of the distance from the epicenter of a fault, the thickness and areal extent of surficial deposits, the lithology and degree of consolidation of these deposits, and the nature of the disposal unit itself. A geotechnical investigation and analysis of the site may be undertaken to show that the disposal unit will withstand the maximum likely ground motion for the site, or a simplified analysis may be undertaken based on the assumption

of complete failure of the disposal unit. The first approach would have to show that catastrophic failure would not occur while the second approach would have to show that in the event of catastrophic failure, the natural site features would still contain the hazardous constituents such that human health and the environment are protected.

The Agency will deny any petition where the disposal unit is sited within a fault zone where surface displacement has occurred in the past 10,000 years (Holocene). In a seismically active zone the petitioner will be required to establish that evidence of Holocene surface displacement is not any less than 1 km from the site boundaries. Evidence of Holocene displacement must be established by using available data from the U.S. or State Geological Surveys, published maps and reports. The petitioner will also be advised to obtain the services of a qualified registered geologist to perform a geologic reconnaissance of the area within 1 km of the site. The geologist report must also include a discussion on how any changes in the natural drainage due to displacement might affect a site, if there is evidence of Holocene surface displacement.

In seismically active zones the petitioner may be required to assess the potential impact of seismically induced ground failure. A geotechnical investigation and analysis should be designed to estimate the likelihood of ground failures caused by liquefaction which might result in lateral spread of large blocks of soil, flow failures, or loss of bearing strength.

If a site is located on or adjacent to moderate to steep slopes, the potential for landslides must be assessed. The investigation must show that either ground failure will not occur, or, assuming worst case conditions, that a catastrophic failure will not endanger human health or the environment.

The historical record for tsunamis will provide the petitioner whose site is located in a coastal setting an indication of the vulnerability of the site. The petitioner must show that the site is out of reach of a tsunami because of topagraphic barriers or height, or that the disposal unit is designed to withstand the impact of a tsunami. A petitioner whose site is located in a seismically active area and is adjacent to a lake will have to make a demonstration similar to that for a tsunami. The petitioner and the petition reviewer will agree upon the extent of the investigation that is reasonable for the actual conditions of the subject disposal unit.

C. Components

Following are brief descriptions of the possible components of a 3rd Tier analysis. Various appendices provide more detail on the data and analyses, and provide references to source material and Agency guidance documents. The contents of the petition should include but not necessarily be limited to the following topics which are more fully discussed in separate sections in this manual.

1. Synopsis (including checklist). The synopsis is the first section in the petition and should be in the form of an executive summary. It should include facility identification, discussions of the contents of the petition and the conclusions drawn from the analyses. It should also include a directory (in the form of checklists) to guide the petition reviewer in locating specific elements. The synopsis should include a discussion of any deviations from the recommended format. (See discussion below.)
2. Facility Description. In this section the facility should be characterized by physical description, natural setting, design, construction, and operation. Also, there should be site plans, closure and post-closure care plans and QA/QC for design, construction and operation of the facility included, where appropriate
3. Waste Characterization. This section should include the completed forms shown in Section II and appropriate discussion of the waste(s) and its hazardous constituents.
4. Waste Interactions and Effects. This section should discuss the changes in waste characteristics, both physical and chemical, that may occur as a result of waste interactions within the unit. Four major categories of interaction are described in this manual which gives specific guidance in writing this section.

5. Waste Mobility in the Unsaturated Zone. Using information on site characteristics, waste characteristics and waste interactions, this part of the petition should discuss the probable movement of the waste constituents through the soil zone, intermediate unsaturated zone, and the capillary fringe. It should include a complete discussion of the model(s) used and describe the QA/QC procedures used.

6. Waste Mobility in the Saturated Zone. This section should describe the probable movement of the hazardous constituents of the wastes within the saturated zone. If the waste remains hazardous during its passage through the unsaturated zone, this section should demonstrate that the waste will not migrate beyond the area of effective control in a hazardous form via the saturated zone. It should include a complete discussion of the model(s) used and describe the QA/QC procedures used.

7. Waste Mobility in Surface Waters. This section should demonstrate that hazardous constituents of the waste will not migrate beyond the area of effective control in dissolved or suspended form in surface waters. It should include a complete discussion of the model(s) used and describe the QA/QC procedures used.

8. Waste Mobility in the Air. This section should demonstrate that hazardous constituents of the waste will not migrate beyond the area of effective control through the air. It should include a complete discussion of the models used and describe the QA/QC procedures used.

9. Human Health Risk Assessment. Using data presented in the previous sections and other information as appropriate, this section should present an assessment of potential risks to human health arising from the land disposal of the subject waste. This should include risks to facility personnel as well as the human population at large. Probable exposure pathways for hazardous constituents should be developed and then the effects of exposure estimated. Section V provides more specific guidance on this topic.

10. Potential Damage to Wildlife and Vegetation. Information from previous sections should be used to evaluate probable pathways by which wildlife and plant populations could be exposed to the hazardous constituents of the waste and also the effects of exposure on the fauna and flora should exposure occur. Both terrestrial and aquatic/marine communities should be included in the assessment.

11. Documentation. Data, modeling results, procedures, and associated QA/QC for facility design, construction and operation should be documented in one or more appendices as needed. Reference to the various appendices should be made in the text of the petition, as appropriate.

D. Model Validation

The petitioner is responsible for performing adequate validation of the use of any models other than the unmodified versions of the Screening/Treatment Level models. Validation may involve comparison of various analytical model results to the results of the models used in the petition, or it may involve history matching of field data collected over a certain period of time with detailed modeling of the same time period, assuming the initial and boundary conditions existing at the field site.

The petitioner should include sufficient information to demonstrate the accuracy of the model results for the particular application. The goals of this demonstration may be summarized as follows:

a. The model reasonably represents the actual physical system; and

b. There are no computational errors in the computer code.

To achieve these goals, the petitioner should address each of the following areas:

1. Identification of objectives of the modeling study;
2. Description of the conceptual approach;
3. Description of the solution methodology employed to predict contaminant migration; and
4. Description of the rationale for the selection of input parameters.

The petitioner should present adequate information addressing each of the above, consistent with the type and level of modeling contemplated.

If the petition demonstration involves the use of an analytical groundwater flow model, for example, the petitioner should verify the model results by comparison to other analytical flow models, and by comparison to solutions presented in the original references. A numerical groundwater flow and transport model may involve more detailed verification, such as the following steps:

1. Identification of the capabilities, assumptions, and limitations of the numerical code;
2. Justification of the grid and time increments through description of the geometry and flow characteristics of the site;
3. Justification of the compatibility of each code, when two or more codes are used to solve the flow and transport problems.
4. Demonstration of a high degree of predictive correlation between the model results and actual measured data.

The Agency is aware of a variety of models that simulate the fate and transport of hazardous constituents in the air, in surface water, and in ground-water. Available models cover the range from very simple to very sophisticated, from requiring a few, simple parameters to requiring large volumes of specific data, from very general results with large uncertainty to very specific results with less uncertainty. The petitioner will be responsible for selecting the most appropriate modeling approach for the situation to be simulated. If the problem at hand calls for an analytical ground-water flow model, the petitioner may select such a model from the many that are available or develop a new model that is suitable to the situation. If a more complex problem is to be analyzed, a more sophisticated model, capable of managing large volumes of site-specific data, may be more appropriate. Where interactions or inter-media transfers occur, such as at the soil-air interface, or where ground water discharges to surface water, a combination of models may be integrated. The Agency will accept any type of simulation model, or combinations of models, for the purpose of predicting the ultimate face of hazardous constituents of the subject waste, as long as the overall modeling approach can be technically supported as being most appropriate to the waste and site conditions and most capable of producing accurate and reliable results.

The Agency will use the following general criteria in determing if a proposed modeling approach is appropriate and will produce results with the desired quality. First, the model

must be compatible with the quality and type of input data available. Second, the model must have been demonstrated to be applicable to the environmental conditions at the site of the subject disposal unit. Third, the computer code must have been subjected to an independent quality assurance audit, or have been subjected to a level of professional peer review equivalent to that for publication in a scientific or technical journal. Fourth, the approach must be internally consistent in the use of boundary and initial conditions, time stepsm assumptions, and code modifications. Fifth, fully documented support for the modeling approach selected by the petitioner must be available to the Agency.

E. Format

The petitioner should present each of the items listed above as a section of the petition. Each section should be as self-contained as possible. They should include all data, figures, drawings, etc., needed to support the specific aspect of the petition being addressed. If necessary, separate binders for some sections may be advisable.

The synopsis should contain complete identification of the facility for which a variance is being requested. This should include all the information required on EPA Form 3510-1, the general information portion of a RCRA Part A permit application. A copy of Form 3510-1 may be included in the synopsis.

Conclusions that have been drawn from the petition information should be included in the synopsis and they should be briefly explained in relation to the performance standard. If conclusions are drawn based on rationale, data, or models that are different from the guidance explained in this document, such deviations should be briefly explained in the synopsis. Detailed discussions and explanations should be confined to the appropriate sections of the petition.

The synopsis should be general in nature as compared to the other sections of the petition. The other sections address specific technical areas. Each area presented should be presented in a self-contained section. Each should contain the information, data, maps, calculations, logs, etc. to fulfill the petition requirements for a specific feature of the proposed waste disposal facility. The synopsis should refer to the self-contained sections such that the petition reviewer can easily relate the synopsis to the sections.

The self-contained sections will greatly aid the evaluation and review of petitions, as well as any subsequent writing and issuance of variances. Reviewers and variance writers will, in turn, assess these sections and incorporate them into the variance. Sections acceptable to EPA as proposed by the petitioner, may be incorporated without change into the variance.

If during review, additional information is required, EPA will identify such information or return the appropriate sections to the petitioner for revisions rather than return the entire petition. The resulting variance may contain the sections prepared by the petitioner, either as originally written or as modified by EPA or the State.

Sections should be clearly identified with either a letter or number and appropriate title. Sections should have page numbers, figure numbers, etc., that relate to the section identifier letter or number. Sufficient petitioner and facility information should be provided on the first page of each section to uniquely identify the petition of which it is a part.

The use of color-coded pages should be given consideration for confidential business information (CBI). CBI should be identified clearly as was done in the related RCRA Part B permit application.

The use of figures, tables, and other illustrative techniques are encouraged where their use would aid the evaluation, review, and variance writing. The use of color graphics should also be considered in this regard.

Petitions should contain tables of content for the overall petition, as well as each section. The inclusion of such items as indices and cross references should be considered in the development of the petition.

All portions should be legible and reproducible. Appropriate margins and spacings will ease evaluation and review of the petition. Maps, plans, etc., should be provided at an appropriate scale. Each page should contain a date of original issuance or date of revision on the upper right corner.

E. Technical Assistance

In the preparation of a petition, most petitioners will likely require technical assistance from specialists, including but not limited to: engineers, geologists, hydrogeologists, and soil scientists. These specialists may be part of the petitioner's staff or outside consultants. The EPA feels that petitioners will obtain the best service (designs, plans, etc.) and thus the most complete petition, if they use only fully qualified technical expertise. Particularly important is experience in hazardous waste management closely related to the proposed facility and wastes.

The use of registered, professional engineers in the preparation of a variance petition is encouraged. Part 264 requires certification by a registered, professional engineer that a facility has been closed in accordance with an approved closure plan. Engineers are registered by all 50 States. Registration is based on combinations of education, experience, and examinations. Registration licenses engineeers to practice their profession and includes legal and ethical restrictions regarding the technical extent to which services may be offered. Registered engineers may not practice beyond their areas of

expertise. Additionally, registered engineers are required by law to place public health, safety, and welfare before other aspects of their assignments.

The petitioner should obtain the best assistance possible in the preparation of a petition. EPA recommends that engineers experienced in hazardous waste management be involved with preparation of petitions. Also, it highly recommends that registered, professional engineers (registered in the State in which the facility is located) be utilized in the development of necessary designs, specifications, certifications, etc. The combination of applicable experience and registration on behalf of engineers involved should result in a petition (and resultant facility) that meets the technical requirements and spirit of the regulations. Proper qualifications are most important; however, professional registration is also considered an important credential. If the regulations require a registered engineer, even the best qualified, non-registered engineer will not meet the requirements.

Again, experience in land-based hazardous waste management is the most important credential for geologists, hydrogeologists, and soil scientists. Some States and professional organizations register geologists and hydrogeologists in a manner similar to engineers. It is recommended that experienced, registered professionals be involved with the petition.

In lieu of registration, several national organizations certify geologists, hydrogeologists, and soil scientists. Certification generally indicates that an individual has the basic educational requirement and (usually) experience to be considered a member of that profession.

Whenever an exposure and population analysis is included in a petition demonstration, the services of a qualified toxicologist or public health professional is desirable. These professionals should be familiar with the Agency's policies for developing health effects criteria and should have had experience in conducting a human health risk assessment for environmental exposure scenarios.

F. Related Guidance Documents

The EPA has published several guidance documents related to the submittal of RCRA Part B permit applications and to the performance of risk assessments. These documents address preparation of the applications and technical aspects related to the design and operation of land-based hazardous waste facilities. These documents may be helpful in the preparation of a variance petition. A list of selected documents follows.

Publications with source shown as NTIS can be ordered from the National Technical Information Services in Springfield, Virginia, at (703) 487-4650. Publications from the Government Printing Office (GPO) may be ordered by calling (202) 783-3238. Stock numbers are shown for GPO publications and publication numbers are shown for those from NTIS.

Title	Source
Permit Applicant's Guidance Manual for Hazardous Waste Land Treatment, Storage, and Disposal Facilities (530 SW-84-004)	GPO (055-00-00240-1)
Evaluating Cover Systems for Solid and Hazardous Waste (SW-867)	GPO (055-00-00228-2)
Hydrologic Simulation Waste Disposal Sites (SW-868)	GPO (055-00-00225-8)
Landfill and Surface Impoundments Performance Evaluation (SW-870)	GPO (055-00-00233-9)
Lining of Waste Impoundment and Disposal Facilities (SW-870)	GPO (055-00-00231-2)
Management of Hazardous Waste Leachate (SW-871)	GPO (055-00-00224-0)
Guide to the Disposal of Chemically Stabilized and Solidified Waste (SW-872)	GPO (055-000-00226-6)
Closure of Hazardous Waste Surface Impoundments (SW-873)	GPO (055-000-00227-4)
Hazardous Waste Land Treatment (SW-874)	GPO (055-000-00232-1)
Test Methods for Evaluating Solid Wastes (SW-846)	GPO (055-002-81001-2)
A Method for Determining the Compatibility of Hazardous Wastes (EPA-600/2-80-076)	NTIS (PB80-221005)
Soil Properties, Classification, and Hydraulic Conductivity Testing, Draft Technical Resource Document (SW-925; 1984)	RCRA Hotline (800) 424-9346
Solid Waste Leaching Procedure, Draft Technical Resource Document (SW-924; 1984)	RCRA Hotline (800) 424-9346
Procedures for Modeling Flow Through Clay Liners, Draft Document (EPA/530-SW-84-001; April 1, 1984)	RCRA Hotline (800) 424-9346

Title	Source
Superfund Public Health Evaluation Manual	U.S. EPA Office of Solid Waste and Emergency Response
Superfund Exposure Assessment Manual	U.S. EPA Office of Solid Waste and Emergency Response
Background Document for the Ground-Water Screening Procedure to Support the 40 CFR Part 268 Land Disposal Restrictions	U.S. EPA, Office of Solid Waste
Background Document on the Development and Use of Reference Doses to Support 40 CFR Part 268 Land Disposal Restrictions	U.S. EPA, Office of Solid Waste
Background Document for the Surface Water Screening Procedure to Support 40 CFR Part 268 Land Disposal Restrictions	U.S. EPA, Office of Solid Waste

V. Summary of the Conditions of an Approved Petition

For every petition that the Agency or authorized state approves, certain minimum conditions regarding the subject waste, the disposal unit, and relevant management practices will be specified. Additionally, certain specific conditions that identify grounds for revocation of the approved petition and possible enforement action will also be specified. Although all of these conditions will be very dependent on the individual petition, there are certain general components that would be included in every approved petition. These components are briefly described in the following paragraphs.

Each approved petition will contain precise descriptions of the subject waste, in chemical and physical characteristics, the concentration of hazardous constituents and the range of variables of these concentrations, and the volume or weight of the waste to be managed in the subject disposal unit. The petition will also contain a complete description of the disposal unit, in terms of physical location and dimensions, and current ownership. The petition will specify the length of time over which the approval is effective and will state exact dates by which a renewal or re-application is required. This latter information will be dependent upon the status of the operating permit of the disposal unit at the time of petition approval. In addition, if any petition is approved on a conditional basis, (e.g., conditional on the basis of additional monitoring results, or the results of some long-term analyses) the details of the condition and the petitioner's responsibilities would be specified.

Under certain circumstances, an approved petition may be revoked, and possible enforcement action, to include fines and imprisonment, may be necessary. In general, such circumstances would include significant changes in the subject waste or in the site characteristics that could not have been foreseen at the time that the petition was approved, or the subsequent obtaining or developmentof relevant information that was not available to the petitioner or the Agency at the time the petition was approved. Additionally, if the petitioner fails to obtain the required operating permits, or is not in compliance with current permit requirements, the Agency may decide to commence enforcement action, and this may result in petition revocation. In the case of a significant changes in the physical characteristics of a waste that are either to process changes that involve different raw materials or to mixture of the waste with other materials, the generator of the waste or the person who is knowledgeable of these changes is responsible for reporting the change in waste characteristics to the Agency or to the state that had approved the petition.

APPENDIX I

SCREENING FACTORS

APPENDIX I

I. Approval and Rejection Criteria

A. Approval Criterion

A petition for removing restrictions on the land disposal of a previously restricted hazardous waste is approved for a specific disposal unit if the disposal unit owner or operator can demonstrate that no exposure to humans or to environmental species or systems will occur through any pathway for as long as the wastes remain hazardous.

B. Rejection Criteria

A petition for removing restrictions on the land disposal of a previously restricted hazardous waste is rejected for a specific disposal unit if:

1. The petitioner fails to submit an analysis documenting the validity of any fate and transport model, other than the unmodified version of the Screening/ Treatment Standard models, to be used in evaluating the disposal unit site.
2. The petitioner fails to submit for Agency approval a comprehensive quality assurance/quality control plan for all sampling and analytical techniques to be used in developing the petition demonstration.
3. The owner or operator of the disposal unit has not provided to the Agency or State all relevant Part B information, including all relevant Part 270.14(c) information.

II. Approval for Performing a 2nd Tier Simplified Analysis

Approval is granted for performing a 2nd Tier Simplified Site Analysis for a petition for removing restrictions on the land disposal of a previously restricted hazardous waste if:

1. The disposal unit is not located within 1 Km of a fault which has had displacement in Holocene time.
2. The disposal unit is not located in a 100-year floodplain, unless granted a variance as required under Part 264.18(b).
3. The disposal unit is located at a site where the inherent geologic, hydrologic, and pedologic features can be adequately characterized, to ensure that all significant ground water flow paths can be monitored.
4. The disposal unit is not located at a site in close proximity to karst topography, subsurface fractures and bedding planes, active volcanic impact zones, landslide-susceptible areas, subsidence-prone areas, or weak or unstable soils.
5. The disposal unit is not located at a site where ground water withdrawal, natural infiltration, or any type of subsurface injection significantly affects the ground-water flow systems to the extent that the integrity of the disposal unit is threatened by contact with the ground water.

6. The owner or operator of the disposal unit is not required to perform compliance monitoring under Subpart F unless an ACL has been granted, or is not performing corrective action.

APPENDIX II

PROPOSED LAND DISPOSAL RESTRICTIONS

PART 268—LAND DISPOSAL RESTRICTIONS

VI. In Part 268, proposed in the Federal Register of May 31, 1985 (50 FR 23255):

1. The authority citation for proposed Part 268 is revised to read as follows:

Authority: Secs. 1006, 2002(a), 3001, and 3004 of the Solid Waste Disposal Act, as amended by the Resource Conservation and Recovery Act of 1976, as amended by the Hazardous and Solid Waste Amendments of 1984 (42 U.S.C. 6905, 6912(a), 6921, and 6924).

2. By adding Subpart A to proposed Part 268 to read as follows:

Subpart A—General

Sec.

Subpart A—General

§ 268.1 Purpose, scope and applicability.

(a) This part identifies hazardous wastes that are restricted from land disposal and those limited circumstances under which an otherwise prohibited waste may continue to be land disposed.

(b) Except as specifically provided otherwise in this part or Part 261 of this chapter, the requirements of this part apply to persons who generate or transport hazardous waste and owners and operators of hazardous waste treatment, storage, and disposal facilities.

(c) The requirements of Subparts A, C D and E of this part do not apply to the disposal of hazardous waste by underground injection.

(d) The requirements of this part appl to a person who generates, transports, treats, stores, or disposes of hazardous waste in a State which is authorized under Subpart A or B of Part 271 of this chapter if the State has not been authorized to carry out the requiremen and prohibitions applicable to the generation, transport, treatment, storag or disposal of hazardous waste which are imposed pursuant to the Hazardou and Solid Waste Amendments of 1984 The requirements and prohibitions tha are applicable until a State receives authorization to carry them out includ all Federal program requirements identified in § 271.1(j) of this chapter.

(e) The requirements of this part do not apply to persons placing hazardou wastes in a surface impoundment provided that:

(1) Treatment of such wastes occur the impoundment.

(2) The contents of the impoundme must be analyzed, through use of the test methods described in SW–846 a the residues of such treatment (inclu any liquid waste) that do not meet th treatment standards promulgated un Subpart D of this part, or are not delisted under § 260.22 of this chapt must be removed at least annually a may not be placed in a surface impoundment for subsequent treatm The procedures and schedule for (i) sampling of impoundment contents, the analysis of test data, and (iii) th annual removal of residue which do not meet Subpart D treatment stand must be specified in the facility's w analysis plan as required under §§ 264.13 or 265.13 of this chapter.

(3) The impoundment meets the requirements of § 264.221(c) or § 265.221(a) of this chapter, unless:

xempted pursuant to § 264.221 (d) of this chapter, or § 265.221 (c) or this chapter, or

Upon application of the owner or tor prior to November 8, 1988, the nistrator has granted a waiver of quirements on the basis that the e impoundment:

Has at least one liner, for which is no evidence that such liner is ge;

Is located more than one-quarter rom an underground source of ing water; and

Is in compliance with the generally cable ground water monitoring rements for facilities with permits;

Upon application of the owner or tor prior to November 8, 1988, the nistrator has granted a dication of the requirements on the of a demonstration that the e impoundment is located, ned, and operated so as to assure here will be no migration of any rdous constituent into ground water rface water at any future time.

The requirements of this part do pply to:

Persons who have been granted a use from a prohibition pursuant to 15, with respect to those wastes and covered by the variance; or,

any land disposal of contaminated or debris resulting from a response n taken under section 102 or 106 of Comprehensive Environmental ponse, Compensation, and Liability of 1980 or a corrective action ired under Part 264 or 265 of this ter until November 8, 1988.

A generator or an owner or ator of a facility otherwise lated by this part must comply with pplicable requirements of this ter.

1.2 Definitions applicable to this part.

) When used in this part the rwing terms have the meanings given w:

Area of effective control" means an where perpetual restrictions exist he use of any air or water resources manner that would not be ective of human health and the ironment. If this area extends ond the waste management area, as ned at § 264.95(b) of this chapter, petual restrictions on the use of any or water resources must be ablished by an act of the local or te legislature.

Hazardous constitutent or stituents" means those constituents ed in Appendix VIII to Part 261 of chapter.

"Land disposal" means placement in or on the land and includes, but is not limited to, placement in a landfill, surface impoundment, waste pile, injection well, land treatment facility, salt dome formation, salt bed formation, underground mine or cave, concrete vault or bunker intended for disposal purposes and placement in or on the land by means of open detonation. The term "land disposal" does not encompass ocean disposal.

(b) All other terms have the meanings given under §§ 260.10, 261.2, 261.3, or 270.2 of this chapter.

268.3 Dilution prohibited as a substitute for treatment.

No generator or owner or operator of a treatment, storage, or disposal facility shall in any way attempt to dilute a waste as a substitute for adequate treatment to achieve compliance with Subpart D of this part.

§ 268.4 Procedures for extensions to an effective date.

(a) Any person who generates, treats, stores, or disposes of a hazardous waste restricted (or proposed to be restricted) from land disposal pursuant to Subpart C of this part may submit an application to the Administrator for an extension to the effective date of any applicable restriction established under §§ 268.30, 268.31, or 268.40. The applicant must demonstrate the following:

(1) He has entered into a contract to construct or otherwise provide alternative treatment, recovery (recycling), or disposal capacity that protects human health and the environment. The contract must contain a penalty for cancellation that, in the Agency's judgment, is sufficient to discourage cancellation by the applicant.

(2) Due to circumstances beyond the applicant's control, such alternative capacity cannot reasonably be made available by the applicant by the applicable effective date.

(3) The applicant has made a good-faith effort to locate and contract with treatment, recovery, or disposal facilities nationwide to manage his waste in accordance with §§ 268.30 or 268.31.

(4) The capacity being constructed or otherwise provided by the applicant will be sufficient to manage all of the waste that is the subject of the application.

(5) The applicant has prepared and submitted to the Administrator a detailed schedule for obtaining required operating permits and construction or an outline of how and when alternative capacity will be provided.

(6) The applicant has arranged for adequate capactiy to manage his waste during an extension and has documented in the application the location of all sites at which the waste will be managed.

(7) Any waste managed in a surface impoundment or landfill during the extension period will meet the requirements of paragraph (i) (2) of this section.

(b) Any person signing an application described under paragraph (a) of this section shall make the following certification:

I certify under penalty of law that I have personally examined and am familiar with the information submitted in this document and all attachments and that, based on my inquiry of those individuals immediately responsible for obtaining the information, I believe that the information is true, accurate, and complete. I am aware that there are significant penalties for submitting false information, including the possibility of fine and imprisonment.

(c) On the basis of the information referred to in paragraph (a) of this section, after notice and opportunity for comment, and after consultation with appropriate State agencies in all affected States, the Administrator may grant an extension of up to 1 year from the effective date. The Administrator may renew this extension for up to 1 additional year upon the request of the applicant. In no event will an extension extend beyond 48 months from the applicable statutory effective date specified in section 3004(d), (e), or (g) of the Act (42 U.S.C. 6924(d), (e), or (g)).

(d) The length of any extension authorized in paragraph (c) of this section will be determined by the Administrator based on the time required to construct or obtain the type of capacity needed by the applicant as described in the completion schedule discussed in paragraph (a)(5) of this section.

(e) The Administrator will provide the successful applicant with written notice of the extension. This notice will describe the manufacturing process that is the source of the waste subject to the extension, the volume of such waste, the duration of the extension, and the name and the location of the facility designated in paragraph (a)(6) of this section to manage the waste during the period of the extension. The applicant must retain a copy of the notice during the period of the extension and for at least 3 years after the extension expires.

(f) The applicant must provide a copy of the notice to the facility designated in paragraph (a)(6) of this section. The notice must be provided to the

designated facility prior to the first shipment of waste which is the subject of the extension. The owner or opreator of the facility shall retain a copy of the notice during the period of the extension and for at least 3 years after the extension expires.

(g) The successful applicant must immediately notify the Administrator as soon as he has knowledge of any changes in the conditions certified to in the application.

(h) The successful applicant must submit written progress reports at intervals designated by the Administrator. Such reports must describe the overall progress made toward constructing or otherwise providing alternative treatment, recovery or disposal capacity; must identify any event which may cause or has caused a delay in the development of the capacity; and must summarize the steps taken to mitigate the delay. The Administrator can revoke the extension at any time if the applicant does not demonstrate a good-faith effort to meet the schedule for completion, if the Agency denies or revokes any required permit, if conditions certified in the application change, or for any violation of this part.

(i) Whenever the Administrator establishes an extension to an effective date under this section, during the period for which such extension is in effect:

(1) The storage restrictions under § 268.50(a)(1) do not apply, and

(2) Such hazardous waste may be disposed of in a landfill or surface impoundment, only if:

(i) The landfill, if in interim status, meets the requirements of Subpart F of Part 265 and § 265.301 (a) through (e) of this chapter.

(ii) The landfill, if permitted, meets the requirements of Subpart F of Part 264 and § 264.301 (c) through (e) of this chapter.

(iii) The surface impoundment, if in interim status, meets the requirements of Subpart F of Part 265 and § 265.221 (a) through (e) of this chapter; or

(iv) The surface impoundment, if permitted, meets the requirements of Subpart F of Part 264 and § 264.221 (c) through (e) of this chapter.

§ 268.5 Petitions to allow land disposal of a waste prohibited under Subpart C of Part 268.

(a) Any person seeking a variance from a prohibition under Subpart C of this part for the disposal of a restricted hazardous waste in a particular unit or units must submit a petition to the Administrator demonstrating that any hazardous constituents of the waste are at levels that ensure, to a reasonable degree of certainty, that there will be no migration of any such hazardous constituents of the waste from the area of effective control into the air, ground water, surface water, or soil in concentrations that exceed the applicable screening level, or that result in adverse effects upon the environment.

(1) The Administrator will use the following criteria for determining whether the established screening levels may be exceeded for any threshold constituents:

(i) Exposure criteria:

(A) Other potential or actual sources of exposure to the same or similar constituents.

(B) The level and type of uncertainty inherent in the models used to predict potential exposure to the surrounding population.

(C) The nature of the potentially exposed population.

(ii) Toxicological criteria:

(A) The slope or slopes of dose response curves for the health effects attributable to a threshold constituent.

(B) The frequency and magnitude of potential exposure to a threshold constituent.

(2) The Administrator will use the following criteria for determining a health effects level for any non-threshold constituents:

(i) Exposure criteria:

(A) Other potential or actual sources of exposure to the same or similar constituents.

(B) The level and type of uncertainty inherent in the models used to predict potential exposure to the surrounding population.

(C) The potential current and future risk to individuals from the activities of the disposal unit.

(D) The size and nature of the potentially exposed population.

(ii) Toxicological criteria: the level and type of uncertainty inherent in the data used to estimate health risks.

(b) The demonstration referred to in paragraph (a) of this section must include an analysis of the total number of people that could potentially be exposed to any hazardous constituent of the specified waste for as long as the specified waste remains hazardous.

(c) The demonstration referred to in paragraph (a) of this section must include assurances that land disposal of the specified waste will not cause adverse effects on any aquatic biota, wildlife, vegetation, protected lands, or other areas of potential ecological or economic significance.

(d) The demonstration referred to in paragraphs (a), (b), and (c) of this section may include the following components:

(1) An identification of the specific waste and the specific unit for which th demonstration will be made.

(2) A waste analysis, using methods described in SW-846, where appropriate, or equivalent methods approved by the Administrator in accordance with § 260.21 of this chapter, to describe fully the chemical and physical characteristics of the subject waste, including the waste's toxicity, mobility, persistence, and propensity to bioaccumulate.

(3) An evaluation of the performance of the engineered components of the disposal unit.

(4) A comprehensive characterization of the disposal unit site and area of effective control, including an analysis of background air, soil, and water quality.

(5) Predictions of the ultimate fate of hazardous constituents in the air, soil, surface water, and ground water, at the point or points of potential human and environmental exposure.

(e) The demonstration referred to in paragraphs (a), (b), and (c) of this section must meet the following criteria:

(1) All waste and environmental sampling or test data must be accurate, and reproducible.

(2) All sampling, testing, and estimation techniques for chemical and physical properties of the waste and all environmental parameters must have been approved by the Administrator.

(3) Simulation models may need to be calibrated for the specific waste and site conditions, and verified for accuracy by comparison with actual measurements.

(4) A quality assurance and quality control plan that addresses all aspects of the demonstration must be approved by the Administrator.

(5) An analysis may need to be performed to identify and quantify any aspects of the demonstration that contribute significantly to uncertainty. This analysis must include an evaluation of the consequences of predictable future events, including, but not limited to earthquakes, floods, severe storm events, droughts, or other natural phenomena.

(f) Each petition must be submitted to the Administrator by certified mail.

(g) Each petition must include the following statement signed by the petitioner or an authorized representative:

I certify under penalty of law that I have personally examined and am familiar with the information submitted in this petition and all attached documents, and that, based on my inquiry of those individuals immediately

...ilable for obtaining the information. I ...e that the submitted information is true, ...te, and complete. I am aware that there ...gnificant penalties for submitting false ...rmation, including the possibility of fine ...prisonment.

...After receiving a petition, the ...nistrator may request any ...tional information that may ...nably be required to evaluate the ...petition.

...If approved, the petition will apply ...al disposal of the specific restricted ...te at the individual disposal unit ...ified in the demonstration and will ...pply to any other restricted waste ...t disposal unit.

...The Administrator shall give public ...ice of the intent to approve or deny a ...tion and provide an opportunity for ...public comment. The Administrator ...ll give public notice of the final ...ision on a petition in the Federal ...ister.

...(3) The Administrator will provide ...ten notice to the petitioner upon ...proval or denial of a petition. If ...proval is given, the notice will ...ecify the land disposal unit, the ...ste that may be disposed therein, ...olume limit, and the duration of the ...approval.

...The petitioner shall retain the ...ice for the term of the approval as ...ired by paragraph (1) of this section.

...The term of an approved petition ...not be no longer than the term of the ...RCRA permit if the disposal unit is ...erating under a RCRA permit, or up to ...maximum of 10 years from the date of ...notice provided under paragraph ...(3) of this section if the unit is ...erating under interim status. In either ...case, the term of the approved petition ...will expire upon the termination or ...denial of a RCRA permit, or upon the ...termination of interim status or when ...the volume limit specified in the petition ...is reached.

...268.8 Waste analysis.

...(a) The owner or operator of any land ...disposal facility accepting any waste ...subject to restrictions under this part, ...must have records of either the ...treatment certification specified in ...paragraph (b) of this section or of ...sufficient waste analysis through testing ...the waste for the constituents listed in ...Table CCWE in § 268.42 to determine ...whether the wastes are in compliance ...with the applicable treatment standards ...specified in Subpart D of this part. The ...waste must be tested using the methods ...described in SW-846 or equivalent ...methods approved by the Administrator ...in accordance with §§ 260.20 and 260.21 ...of this chapter.

(b) Where the applicable treatment standard for a waste is treatment by a specific technology (i.e., § 268.41(a)), the owner or operator of the treatment facility must submit a certification to the land disposal facility stating that the waste has been treated using the specified technology. The certification is subject to the following requirements:

(1) The certification must be signed by the treater or his authorized representative and must state the following:

I certify under penalty of law that I have personally examined and am familiar with the treatment technology and operation of the treatment process used to support this certification and that, based on my inquiry of those individuals immediately responsible for obtaining this information, I believe that the treatment process has been operated and maintained properly so as to achieve the treatment standards of the specified technology without dilution of the prohibited waste. I am aware that there are significant penalties for submitting a false certification including the possibility of fine and imprisonment.

(2) The certification must be sent to the land disposal facility before the treated waste (including treatment residues) is shipped by the treater and must be kept on site for 3 years after the waste is placed in a land disposal unit at the facility.

§ 268.9 Incorporations by reference.

The following material is incorporated by reference and is available for inspection at the Office of the Federal Register Information Center, Rm. 8301, 1100 L St., NW., Washington, DC 20408. These incorporations by reference were approved by the Director of the Office of the Federal Register. The material is incorporated as it exists on the date of approval and a notice of any change in the material will be published in the Federal Register.

(a) "Test Methods for Evaluating Solid Waste, Physical/Chemical Methods," EPA Publication SW-846 (First Edition, 1980, as updated by Revision A (August 1980), B (July 1981), and C (February 1982) or Second Edition, 1982). The first edition of SW-846 is no longer in print. Revisions A and B are available from NTIS, 5285 Port Royal Road, Springfield, Virginia 22161. The second edition of SW-846 includes material from the first edition and Revisions A, B, and C in a reorganized format. It is available from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402 (202-783-3238), on a subscription basis, and future updates will automatically be mailed to the subscriber. The material is cited in the following sections of Part 268: §§ 268.1(e)(2), 268.5(c)(2), 268.6(a), and 268.42(a).

(b) [Reserved.]

3. By adding Subpart C to proposed Part 268 to read as follows:

Subpart C—Prohibitions on Land Disposal

Sec.

Subpart C—Prohibitions on Land Disposal

§ 268.30 Waste specific prohibitions—Group I.

(a) Effective November 8, 1986, the wastes listed in paragraph (b) of this section are prohibited from land disposal, except in an injection well, unless:

(1) The wastes are treated to meet the standards of Subpart D of this part, or

(2) The wastes are subject to a successful petition under § 268.5, or

(3) An extension has been granted under § 268.4.

(b) Prohibited are the following solvent containing wastes containing greater that 1 percent (by weight) total organic constituents, except for solvent contaminated soils:

F001—The following spent halogenated solvents used in degreasing: tetrachloroethylene, trichloroethylene, methylene chloride, 1,1,1-trichloroethane, carbon tetrachloride, and chlorinated fluorocarbons; all spent solvent mixtures/blends used in degreasing containing, before use, a total of 10 percent or more (by volume) of one or more of the above halogenated solvents or those solvents listed in F002, F004, and F005; and still bottoms from the recovery of these spent solvents and spent solvent mixtures.

F002—The following spent halogenated solvents: tetrachloroethylene, methylene chloride, trichloroethylene, 1,1,1-trichloroethane, chlorobenzene, 1,1,2-trichloro-1,2,2-trifluoroethane, ortho-dichlorobenzene, and trichlorofluoromethane; all spent solvent mixtures/blends containing, before use, a total of 10 percent or more (by volume) of one or more of the above halogenated solvents or those solvents listed in F001, F004, and F005; and still bottoms from the recovery of these spent solvents and spent solvent mixtures.

F003—The following spent non-halogenated solvents: xylene,

acetone, ethyl acetate, ethyl benzene, ethyl ether, methyl isobutyl ketone, n-butyl alcohol, cyclohexanone, and methanol; all spent solvent mixtures/blends containing, solely the above spent non-halogenated solvents; and all spent solvent mixtures/blends containing, before use, one or more of the above non-halogenated solvents, and a total of 10 percent or more (by volume) of one or more of those solvents listed in F001, F002, F004, and F005; and still bottoms from the recovery of these spent solvents and spent solvent mixtures.

F004—The following spent non-halogenated solvents: cresols and cresylic acid and nitrobenzene; all spent solvent mixtures/blends containing, before use, a total of 10 percent or more (by volume) of one or more of the above non-halogenated solvents or those solvents listed in F001, F002, and F005; and still bottoms from the recovery of these spent solvents and spent solvent mixtures.

F005—The following spent non-halogenated solvents: toluene, methyl ethyl ketone, carbon disulfide, isobutanol, and pyridine; all spent solvent mixtures/blends containing, before use, a total of 10 percent or more (by volume) of one or more of the above non-halogenated solvents or those solvents listed in F001, F002, and F004; and still bottoms from the recovery of these spent solvents and solvent mixtures.

P022—Carbon disulfide
U002—Acetone
U031—n-Butyl alochol
U037—Chlorobenzene
U052—Cresols and cresylic acid
U057—Cyclohexanone
U070—o-Dichlorobenzene
U080—Methylene chloride
U112—Ethyl acetate
U117—Ethyl ether
U121—Trichlorofluoromethane
U140—Isobutanol
U154—Methanol
U159—Methyl ethyl ketone
U161—Methyl isobutyl ketone
U169—Nitrobenzene
U196—Pyridine
U210—Tetrachloroethylene
U211—Carbon tetrachloride
U220—Toluene
U226—1,1,1-Tricnloroethane
U228—Trichloroethylene
U239—Xylene

§ 268.31 Waste specific prohibitions—Group II.

(a) Effective November 8, 1988, the wastes listed in paragraph (c) of this section are prohibited from land disposal, except in an injection well, unless:

(1) The wastes are treated to meet the standards of Subpart D of this part, or

(2) The Wastes are subject to a successful petition under § 268.5, or

(3) An extension has been granted under § 268.4.

(b) Between November 8, 1988, and November 8, 1989, wastes identified in paragraph (c) of this section may be disposed of in a landfill or surface impoundment only if the facility is in compliance with the minimum technological requirements of § 268.4 (i)(2).

(c) Prohibited are:

(1) The following solvent-containing wastes (containing less than 1 percent (by weight) total organic constituents) and solvent contaminated soils.

F001—The following spent halogenated solvents used in degreasing: tetrachloroethylene, trichloroethylene, methylene chloride, 1,1,1-trichloroethane, carbon tetrachloride, and chlorinated fluorocarbons; all spent solvent mixtures/blends used in degreasing containing, before use, a total of 10 percent or more (by volume) of one or more of the above halogenated solvents or those solvents listed in F002, F004, and F005; and still bottoms from the recovery of these spent solvents and spent solvent mixtures.

F002—The following spent halogenated solvents: tetrachloroethylene, methylene chloride, trichloroethylene, 1,1,1-trichloroethane, chlorobenzene, 1,1,2-trichloro-1,2,2-trifluoroethane, ortho-dichlorobenzene, and trichlorofluoromethane; all spent solvent mixtures/blends containing, before use, a total of 10 percent or more (by volume) of one or more of the above halogenated solvents or those solvents listed in F001, F004, and F005; and still bottoms from the recovery of these spent solvents and spent solvent mixtures.

F003—The following spent non-halogenated solvents: xylene, acetone, ethyl acetate, ethyl benzene, ethyl ether, methyl isobutyl ketone, n-butyl alcohol, cyclohexanone, and methanol; all spent solvent mixtures/blends containing solely the above spent non-halogenated solvents; and all spent solvent mixtures/blends containing, before use, one or more of the above non-halogenated solvents, and a total of 10 percent or more (by volume) of one or more of those solvents listed in F001, F002, F004, and F005; and still bottoms from the recovery of these spent solvents and spent solvent mixtures.

F004—The following spent non-halogenated solvents: cresols and cresylic acid and nitrobenzene; all spent solvent mixtures/blends containing, before use, a total of 10 percent or more (by volume) of one or more of the above non-halogenated solvents or those solvents listed in F001, F002, and F005; and still bottoms from the recovery of these spent solvents and spent solvent mixtures.

F005—The following spent non-halogenated solvents: toluene, methyl ethyl ketone, carbon disulfide, isobutanol, and pyridine; all spent solvent mixtures/blends containing, before use, a total of 10 percent or more (by volume) of one or more of the above non-halogenated solvents or those solvents listed in F001, F002, and F004; and still bottoms from the recovery of these spent solvents and spent solvent mixtures.

P022—Carbon disulfide
U002—Acetone
U031—n-Butyl alcohol
U037—Chlorobenzene
U052—Cresols and cresylic acid
U057—Cyclohexanone
U070—o-Dichlorobenzene
U080—Methylene chloride
U112—Ethyl acetate
U117—Ethyl ether
U121—Trichlorofluoromethane
U140—Isobutanol
U154—Methanol
U159—Methyl ethyl ketone
U161—Methyl isobutyl ketone
U169—Nitrobenzene
U196—Pyridine
U210—Tetrachloroethylene
U211—Carbon tetrachloride
U220—Toluene
U226—1,1,1-Trichloroethane
U228—Trichloroethylene
U239—Xylene

(2) The following dioxion-containing wastes:

F020—Wastes (except wastewater and spent carbon from hydrogen chloride purification) from the production and manufacturing use (as a reactant, chemical intermediate, or component in a formulating process) of tri-, or tetrachlorophenol or of

intermediates used to produce their pesticide derivatives. (This listing does not include wastes from the production of hexachlorophene from highly purified 2,4,5-trichlorophenol.)

022—Wastes (except wastewater and spent carbon from hydrogen chloride purification) from the production or manufacturing use (as a reactant, chemical intermediates, or component in a formulating process) of pentachlorophenol, or of intermediates used to produce its derivatives.

022—Wastes (except wastewater and spent carbon from hydrogen chloride purification) from the manufacturing use (as a reactant, chemical intermediate, or component in a formulating process) of tetra-, penta-, or hexachlorobenzenes under alkaline conditions.

023—Wastes (except wastewater and spent carbon from hydrogen chloride purification) from the production of materials on equipment previously used for the production or manufacturing use (as a reactant, chemical intermediate, or component in a formulating process) of tri-, and tetrachlorophenols. (This listing does not include wastes from equipment used only for the production or use of hexachlorophene made from highly purified 2,4,5-trichlorophenol.)

026—Wastes (except wastewater and spent carbon from hydrogen chloride purification) from the production of materials on equipment previously used for the manufacturing use (as a reactant, chemical intermediate, or component in a formulation process) of tetra-, penta-, or hexachlorobenzene under alkaline conditions.

027—Discarded unused formulations containing tri-, tetra- or pentachlorophenol, or compounds derived from these chlorophenols. (This listing does not include formulations containing hexachlorophene synthesized from prepurified 2,4,5-trichlorophenol as the sole component.)

4. By adding Subpart D to proposed art 268 to read as follows:

ubpart D—Treatment Standards

=

8.40 Applicability of treatment standards.
8.41 Treatment standards expressed as a specified technology.

Sec.
268.42 Treatment levels expressed as concentrations in waste extract.
268.43 Treatment standards expressed as waste concentrations. [Reserved]

Subpart D—Treatment Standards

§ 268.40 Applicability of treatment standards.

(a) Prior to land disposal, any waste for which an identified technology is specified as the treatment standard § 268.41(a), must be treated using that technology or treated using an equivalent treatment method approved by the Administrator or under the procedures set forth in § 268.41(b), unless the hazardous constituents in an extract of the waste or in the waste are less than the concentration levels indicated in § 268.42 or § 268.43, respectively.

(b) For land disposal of a waste listed in Subpart C of this part but not specifically identified in § 268.41, the concentrations of hazardous constituents in the waste extract must not equal or exceed the value given for any hazardous constituent listed in Table CCWE in § 268.42(a). If none of the concentrations of hazardous constituents in the waste extract equal or exceed the specified concentrations listed in Table CCWE in § 268.42(a), the waste may be land disposed without further treatment. If the concentration of any hazardous constituent in the waste extract equals or exceeds a level indicated in Table CCWE in § 268.42(a) for that constituent, the waste must undergo treatment to bring the level below the applicable concentration level before being land disposed.

§ 268.41 Treatment standards expressed as a specified technology.

(a) The following wastes must be treated using the identified technology or technologies, or an equivalent method approved by the Assistant Administrator for Solid Waste and Emergency Response:
[Wastes and designated treatment technologies will be specified in future actions.]

(b) Any person may submit an application to the Assistant Administrator for Solid Waste and Emergency Response demonstrating that an alternative treatment method can achieve a level of performance equivalent to that achieved by methods specified in paragraph (a) of this section. The applicant must show that his treatment method will not present an unreasonable risk of injury to health or the environment. On the basis of such information and any other available information, the Assistant Administrator for Solid Waste and Emergency Response may, in his discretion, approve the use of the alternative treatment method if he finds that the alternative treatment method provides a level of performance equivalent to that achieved by methods specified in paragraph (a) of this section. Any approval must be stated in writing and may contain such provisions and conditions as the Assistant Administrator for Solid Waste and Emergency Response deems appropriate. The person to whom such certification is issued must comply with all limitations contained in such determination.

§ 268.42 Treatment levels expressed as concentrations in waste extract.

Using the test methods described in SW-846 or equivalent methods approved by the Administrator under the procedures set forth in §§ 260.20 and 260.21 of this chapter, the extract from a representative sample of a waste identified in Subpart C of this part, or from the residue of treatment of such a waste, must not contain any of the constituents listed in Table CCWE at a concentration greater than the respective value given in that table. Where the waste contains less than 0.5 percent filterable solids, the waste itself, after filtering, is considered to be the extract for the purposes of this section.

TABLE CCWE—CONSTITUENT CONCENTRATION IN WASTE EXTRACT

Hazardous constituent	Concentration (in mg/l)
Acetone	2.0
n-Butyl alcohol	2.0
Carbon disulfide	2.0
Carbon tetrachloride	0.1
Chlorobenzene	2.0
Cresols	2.0
Cyclohexanone	2.0
Ethyl acetate	2.0
Ethyl benzene	2.0
Ethyl ether	2.0
HxCDD—All Hexachlorodibenzo-p-dioxins	.001 (1ppb)
HxCDF—All Hexachlorodibenzofurans	.001 (1ppb)
Isobutanol	2.0
Methanol	2.0
Methylene chloride	1.2
Methyl ethyl ketone	2.0
Methyl isobutyl ketone	2.0
Nitrobenzene	0.09
PeCDD—All Pentachlorodibenzo-p-dioxins	.001 (1ppb)
PeCDF—All Pentachlorodibenzofurans	.001 (1ppb)
Pentachlorophenol	1.0
Pyridine	3.7
TCDD—All Tetrachlorodibenzo-p-dioxins	.001 (1ppb)
TCDF—All Tetrachlorodibenzofurans	.001 (1ppb)
Tetrachloroethylene	0.015
2,3,4,6 Tetrachlorophenol	2.0
Toluene	2.0
1,1,1-Trichloroethane	2.0
1,2,2-Trichloro- 1,2,2-trifluoroethane	2.0
Trichloroethylene	0.1
Trichlorofluoromethane	2.0
2,4,5 Trichlorophenol	8.0
2,4,6 Trichlorophenol	0.04
Xylene	2.0

§ 268.43 Treatment standards expressed as waste concentrations. [Reserved]

5. By adding Subpart E consisting at this time of § 268.50 to proposed Part 268 to read as follows:

Subpart E—Prohibitions on Storage

§ 268.50 Prohibitions on storage of restricted wastes.

(a) A hazardous waste prohibited from land disposal under Subpart C of this part may not be stored in tanks or containers after the prohibition effective date unless:

(1) The owner or operator of a hazardous waste treatment, storage, or disposal facility stores such waste for 90 days or less; or

(2) A transporter stores manifested shipments of such waste in containers at a transfer facility for 10 days or less; or,

(3) Such waste is accumulated on site by the generator and does not exceed the applicable time limitations set forth in § 262.34 of this chapter.

(b) The prohibition in paragraph (a) of this section does not apply to the conditions of an approved petition under § 268.5 or an approved case-by-case extension under § 268.4.

(c) The prohibition in paragraph (a) of this section does not apply to hazardous wastes that meet the treatment standards specified under Subpart D of this part.

APPENDIX III

AGENCY RISK ASSESSMENT

GUIDELINES

federal register

Wednesday
January 9, 1985

Part III

Environmental Protection Agency

Proposed Guidelines for the Health Risk Assessment of Chemical Mixtures and Request for Comments; Notice

ENVIRONMENTAL PROTECTION AGENCY

[FRL-2742-8]

Proposed Guidelines for the Health Risk Assessment of Chemical Mixtures

AGENCY: Environmental Protection Agency (EPA.

ACTION: Proposed guidelines for the Health Risk Assessment of Chemical Mixtures and request for comments.

SUMMARY: The U.S. Environmental Protection Agency is proposing Guidelines for the Health Risk Assessment of Chemical Mixtures (Guidelines). These Guidelines are proposed for use within the policy and procedural framework provided by the various statutes that EPA administers to guide Agency analysis of health effects data. We solicit public comment and will take public comment into account in revising these Guidelines. These Guidelines will be reviewed by the Science Advisory Board in meetings now tentatively scheduled for April 1985.

These proposed Guidelines were developed as part of a board guidelines development program under the auspices of the Office of Health and Environmental Assessment (OHEA), located in the Agency's Office of Research and Development. Consonant with the role of OHEA's Environmental Criteria and Assessment Office in Cincinnati (ECAO–Cin) as the Agency's senior health committee for health risk assessment of chemical mixtures, the Guidelines were developed by an Agency-wide working group chaired by the Director of ECAO–Cin.

DATE: Comments must be postmarked by March 11, 1985.

ADDRESS: Comments may be mailed or delivered to: Dr. Jerry Stara, Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency, 26 West St. Clair, Cincinnati, OH 45268.

FOR FURTHER INFORMATION CONTACT: Dr. Richard Hertzber, Telephone: 513–684–7531.

SUPPLEMENTARY INFORMATION: Preliminary drafts of these Guidelines were sent for review to approximately 20 scientists in the fields of toxicology, pharmacokinetics and statistics within the Agency and a later draft was sent for external review to 12 scientists within government, academia and the private sector. Comments received from these reviewers, generally favorable, were considered in developing the Guidelines proposed here.

References and supporting documents used in the preparation of these guidelines as well as comments received are available for inspection and copying at the Public Information Reference Unit (202–382–5926), EPA Headquarters Library, 401 M Street, SW., Washington, DC, between the hours of 8:00 a.m. and 4:30 p.m.

Dated: January 2, 1985.

William D. Ruckelshaus,

Administrator.

Contents

I. Introduction

The primary purpose of this document is to generate a consistent Agency approach for evaluating data on the chronic and subchronic effects of chemical mixtures. It is a procedural guide which emphasizes broad underlying principles of the various science disciplines (toxicology, pharmacology, statistics) necessary for assessing health risk from chemical mixture exposure. Approaches to be used with respect to the analysis and evaluation of the various data are also discussed.

It is not the intent of these Guidelines to regulate any social or economic aspects concerning risk of injury to human health or the environment caused by exposure to a chemical agents(s). All such action is addressed in specific statutes and federal legislation and is independent of these Guidelines.

While some potential environmental hazards involve significant exposure to only a single compound, most instances of environmental contamination involve concurrent or sequential exposures to a variety of compounds that my induce similar or dissimilar effects over exposure periods ranging from short-term to lifetime. In some instances, the mixtures are highly complex consisting of scores of compounds that are generated simultaneously as by-products from a single source or process (e.g., coke oven emissions and diesel exhaust). In other cases, complex mixtures of related compounds are produced as commercial products (e.g., PCBs, gasoline and pesticide formulations) and eventually released to the environment. Another class of mixtures consists of compounds, often unrelated chemically or commercially, which are placed in the same area for disposal or storage, eventually come into contact with each other, and are released as a mixture to the environment. The quality and quantity of pertinent information available for risk assessment varies considerably for different mixtures. Occasionally, the chemical compositions of a mixture is well characterized, levels of exposure to the population are known, and detailed toxicologic data on the mixture are available. Most frequently, not all components of the mixture are known, exposure data are uncertain, and toxicologic data on the known components of the mixture are limited. Nonetheless, the Agency may be required to take action because of the number of individual at potential risk or because of the known toxicologic effects of these compounds that have been identified in the mixture.

Guidelines for single compound risk assessments have been developed for subchronic and chronic exposures to both systemic toxicants and carcinogens. In the current document, these approaches are extended to provide compatible guidelines for assessing the effects of multiple toxicant or multiple carcinogen exposures.

The ability to predict how specific mixtures of toxicants will interact must be based on an understanding of the mechanisms of such interactions. Most reviews and texts that discuss toxicant interactions make some attempt to discuss the biological or chemical bases of the interactions (e.g., Klaassen and Doull, 1980; Levine, 1973; Goldstein et al., 1974; NRC, 1980a; Veldstra, 1958; Withey, 1981). Although different authors use somewhat different classification schemes for discussing the ways in which toxicants interact, it generally is recognized that toxicant interactions may occur during any of the toxicologic processes that take place with a single compound: absorption, distribution, metabolism, excretion, and activity at the receptor site(s). In addition, compounds may interact chemically, causing a change in the biological effect or they may interact by causing different effects at different receptor sites.

Because of the uncertainties inherent in any approach to predicting the magnitude and nature of toxicant interactions, any assessment of health risk from chemical mixture must include a thorough discussion of all assumptions. No single approach is recommended in these Guidelines. Instead, guidance is given for modifying a few simple approaches involving risk addition or dose addition. The mathematical details are presented in Section IV.

III. Proposed Approach

No single approach can be recommended to risk assessments for multiple chemical exposures. Nonetheless, general guidelines can be recommended depending on the type of mixture, the known toxic effects of the components in the mixture, the availability of toxicity data on the mixture or similar mixtures, the known or anticipated interactions among components in the mixture, and the quality of the exposure data. Given the complexity of this issue and the relative paucity of empirical data from which sound generalizations can be constructed, emphasis must be placed on flexibility, judgment, and a clear articulation of the assumption and limitations in any risk assessment that is developed. The proposed approach is summarized in Table I and detailed below.

A. Data Available on Similar Mixtures

For predicting the effects of subchronic or chronic exposure to mixtures, the preferred approach is to use subchronic or chronic health effects data on the mixture of concern and adopt the same procedures as those used for single compounds, either systemic toxicants or carcinogens. Such data are most likely to be available on highly complex mixtures, such as coke oven emission or diesel exhaust, which are generated in large quantities and associated with or suspected of having adverse health effects. Even if such data are available, attention should be given to the persistence of the mixture in the environment as well as the variability of composition of the mixture over time or from different sources of emissions. If the components in the mixture are known to partition into different environmental compartments or to degrade or transform at different rates in the environment, then those factors must also be taken into account, or the confidence in and applicability of the risk assessment is diminished.

TABLE 1.—OUTLINE OF THE RISK ASSESSMENT APPROACH FOR CHEMICAL MIXTURES

1. Health effects information is available on the chemical mixture of concern.
   a. If yes, proceed to Step 5.
   b. If no, proceed to Step 2.
2. Assess the similarity of the mixture on which health effects data are available to the mixture of concern, with emphasis on any differences in components, proportions of components, and environmental partitioning.
   a. If sufficiently similar, proceed to Step 5.
   b. If not sufficiently similar or if no such data exist, proceed to Step 3.
3. Derive appropriate indices of acceptable exposure and/or potency factors for carcinogenicity on the individual components in the mixture and proceed to Step 4.
4. Assess data on interactions of components in the mixture.
   a. If sufficient quantitative information is available on the interactions (including mechanisms) of two or more toxicants from subchronic or chronic studies, proceed to Step 6.
   b. If qualitative information is available on acute interactions, attempt to qualitatively indicate the nature of potential interactions and proceed to Step 7.
5. Conduct risk assessment on the mixture of concern based on health effects data on the mixture, using the same procedures as those for single compounds. Proceed to Step 9.
6. Use an appropriate interaction model to combine risk assessment on compounds for which the data are adequate and use assumption of dose addition for remaining toxicants. Proceed to Step 8.
7. Use an additivity assumption for all compounds in the mixture. Proceed to Step 8.
8. Develop an integrated summary of the qualitative and quantitative assessments with special emphasis on uncertainties and assumptions.

Similarly, if the risk assessment is conducted based on data from a single mixture which is known to be generated with varying compositions depending on time or different emission sources, then the confidence in the applicability of the data to a risk assessment also is diminished. This can be offset to some degree if data are available on several mixtures of the same components but having different ratios of the components which encompass the differences in composition seen with time or from different emission sources. If such data are available, an attempt should be made to determine if significant and systematic differences exist among the chemical mixtures. If significant differences are noted, ranges of risk can be estimated based on toxicologic data from the various mixtures. If no significant differences are noted, then a single risk assessment may be adequate, although some statement should be made giving the range of ratios of the components in the mixtures to which the risk assessment applies.

If no data are available on the mixtures of concern but health effects data are available on a similar mixture (i.e., a mixture having the same components but at slightly different ratios, or having several common components but lacking one or more components, or having one or more additional components) a decision must be made whether the mixture on which health effects data are available is or is not "sufficiently similar" to the mixture of concern to permit a risk assessment. The determination of "sufficient similarity" must be made on a case-by-case basis, considering not only the uncertainties associated with using data on a dissimilar mixture but also the uncertainties of using approaches based on additivity, which are detailed later. In determining reasonable similarity, consideration should be given to any information on the components which differ or are contained in markedly different proportions between the mixture on which health effects data are available and the mixture of concern.

B. Data Available Only on Mixture Components

If data are not available on an identical or reasonably similar mixture, the risk assessment may be used on the toxic or carcinogenic properties of the components in the mixture. When little or no quantitative information is available on the potential interaction among the components, dose additive models are recommended for systemic toxicants (defined later). Several studies have demonstrated that dose additive models often predict reasonably well the toxicities of mixtures composed of a substantial variety of both similar and dissimilar compounds (Pozzani et al., 1959; Smyth et al., 1969, 1970; Murphy, 1980). The problem of multiple toxicant exposure has been addressed by the American Conference of Governmental Industrial Hygienists (ACGIH, 1983), the Occupational Safety and Health Administration (OSHA, 1983), the World Health Organization (WHO, 1981), and the National Research Council (NRC, 1980a,b). Although the focus and purpose of each group was somewhat different, all groups that recommended an approach elected to adopt some type of dose additive model. Nonetheless, as discussed in Section IV, dose additive models are not the most biologically plausible approach if the compounds do not have the same mode of toxicologic action. Consequently, depending on the nature of the risk assessment and the available information or modes of action and patterns of joint action, the most reasonable additive model should be used.

1. Systemic Toxicants

For systemic toxicants, the current risk assessment methodology used by the agency for single compounds most often results in the derivation of an exposure level which is considered acceptable or which is not anticipated to cause adverse effects. Depending on the route of exposure, media of concern, and the legislative mandate guiding the risk

assessments, the exposure levels may be expressed in a variety of ways such as Acceptable Daily Intakes (ADIs), levels associated with various Margins Of Safety (MOS), or Ambient Air Standards. For the purpose of this discussion, the term "Acceptable Level" (AL) will be used to indicate any of the criteria, standards, or advisories derived by the Agency. For such estimates, the "hazard index" (HI) of a mixture based on the assumption of dose additivity may be defined as:

$$HI = E_1/AL_1 + E_2/AL_2 + \ldots + E_i/AL_i \quad \text{(II-1)}$$

where:

E_i = exposure level to the i^{th} toxicant, and
AL_i = maximum acceptable level for the i^{th} toxicant

Since the inverse of the acceptable level can be used as an estimate of toxic potency, Equation II-1 can be interpreted as a normalized weighted-average dose, with each component dose scaled by its potency. As this index approaches unity, concern for the potential hazard of the mixture increases. If HI>1, the concern for the potential hazard is the same as if an acceptable level were exceeded for an individual compound, i.e., if E_i/AL_i exceeded 1. If the variabilities of the acceptable levels are known, or if the acceptable levels are given as ranges (e.g., associated with different margins of safety), then HI should be presented with estimates of variation or as a range.

The hazard index is not a mathematical prediction of incidence of effects or severity. Statistical properties of this index and its dependence on the shape of the dose-response curves for the components are not yet known. Much additional research is required to determine the accuracy of the hazard index as a numerical prediction of toxic severity. The hazard index is only a numerical indicator of the transition between acceptable and unacceptable exposure levels and should not be overinterpreted.

As discussed in Section IV, the assumption of additivity is most properly applied to compounds that induce the same effect by the same mechanism. Consequently, the application of Equation II-1 to a mixture of compounds that does not interact and is not expected to induce the same types of effects could overestimate hazard. Thus, if the application of Equation II-1 results in an index near to or greater than unity, it may be desirable to segregate the compounds in the mixture by critical effect and derive separate indices for each effect. Conversely, if the dissimilar effects influence one another (e.g., liver failure diminishing the function of another organ), then simple dose addition could underestimate the total hazard; this is discussed more fully in Section III.

The Agency has developed methods for estimating dose-response curves for single chemicals, e.g. carcinogens (U.S. EPA, 1984). In attempting to assess the response to mixtures using dose-response curves for the components of the mixture, dose-additive or response-additive assumptions can be used, with preference given to the most biologically plausible assumption.

2. Carcinogens

For carcinogens, whenever linearity of the dose-response curve can be assumed (usually restricted to low doses), the increase in incremental risk P, caused by exposure d, is related to carcinogenic potency B, as:

$$P = d\,B. \quad \text{(II-2)}$$

For multiple compounds, this equation may be generalized to:

$$P = \Sigma\, d_i B_i. \quad \text{(II-3)}$$

This equation assumes independence of action by the several carcinogens and is equivalent to the assumption of dose addition as well as to response addition with completely negative correlation of tolerance (see Section IV). Analogous to the procedure used in Equation II-1 for systemic toxicants, an index could be developed by dividing exposure levels (E) by doses (DR) associated with varying levels of risk:

$$HI = E_1/DR_1 + E_2/DR_2 + \ldots = E_i/DR_i \quad \text{(II-4)}$$

It should be emphasized that because of the uncertainties in estimating dose response relationships for single compounds and the additional uncertainties in combining the individual estimate to assess response from exposure to mixtures, response rates and hazard indices may have merit in comparing risks but should not be regarded as measures of absolute risk.

3. Interactions

None of the above equations incorporates any form of synergistic or antagonistic interaction. Some types of information, however, may be available that suggest that two or more components in the mixture may interact. Such information must be assessed in terms of both its relevance to subchronic or chronic hazard and its suitability for quantitatively altering the risk assessment.

For example, if chronic or subchronic toxicity or carcinogenicity studies have been conducted that permit a quantitative estimation of interaction for two chemicals, then it may be desirable to consider using equations detailed in Section IV, or modifications of these equations, to treat the two compounds as a single toxicant with greater or lesser potency than would be predicted from additivity. Other compounds in the mixture, on which no such interaction data are available, could then be treated in an additive manner. Before such a procedure is adopted, however, a discussion should be presented of the likelihood that other compounds in the mixture may interfere with the interaction of the two toxicants on which quantitative interaction data are available. If the weight of evidence suggests that interference is likely, then an attempt to quantitatively alter the risk assessment may not be justified. In such cases, the discussion of the risk assessment may only indicate the likely nature of interactions, either synergistic or antagonistic, but not attempt to quantify the magnitude of this interaction.

Other types of available information, such as those relating to mechanisms of toxicant interaction, or quantitative estimates of interaction between two chemicals derived from acute studies, are even less likely to be of quantitative use in the assessment of long-term health risks. Usually it will be appropriate only to discuss these types of information, indicate the relevance of the information to subchronic or chronic exposure, and, as above, indicate, if possible, the nature of any potential interaction, without attempting to quantify the magnitude of the interaction.

4. Uncertainties

In addition to uncertainties on the nature and magnitude of toxicant interactions in the mixture, data may be inadequate to assess exposure to human populations or the potential health effects of one or more components of the mixture. In such a case, the less studied chemicals must not be assumed to be harmless. Instead the uncertainty is increased. Confidence in the risk assessment is reduced because the contribution of these components to the toxicity of the mixture and, consequently, the toxicity of the mixture itself are not known.

a. *Health Effects.* In some cases, when health effects data are incomplete, it may be possible to argue by analogy or quantitative structure-activity relationships that the compounds on which no health effects data are available are not likely to significantly affect the toxicity of the mixture. If a risk assessment is conducted based on such an argument, the limitations of the approach must be clearly articulated.

Since a methodology has not been adopted for estimating an acceptable level (e.g., ADI) or carcinogenic potency for single compounds based either on quantitative structure-activity relationships or on the results of short-term screening tests, such methods are not presently recommended as the sole basis of a risk assessment on chemical mixtures.

b. *Exposure Uncertainties.* If levels of exposure to certain compounds known to be in the mixture are not available, but information on health effects and environmental persistence and transport suggest that these compounds are not likely to be significant in affecting the toxicity of the mixture, then a risk assessment can be conducted based on the remaining compounds in the mixture, with appropriate caveats. If such an argument cannot be supported, no final risk assessment can be performed until adequate monitoring data are available. As an interim procedure, a risk assessment may be conducted for those components in the mixture for which adequate exposure and health effects data are available. If the results of the interim risk assessment suggest that a hazard already exists, resources might be better expended on remedial action as part of the a risk management decision rather than on further assessment. Concern is not reduced if the interim risk assessment does not suggest a hazard because not all components in the mixture have been considered.

c. *Uncertainties Regarding Composition of the Mixture.* As a worst case scenario, information may be lacking not only on health effects and levels of exposure, but also on the identity of some components in the mixture. Analogous to the procedure described in the previous paragraph, an interim risk assessment can be conducted on the components of the mixture for which adequate health effects and exposure information are available. If a hazard is indicated, then the resulting partial assessment should be carefully qualified to avoid over interpretation of the accuracy of the assessment. If no hazard is indicated, the risk assessment should not be quantified until better health effects and monitoring data are available.

III. Assumptions and Limitations

Most of the data available on toxicant interactions are derived from acute toxicity studies using experimental animals in which mixtures of two compounds were tested, often in only a single combination. Major areas of uncertainty with such data involve the appropriateness of interaction data from an acute toxicity study to quantitatively alter a risk assessment for subchronic or chronic exposure, the appropriateness of interaction data on two component mixtures to quantitatively alter a risk assessment on a mixture of several compounds, and the predictability of interaction data on experimental animals to quantitatively assess interactions in humans.

The use of interaction data from acute toxicity studies to assess the potential interactions on chronic exposure would be highly questionable unless the mechanism(s) of the interaction on acute exposure were known to apply to low dose chronic exposure. However, most known biological mechanisms for toxicant interactions involve some form of competition between the chemicals or phenomena involving saturation of a receptor site or metabolic pathway. As the doses of the toxicants are decreased, it is likely that these mechanisms either no longer will exert a significant effect or will be decreased to an extent which cannot be measured or approximated.

The use of information from two component mixtures to assess the interactions in a mixture containing more than two compounds also is questionable from a mechanistic perspective. For example, if two compounds are known to interact, either synergistically or antagonistically, because of the effects of one compound on the metabolism or excretion of the other, the addition of a third compound which either chemically alters or affects the absorption of one of the first two compounds could substantially alter the degree of the toxicologic interaction. Usually, detailed studies quantifying toxicant interactions are not available on multicomponent mixtures, and the few studies that are available on such mixtures (e.g., Gullino et al., 1956) do not provide sufficient information to assess the effects of interactive interference.

Concerns with the use of interaction data on experimental mammals to assess interactions in humans is based on the increasing appreciation for systematic differences among species in their response to individual chemicals. If systematic differences in interspecies sensitivity exist among species, then it seems reasonable to suggest that the magnitude of toxicant interactions among species also may vary in a systematic manner. Consequently, even if excellent chronic data are available on the magnitude of toxicant interactions in a species of experimental mammal, there is uncertainty that the magnitude of the interaction will be the same in humans. Again, data are not available to properly assess the significance of this uncertainty.

Last, it should be emphasized that none of the models for toxicant interaction can predict the magnitude of toxicant interactions in the absence of extensive data. If sufficient data are available to estimate interactive coefficients as described in Section IV, then the magnitude of the toxicant interactions for various proportions of the same components can be predicted. The availability of an interaction ratio (observed response divided by predicted response) is useful only in assessing the magnitude of the toxicant interaction for the specific proportions of the mixture which were used to generate the interaction ratio.

The basic assumption in the recommended approach is the risk assessments on chemical mixtures are best conducted using toxicologic data on the mixture of concern or a reasonably similar mixture. While such risk assessments do not formally consider toxicologic interactions as part of a mathematic model, it is assumed that responses in experimental mammals or human populations noted after exposure to the chemical mixture can be used to conduct risk assessments on human populations. In bioassays of chemical mixtures using experimental mammals, the same limitations inherent in species-to-species extrapolation for single compounds apply to mixtures. When using health effects data on chemical mixtures from studies on exposed human populations, the limitations of epidemiologic studies in the risk assessment of single compounds also apply to mixtures. Additional limitations may be involved when using health effects data on chemical mixtures if the components in the mixture are not constant or if the components partition in the environment.

If sufficient data are not available on the effects of the chemical mixture of concern or a reasonably similar mixture, the proposed approach is to assume additivity. Dose additivity is based on the assumption that the components in the mixture have the same mode of action and elicit the same effects. This assumption will not hold true in most cases, at least for mixtures of systemic toxicants. For systemic toxicants, however, most single compound risk assessments will result in the derivation of acceptable levels, which, as currently defined, cannot be adapted to the different forms of response additivity as described in Section IV.

Additivity models can be modified to incorporate quantitative data on toxicant interactions from subchronic or

chronic studies using the models given in Section IV or modifications of these models. If this approach is taken, however, it will be under the assumption that other components in the mixture do not interfere with the measured interaction. In practice, such subchronic or chronic interactions data seldom will be available, and most risk assessments, in the absence of health effects data on the mixture of concern, will be based on an assumption additivity.

Dose-additive and response-additive assumptions can lead to substantial errors in risk estimates if synergistic or antagonistic interactions occur. Although dose additivity has been shown to predict the acute toxicities of many mixtures of similar and dissimilar compounds (e.g., Pozzani et al., 1959; Smyth et al., 1969, 1970; Murphy, 1980), some marked exceptions have been noted. For example, Smyth et al. (1970) tested the interaction of 53 pairs of industrial chemicals based on acute lethality in rats. For most pairs of compounds, the ratio of the predicted LD_{50} to observed LD_{50} did not vary by more than a factor of 2. The greatest variation was seen with an equivolume mixture of morpholine and toluene, in which the observed LD_{50} was about five times less than the LD_{50} predicted by dose addition. In a study by Hammond et al. (1979), the relative risk of lung cancer attributable to smoking was 11, while the relative risk associated with asbestos exposure was 5. The relative risk of lung cancer from both smoking and asbestos exposure was 53, indicating a substantial synergistic effect. Consequently, in some cases, additivity assumptions may substantially underestimate risk. In other cases, risk may be overestimated. While this is certainly an unsatisfactory limitation, it is a limitation associated more with the nature and quality of the available data on toxicant interaction than with the proposed approach itself.

IV. Mathematical Models and the Measurement of Joint Action

The simplest mathematical models for joint action assume no interaction in any mathematical sense. They describe either dose addition or response addition and are motivated by data on acute lethal effects of mixtures of two compounds.

A. Dose Addition

Dose addition assumes that the toxicants in a mixture behave as if they were dilutions or concentrations of each other, thus the slopes of the dose-response curves for the individual compounds are identical, and the response elicited by the mixture can be predicted by summing the individual doses after adjusting for differences in potency; this is defined as the ratio of equitoxic doses. Probit transformation typically makes this ratio constant at all doses when parallel straight lines are obtained. Although this assumption can be applied to any model (e.g., the one-hit model in NRC, 1980b), it has been most often used in toxicology with the log-dose probit-response model, which will be used to illustrate the assumption of dose additivity. Suppose that two toxicants show the following log-dose probit-response equations:

$$Y_1 = 0.3 + 3 \log Z_1 \qquad \text{(IV-1)}$$

$$Y_2 = 1.2 + 3 \log Z_2 \qquad \text{(IV-2)}$$

where Y_i is the probit response associated with a dose of Z_i ($i = 1,2$).

The potency, p, of toxicant-2 with respect to toxicant-1 is defined by the quantity Z_1/Z_2 when $Y_1 = Y_2$ (that is what is meant by equitoxic doses). In this example, the potency, p, is approximately 2. Dose addition assumes that the response, Y, to any mixture of these two toxicants can be predicted by:

$$Y = 0.3 + 3 \log (Z_1 + pZ_2) \qquad \text{(IV-3)}$$

Thus, since p is defined as Z_1/Z_2, Equation IV-3 essentially converts Z_2 into an equivalent dose of Z_1 by adjusting for the difference in potency. A more generalized form of this equation for any number of toxicants is:

$$Y = a_1 + b \log (f_1 + \Sigma f_i p_i) + b \log Z \qquad \text{(IV-4)}$$

where a_1 is the y-intercept of the dose-response equation for toxicant-1, b is the slope of the dose-response lines for the toxicants, f_i is the proportion of the i^{th} toxicant in the mixture, p_i is the potency of the i^{th}-toxicant with respect to toxicant-1 (Z_1/Z_i), and Z is the sum of the individual doses in the mixture. A more detailed discussion of the derivation of the equations for dose addition is presented by Finney (1971).

B. Response Addition

The other form of additivity is referred to as response addition. As detailed by Bliss (1939), this type of joint action assumes that the two toxicants act on different receptor systems and that the correlation of individual tolerances may range from completely negative ($r = -1$) to completely positive ($r = +1$) correlation. Response addition assumes that the response to a given concentration of a mixture of toxicants is completely determined by the responses to the components and the correlation coefficient. Taking P as the proportion of organisms responding to a mixture of two toxicants which evoke individual responses of P_1 and P_2, then

$P = P_1$ if $r = 1$ and $P_1 > P_2$ (IV-5)

$P = P_2$ if $r = 1$ and $P_1 < P_2$ (IV-6)

$P = P_1 + P_2 (1 - P_1)$ if $r = 0$ (IV-7)

$P = P_1 + P_2$ if $r = -1$ and $P <$ (IV-8)

More generalized mathematical models for this form of joint action have been given by Plackett and Hewlett (1948).

C. Interactions

All of the above models are noninteractive and do not allow for the measurements of synergistic or antagonistic effects. For measuring toxicant interactions for mixtures of two compounds, Finney (1942) proposed the following modification of Equation IV-4 for dose addition:

$$Y = a_1 + b \log (f_1 + pf_2 + K [pf_1f_2]^{0.5}) + b \log Z \qquad \text{(IV-9)}$$

where a_1, b, f_2, p and Z are defined as before and K is the coefficient of interaction. A positive value of K indicates synergism, a negative value indicates antagonism, and a value of zero corresponds to dose addition as in Equation IV-4. Like other proposed modifications of dose addition (Hewlett, 1969), the equation assumes a consistent interaction throughout the entire range of proportions of individual components. To account for such asymmetric patterns of interaction as those observed by Alstott et al. (1973), Durkin (1981) proposed the following modification to Equation IV-9:

$$Y = a_1 + b \log (f_1 + pf_2 + K_1 f_1 [pf_1f_2]^{0.5} + K_2 f_2 [pf_1f_2]^{0.5}) + b \log Z \qquad \text{(IV-10)}$$

in which $K(pf_1f_2)^{0.5}$ is divided into two components, $K_1f_1(pf_1f_2)^{0.5}$ and $K_2f_2(pf_1f_2)^{0.5}$. Since K_1 and K_2 need not have the same sign, apparent instances of antagonism at one receptor site and synergism at another receptor site can be estimated. When K_1 and K_2 are equal, Equation IV-10 reduces to Equation IV-9.

It should be noted that to obtain a reasonable number of degrees of freedom in the estimation of K in Equation IV-9 or K_1 and K_2 in Equation IV-10 requires that the toxicity of several different combinations of the two components must be assayed along with assays of the toxicity of the individual components. Since this requires experiments with large numbers of animals, such analyses have been restricted for the most part to data from acute bioassays using insects (e.g., Finney, 1971) or aquatic organisms (Durkin, 1979). Also, because of the complexity of experimental design and the need for large numbers of animals, neither Equation IV-9 nor Equation IV-10 has been generalized or applied to mixtures of more than two toxicants. Modifications of response-additive models to include interactive terms have

also been proposed, along with appropriate statistical tests for the assumption of additivity (Korn and Liu, 1983; Wahrendorf et al., 1981).

In the epidemiologic literature, measurements of the extent of toxicant interactions (S) can be expressed as the ratio of observed relative risk to relative risk predicted by some form of additivity assumption. Analogous to the ratio of interaction in classical toxicology studies, S=1 indicates no interaction, S<1 indicates synergism, S>1 indicates antagonism. Several models for both additive and multiplicative risks have been proposed (e.g., Hogan et al., 1978; NRC, 1980b; Walter, 1978). For instance, Rothman (1976) has discussed the use of the following measurement of toxicant interaction based on the assumption of risk additivity:

$$S=(R_{11}-1)/(R_{10}+R_{01}-2) \quad \text{(IV-11)}$$

where R_{10} is the relative risk from compound-1 in the absence of compound-2, R_{01} is the relative risk from compound-2 in the absence of compound-1, and R_{11} is the relative risk from exposure to both compounds. A multiplicative risk model adapted from Walter and Holford (1978, Eq. 4) can be stated as:

$$S=R_{11}/(R_{10}R_{01}) \quad \text{(IV-12)}$$

As discussed by both Walter and Holford (1978) and Rothman (1976), the risk-additive model is generally applied to agents causing diseases while the multiplicative model is more appropriate to agents that prevent disease. The relative merits of these and other indices have been the subject of considerable discussion in the epidemiologic literature (Hogan et al., 1978; Kupper and Hogan, 1978; Rothman, 1978; Rothman et al., 1980; Walter and Holford, 1978) which has not yet been resolved.

Both the additive and multiplicative models assume statistical independence in that the risk associated with exposure to both compounds in combination can be predicted by the risks associated with separate exposure to the individual compounds. As illustrated by Siemiatycki and Thomas (1981) for multistage carcinogenesis, the better fitting statistical model will depend not only upon actual biological interactions but also upon the stages of the disease process which the compounds affect. Consequently, there is no *a priori* basis for selecting either type of model in a risk assessment. As discussed by Stara et al. (1983), the concepts of multistage carcinogenesis and the effects of promoters and cocarcinogens on risk are extremely complex issues. Although risk models for promoters have been proposed (e.g., Burns et al., 1983) no single approach can be recommended at this time.

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Friday
November 23, 1984

Part VIII

Environmental Protection Agency

Proposed Guidelines for Exposure Assessment; Request for Comments

ENVIRONMENTAL PROTECTION AGENCY

[FRL-2702-3]

Proposed Guidelines for Exposure Assessment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed Guidelines for Exposure Assessment and Request for Comments.

SUMMARY: The U.S. Environmental Protection Agency is proposing Guidelines for Exposure Assessment (Guidelines). These Guidelines are proposed for use within the policy and procedural framework provided by the various statutes which EPA administers to guide Agency analysis of exposure data. We solicit public comment and will take public comment into account in revising these Guidelines. These Guidelines will be reviewed by the Science Advisory Board in meetings now tentatively scheduled for April 1985.

These proposed Guidelines were developed as part of a broad guidelines development program under the auspices of the Office of Health and Environmental Assessment (OHEA), located in the Agency's Office of Research and Development. Consonant with the role of OHEA's Exposure Assessment Group (EAG) as the Agency's senior health committee for exposure assessment, the Guidelines were developed by an Agency-wide working group chaired by the Director of EAG.

DATE: Comments must be postmarked by January 22, 1985.

ADDRESSES: Comments may be mailed or delivered to: Dr. James W. Falco, Exposure Assessment Group (RD-689), Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, 401 M Street S.W., Washington, DC 20460.

FOR FURTHER INFORMATION CONTACT: Dr. James W. Falco, Telephone: 202-475-8909.

SUPPLEMENTARY INFORMATION: Preliminary drafts of these Guidelines were sent out for review to 15 scientists and engineers in the field of exposure assessment within government, universities in the United States and abroad, and the private sector. Comments received from these reviews, generally favorable, were taken into account in developing the Guidelines proposed here.

In addition, as a result of the reviews, four areas requiring further research were identified as follows:

(1) Development of Mathematical Model Selection Criteria.

A large number of mathematical models are used to estimate a wide variety of parameters needed for estimating exposures. Guidance in the form of selection criteria are needed to ensure that the most appropriate mathematical model is used for each exposure parameter estimate.

(2) Development of Guidance for Analysis of Metabolism Data.

Guidance is needed to provide appropriate consideration of metabolism data in the calculation of whole body dose and in the extrapolation of whole organism dose from one species to another.

(3) Definition of the Relationship Between Exposure Assessment and Epidemiology.

Guidance is needed to ensure that pertinent parameters of exposure are measured in prospective epidemiologic studies. Methods providing the best estimates of exposure for retrospective and historical epidemiologic studies must be defined.

(4) Development of Methods to Relate Exposures Measured by Personal Monitoring to Source Contributions.

Guidance is needed to establish methods to relate exposures as measured by personal monitoring to controllable sources and to discriminate among possible sources and between background and anthropogenic sources.

It is the Agency's intent to revise the Guidelines periodically to incorporate the results obtained in the four research areas defined above as they become available.

In addition to the publication of the Guidelines, the Agency also will provide technical support documents that contain detailed technical information needed to implement the Guidelines. Two of these technical reports entitled "Development of Statistical Distribution or Ranges of Standard Factors Used in Exposure Assessments" and "Methodology for Characterization of Uncertainty in Exposure Assessments" are currently available. Technical reports for the four new guideline areas described above will be available at the time of publication of the corresponding guideline section. These technical support documents will be revised periodically to reflect improvements in exposure assessment methods and new information or experience.

Support documents used in the preparation of these Guidelines as well as comments received are available for inspection and copying at the Public Information Reference Unit (202-382-5926), EPA Headquarters Library, 401 M Street S.W., Washington, DC, between the hours of 8:00 a.m. and 4:30 p.m.

Dated: November 9, 1984.

William D. Ruckelshaus,

Administrator.

Contents

I. Introduction

These Guidelines provide the Agency with a general approach and framework for carrying out human or nonhuman exposure assessments for specified pollutants. The Guidelines have been developed to assist future assessment activities and encourage improvement in those EPA programs that require, or could benefit from the use of exposure assessments. The Guidelines are procedural. They should be followed to the extent possible in instances where exposure assessment is a required element in the regulatory process or where exposure assessments are carried out on a discretionary basis by EPA management to support regulatory or programmatic decisions.

This document, by laying out a set of questions to be considered in carrying out an exposure assessment, should help avoid inadvertent mistakes of omission. EPA recognizes that gaps in data will be common, but the Guidelines will nevertheless serve to assist in organizing the data that are available, including any new data developed as part of the exposure assessment. It is understood that exposure assessments may be performed at many different levels of detail depending on the scope of the assessment.

These Guidelines should also promote consistency among various exposure assessment activities that are carried out by the Agency. Consistency with respect to common physical, chemical, and biological parameters, with respect to assumptions about typical exposure

situations, and with respect to the characterization of uncertainty of estimates, will enhance the comparability of results and enable the Agency to improve the state-of-the-art of exposure assessment over time through the sharing of common data and experiences.

It is recognized that the main objective of an exposure assessment is to provide reliable data and/or estimates for a risk assessment. Since a risk assessment requires the coupling of exposure information and toxicity or effects information, the exposure assessment process should be coordinated with the toxicity/effects assessment. This document provides a common approach to format, which should simplify the process of reading and evaluating exposure assessments and thereby increase their utility in assessing risk.

As the Agency performs more exposure assessments, the Guidelines will be revised to reflect the benefit of experience.

II. General Guidelines and Principles

A. Exposure and Dose

Exposure has been defined by Committee E-47, Biological Effects and Environmental Fate, of the American Society for Testing and Materials, as the contact with a chemical or physical agent. The magnitude of the exposure is determined by measuring or estimating the amount of an agent available at the exchange boundaries, i.e., lungs, gut, skin, during some specified time. Exposure assessment is the determination or estimation (qualitative or quantitative) of the magnitude, frequency, duration, and route of exposure. Exposure assessments may consider past, present, and future exposures with varying techniques for each phase, i.e., modeling of future exposures, measurements of existing exposure, and biological accumulation for past exposures. Exposure assessments are generally combined with environmental and health effects data in performing risk assessments.

In considering the exposure of a subject to a hazardous agent, there are several related processes. The contact between the subject of concern and the agent may lead to the intake of some of the agent. If absorption occurs, this constitutes an uptake (or an absorbed dose) which then may lead to health effects. When biological tissue or fluid measurements indicate the presence of a chemical, exposures can be estimated from these data. Presence of a chemical in such biological samples is the most direct indication that an exposure has occurred. The route of exposure generally impacts the overall exposure and should be considered in performing risk assessments.

B. Decision Path to Determine Scope of the Assessment

The first step in preparing an exposure assessment should be the circumscription of the problem at hand to minimize effort by use of a narrowing process. A decision logic path that describes this process is shown in Figure 1. As illustrated in Figure 1, the preliminary assessment and the in-depth assessment are two major phases in this logic path.

The preliminary assessment phase should commence by considering what risk is under study and what law might regulate the exposure to the agent. Within this framework, a preliminary data base should be compiled from readily available scientific data and exposure information based on manufacturer, processor, and user practices. Next, the most likely areas of exposure (manufacuring, processing, consumer, distribution, disposal, ambient, water and food, etc.) should be identified. Since a complete data search has not been conducted, well-identified assumptions and order of magnitude estimates are used to further narrow the exposure areas of concern.

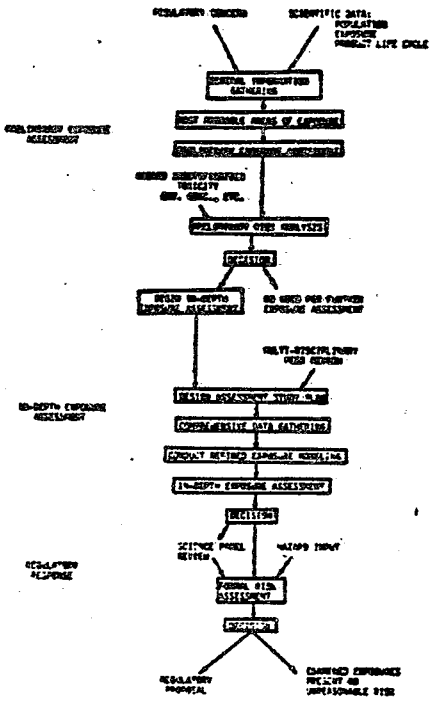

FIGURE 1. DECISION PATH FOR EXPOSURE ASSESSMENT

Data from this preliminary exposure assessment can then be coupled with toxicity information to perform a preliminary risk analysis. As a result of this analysis, a decision will be made that either an in-depth exposure assessment is necessary or that there is no need for further exposure information. The organization and contents of an in-depth exposure assessment are given in the following section.

In assembling the information base for either a preliminary assessment or a more detailed assessment, its adequacy should be ascertained by addressing the following considerations:

—Availability of information in every area needed for an adequate assessment;
—Quantitative and qualitative nature of the data;
—Reliability of information;
—Limitations on the ability to assess exposure.

C. Uncertainty

Exposure assessments are based on monitoring data, simulation model estimates, and assumptions about parameters used in approximating actual exposure conditions. Both data and assumptions contain varying degrees of uncertainty which influence the accuracy of exposure assessments. An evaluation of these uncertainties is important when the assessment is the basis for regulatory action.

The uncertainty analyses performed will vary depending on the scope of the assessment, the quantity and quality of monitoring data collected, and the type and complexity of mathematical models used. A discussion of the types of analysis used for quantifying uncertainties in exposures is presented in the next section.

III. Organization and Contents of an Exposure Assessment

A. Overview

A suggested outline for an exposure assessment document is given in Exhibit 1. The five major topics to be addressed within most exposure assessments are as follows: Source(s); Exposure Pathways; Monitored or Estimated Concentration Levels and Duration; Exposed Population(s); and Integrated Exposure Analysis. These five topics are appropriate for exposure assessments in general, whether the assessments are of global, national, regional, local, site-specific, workplace-related, or other scope. The topics are appropriate for exposure assessments on new or existing chemicals and radionuclides.

They are also applicable to both single media and multimedia assessments. Since exposure assessments are performed at different levels of detail, the extent to which any assessment contains items listed in Exhibit 1 depends upon its scope. The outline is a guide to organize the data whenever they are available.

B. Detailed Explanation of Outline

1. Executive Summary

The "Executive Summary" should be written so that it can stand on its own as a miniature report. Its main focus should be on a succinct description of the procedures used, assumptions employed, and summary tables or charts of the results. A brief discussion of the uncertainties associated with the results should be included.

2. Introduction (Purpose and Scope)

This section should state the intended purpose of the exposure assessment and identify the agent being investigated, the types of sources and exposure routes included, and the populations of concern.

Exhibit 1.—Suggested Outline for an Exposure Assessment

1. EXECUTIVE SUMMARY
2. INTRODUCTION
   a. Purpose
   b. Scope
3. GENERAL INFORMATION
   a. Identity
      (1) Molecular formula and structure, CAS number, TSL number
      (2) Description of technical grades, contaminants, additives
      (3) Other identifying characteristics
   b. Chemical and Physical Properties
4. SOURCES
   a. Characterization of Production and Distribution
      (1) Production and processing
      (2) Distribution in commerce
   b. Uses
   c. Disposal
   d. Summary of Environmental Releases
5. EXPOSURE PATHWAYS AND ENVIRONMENTAL FATE
   a. Transport and Transformation
   b. Identification of Principal Pathways of Exposure
   c. Predicting Environmental Distribution
6. MONITORED OR ESTIMATED CONCENTRATION LEVELS
   a. Summary of Monitoring Data
   b. Estimation of Environmental Concentrations
   c. Comparison of Concentration Estimates with Monitoring Data
7. EXPOSED POPULATIONS
   a. Human Populations (Size, Location, and Habits)
      (1) Population size and characteristics
      (2) Population location
      (3) Population habits
   b. Nonhuman Populations (where appropriate)
      (1) Population size and characteristics
      (2) Population location
      (3) Population habits
8. INTEGRATED EXPOSURE ANALYSIS
   a. Calculation of Exposure
      (1) Identification and characterization of the exposed populations and critical elements of the ecosystem
      (2) Pathways of exposure
   b. Human Dosimetry and Monitoring
   c. Development of Exposure Scenarios and Profiles
   d. Evaluation of Uncertainty
9. REFERENCES
10. APPENDICES

3. General Information

a. *Identity.* (1) Molecular formula and structure, synonyms, Chemical Abstract Service number, Toxic Substance List number.

(2) Description of technical grades, contaminants, additives.

(3) Other identifying characteristics.

b. *Chemical and Physical Properties.* This subsection should provide a summary description of the chemical and physical properties of the agent. Particular attention should be paid to the features that would affect its behavior in the environment. Examples of factors to be included are molecular weight, density, boiling point, melting point, vapor pressure, solubility, pK_a, partition coefficients, and half-lives.

4. Sources

The points at which a hazardous substance is believed to enter the environment should be described, along with any known rates of entry. Points of entry may be indoors as well as outdoors, and environments include indoor settings such as offices as well as outdoor environments. A detailed exposure assessment should include a study of sources, production, uses, destruction/disposal, and environmental release of a substance. The studies should include a description of human activities with respect to the substance and the environmental releases resulting from those activities. It should account for the controlled mass flow of the substance from creation to destruction and provide estimates of environmental releases at each step in this flow. Seasonal variations in environmental releases should also be examined. All sources of the substances should be accounted for with the sum of the uses, destruction, and the environmental releases. The environmental releases can be described in terms of geographic and temporal distribution and the receiving environmental media, with the form identified at the various release points.

a. *Characterization of Production and Distribution.* All sources of the substance's release to the environment, consistent with the scope of the assessment, should be included, such as production, extraction, processing, imports, stockpiles, transportation, accidental/incidental production as a side reaction, and natural sources. The sources should be located, and activities involving exposure to the substance should be identified.

b. *Uses.* The substance should be traced from its sources through various uses (with further follow-up on the products made to determine the presence of the original material as an impurity), exports, stockpile increases, etc.

c. *Disposal.* This subsection should contain an evaluation of disposal sites and destruction processes, such as incineration of industrial chemical wastes, incineration of the substance as part of an end-use item in municipal waste, landfilling of wastes, biological destruction in a secondary wastewater treatment plant, or destruction in the process of using the end product. Hazardous contaminants of the substance may be included, and products containing the substance as a contaminant may be followed from production through destruction/disposal.

d. *Summary of Environmental Releases.* Estimates should be made of the quantities of the substances released to the various environmental media. Sources of release to the environment include production, use, distribution/transport, natural sources, disposal, and contamination of other products. Environmental releases should be presented at a reasonable level of detail. Extremely detailed exposure estimates would attempt to specify the following information for each significant emission source: Location, amount of the substances being released as a function of time to each environmental medium, physical characteristics of the emission source, and the physical and chemical form of the substance being released. Evaluation of the uncertainties associated with the emission estimates should be given. A detailed discussion of procedures for estimating uncertainty is presented in section 8.d.

5. Exposure Pathways and Environmental Fate

The exposure pathways section should address how a hazardous agent moves from the source to the exposed population or subject. For a less detailed assessment, broad generalizations on environmental pathways and fate may be made. In the absence of data, e.g., for new substances, fate estimates may

have to be predicted by analogy with data from other substances. Fate estimates may also be made by using models and/or monitoring data and laboratory-derived process rate coefficients. At any level of detail, certain pathways may be judged insignficiant and not pursued further.

For more detailed assessments involving environmental fate, the sources analysis described previously should provide the amount and rate of emissions to the environment, and possibly the locations and form of the emissions. The environmental pathways and fate analysis follows the substance from its point of initial environmental release, through the environment, to its ultimate fate. It may result in an estimation of the geographic and temporal distribution of concentrations of the substance in the various contaminated environmental media.

a. *Transport and transformation.* The substance, once released to the environment, may be transported (e.g., convected downstream in water or on suspended sediment, through the atmosphere, etc.) or physically transformed (e.g., volatilized, melted, absorbed/desorbed, etc.); may undergo chemical transformation such as photoysis, hydrolysis, oxidation, reduction; may undergo biotransformation such as biodegradation; or may accumulate in one or more media. Thus, the environmental behavior of a substance should be evaluated before exposures are assessed. Factors that should be addressed include:

- How does the agent behave in air, water, soil, and biological media? Does it bioaccumulate or biodegrade? Is it absorbed or taken up by plants?
- What are the principal mechanisms for change or removal in each of the environmental media.
- Does the agent react with other compounds in the environment?
- Is there intermedia transfer? What are the mechanisms for intermedia transfer? What are the rates of the intermedia transfer or reaction mechanisms?
- How long might the agent remain in each environmental medium? How does its concentration change with time in each medium?
- What are the products into which the agent might degrade or change in the environment? Are any of these degradation products ecologically or biologically harmful? What is the environmental behavior of the harmful products?
- Is a steady-state concentration distribution in the environment or in specific segments of the environment, achieved? If not, can the nonsteady-state distribution be described?
- What is the resultant distribution in the environment—for different media, different types or forms of the agent, for different geographical areas, at different times or seasons?

b. *Identification of Principal Pathways of Exposure.* The principal pathway analysis should evaluate the sources, locations, and types of environmental releases, together with environmental behavioral factors, to determine the significant routes of human and environmental exposure to the substance. Thus, by listing the important characteristics of the environmental release (entering media, emission rates, etc.) and the agent's behavior (intermedia transfer, persistence, etc.) after release to each of the entering media, it should be possible to follow the movement of the agent from its initial release to its subsequent fate in the environment. At any point in the environment, human or environmental exposure may occur. Pathways that result in major concentrations of the agent and high potential for human or environmental contact are the principal exposure pathways.

c. *Predicting Environmental Distribution.* Models may be used to predict environmental distributions of chemicals. Many modeling estimates of environmental distribution of chemicals are based in part on monitoring data. In predicting environmental distributions of chemicals, available monitoring data should be considered.

In this section an estimation is made, using appropriate models, of representative concentrations of the agent in different environmental media, and its time-dependence in specific geographical locations (e.g., river basins, streams, etc.).

6. Monitored or Estimated Concentration Levels

a. *Summary of Monitoring Data.* Monitoring data are used to identify releases (source terms) and, in the exposure pathways and fate assessments, to quantitatively estimate both release rates and environmental concentrations. Some examples of uses of monitoring data are: Sampling of stacks of discharge pipes for emissions to the environment; testing of products for chemical or radionuclide content; testing of products for chemical or radioactive releases; sampling of appropriate points within a manufacturing plant to determine releases from industrial processes or practices; and sampling of solid waste for chemical or radionuclide content. These data should be characterized as to accuracy, precision, and representativeness. If actual environmental monitoring data are unavailable, concentrations can be estimated by various means, including the use of fate models (see previous section) or, in the case of new chemicals, by analogy with existing chemicals.

The analysis of monitoring data should be considered a complement to environmental pathway and fate analysis for the following reasons: For most pollutants, particularly organic and new chemicals, monitoring data are limited; analysis of monitoring data does not often yield relationships between environmental releases and environmental concentration distribution in media or geographic locations that have not been monitored; analysis of monitoring data does not provide information on how and where biota influence the environmental distribution of a pollutant; and monitored concentrations may not be traceable to individual sources that EPA can regulate. Monitoring data are, however, a direct source of information for exposure analysis and, furthermore, they can be used to calibrate or extrapolate models or calculations to assess environmental distribution.

b. *Estimation of Environmental Concentrations.* Concentrations of agents should be estimated for all environmental media that might contribute to significant exposures. Generally, the environmental concentrations are estimated from monitoring data, mathematical models, or a combination of the two.

The concentrations must be estimated and presented in a format consistent with available dose-response information. In some cases an estimate of annual average concentration will be sufficient, while in other cases the temporal distribution of concentrations may be required. Future environmental concentrations resulting from current or past releases may also be projected. In some cases, both the temporal and geographic distributions of the concentration may be assessed. Moreover, if the agent has natural sources, the contribution of these to environmental concentrations may be relevant. These "background" concentrations may be particularly important when the results of tests of toxic effects show a threshold or distinctly nonlinear dose-response.

The uncertainties associated with the estimated concentrations should be evaluated by an analysis of the

uncertainties of the model parameters and input variables. When the estimates of the environmental concentrations are based on mathematical models, the model results should be compared to available monitoring data, and any significant discrepancies should be discussed. Reliable, analytically-determined values should be given precedence over estimated values whenever significant discrepancies are found.

7. Exposed Populations

Populations selected for study may be done *a priori*, but frequently the populations will be identified as a result of the sources and fate studies. From an analysis of the distribution of the agent, populations exposed and subpopulations (i.e., collections of subjects) at potentially high exposure can be identified, which will then form the basis for the populations studied. Subpopulations of high sensitivity, such as pregnant women, infants, chronically ill, etc., may be studied separately.

In many cases, exposed populations can be described only generally. In some cases, however, more specific information may be available on matters such as the following:

a. *Human Populations. (1) Population size and characteristics (e.g., trends, sex/age distribution)*

(2) Population location

(3) Population habits—transportation habits, eating habits, recreational habits, workplace habits, product use habits, etc.

b. *Nonhuman Populations (where appropriate).* (1) Population size and characteristics (e.g., species, trends)

(2) Population location

(3) Population habits

Census and other survey data may be used to identify and describe the population exposed to various contaminated environmental media. Depending on the characteristics of available toxicological data, it may be appropriate to describe the exposed population by other characteristics such as species, race-age-sex distribution, and health status.

8. Integrated Exposure Analysis

The integrated exposure analysis combines the estimation of environmental concentrations (sources and fate information) with the description of the exposed population to yield exposure profiles. Data should be provided on the size of the exposed populations; duration, frequency, and intensity of exposure; and routes of exposure. Exposures should be related to sources.

For more detailed assessments, the estimated environmental concentrations should be considered in conjunction with the geographic distribution of the human and environmental populations. The behavioral and biological characteristics of the exposed populations should be considered and the exposures of populations to various concentration profiles should be estimated. The results can be presented in tabular or graphic form, and an estimate of the uncertainty associated with them should be provided.

a. *Calculations of Exposure. The calculation of exposure involves two major aspects:*

(1) Identification of the Exposed Population and Critical Elements of the Ecosystem.

The estimate of environmental concentrations also should give the geographical areas and environmental media contaminated. The stated purpose of the assessment should have prescribed the human and environmental subjects for which exposures are to be calculated. If the subjects are not listed, the contaminated geographical areas and environmental media can be evaluated to determine subject populations. The degree of detail to be used in defining the exposed population distribution depends on the concentration gradient over geographic areas.

(2) Identification of pathways of exposure.

(a) Identification and description of the routes by which the substances travel from production site, through uses, through environmental releases/sources, through transport and fate processes, to the target population.

(b) Quantitative estimates of the amounts of the chemical following each exposure pathway. Such estimates allow the various pathways to be put in the perspective of relative importance.

From the geographic and tempral distribution of environmental concentrations, the exposed population, the behavioral characteristics, and the critical elements of the ecosystem, exposure distributions can be estimated. The results of exposure calculation should be presented in a format that is consistent with the requirements of the dose-response functions which may later be used in a risk assessment. For example, when health risks caused by exposure over extended durations are considered, average daily exposure over the duration of exposure usually is calculated. When lifetime risks are considered, average daily exposure over a lifetime usually is calculated. In contrast, when health risks caused by exposures over short durations are considered, exposure rates are calculated over short time intervals to ensure that peak risks are defined. Many exposure assessments are based on the average exposure occurring over the exposure period. The range of possible exposures is usually divided into intervals, and the exposures within each interval are counted. The results can be presented in a tabular form or as a histogram.

The population residing in a specific geographic area may be exposed to a substance from several exposure routes. For each exposure route, exposure of individuals in these populations may be determined by summing the contribution of all sources to the exposure route. When exposures involve more than one exposure route, the relative amounts of a substance absorbed is usually route dependent. Consequently, total absorbed dose estimates must account for these differences. Because EPA regulates sources of releases, the contribution to exposures from each type of source being considered should be displayed. Exposure estimates should be presented for each significant exposure route (i.e., those routes consistent with the regulatory purpose), and the results should be tabulated in such a way that total externally applied and absorbed dose can be determined.

b. *Human Dosimetry and Monitoring.* Biological monitoring of human body fluids and tissues for substances or their metabolites can be used to estimate current or past exposure to chemicals. When analytical methods are available, chemicals that have been absorbed into the body can be measured in body tissue and fluid. Such measurements can be used to estimate exposure. However, the substances to which humans are exposed are highly variable in the degree to which they leave in the body reliable indicators of exposure. Furthermore, although a compound may be relatively easy to detect in body tissue, for some compounds, attributing body burdens to specific environmental releases may be difficult because of limited ability to obtain environmental monitoring data.

c. *Development of Exposure Scenarios and Profiles.* Depending on the scope of the exposure assessment, the total exposure may be fractionated into one or more "exposure scenarios" to facilitate quantification. As an example, Table 1 lists seven very broad scenarios: Occupational, Consumer, Transportation, Disposal, Food, Drinking Water, and Ambient. For each of the scenarios, the major topics necessary to quantify exposure include sources, pathways, monitoring, and population

characteristics. Investigation of only one scenario may be necessary for the scope of some assessments. For example, a pesticide application exposure assessment may consider the occupational scenario which would address the exposure to applicators and populations in the vicinity of the site. An exposure assessment around a hazardous waste site may focus on the disposal scenario. The exposure assessment also may consider other scenarios. The more extensive and comprehensive the scope, the more scenarios are usually involved.

TABLE 1. EXPOSURE ASSESSMENT NEEDS FOR VARIOUS EXPOSURE SCENARIOS

Exposure scenario	Source needs	Fate needs	Population characteristics needs	Monitoring needs
Occupational (chemical production)	Site/plant locations in-plant/on-site materials balance.	Physical and chemical properties models.	Workers, families, population around sites/plants.	In-plant/on-site releases, ambient levels surrounding site/plants, human monitoring.
Consumer (direct use of chemical or inadvertent use).	Consumption rates, distribution patterns amounts in products.	Physical and chemical properties, shelf life release rates, models.	Consumers	Levels in products releases.
Transportation/storage/spills	Patterns of distribution and transportation; models for spills.	Physical and chemical properties, environmental fate models.	Storage, transportation workers, general population in area.	Releases, ambient levels.
Disposal (include incineration, land-fill).	Materials balance around disposal method, efficiency, releases to environment.	Fate within disposal process; environmental fate of releases; models.	Workers at site of disposal, general population around site.	Releases, levels at various points within process, ambient levels.
Food	Food chain, packaging, additives	Food chain models, fate during preparation or processing of food.	General population, nonhuman population.	Levels in food, feedstuff; food chain sampling.
Drinking water	Groundwater, surface water, distribution system.	Leach rates from pipes, chlorination processes, fate in water; models.	General population	Levels in drinking water, groundwater, surface water, treatment plants.
Ambient	Releases to environment; air, land, water.	Environmental fate models	General population, nonhuman population.	Ambient Air, water, soil, etc.; human monitoring.

It will usually be advantageous in performing an exposure assessment to identify exposure scenarios, quantify the exposure in each scenario, and then integrate the scenarios to estimate total exposure. In this "integrated exposure analysis," summation of independent exposures from different scenarios (keeping exposure routes separate) often will result in a breakout of exposure by subpopulations, since the individual scenarios usually treat exposure by subpopulation. Therefore, the integration of the scenarios, or integrated exposure analysis, will often result in an exposure profile.

For each exposed subpopulation, exposure profiles should include the size of the group, the make-up of the group (age, sex, etc.), the source of the agent, the exposure pathways, the frequency and the intensity of exposure by each route (dermal, inhalation, etc.), duration of exposure, and the form of the agent when exposure occurs. Assumptions and uncertainties associated with each scenario and profile should be clearly discussed.

d. *Evaluation of Uncertainty.* (1) *Introduction.* Often an exposure assessment progresses through several stages of refinement. The purpose of these Guidelines is to present methods appropriate for characterization of uncertainty for assessments at various stages of refinement, from assessments based upon limited initial data to those based upon extensive data.

The appropriate method for characterizing uncertainty for an exposure assessment depends upon the underlying parameters being estimated, the type and extent of data available, and the estimation procedures utilized. The uncertainty of interest is always with regard to the population characteristic being estimated. For example, when the population distribution of exposures is being estimated, characterization of uncertainty addresses the possible differences between the estimated distribution of exposure and the true population distribution of exposure.

An exposure assessment quantifies contact of a substance with affected population members (human or nonhuman subjects). The measure of contact (e.g., environmental level of absorbed dose) depends upon what is needed to predict risk. An integrated exposure assessment quantifies this contact via all routes of exposure (inhalation, ingestion, and dermal) and all exposure pathways (e.g., occupational exposure, exposure from consumption of manufactured goods, etc.). The exposed-population generally is partitioned into subpopulations such that the likely exposure of all members of a subpopulation is attributable to the same sources. The exposure for each member of a subpopulation is then the sum of exposures over a fixed set of sources and pathways. The measured or estimated exposures for members of a subpopulation are ideally used to estimate the subpopulation distribution of exposure or characteristics thereof. However, a lack of sufficient information sometimes precludes estimation of the subpopulation distributions of exposure and only summary measures of this distribution, such as the mean, minimum, maximum, etc., are estimated. In each case characterization of uncertainty for the exposure assessment primarily addresses limitations of the data and the estimation procedures. The proportions of the population members in the individual subpopulations are usually estimated and can be used (by combining estimated distributions for the subpopulations) to estimate the distribution of exposure for the total population. Uncertainty concerning the sizes of the subpopulations should be addressed by discussing limitations of the data and estimation methods as well as by tabulating confidence interval estimates for the population sizes whenever possible.

(2) *Assessments Based Upon Limited Initial Data.* The initial exposure assessment for a substance may be based upon limited data for exposure and/or input variables for an exposure prediction model (i.e., an equation that expresses exposure as a function of one or more input variables). These data might be either extant data or data produced by an initial small-scale study. The initial limited data frequently are insufficient to permit estimation of the entire distribution of exposure. Instead, summary measures of this distribution, such as the mean, minimum, and maximum, are usually estimated.

If the assessment is based upon measured exposures, the methods used to characterize uncertainty depend mainly upon whether or not the data result from a probability sample for which the probability of inclusion is known for each sample member. Characterization of uncertainty for an assessment based upon a probability sample of exposures is discussed later in section 8. d. (5). If the measured exposures are not based upon a probability sample, acknowledgement

that no strictly valid statistical inferences can be made beyond the units actually in the sample is one aspect of the characterization of uncertainty. If inference procedures are implemented, the assumptions upon which these inferences are based (e.g., treatment of the sample as if it was a simple random sample, or assumption of an underlying model) should be explicitly stated and justified. The data collection methods and inherent limitations of the data should also be discussed.

An initial exposure assessment also may be based upon limited data, such as estimated ranges, for input variables for an exposure prediction model. The exposure prediction model would be derived from a postulated exposure scenario that describes the pathways from sources to contact with population members. If the data were only sufficient to support estimates of the ranges of the input variables, the exposure assessment might be limited to a sensitivity analysis. The purpose of the sensitivity analysis would be to identify influential model input variables and develop bounds on the distribution of exposure. A sensitivity analysis would estimate the range of exposures that would result as individual model input variables were varied from their minimum to their maximum possible values with the other input variables held at fixed values, e.g., their midranges. The overall minimum and maximum possible exposures usually would be estimated also. For an exposure assessment of this type, the uncertainty would be characterized by describing the limitations of the data used to estimate plausible ranges of model input variables and by discussing justification for the model. Justification of the model should include a description of the exposure scenario, choice of model input variables, and the functional form of the model. Sensitivity to the model formulation also can be investigated by replicating the sensitivity analysis for plausible alternative models.

If the maximum possible exposure estimated by the sensitivity analysis presented no significant health risk, there might be no need to refine the assessment. If both the minimum and maximum exposures presented a potentially significant health risk, it would be known that the exposure scenario represented a significant health problem without refining the assessment. When the minimum exposure estimate does not present a potentially significant health risk and maximum dose, then greater importance is placed on choosing a summary parameter of the exposure distribution (e.g., the mean or percentile) as the basis for a regulatory decision. Refining the exposure assessment to estimate the distribution of exposure permits selection of any summary parameter (minimum, maximum, mean, or percentile, etc.) as the basis for regulatory decision.

The sensitivity analysis can be enhanced by computing the predicted exposures that result from all possible input variable combinations. If each input variable has only a finite set of possible values, the set of all possible combinations of the input variables can be formed, and the predicted exposure can be computed for each combination. These exposure predictions can be used to form a distribution of exposures by counting the number of occurrences of each exposure level or interval of exposures. This is equivalent to estimating the distribution of exposures that results from treating all input variable combinations as equally likely. This procedure can also be applied by discretizing continuous input variables and representing them by equally-spaced points. In the limit, as the equal spaces become small and the number of points becomes large, the distribution of exposure that results from counting occurrences of exposure levels is equivalent to estimating the distribution of exposures that results from statistically-independent, continuous input variables with uniform distributions on the estimated ranges. This estimated distribution of exposure values can be produced by the methods of mathematical statistics or Monte Carlo simulation. The Monte Carlo method consists of randomly generating input variate values and using these to compute corresponding exposure levels, generating an exposure distribution via many iterations. Interpretation of statistics based upon this exposure distribution would be in terms of the equally likely input variable combinations. For example, the 95th percentile of this distribution would be the exposure level exceeded by only 5% of the exposures resulting from treating all combinations of input variable values as equally likely. Although this distribution of exposures cannot be interpreted as an estimate of the population distribution (unless the input variables actually are statistically independent and uniformly distributed), it provides additional information for making regulatory decisions. Characterization of uncertainty would include a discussion of limitations of the data and justification for the model as discussed above. Sensitivity to model formulation could also be investigated by estimating the distribution of exposure that results from using the same uniform input variable distributions with plausible alternative models and comparing the estimated percentiles.

(3) *Assessments Based Upon Subjective Estimates of Input Variable Distributions.* If a model has been formulated that expresses exposure as a function of one or more input variables, the methods of mathematical statistics or Monte Carlo simulation can be used to estimate the population distribution of exposure from an estimate of the joint distribution of the model input variables. Ideally model input variables should be represented by empirically validated probability distributions. In some cases, it may be possible to formulate an estimate of the joint distribution of model input variables from discussions with subject-matter experts (e.g., via histograms for statistically-independent input variables). The estimated population distribution of exposure will be equivalent to the distribution discussed in section 8. d. (2) for equally likely combinations of input variable values only when the input variable distributions supported are independent uniform distributions. When qualitative knowledge of input variable distributions is used to estimate the population distribution of exposure, uncertainty is characterized by discussing justification for the presumed model and input variable distributions. Alternative models and/or alternative input variable distributions also should be discussed. Sensitivity to these alternatives can be investigated by estimating the distributions of exposure that result from plausible alternatives and comparing the percentiles of the estimated exposure distributions. All available data, even if data are limited, should be used to validate the presumed input variable distributions and the predicted distribution of exposure.

(4) *Assessments Based Upon Data for Model Input Variables.* The exposure assessment based upon an estimate of the joint probability distribution for model input variables can be refined by collecting sample survey data for model input variables for a sample of population members. The population distribution of exposure can then be estimated by computing the expected exposure for each sample member based upon the model. These expected exposures can be used to directly compute confidence interval estimates for percentiles of the exposure

distribution. Alternatively, the sample survey data can be used to compute joint confidence interval estimates for percentiles of the input variable distribution, which can then be used to generate confidence interval estimates for percentiles of the exposure distribution. In either case, the interval estimates for percentiles of the exposure distribution are a useful quantitative characterization of uncertainty.

Characterization of uncertainty for the exposure assessment would contain a thorough discussion of limitations of the data and justification for the model used to compute expected exposures. The design of the sample survey used to produce the data base should also be discussed. If a probability sample were not used, the lack of a probability sample would be an additional source of uncertainty. Any assumptions used in computing the confidence interval estimates, such as independence of model input variables, should be explicitly stated and justified. Sensitivity to model formulation can be investigated by estimating the distribution of exposure for plausible alternative models and comparing the estimated percentiles, if sample survey data have been collected for the input variables of the alternative models. Appropriate available data for exposure should be used to validate the predicted distribution of exposure. If specific probability distributions have been presumed for any model input variables, the data for these variables should be used to test for goodness of fit for these distributions.

(5) *Assessments Based Upon Data for Exposure.* A major reduction in the uncertainty associated with an exposure assessment can be achieved by directly measuring the exposure for a sufficiently large sample of members of the affected population. This reduction in uncertainty is achieved by eliminating the use of a model to predict exposure. The measured exposure levels can be used to directly estimate the population distribution of exposure and confidence interval estimates for percentiles of the exposure distribution. Direct confidence interval estimates also can be computed for other characteristics of the exposure distribution, such as the mean exposure.

These confidence interval estimates are then the primary characterization of uncertainty for the exposure assessment. Limitations of the data and design of the sample survey used to collect the data also should be discussed. If the sample was not a probability sample, this would again be an additional source of uncertainty.

(6) *Summary.* A summary of the primary methods recommended for characterizing uncertainty in exposure assessments is presented in Table 2. Virtually all exposure assessments, except those based upon measured exposure levels for a probability sample of population members, rely upon a model to predict exposure. The model may be any mathematical function, simple or complex, that expresses an individual's exposure as a function of one or more input variables. Whenever a model that has not been validated is used as the basis for an exposure assessment, the uncertainty associated with the exposure assessment may be substantial. The primary characterization of uncertainty is at least partly qualitative in this case, i.e., it includes a description of the assumptions inherent in the model and their justification. Plausible alternative models should be discussed. Sensitivity of the exposure assessment to model formulation can be investigated by replicating the assessment for plausible alternative models.

TABLE 2.—SUMMARY OF PRIMARY METHODS FOR CHARACTERIZING UNCERTAINTY FOR EXPOSURE ASSESSMENTS

Type and extent of data	Population characteristic being estimated	Primary methods for characterizing uncertainty	
		Qualitative methods	Quantitative methods
Measured exposures for a large sample of population members.	Distribution of exposure	1. Limitations of the survey design and measurement techniques.	1. Confidence interval estimates for percentiles of the exposure distribution. 2. Goodness of fit for exposure models, if any have been postulated.
Measured exposures for a small sample of population members.	Summary parameter(s) of the exposure distribution, e.g., mean or a percentile.	1. Limitations of the survey design and measurement techniques.	1. Confidence interval estimates for the summary parameter(s). 2. Goodness of fit for exposure models, if any have been postulated.
Measured model input variables for a large sample of population members.	Distribution of exposure	1. Limitations of the survey design and measurement technique. 2. Validity of the exposure model	1. Confidence interval estimates for percentiles of the exposure distribution. 2. Goodness of fit for input variable distribution functions, if any have been postulated. 3. Estimated distribution of exposure based upon alternative models.
Estimated distributions of model input variables.	Distribution of exposure	1. Validity of the exposure model 2. Limitations of the data or other basis for the input variable distributions.	1. Confidence interval estimates for percentiles of the exposure distribution. 2. Goodness of fit for input variable distributions, if input variable data are available. 3. Estimated distribution of exposure based upon alternative models.
Limited data for model input variables	Minimum, maximum, and range of the exposure distribution.	1. Limitations of the data 2. Validity of the exposure model	If input variable data are very limited, e.g., some extent data collected for other purposes, quantitative characterization of uncertainty may not be possible.

When an exposure assessment is based upon directly measured exposure levels for a probability sample of population members, uncertainly can be greatly reduced and described quantitatively. In this case, the primary sources of uncertainty are measurement errors and sampling errors. The effects of these sources of error are measured quantitatively by confidence interval estimates of percentiles of the exposure distribution. Moreover, the sampling errors can be limited by taking a large sample.

Whenever the latter is not feasible, it is sometimes possible to obtain at least some data for exposure and model input variables. These data should be used to assess goodness of fit of the model and/or presumed distributions of input variables. This substantially reduces the amount of quantitative uncertainty for estimation of the distribution of exposure and is strongly recommended. It is recognized, however, that it may not be feasible to collect such data.

9. References

The references should contain a listing of all reports, documents, articles, memoranda, contacts, etc. that have been cited in the report.

10. Appendices

The appendices may contain such items as memoranda and letters that are not readily accessible, other tables of monitoring data, detailed lists of emission sources, detailed tables of exposures, process flow diagrams, mathematical model formulations, or any other item that may be needed to describe or document the exposure assessment.

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Part VII

Environmental Protection Agency

Proposed Guidelines for Carcinogen Risk Assessment; Request for Comments

ENVIRONMENTAL PROTECTION AGENCY

[FRL-2706-4]

Proposed Guidelines for Carcinogen Risk Assessment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed Guidelines for Carcinogen Risk Assessment and Request for Comments.

SUMMARY: The U.S. Environmental Protection Agency is proposing Guidelines for Carcinogen Risk Assessment (Guidelines). These Guidelines are proposed for use within the policy and procedural framework provided by the various statutes that EPA administers to guide Agency analysis of carcinogenicity data. We solicit public comment and will take public comment into account in revising these Guidelines. These Guidelines will be reviewed by the Science Advisory Board in meetings now tentatively scheduled for April 1985.

These proposed Guidelines were developed as part of a broad guidelines development program under the auspices of the Office of Health and Environmental Assessment (OHEA), located in the Agency's Office of Research and Development. Consonant with the role of OHEA's Carcinogen Assessment Group (CAG) as the Agency's senior health committee for carcinogenicity assessment, the Guidelines were developed by an Agency-wide working group chaired by the Chairman of CAG.

DATE: Comments must be postmarked by January 22, 1985.

ADDRESS: Comments may be mailed or delivered to: Dr. Robert McGaughy, Carcinogen Assessment Group (RD-689), Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, 401 M Street SW., Washington, D.C. 20460.

FOR FURTHER INFORMATION CONTACT: Dr. Robert McGaughy, Telephone: 202-382-5952.

SUPPLEMENTARY INFORMATION: This is the first proposed revision of the 1976 Interim Procedures and Guidelines for the Health Risk Assessment of Suspected Carcinogens (Federal Register 41:21402-21405, 1976). This revision incorporates concepts and approaches to carcinogen assessment that have been developed during the last eight years. These proposed revised Guidelines describe salient principles for evaluating the nature and magnitude of the cancer hazard from suspect carcinogens and general framework to be followed in developing analyses of carcinogenic risk.

These Guidelines were sent to 38 scientists in the field of carcinogenesis from universities, environmental groups, industry, labor, and governmental agencies. We have decided to delay incorporating suggestions from the 25 reviewers who submitted comments into the Guidelines published here until comments submitted during this public comment period are received.

References and supporting documents used in the preparation of these Guidelines as well as comments received are available for inspection and copying at the Public Information Reference Unit (202-382-5926), EPA Headquarters Library, 401 M Street SW., Washington, DC, between the hours of 8:00 and 4:30 p.m.

Dated: November 9, 1984.

William D. Ruckelshaus,

Administrator.

Contents

I. Introduction

This is the first revision of the 1976 Interim Procedures and Guidelines for Health Risk Assessments of Suspected Carcinogens (U.S. EPA, 1976; Albert et al., 1977). The impetus for this revision is the need to incorporate into these Guidelines the concepts and approaches to carcinogen risk assessment that have been developed during the last eight years. The purpose of these Guidelines is to promote quality and consistency of carcinogen risk assessments within the EPA and to inform those outside the EPA about its approach to carcinogen risk assessment. These Guidelines emphasize the broad but essential aspects of risk assessment that are needed by the experts in the various disciplines required (e.g., toxicology, pathology, pharmacology, and statistics) for carcinogen assessment. Guidance is given in general terms since the science of carcinogenesis is in a state of rapid advancement, and overly specific approaches may rapidly become obsolete.

These Guidelines describe the general framework to be followed in developing an analysis of carcinogenic risk and some salient principles to be used in evaluating the quality of data and in formulating judgments concerning the nature and magnitude of the cancer hazard from suspect carcinogens.

A summary of the current state of knowledge in the field of carcinogenesis and a statement of broad scientific principles of carcinogen risk assessment, which was developed by the Office of Science and Technology Policy (OSTP, 1984), forms an important basis for these Guidelines; the format of these Guidelines is similar to that proposed by the National Research Council (NRC) of the National Academy of Sciences in a report entitled "Risk Assessment in the Federal Government" (NRC, 1983).

These Guidelines are to be used within the policy framework already provided by applicable EPA statutes and do not alter such policies. These Guidelines provide general directions for analyzing and organizing available data. They do not imply that one kind of data or another is a prerequisite for regulatory action to control, prohibit, or allow the use of a carcinogen. The analysis of carcinogenic risks will be carried out independently from considerations of the socioeconomic consequences of regulatory action.

Regulatory decisionmaking involves two components: Risk assessment and risk management. Risk assessment defines the adverse health consequences of exposure to toxic agents; risk management combines the risk assessment with the directives of the enabling regulatory legislation, together with socioeconomic, technical, political, and other considerations, to reach a decision as to whether or how much to control future exposure to the suspected toxic agents.

Risk assessment includes one or more of the following components: hazard identification, dose-response

assessment, exposure assessment, and risk characterization (NRC, 1983).

Hazard identification is a qualitative risk assessment, dealing with the process of determining whether exposure to an agent has the potential to increase the incidence of cancer. For purposes of these Guidelines, malignant and benign tumors are used in the evaluation of the carcinogenic hazard. The hazard identification component qualitatively answers the question of how likely an agent is to be a human carcinogen.

Traditionally, quantitative risk assessment has been used as an inclusive term to describe all or parts of dose-response assessment, exposure assessment, and risk characterization. Quantitative risk assessment can be a useful general term in some circumstances, but the more explicit terminology is usually preferred. The dose-response assessment defines the relationship between the dose of an agent and the probability of induction of a carcinogenic effect. This component usually entails an extrapolation from the generally high doses administered to experimental animals or exposures noted in epidemiologic studies to the exposure levels expected from human contact with the agent in the environment; it also includes considerations of the validity of these extrapolations.

The exposure assessment identifies populations exposed to the agent, describes their composition and size, and presents the types, magnitudes, frequencies, and durations of exposure to the agent.

In risk characterization, the outputs of the exposure assessment and the dose-response assessment are combined to estimate quantitatively some measure of the carcinogenic risk. As part of risk characterization, a summary of the strengths and weaknesses in the hazard identification, dose-response assessment, exposure assessment, and the public health risk estimates are presented. Major assumptions, scientific judgments, and, to the extent possible, estimates of the uncertainties embodied in the assessment are also presented, distinguishing clearly between fact, assumption, and science policy.

II. Hazard Identification (Qualitative Risk Assessment)

A. Overview

The qualitative assessment or hazard identification part of risk assessment contains a review of the relevant biological and chemical information bearing on whether or not an agent may pose a carcinogenic hazard. Since chemical agents seldom occur in a pure state and are often transformed in the body, the review should include information on contaminants, degradation products, and metabolites.

Studies are evaluated according to sound biological and statistical considerations and procedures. These have been described in several publications (Interagency Regulatory Liaison Group, 1979; OSTP, 1984; Peto et al., 1980; Mantel, 1980; Mantel and Haenszel, 1959; Interdisciplinary Panel on Carcinogenicity, 1984; National Center for Toxicological Research, 1981; National Toxicology Program, 1984; U.S. EPA, 1983a; 1983b; 1983c). Results and conclusions concerning the agent, derived from different types of information, whether indicating positive or negative responses, are melded together into a weight-of-evidence determination. The strength of the evidence supporting a potential human carcinogenicity judgment is developed in a weight-of-evidence stratification scheme.

B. Elements of Hazard Identification

1. Physical-Chemical Properties and Routes and Patterns of Exposure

Parameters relevant to carcinogenesis, including physical state, physical-chemical properties, and exposure pathways in the environment should be described.

2. Structure-Activity Relationships

This section should summarize relevant structure-activity correlations that support the prediction of potential carcinogenicity.

3. Metabolic and Pharmacokinetic Properties

This section should summarize relevant metabolic information. Information such as whether the agent is direct-acting or requires conversion to a reactive carcinogenic (e.g., an electrophilic) species, metabolic pathways for such conversions, macromolecular interactions, and transport in, fate in, and excretion from the body as well as species differences in metabolism should be discussed.

4. Toxicologic Effects

Toxicologic effects other than carcinogenicity (e.g., suppression of the immune system, endocrine disturbances, organ damage), which are relevant to the evaluation of carcinogenicity, should be summarized. Prechronic and chronic toxicity evaluations, as well as other test results, may yield information on target organ effects, pathophysiological reactions, and preneoplastic lesions that bear on the evaluation of carcinogenicity. Dose-response and time-to-response analyses of these reactions may also be helpful.

5. Short-Term Tests

Tests for point mutations, numerical and structural chromosome aberrations, DNA damage/repair, and *in vitro* transformation provide supportive evidence of carcinogenicity and may give information on potential carcinogenic mechanisms. A range of tests from each of the above end points helps to characterize an agent's response spectrum.

Short-term *in vivo* and *in vitro* tests that can give indication of initiation and promotion activity may also provide supportive evidence for carcinogenicity.

6. Long-Term Animal Studies

Criteria for the technical adequacy of animal carcinogenicity studies have been published (e.g., U.S. Food and Drug Administration, 1982; Interagency Regulatory Liaison Group, 1979; National Toxicology Program, 1984; OSTP, 1984; U.S. EPA, 1983a; 1983b; 1983c; Peron et al., 1980; Mantel, 1980) and should be used to judge the acceptability of individual studies.

The strength of the evidence that an agent is carcinogenic increases with the increase in number of tissue sites affected by the agent; the increase in number of animal species, strains, and sexes showing a carcinogenic response; the occurrence of clear-cut dose-response relationships as well as a high level of statistical significance of the increased tumor incidence is treated with respect to control groups; the dose-related shortening of the time-to-tumor occurrence or time to death with tumor, and a dose-related increase in the proportion of tumors that are malignant.

Long-term animal studies at or near the maximum tolerated dose level (MTD) are used to ensure an adequate power for the detection of carcinogenic activity. Negative long-term animal studies at exposure levels above the MTD or partial lifetime exposures at the MTD may not be acceptable because of toxicity, or if animal survival is so impaired that the sensitivity of the study is significantly reduced below that of a conventional chronic animal study at the MTD. Positive studies at levels above the MTD should be carefully reviewed to ensure that the responses are not due to factors which do not operate at exposure levels below the MTD. Evidence indicating that high-dose testing produces tumor responses by indirect mechanisms that may be

unrelated to effects at lower doses should be dealt with on an individual basis.

The mechanism of the carcinogenic responses under conditions of the experiment should be reviewed carefully as it relates to the relevance of the evidence to human carcinogenic risks (e.g., the occurrence of bladder tumors in the presence of bladder stones and injection site sarcomas). Interpretation of animal studies is aided by the review of target organ toxicity and other effects (e.g., changes in the immune and endocrine systems) that may be noted in prechronic or other toxicological studies. Time and dose-related changes in the incidence of preneoplastic lesions may also be helpful in interpreting animal studies.

Historical control data are often valuable and could be used along with concurrent control data in the evaluation of carcinogenic responses. For the evaluation of rare tumors, even small tumor responses may be significant compared to historical data. In the case of tumors with relatively high spontaneous rates, a response that is significant with respect to the experimental control group becomes questionable if the historical control data indicate that the experimental control group had an unusually low background incidence.

Agents that are positive in long-term animal experiments and also show evidence of promoting or cocarcingenic activity in specialized tests should be considered as complete carcinogens unless there is evidence to the contrary. Agents that show positive results in special tests for initiation, promotion, or cocarcingenicity and no indication of tumor response in well-conducted and well-designed long-term animal studies should be dealt with on an individual basis.

There are widely diverging scientific views (OSTP, 1984; Ward et al. 1979a; 1979b; Tomatis, 1977; Nutrition Foundation, 1983) about the validity of mouse liver tumors when such tumors occur in strains with high spontaneous background incidence and when they constitute the only tumor response to an agent. These Guidelines take the position that the mouse-liver-only tumor response, when other conditions for a classification of "sufficient" evidence in animal studies are met, should be considered as "sufficient" evidence of carcinogenicity with the understanding that this classification could be changed to "limited" if warranted when a number of factors such as the following are observed: The occurrence of tumors only in the highest dose group and/or only at the end of the study; no substantial dose-related increase in the proportion of tumors that are malignant; the occurrence of tumors that are predominately benign, showing no evidence of metastases or invasion; no dose-related shortening of the time to the appearance of tumors; negative or inconclusive results from a spectrum of short-term tests for mutagenic activity; the occurrence of excess tumors only in a single sex.

Positive carcinogenic responses in one species/strain/sex are not generally negated by negative results in other species/strain/sex. Replicate negative studies that are essentially identical in all other respects to a positive study may indicate that the positive results are spurious.

Evidence for carcinogenic action should be based on the observation of statistically significant tumor responses in specific organs or tissues. Appropriate statistical analysis should be performed on data from long-term studies to help determine whether the effects are treatment-related or possibly due to chance. These should at least include a statistical test for trend, including appropriate correction for differences in survival. The weight to be given to the level of statistical significance (the p-value) and to other available pieces of information is a matter of overall scientific judgment. A statistically significant excess of tumors of all types in the aggregate, in the absence of a statistically significant increase of any individual tumor type should be regarded as minimal evidence of carcinogenic action unless there are persuasive reasons to the contrary.

7. Human Studies

Epidemiologic studies provide unique information about the response of humans who have been exposed to suspect carcinogens. Descriptive epidemiologic studies are useful in generating hypotheses and providing supporting data, but can rarely be used to make a causal inference. Analytical epidemiologic studies of the case-control or cohort variety, on the other hand, are especially useful in assessing risks to exposed humans.

Criteria for the adequacy of epidemiologic studies are well recognized and include factors such as the proper selection and characterization of exposed and control groups, the adequacy of duration and quality of follow-up, the proper identification and characterization of confounding factors and bias, the appropriate consideration of latency effects, and the valid ascertainment of the causes of morbidity and death.

The strength of the epidemiological evidence for carcinogenicity depends on the magnitude, specificity, and statistical significance of the response and increases rapidly with the number of adequate studies which show the same results on populations exposed to the same agent under different conditions.

It should be recognized that epidemiologic studies are inherently capable of detecting only comparatively large increases in the relative risk of cancer. Negative results from such studies cannot prove the absence of carcinogenic action; however, negative results from a well-designed and conducted epidemiologic study that contains usable exposure data can serve to define upper limits of risk which are useful if animal evidence indicates that the agent is potentially carcinogenic.

C. Weight of Evidence

Evidence of possible carcinogenicity in humans comes primarily from two sources: Long-term animal tests and epidemiologic investigations. Results from these studies are supplemented with information from short-term tests, pharmacokinetic studies, comparative metabolism studies, structure-activity relationships, and other relevant toxicologic studies. The question of how likely an agent is to be a human carcinogen should be answered in the framework of a weight-of-evidence judgment. Judgments about the weight of evidence involve considerations of the quality and adequacy of the data and the kinds of responses induced by a suspect carcinogen. There are three major steps to characterizing the weight of evidence for carcinogenicity: (1) Characterization of the evidence from human studies and from animal studies individually, (2) combination of the characterizations of these two types of data into a final indication of the overall weight of evidence for human carcinogenicity, and (3) evaluation of all supportive information to determine if the overall weight of evidence should be modified.

A system for stratifying the weight of evidence is recommended, and EPA has developed a scheme (see the Appendix). The EPA scheme is modeled after the classification system developed by the International Agency for Research on Cancer (IARC, 1982). In the IARC classification method, the evidence that an agent produces cancer in humans is divided into three categories: Sufficient, limited, and inadequate. A similar characterization of evidence is provided for animal data.

The EPA classification system is, in general, an adaptation of the IARC approach for classifying the weight of

evidence for human data and animal data. The EPA classification system for the characterization of the overall weight of evidence for carcinogenicity (animal, human, and other supportive data) includes: Group A—Carcinogenic to Humans; Group B—Probably Carcinogenic to Humans; C—Possibly Carcinogenic to Humans; Group D—Not Classifiable as to Human Carcinogenicity; and Group E—No Evidence of Carcinogenicity for Humans.

In addition, the following modifications of the IARC approach have been made for classifying human and animal studies. For human studies: (1) The observation of a statistically significant association between an agent and life-threatening benign tumors in humans is included in the evaluation of risks to humans. (2) A "no evidence" category is added. This category indicates that no association was found between exposure and increased risk of cancer in well-conducted, well-designed, independent analytical epidemiologic studies. For animal studies: (1) An increased incidence of combined benign and malignant tumors will be considered to provide sufficient evidence of carcinogenicity if the other criteria defining the "sufficient" category of evidence are met. Benign and malignant tumors will be combined unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same morphologic type. (2) An increased incidence of benign tumors alone as "limited" evidence of carcinogenicity is added. (3) Under specific circumstances, such as the production of neoplasms that occur with high spontaneous background incidence, the evidence may be decreased to "limited" if warranted (e.g., there are widely diverging scientific views regarding the validity of the mouse liver tumors as an indicator of potential human carcinogenicity when this is the only response observed, even in replicated experiments, in the absence of other short-term evidence). (4) A "no evidence" category is also added. This operational category would include substances for which there is no increased incidence of neoplasms in at least two well-designed and well-conducted animal studies of adequate power and dose in different species.

D. Guidance For Quantitative Assessment

The qualitative evidence for carcinogenesis should be discussed for purposes of guiding the dose-response assessment. The guidance should be given in terms of the appropriateness and limitation of specific studies as well as pharmacokinetic considerations that should be factored into the dose-response assessment. The appropriate method of extrapolation should be factored in when the experimental route of exposure differs from that occurring in humans.

Agents that are judged to be in the EPA weight-of-evidence stratification Groups A and B would be regarded as suitable for quantitative risk assessments. The appropriateness of quantifying the risks from agents in Group C, specifically those agents that are at the boundary of Groups C and D, would be judged on a case-by-case basis. Agents that are judged to be in Groups D and E would generally not have quantitative risk assessments.

E. Summary and Conclusion

The summary should present all of the key findings in all of the sections of the qualitative assessment and the interpretive rationale that forms the basis for the conclusion. Uncertainties in the evidence as well as factors that may affect the relevance of the chronic animal study to humans should be discussed. The conclusion should present both the weight-of-evidence ranking and a description that brings out the more subtle aspects of the evidence that may not be evident from the ranking alone.

III. Dose-Response Assessment, Exposure Assessment, and Risk Characterization

After data concerning the carcinogenic properties of a substance have been collected, evaluated, and categorized, it is frequently desirable to estimate the likely range of excess cancer risk associated with given levels and conditions of human exposure. The first step of the analysis needed to make such estimations is the development of the likely relationship between dose and response (cancer incidence) in the region of human exposure. This information on dose-response relationships is coupled with information on the nature and magnitude of human exposure to yield an estimate of human risk. The risk-characterization step also includes an interpretation of these estimates in light of the biological, statistical, and exposure assumptions and uncertainties that have arisen throughout the process of assessing risk.

The elements of dose-response assessment are described in section III.A. Guidance on human exposure assessment is provided in another EPA document (U.S. EPA, 1984); however, section III.B. of these Guidelines includes a brief description of the specific type of exposure information that is necessary for use in carcinogenic risk assessment. Finally, in section III.C. there is a description of the type of information and its interpretation necessary for accurately characterizing risk and the degree to which it can be known.

It should be emphasized that calculation of quantitative estimates of cancer risk does not require that an agent be a human carcinogen. The likelihood that an agent is a human carcinogen is a function of the weight of evidence, as this has been described in the hazard identification section of these Guidelines. It is nevertheless important to present quantitative estimates, appropriately qualified and interpreted, in those circumstances in which there is likelihood that the agent is a human carcinogen. Appropriately qualified quantitative estimates of risk, together with estimates of their uncertainty, are useful in cost-benefit analyses, in setting regulatory priorities, and for evaluating residual risks associated with the application of regulatory controls.

It should be emphasized in every quantitative risk estimation that the results are uncertain. The uncertainties due to experimental and epidemiologic variability as well as uncertainty in the exposure assessment can be important. There are major uncertainties in extrapolating both from animals to humans and from high to low doses. There are important species differences in uptake, metabolism, and organ distribution of carcinogens, as well as species and strain differences in target site susceptibility. Human populations are variable with respect to genetic constitution, diet, occupational and home environment, activity patterns, and other cultural factors. Risk estimates should be presented together with the associated hazard assessment (section III.C.3.) to ensure that there is an appreciation of the weight of evidence for carcinogenicity that underlies the quantitative risk estimates.

A. Dose-Response Assessment

1. Selection of Data

As indicated in section II.D. guidance needs to be given by the individuals doing the qualitative assessment (toxicologists, pathologists, pharmacologists, etc.) to the statisticians doing the quantitative assessment as to the appropriate data to be used in the dose-response assessment. This is determined by the quality of the data, its relevance to human modes of exposure, and other technical details.

If available, estimates based upon human epidemiologic data are preferred. If adequate exposure data exist in a well-designed and conducted negative epidemiologic study, an upper-bound estimate of risk should be used in preference to higher risks estimated from animal data. In the absence of human data, data from a species that responds most like humans should be used, if information to this effect exists. Where, for a given agent, several studies are available which may involve different animal species, strains, and sexes, at several doses and by different routes of exposure, the following approach to selecting the data sets is used. The tumor incidence data are separated according to organ site and tumor type. All biologically and statistically acceptable data sets are presented. The range of the risk estimates is identified with due regard to biological relevance (particularly in the case of animal studies) and appropriateness of route of exposure. Because it is possible that human sensitivity is as high as the most sensitive responding animal species, in the absence of evidence to the contrary, the biologically acceptable data set from long-term animal studies showing the greatest sensitivity should generally be given the greatest emphasis, again with due regard to biological and statistical considerations.

When the exposure route in the species from which the dose-response information is obtained differs from the route occurring in environmental exposures, uncertainties about the dose delivered to the target organs from different exposure media should be explicitly considered, and the assumptions should be carefully stated.

Where two or more significantly elevated tumor sites or types are observed in the same study, extrapolations may be conducted on selected sites or types. These selections will be made on biological grounds. To obtain a total estimate of carcinogenic risk, animals with one or more tumor sites or types showing significantly elevated tumor incidence should be pooled and used for extrapolation; if the tumor sites or types are occurring independently, this procedure is the same as summing the risks from the several kinds of statistically significant tumors. The pooled estimates will generally be used in preference to risk estimates based on single sites or types.

Benign tumors should generally be combined with malignant tumors for risk estimates unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same morphologic type. However, the contribution of the benign tumors to the total risk should be indicated.

2. Choice of Mathematical Extrapolation Model

Since risks at low exposure levels cannot be measured directly either by animal experiments or by epidemiologic studies, a number of mathematical models have been developed to extrapolate from high to low dose. However, different extrapolation models may fit the observed data reasonably well but may lead to large differences in the projected risk at low doses.

No single mathematical procedure is recognized as the most appropriate for low-dose extrapolation in carcinogenesis. When relevant biological evidence on mechanism of action exists, the models or procedures employed should be consistent with the evidence. However, when data and information are limited, as is the usual case given the high degree of uncertainty associated with the selection of a low-dose extrapolation model, specific guidance on model selection is necessary to provide a desirable degree of consistency in risk assessments. The choice of low-dose extrapolation models should be consistent with current understanding of the mechanisms of carcinogenesis and not solely on goodness of fit to the observed tumor data. Although mechanisms of the carcinogenesis process are largely unknown, at least some elements of the process have been elucidated, e.g., linearity of tumor initiation. In further support of a linear model, it has been shown that, if a carcinogenic agent acts by accelerating the same stages of the carcinogenic process that lead to the background occurrence of cancer, the added effect of the carcinogen at low dose is virtually linear. Thus, a model that is linear at low dose is plausible.

The linearized multistage model procedure for low-dose extrapolation (U.S. EPA, 1980) is therefore recommended in most cases unless there is evidence on carcinogenesis mechanisms or other biological evidence that indicates the greater suitability of an alternative extrapolation model, or there is statistical or biological evidence that excludes the use of the linearized multistage model.

It should be emphasized that the linearized multistage model leads to a plausible upper limit to the risk which is consistent with some mechanisms of carcinogenesis. However, such an estimate does not necessarily give a realistic prediction of the risk. In certain cases, the linearized multistage model cannot be used successfully with the observed data as, for example, when the data are nonmonotonic or flatten out at high doses. In these cases it may be necessary to make adjustments to the procedure to achieve low-dose linearity.

When pharmacokinetic or metabolism data are available, or when other substantial evidence on the mechanistic aspects of the carcinogenesis process exists, a different low-dose extrapolation model might be considered more appropriate on biological grounds. When a different model is chosen, the risk assessment should clearly discuss the nature and strength of the evidence that lead to the choice. In most cases, considerable uncertainty will remain concerning response at low doses; therefore, an upper-limit risk estimate using the linearized multistage model should also be presented.

3. Equivalent Exposure Units Among Species

Low-dose risk estimates derived from laboratory animal data extrapolated to humans are complicated by a variety of factors that differ among species and potentially affect the response to carcinogens. Included among these factors are differences between humans and experimental test animals with respect to life span, body size, genetic variability, population homogeneity, existence of concurrent disease, pharmacokinetic effects such as metabolism and excretion patterns, and the exposure regimen.

The usual approach for making interspecies comparisons has been to use standardized scaling factors. Commonly employed standardized dosage scales include mg per kg body weight per day, ppm in the diet or water, mg per m^2 body surface area per day, and mg per kg body weight per lifetime. In the absence of comparative toxicological, physiological, metabolic, and pharmacokinetic data for a given suspect carcinogen, the extrapolation of body weight to the 0.67 power is considered to be appropriate.

B. Exposure Assessment

In order to obtain a quantitative estimate of the risk, the results of the dose-response assessment must be combined with an estimate of the exposures to which the populations of interest are likely to be subject. While the reader is referred to the Proposed Guidelines for Exposure Assessment (U.S. EPA, 1984) for specific details, it is important that the cancer risk assessor and the decision-maker have an appreciation of the impact of the

strengths and weaknesses of exposure assessment on the overall cancer risk assessment process.

At present there is no single approach to exposure assessment that is appropriate for all cases. On a case-by-case basis, appropriate methods are selected to match the data on hand and the level of sophistication required (e.g., preliminary assessment using crude data and worst case assumptions versus a final assessment using extensive monitoring data). The assumptions, approximations, and uncertainties need to be clearly stated because, in some instances, these will have a major effect on the risk assessment.

In general, the magnitude, duration, and frequency of exposure provide fundamental information for estimating the concentration of the carcinogen to which the organism is exposed. These data are generated from monitoring information, modeling results, and/or reasoned estimates. An appropriate treatment of exposure should consider the potential for exposure via ingestion, inhalation, and dermal penetration from relevant sources of exposures. Where feasible, an attempt should be made to assess the dose to the target organ, either through experimental evidence or reasonable assumptions and modeling.

Special problems arise when the human exposure situation of concern suggests exposure regimens, e.g., route and dosing schedule, which are substantially different from those used in the relevant animal studies. Unless there is evidence to the contrary in a particular case, the cumulative dose received over a lifetime, expressed as average daily exposure prorated over a lifetime, is recommended as the appropriate measure of exposure to a carcinogen. That is, the assumption is made that a high dose of a carcinogen received over a short period of time is equivalent to a corresponding low dose spread over a lifetime. This approach becomes more problematical as the exposures in question become more intense but less frequent, especially when there is evidence that the agent has shown dose-rate effects.

An attempt should be made to assess the level of uncertainty associated with the exposure assessment which is to be used in a cancer risk assessment. This measure of uncertainty should be included in the risk characterization (section III.C.) in order to provide the decision-maker with a clear understanding of the impact of this uncertainty on any final quantitative risk estimate.

C. Risk Characterization

1. Options for Numerical Risk Estimates

Depending on the needs of the individual program offices, numerical estimates can be presented in one or more of the following three ways.

a. Unit Risk—Under an assumption of low-dose linearity, the unit cancer risk is the excess lifetime risk due to a continuous constant lifetime exposure of one unit of carcinogen concentration. Typical exposure units include ppm or ppb in food or water, mg/kg/day by ingestion, or ppm or ug/m^3 in air.

b. The Dose Corresponding to a Given Level of Risk—This approach can be useful, particularly when using nonlinear extrapolation models where the unit risk would differ at different dose levels.

c. Individual and Population Risks—Risk may be characterized either in terms of the excess individual lifetime risks or the excess number of cancers produced per year in the exposed population or both.

Irrespective of the options chosen, the degree of precision and accuracy in the numerical risk estimates currently do not permit more than one significant figure to be presented.

2. Concurrent Exposure

In characterizing the risk due to concurrent exposure to several carcinogens, the risks are combined on the basis of additivity unless there is specific information to the contrary. Interactions of cocarcinogens, promoters, and inititators with known carcinogens should be considered on a case-by-case basis.

3. Summary of Risk Characterization

Whichever method of presentation is chosen, it is critical that the numerical estimates not be allowed to stand alone, separated from the various assumptions and uncertainties upon which they are based. The risk characterization should contain a discussion and interpretation of the numerical estimates that affords the risk manager some insight into the degree to which the quantitative estimates are likely to reflect the true magnitude of human risk, which generally cannot be known with the degree of quantitative accuracy reflected in the numerical estimates. The final risk estimate will be generally rounded to one significant figure and will be coupled with the EPA classification of the qualitative weight of evidence. For example, a lifetime individual risk of 2×10^{-4} resulting from exposure to a "possible human carcinogen" (Group C) should be designated as:

2×10^{-4} [C]

This bracketed designation of the qualitative evidence should be included with all numerical risk estimates (i.e., unit risks, which are risks at a specified concentration, or concentrations corresponding to a given risk). Agency statements, such as Federal Register notices, briefings, and action memoranda, frequently include numerical estimates of carcinogenic risk. It is recommended that whenever these numerical estimates are used, the qualitative weight-of-evidence classification should also be included.

IV. Appendix—EPA Classification System for Evidence of Carcinogenicity From Human Studies and From Animal Studies (Adapted From IARC)

A. Assessment of Evidence for Carcinogenicity From Studies in Humans

Evidence of carcinogenicity from human studies comes from three main sources:

1. Case reports of individual cancer patients who were exposed to the agent(s).

2. Descriptive epidemiolcgic studies in which the incidence of cancer in human populations was found to vary in space or time with exposure to the agent(s).

3. Analytical epidemiologic (case-control and cohort) studies in which individual exposure to the agent(s) was found to be associated with an increased risk of cancer.

Three criteria must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias which could explain the association.

2. The possibility of confounding has been considered and ruled out as explaining the association.

3. The association is unlikely to be due to chance.

In general, although a single study may be indicative of a cause-effect relationship, confidence in inferring a causal association is increased when several independent studies are concordant in showing the association, when the association is strong, when there is a dose-response relationship, or when a reduction in exposure is followed by a reduction in the incidence of cancer.

The degrees of evidence for carcinogenicity* from studies in humans are categorized as:

1. Sufficient evidence of

*For purposes of public health protection, agents associated with life-threatening benign tumors in humans are included in the evaluation.

carcinogenicity, which indicates that there is a causal relationship between the agent and human cancer.

2. Limited evidence of carcinogenicity, which indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding, could not adequately be excluded.

3. Inadequate evidence, which indicates that one of two conditions prevailed: (a) There were few pertinent data, or (b) the available studies, while showing evidence of association, did not exclude chance, bias, or confounding.

4. No evidence, which indicates that no association was found between exposure and an increased risk of cancer in well-designed and well-conducted independent analytical epidemiologic studies.

5. No data, which indicates that data are not available.

B. Assessment of Evidence for Carcinogenicity From Studies in Experimental Animals

These assessments are classified into five groups:

1. Sufficient evidence+ of carcinogenicity, which indicates that there is an increased incidence of malignant tumors or combined malignant and benign tumors§: (a) In multiple species or strains; or (b) in multiple experiments (preferably with different routes of administration or using different dose levels); or (c) to an unusual degree with regard to incidence, site or type of tumor, or age at onset. Additional evidence may be provided by data on dose-response effects, as well as information from short-term tests or on chemical structure.

2. Limited evidence of carcinogenicity, which means that the data suggest a carcinogenic effect but are limited because: (a) The studies involve a single species, strain, or experiment; or (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) an increase in the incidence of benign tumors only.

3. Inadequate evidence, which indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect.

4. No evidence, which indicates that there is no increased incidence of neoplasms in at least two well-designed and well-conducted animal studies in different species.

5. No data, which indicates that data are not available.

The categories "sufficient evidence" and "limited evidence" refer only to the strength of the experimental evidence that these agents(s) are carcinogenic and not to the power of their carcinogenic action.

C. Categorization of Overall Evidence

Group A—Human Carcinogen

This category is used only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to the agent(s) and cancer.

Group B—Probable Human Carcinogen

This category includes agents for which the evidence of human carcinogenicity from epidemiologic studies ranges from almost "sufficient" to "inadequate." To reflect this range, the category is divided into higher (Group B1) and lower (Group B2) degrees of evidence. Usually, category B1 is reserved for agents for which there is at least limited evidence of carcinogenicity to humans from epidemiologic studies. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard agents for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans. Therefore, agents for which there is inadequate evidence from human studies and sufficient evidence form animal studies would usually result in a classification of B2.

In some cases, the known chemical or physical properties of an agent and the results from short-term tests allow its transfer from Group B2 to B1.

Group C—Possible Human Carcinogen

This category is used for agents with limited evidence of carcinogenicity in animals in the absence of human data. It includes a wide variety of evidence: (a) Definitive malignant tumor response in a single well-conducted experiment, (b) marginal tumor response in studies having inadequate design or reporting, (c) benign but not malignant tumors with an agent showing no response in a variety of short-term tests for mutagenicity, and (d) marginal responses in a tissue known to have a high and variable background rate.

In some cases, the known physical or cehmical properties of an agent and results from short-term tests allow a transfer from Group C to B2 or from Group D to C.

Group D—Not Classified

This category is used for agent(s) with inadequate animal evidence of carcinogenicity.

Group E—No Evidence of Carcinogenicity for Humans

This category is used for agent(s) that show no evidence for carcinogenicity in at least two adequate animal tests in different species or in both epidemiologic and animal studies.

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+Under specific circumstances, such as the production of neoplasms that occur with high spontaneous background incidence, the evidence may be decreased to "limited" if warranted (e.g., there are widely diverging scientific views regarding the validity of the mouse liver tumor as an indicator of potential human carcinogenicity when this is the only response observed, even in replicated experiments in the absence of short-term or other evidence).

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Part IX

Environmental Protection Agency

Proposed Guidelines for Mutagenicity Risk Assessment; Request for Comments

ENVIRONMENTAL PROTECTION AGENCY

[FRL-2706-9]

Proposed Guidelines for Mutagenicity Risk Assessment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed Guidelines for Mutagenicity Risk Assessment and Request for Comments

SUMMARY: The U.S. Environmental Protection Agency is proposing Guidelines for Mutagenicity Risk Assessment (Guidelines). These Guidelines are proposed for use within the policy and procedural framework provided by the various statutes that EPA administers to guide Agency analysis of mutagenicity data. We solicit public comment and will take public comment into account in revising these Guidelines. These Guidelines will be reviewed by the Science Advisory Board in meetings now tentatively scheduled for April 1985.

These proposed Guidelines were developed as part of a broad guidelines development program under the auspices of the Office of Health and Environmental Assessment (OHEA), located in the Agency's Office of Research and Development. Consonant with the role of OHEA's Reproductive Effects Assessment Group (REAG) as the Agency's senior health committee for mutagenicity assessment, the Guidelines were developed by an Agency-wide working group chaired by the REAG.

DATES: Comments must be postmarked by January 22, 1985.

ADDRESSES: Comments may be mailed or delivered to: Dr. David Jacobson-Kram, Reproductive Effects Assessment Group (RD-689), Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, 401 M Street SW., Washington, DC 20460.

FOR FURTHER INFORMATION CONTACT: Dr. David Jacobson-Kram, Telephone: 202-382-7336.

SUPPLEMENTARY INFORMATION: Public comments received as a result of the proposed guidelines for Mutagenicity Risk Assessment, which was published in the Federal Register [45(221):74984-74988) on November 13, 1980, have been addressed. The guidelines published here reflect the suggestions that were provided during that initial comment period. A new draft of these Guidelines, taking into account the earlier public comments, was recently sent for review to approximately 14 scientists in the field of chemical mutagenesis within government, universities in the United States, and the private sector. Comments received from these reviews, generally favorable, were also taken into account in developing the Guidelines proposed here.

References and supporting documents used in the preparation of these Guidelines as well as comments received are available for inspection and copying at the Public Information Reference Unit (202-382-5926), EPA Headquarters Library, 401 M Street, SW, Washington, DC, between the hours of 8:00 a.m. and 4:30 p.m.

Dated: November 9, 1984.

William D. Ruckelshaus,

Administrator.

Contents

I. Introduction

On November 13, 1980, the U.S. Environmental Protection Agency (EPA) published purposed guidelines for Mutagenicity Risk Assessment (*1*) and solicited comments on those guidelines. The proposed guidelines of 1980 described the procedures that the Agency would follow to evaluate the genetic risks associated with the exposure of humans to chemical mutagens. These procedures incorporated a weight-of-evidence approach that considered the quality and adequacy of all the available data on a chemical substance in order to make qualitative, and, where possible, quantitative evaluations of mutagenic potential. The Agency stated that mutagenicity risk assessments prepared pursuant to the proposed guidelines would be utilized within the requirements and constraints of the applicable statutes that the Agency administers to arrive at regulatory decisions concerning mutagenicity.

The current proposed Guidelines address the comments received in response to the Agency's proposed mutagenicity risk assessment guidelines and provide the basis for the Agency's risk assessments for mutagenicity. These Guidelines, which adopt the general approach set forth in the 1980 proposal, reflect additional changes made in response to the comments and to new scientific information generated since the time of the proposal.

The current proposed Guidelines reflect changes made in response to the public comments to the proposed guidelines of 1980. These changes dealt primarily with the section addressing the weight-of-evidence approach. This section has been expanded to define "sufficient," "suggestive," and "limited" evidence for potential human germ-cell mutagenicity and to include two categories of evidence, "sufficient" and "suggestive" for chemical interaction with the gonads. Also, in the quantitative assessment section, the dominant skeletal and dominant cataract tests have been added to the list of systems for possible use in estimating the magnitude of genetic risks. Other minor changes have been made in the text for clarification.

A draft of the current proposed Guidelines was submitted for review to individuals from industry, educational institutions, enivornmental groups, and other government agencies. These reviews were useful in revising the Guidelines.

The Agency has not attempted to provide in the current proposed Guidelines a detailed discussion of the mechanisms of mutagenicity or of the various test systems that are currently in use to detect mutagenic potential. Background information on mutagenicity and mutagenic test systems is available in "Identifying and Estimating the Genetic Impact of Chemical Environmental Mutagens," National Academy of Sciences (NAS) Committee on Chemical Environmental Mutagens (*2*), as well as in other recent publications(*3, 4*).

For the information of the reviewer, Chapter II discusses the comments that were received in response to the proposed guidelines of 1980 and the Agency's responses to those comments. The current proposed Guidelines for Mutagenicity Risk Assessment, for which comments are currently invited, are described in Chapter III. The Agency anticipates that, as methods for mutagenicity risk assessment are

refined, and more information becomes available in the area of mutagenicity, revisions to these Guidelines may be desirable or necessary.

II. Comments Received From the Federal Register Publication of the Proposed 1980 Guidelines and Agency Responses to These Comments

As stated in the Introduction, the current Guidelines are being proposed to encourage further public comment. For the information of the reviewer, a summary of the public comments received in response to the proposed guidelines of 1980 and the Agency responses to these comments are presented here.

A total of 34 comments were received, 17 from manufacturers of regulated products, eight from associations, four from individuals, three from educational institutions, and one each from a private consulting laboratory and a government agency. Many responses noted that the proposed guidelines of 1980 were timely and appropriate and praised the Agency for initiating procedures for scientific evaluation of mutagenicity data. Other commenters felt that the proposed guidelines were "premature." Various reasons were given for this position: (1) The mechanisms by which mutations occur are not understood; (2) the data bases for many mutagenicity tests are limited, and hence the tests have not been validated; (3) the Agency should wait until the EPA Gene-Tox Program is completed; and (4) epidemiologic studies have failed to document chemically-induced mutations in humans.

It is the opinion of the Agency that there is a need for mutagenicity guidelines because various statutes administered by the Agency provide the authority to regulate chemicals on the basis of mutagenicity. The purpose of the current proposed Guidelines is to promote Agency-wide consistency in the evaluation of mutagenicity data. In response to the specific concerns enumerated above relating to the issue of prematurity, the Agency has concluded that the comments do not provide an adequate basis for delaying the development of mutagenicity guidelines. Specifically, with regard to the first comment that the mechanisms by which mutations occur are not understood, the Agency does not believe that a full understanding of all aspects of these mechanisms is necessary to evaluate the mutagenic potential of chemicals in the environment. Additionally, the comment ignores the extensive body of data on specific chemical DNA adducts, repair processes, and mutational expression that enable description of the mutational process in specific physiochemical terms (2).

With regard to the second comment, the Agency agrees that the data bases for many mutagenicity tests are limited; however, the Agency does not agree that the validity of a test is a function of the size of the data base. Validity is the extent to which a test measures the particular biological end point of interest and should not be confused with sensitivity, the proportion of known mutagens that are positive in a system, or specificity, the proportion of nonmutagens that are negative. Hence, a mutagenesis assay is validated when its ability to detect a heritable genetic change is demonstrated.

In response to the third comment, the Agency does not believe it is necessary to wait for completion of the Gene-Tox Program before issuing guidelines for evaluating mutagenicity data. The Agency acknowledges that future scientific developments can be expected to affect the methods for the evaluation of mutagenicity data. Such developments may stem from phase II of the Gene-Tox Program (which focuses on test applications) as well as from other collaborative activities in basic and applied research. However, the Agency believes that the current Guidelines, as written, can accommodate new information.

With respect to the fourth comment, the Agency does not agree that the failure to identify a chemical as a known human mutagen is justification for not proposing guidelines to evaluate mutagenicity data. Despite the difficulty in translating changes in mutation rate to alterations in disease frequency, the NAS Committee on Chemical Environmental Mutagens has concluded that the net effect of an increase in mutation rate is harmful because almost all mutants with any detectable effect are deleterious (2).

A. Comments on the Introduction

Many commenters on the proposed guidelines of 1980 were critical of the statement, "Since the prospect of curing most heritable diseases caused by mutagens in the near future is unlikely, minimizing exposure to mutagens is among the best available means to protect against further deterioration of the human gene pool." At the present time there is no direct evidence in humans that heritable diseases are being caused by chemical mutagens, and there is no evidence of deterioration of the gene pool. This sentence has been deleted.

Several commenters objected to the statement, "Mutations are largely recognized as being deleterious," and pointed out that many mutations are silent or have no effect. In the current proposed Guidelines, this sentence has been changed to read, "It is generally recognized that most mutations that are phenotypically expressed are in some ways deleterious to the organism carrying them."

One commenter requested an explanation of how mutagenicity guidelines would be administered and requested a statement indicating requirements for genetic toxicology testing in premarket manufacturing notices. The Agency believes that the language in the current proposed Guidelines clearly states that they will be used to assess risks associated with human exposure to chemical mutagens. Requirements for genetic toxicology testing are the responsibility of the appropriate Agency office.

B. Concepts Relating to Heritable Genetic Risk

One commenter objected to the definition of a mutagen because it was not limited to stable and heritable alternations in the DNA. The Agency agrees that the ultimate end point of concern for the purpose of the current proposed Guidelines is heritable and stable mutation. For gene mutations, heritability is an obvious and necessary component, since all tests used to detect gene mutations actually detect mutant cells or organisms that are descendants of the treated cells. The same is not always true for certain cytogenetic end points, such as chromatid breaks, etc., which may be detected in the same cell generation in which they occur. Since these latter end points provide information relevant to heritable mutation, they will be considered in any mutagenicity assessment. As a result, the Agency feels that the general definition of a mutagen as used in these Guidelines is appropriate.

C. Testing Systems

One commenter felt that most cytogenetic end points that are routinely evaluated (e.g., chromosome breaks, micronuclei) are not transmitted, and therefore, are not germane to the issue of heritable mutation. The Agency disagrees. Although it is clear that cells that carry such aberrations generally do not reproduce, other related aberrations (i.e., balanced translocations, inversions, small duplications, and deficiencies) are compatible with cell survival in germ cells and can be transmitted. Additionally, there is no evidence indicating that the non-transmissible aberrations occur by

hanisms different from transmissible rations.

everal commenters requested that Agency establish minimal criteria by ch assays are to be judged for use in assessment determinations. The ncy believes that to list a specific set riteria that must be met for each y before the Agency evaluates data ld be overly restrictive and propriate. Data generated in any em that measures or correlates with e genetic end point may provide e useful information. The Agency eves that the general protocols and eria for data evaluation established he expert committees of the Phase-I e-Tox Program as well as other ess provide sufficient guidance for e planning to conduct mutagenicity .

Weight-of-Evidence Approach

everal commenters suggested that the ght-of-evidence section required ification of the phrase, "positive onse in any two different point ation test systems," because this se may be subject to various rpretations. The Agency agrees that section as proposed may have been ject to misinterpretation. Therefore, current proposed Guidelines define icient evidence of potential human agenicity to include positive onses in any two different gene ation test systems (one of which zed mammalian cells) or positive onses in two different somatic genetic tests (one of which utilizes nmalian cells), coupled with icient evidence of germ-cell raction in both cases. Alternatively, combination of a positive finding in mammalian gene mutation assay one mammalian cytogenetics test sufficient evidence of germ-cell raction also provides sufficient ience of potential human agenicity. The demonstration of itable effects induced in mammalian n cells is by itself sufficient evidence mutagenicity.

fany commenters objected to the erion that considers a chemical agen a potential human germ-cell agen if there is "evidence for the sence of the test substance and/or its abolites in mammalian gonadal ans." First, they pointed out that the sence of a chemical in the testis or ry does not necessarily mean it has cted with germ-cell DNA. Such dies are generally performed with iolabeled chemicals, and it is sible that metabolism of the npound could result in incorporation he radiolabel into normal cellular cromolecules. The Agency recognizes the shortcomings in the various criteria used to determine whether a mutagen interacts with germ-cell DNA. As a result, in the current Guidelines, two categories of such evidence have been adopted. Sufficient evidence that a mutagen interacts in the mammalian gonad will be the demonstration that an agent interacts with germ-cell DNA or other chromatin constituents, or that it induces such end points as unscheduled DNA synthesis, sister chromatid exchange (SCE), or chromosomal aberrations in germinal cells. Suggestive evidence will include adverse gonadal effects following acute, subchronic, or chronic toxicity testing or adverse reproductive effects, such as decreased fertilization index, reduced sperm count, or abnormal sperm morphology.

One commenter suggested that the Agency develop a scale of weighting tests which would place more emphasis on test systems more relevant to human beings. The Agency has explored the possibility of developing such a scale and has concluded that the assignment of fixed values for each test system could be overly simplistic and might not allow for the consideration of such variables as dose range, route of exposure, and magnitude of respone. The Agency believes that the scheme in the current proposed Guidelines, which generally gives greater weight to mammalian rather than submammalian assays and to germ cell rather than somatic cell data, is currently the most appropriate way to evaluate the information from a variety of systems.

E. Quantitative Assessment of Results

Several commenters expressed the opinion that it is not possible to quantitatively express the risk of genetic disease from exposure to a chemical, and therefore no attempt should be made to do so. The Agency does not suggest that it is necessarily possible to generate a numerical estimate of the genetic risk that will result from exposure to any particular chemical. It is well-recognized and documented that the mutational component of certain categories of human genetic disease is not known. However, mutagenicity data have been used to generate semi-quantitative estimates of the impact of ionizing radiation on genetic disease(*5, 6*). The current proposed Guidelines state the Agency's commitment to utilize existing relevant mutagenicity data to give some estimate of potential human mutagenicity. All such estimates will include a careful delineation of the assumptions and uncertainties associated with the assessment.

Many commenters objected to the use of "linear or nonthreshold models" for low-dose extrapolation on point mutation rates. The Agency acknowledges that linearity and the presence or absence of a threshold are separate issues. The Agency will strive to use the most appropriate extrapolation model for risk analysis and will be guided by the available data in this selection. However, it is anticipated that for whole-animal germ-cell assays, few dose points will be available to define a dose-response function. In these situations there is a theoretical basis for a linear, nonthreshold extrapolation provided that no major germ-cell killing (and thus possible cell selection) has occurred(*2, 7*).

One commenter suggested that for quantitative risk it is more appropriate to rely on tests for structural chromosomal aberrations than on gene mutations, particularly since many diseases can be more readily associated with an identifiable chromosome abnormality. The Agency agrees that associations between diseases and specific chromosomal changes can be estimated. This concept is well documented and has been discussed at length in the NAS report(*2*). However, similar estimates can be made for gene mutations, and such techniques have been used for some time for effects of ionizing radiation(*5, 8*). Because the spectrum of mutational effects induced by different chemicals is known to be variable, the Agency believes that it is necessary to perform estimates on all end points.

One commenter objected to the omission of the dominant skeletal and cataract mutation systems for quantitative risk assessment. The Agency recognizes that these dominant mutation systems do have relevance in the preparation of quantitative risk assessment along with specific-locus test systems. The current proposed Guidelines have been modified to include both types of tests.

III. Proposed Guidelines

A. Introduction

This section describes the procedures that the U.S. Environmental Protection Agency will follow in evaluating the potential genetic risk associated with human exposure to existing industrial chemicals and to pesticides. The central purpose of the health risk assessment is to provide a judgment concerning the weight of evidence that an agent is a potential human mutagen with respect to transmitted genetic changes, and, if so, how great an impact it is likely to have on public health. Regulatory

decision making involves two components: Risk assessment and risk management. Risk assessment estimates the potential adverse health consequences of exposure to toxic chemicals; risk management combines the risk assessment with the directives of the enabling regulatory legislation—together with socioeconomic, technical, political, and other considerations—to reach a decision as to whether or how much to control future exposure to the chemicals. The issue of risk management will not be dealt with in these Guidelines.

Risk assessment is comprised of the following components: Hazard identification, dose-response assessment, exposure assessment, and risk characterization(*8*). Hazard identification is the qualitative risk assessment, dealing with the inherent toxicity of a chemical substance. The qualitative mutagenicity assessment answers the question of how likely an agent is to be a human mutagen. The three remaining components comprise quantitative risk assessment, which provides a numerical estimate of the public health consequences of exposure to an agent. The quantitative mutagenicity risk assessment deals with the question of how much mutational damage is likely to be produced by exposure to a given agent under particular exposure scenarios.

In a dose-response assessment, the relationship between the dose of a chemical and the probability of induction of an adverse effect is defined. The component generally entails an extrapolation from the high doses administered to experimental animals or noted in some epidemiologic studies to the low exposure levels expected from human contact with the chemical in the environment.

The exposure assessment identifies populations exposed to toxic chemicals, describes their composition and size, and presents the types, magnitudes, frequencies, and durations of exposure to the chemcials. This component is developed independently of the other components of the mutagenicity assessment and is addressed in separate Agency guidelines(*9*).

In risk characterization, the outputs of the exposure assessment and the dose-response assessment are combined to estimate quantitatively the mutation risk, which is expressed as either estimated increase of generic disease per generation or per lifetime, or the fractional increase in the assumed background mutation rate of humans. In each step of the assessment, the strengths and weaknesses of the major assumptions need to be presented, and the nature and magnitude of uncertainties need to be characterized.

The procedures set forth in these Guidelines will ensure consistency in the Agency's scientific risk assessments for mutagenci effects. The necessity for a consistent approach to the evaualtion of mutagenic risk from chemical substances arises from the authority conferred upon the Agency by a number of statutes to regulate potential mutagens. As appropriate, these Guidelines will apply to statutes administered by the Agency, including the Federal Insecticide, Fungicide, and Rodenticide Act; the Toxic Substances Control Act; the Clean Air Act; the Federal Water Pollution Control Act; the Safe Drinking Water Act; the Resource Conservation and Recovery Act; and the Comprehensive Environmental Response, Compensation, and Liability Act. Because each statute is administered by separate offices, a consistent Agency-wide approach for performing risk assessments is desirable.

The mutagencity risk assessments prepared pursuant to these Guidelines will be utilized within the requirements and constraints of the applicable statutes to arrive at regulatory decisions concerning mutagenicity. The standards of the applicable statutes and regulations may dictate that additional considerations (e.g., the economic and social benefits associated with use of the chemical substance) will come into play in reaching appropriate regulatory decisions.

The Agency is concerned with the risk associated with both germ-cell mutations and somatic cell mutations. Mutations carried in germ cells are inherited by future generations and may contribute to genetic disease, whereas mutations occurring in somatic cells may be implicated in the etiology of several disease states, including cancer. These Guidelines, however, are only concerned with genetic damage as it relates to germ-cell mutations. The use of mutagenicity test results in the assessment of carcinogenic risk is described in the proposed Guidelines for Carcinogen Risk Assessment(*10*).

As a result of the progress in the control of infectious diseases, increases in average human life span, and better procedures for identifying genetic disorders, a considerable heritable genetic disease burden has been recognized in the human population. It is estimated that at least 10% of all human disease is related to specific genetic states, such as abnormal composition, arrangement, or dosage of genes and chromosomes(*2, 6, 11*). Such genetic diseases can lead to structural or functional health impairments. These conditions may be expressed *in utero*: at the time of birth; or during infancy, childhood, adolescence, or adult life; they may be chronic or acute in nature. As a result, they often have a severe impact upon the affected individuals and their families in terms of physical and mental suffering and economic losses, and upon society in general, which often becomes responsible for institutional care of severely affected individuals. Some examples of genetic conditions are Down's and Klinefelter's syndromes, cystic fibrosis, hemophilia, sickle cell anemia, and achondroplastic dwarfism. Other commonly recognized conditions that are likely to have a genetic component include hypercholesterolemia, hypertension, pyloric stenosis, glaucoma, allergies, several types of cancer, and mental retardation. These disorders are only a few of the thousands that are at least partially genetically determined(*12*).

Estimation of the fraction of human genetic disease that results from new mutation is difficult, although in certain specific cases insights are available(*13*). It is clear that recurring mutation is important in determining the incidence of certain genetic conditions, such as some chromosomal aberration syndromes (e.g., Down's) and rare dominant and X-linked recessive diseases (e.g., achondroplasia and hemophilia A). For other single-factor conditions (e.g., sickle-cell anemia and color blindness) and certain multifactorial conditions (e.g., pyloric stenosis), the contribution of new mutations to disease frequency is probably very small. However, it is generally recognized that most mutations that are phenotypically expressed are in some ways deleterious to the organism receiving them. Adverse effects may be manifested at the biochemical, cellular, or physiological levels of organization. Although mutations are the building blocks for further evolutionary change of species, it is believed that increases in the mutation rate above the spontaneous level could lead to an accumulation of deleterious mutations in the human population and, to a varying extent, an increased frequency of expressed genetic disease.

Life in our technological society results in exposure to many natural and synthetic chemicals. Some have been shown to have mutagenic activity in mammalian and submammalian test systems, and thus may have the potential to increase genetic damage in the human population. Chemicals exhibiting mutagenic activity in various

test systems have been found distributed among foods, tobacco, drugs, food additives, cosmetics, industrial compounds, pesticides, and consumer products. As our knowledge of genetics and disease etiology increases, and techniques for detecting mutations in human beings improve, we may become aware of chemically-induced human genetic effects. The extent to which exposure to natural and synthetic environmental agents may have increased the amount of genetic damage in the present human population and contributed to the mutational "load" that will be transmitted to future generations is unknown at this time. However, for the reasons cited above, it seems prudent to limit exposures to potential human mutagens.

1. Concepts Relating to Heritable Mutagenic Risk

For the purposes of these Guidelines, a mutagen is considered a chemical substance or mixture of substances that can induce alterations in the DNA of either somatic or germinal cells. The mutagenicity of physical agents (e.g., radiations) is not addressed here. There are several mutagenic end points of concern to the Agency. These include point mutations (i.e., submicroscopic changes in the base sequence of DNA) and structural or numerical chromosome aberrations. Structural aberrations include deficiencies, duplications, inversions, and translocations, whereas numerical aberrations are gains or losses of whole chromosomes (e.g., trisomy, monosomy) or sets of chromosomes (haploidy, polyploidy).

It is conceivable that only one or a few molecules of an active compound may be sufficient to cause certain types of heritable changes in DNA. Mutagenic effects may also come about through mechanisms other than chemical alterations of DNA. Among these are interference with normal DNA synthesis, or induction of DNA misrepair, DNA methylation, abnormal nuclear division processes, or lesions in non-DNA targets (e.g., protamine, tubulin).

The best evidence that an agent induces heritable mutations in human beings would be epidemiologic data indicating a strong association between chemical exposure and a heritable response. Such data do not exist at this time because any specific mutation is a rare event, and only a small fraction of the estimated thousands of human genes and conditions are currently useful as markers in estimating mutation rates. Human genetic variability, small numbers of offspring per individual, and long generation times further complicates such studies. In addition, only dominant mutations, some sex-linked recessive mutations, and certain chromosome aberrations can be detected in the first generation after their occurrence. Conditions caused by autosomal recessive mutations (which appear to occur more frequently than dominants) or by interaction of multiple factors may go unrecognized for many generations. Therefore, in the absence of human germ-cell data, it is appropriate to rely on data from experimental animal systems.

Despite species differences in metabolism, DNA repair, and other physiological processes affecting chemical mutagenesis, the virtual universality of DNA as the genetic material and of the genetic code provides a rationale for using various nonhuman test systems to predict the intrinsic mutagenicity of test chemicals. Additional support for the use of nonhuman systems is provided by the observation that chemicals causing genetic effects in one species or test system frequently cause similar effects in other species or systems. There also exists evidence that chemicals can induce genetic damage in somatic cells of exposed humans. For example, high doses of mutagenic chemotherapeutic agents have been shown to cause chromosomal abnormalities(*14*), sister chromatid exchange(*14*), and, quite probably, point mutations in human lymphocytes exposed *in vivo*(*15*). While these results are not in germ cells, they do indicate that it is possible to induce mutagenic events in human cells *in vivo*. Furthermore, a wide variety of different types of mutations have been observed in humans including numerical chromosome aberrations, translocations, base-pair substitutions, and frameshift mutations. Although the cause of these mutations is uncertain, it is clear from these observations that the human germ-cell DNA is subject to the same types of mutational events that are observed in other species and test systems.

Certain test systems offer notable advantages: Cost; anatomical, histological, and/or metabolic similarities to humans; suitability for handling large numbers of test organisms; a large data base; and a basis for characterizing genetic events(*10*).

2. Test Systems

Many test systems are currently available that can contribute information about the mutagenic potential of a test compound with respect to various genetic end points. These tests have recently been evaluated through the EPA Gene-Tox Programs and the results of Phase I have been published(*4*). The Agency's Office of Pesticides and Toxic Substances has published various testing guidelines for the detection of mutagenic effects(*16, 17*).

Test systems for detecting point mutations include those in bacteria, eukaryotic microorganisms, higher plants, insects, mammalian somatic cells in culture, and germinal cells of intact mammals (e.g., the mouse specific-locus test). Positive results in a mouse germinal gene-mutation test argue strongly that a chemical is a potential human mutagen because such tests demonstrate that the mutations occur in mammalian germinal cells and are transmitted to the next generaton. However, because large numbers of offspring must usually be generated, it is not expected that many chemicals will be tested using these systems. To obtain data on a large number of environmental chemicals, it will be necessary to rely on other tests to identify and characterize hazards from gene mutations.

Test systems for detecting structural chromosome aberrations have been developed in a variety of organisms including higher plants, insects, fish, birds, and several mammalian species. Many of these assays can be performed *in vitro* or *in vivo*, and in either germ or somatic cells. Procedures available for detecting structural chromosome aberrations in mammalian germ cells include measurement of heritable translocations or dominant lethality, as well as direct cytogenetic analyses of germ cells and early embryos in rodents.

Some chemicals may cause numerical chromosome changes (i.e., aneuploidy) as their sole mutagenic effect. These agents may not be detected as mutagens if evaluated only in tests for DNA damage, gene mutations, or chromosome breakage and rearrangement. Therefore, it is important to consider tests for changes in chromosome number in the total assessment of mutagenic hazards. Although tests for the detection of variation in the chromosome number are still at an early stage of development, systems exist in such diverse organisms as fungi, Drosophila, mammalian cells in culture, and intact mammals (e.g., mouse X-chromosome loss assay). Nondisjunction and chromosome lagging are recognized sources of numerical aberrations. Aneuploidy can also arise from chromosome breakage and reunion followed by segregation(*18*). The mechanmisms by which nondisjunction occurs are not well understood. However, proteins (e.g., spindle apparatus), rather than DNA, may be

the target molecules for at least some mechanisms of induced nondisjunction.

Other end points that provide information bearing on the mutagenicity of a chemical can be detected by a variety of test systems. Such tests measure DNA damage in eukaryotic or prokaryotic cells, unscheduled DNA synthesis in mammalian somatic and germ cells, mitotic recombination and gene conversion in yeast, and sister-chromatid exchange in mammalian somatic and germ cells. Results in these assays are useful because the induction of these end points often correlates positively with the potential of a chemical to induce mutations.

In general, for all three end points (i.e., point mutations and numerical and structural aberrations) the Agency will place greater weight on tests conducted in germ cells than in somatic cells, on tests performed *in vivo* rather than *in vitro*, in eukaryotes rather than prokaryotes, and in mammalian species rather than in submammalian species. Formal numerical weighting systems have been developed[*19*]; however, the Agency has concluded that these do not readily accommodate such variables as dose range, route of exposure, and magnitude of response.

The Agency anticipates that from time to time data from chemically-exposed human beings will be available (e.g., cytogenetic markers in peripheral lymphocytes). When possible, the Agency will use such data in conjunction with other studies for the purpose of performing risk assessments.

The test systems mentioned previously are not the only ones that will provide evidence of mutagenicity or related DNA effects. These systems are enumerated merely to demonstrate the breadth of the available techniques for characterizing mutagenic hazards, and to indicate the types of data that the Agency will consider in its evaluation of mutagenic potential of a chemical agent. Most systems possess certain limitations that must be taken into account. The selection and performance of appropriate tests for evaluating the risks associated with human exposure to any suspected mutagen will depend on sound scientific judgment and experience, and may necessitate consultation with geneticists familiar with the sensitivity and experimental design of the test system in question. In view of the rapid advances in test methodology, the Agency expects that both the number and quality of the tools for assessing genetic risk to human beings will increase with time. The Agency will closely monitor developments in mutagenicity evaluation and will refine its risk assessment scheme as better test systems become available.

B. Qualitative Assessment (Hazard Identification)

The assessment of potential human germ-cell mutagenic risk is a multistep process. The first step is an analysis of the evidence bearing on a chemical's ability to induce mutagenic events, while the second step involves an analysis of its ability to produce these events in the mammalian gonad. All relevant information is then integrated into a weight-of-evidence scheme which presents the strength of the information bearing on the chemical's potential ability to produce mutations in human germ cells. For chemicals demonstrating this potential, one may decide to proceed with an evaluation of the quantitative consequences of mutation following expected human exposure.

For hazard identification, it is clearly desirable to have data from mammalian germ-cell tests, such as the mouse specific-locus test for point mutations and the heritable translocation or germ-cell cytogenetic tests for structural chromosome aberrations. It is recognized, however, that in most instances such data will not be available, and alternative means of evaluation will be required. In such cases the Agency will evaluate the evidence bearing on the agent's mutagenic activity and the agent's ability to reach and interact with or affect the mammalian gonadal target. When evidence exists that an agent possesses both these attributes, it is reasonable to deduce that the agent is a potential human germ-cell mutagen.

1. Mutagenic Activity

In evaluating chemicals for mutagenic activity, a number of factors will be considered: (1) Genetic end points (e.g., gene mutations, structural or numerical chromosomal aberrations) detected by the test systems, (2) sensitivity and predictive value of the test systems for various classes of chemical compounds, (3) number of different test systems used for detecting each genetic end point, (4) consistency of the results obtained in different test systems and different species, (5) aspects of the dose-response relationship, and (6) whether the tests are conducted in accordance with appropriate test protocols agreed upon by experts in the field.

The array of mutagenicity tests available will be reviewed within the following qualitative perspective: greater weight will be attributed to tests conducted in germ cells than in somatic cells, to studies in mammalian cells than in submammalian cells, and to studies in eukaryotic cells than in prokaryotic cells.

2. Chemical Interactions in the Mammalian Gonad

Evidence for chemical interaction in the mammalian gonad spans a range of different types of findings. Each chemical under consideration needs to be extensively reviewed since this type of evidence may be part of testing exclusive of mutagenicity per se (e.g., reproduction, metabolism, and mechanistic investigations). Although it is not possible to classify clearly each type of information that may be available on a chemical, two possible groups are illustrated.

Sufficient evidence of chemical interaction is given by the demonstration that an agent interacts with germ-cell DNA or other chromatin constituents, or that it induces such end points as unscheduled DNA synthesis, sister-chromatid exchange, or chromosomal aberrations in germinal cells. Positive results in a mammalian germ-cell mutation study also demonstrate the action of the chemical in the gonadal target cells.

b. *Suggestive evidence* will include the finding of adverse gonadal effects following acute, subchronic, or chronic toxicity testing, or findings of adverse reproductive effects, which are consistent with interaction with germ cells.

3. Weight-of-Evidence Determination

The evidence for a chemical's ability to produce mutations and to interact with the germinal target are integrated into a weight-of-evidence judgment that the agent may pose a hazard as a potential human germ-cell mutagen. All information bearing on the subject, whether indicative of potential concern or not, must be evaluated. Whatever evidence may exist from humans must also be factored into the assessment.

Information available will vary greatly from chemical to chemical because there are many mutagenicity test systems, and there has been no systematic attempt to develop information on all chemicals of concern. The responses noted for different tests may also vary from chemical to chemical since often one does not find consistent positive or negative results across all tests. Chemicals may show positive effects for some end points in some test systems, but negative responses in others. Each review must take into account the limitations in the testing and in the types of responses that may exist.

To provide guidance as to the categorization of the weight of evidence, a classification scheme is presented to illustrate, in a simplified sense, the strength of the information bearing on the potential for human germ-cell mutagenicity (Table 1). It is not possible to illustrate all potential combinations of evidence, and considerable judgment must be exercised in reaching conclusions. The factors illustrated in Table 1 and discussed previously in sections 1, 2, and 3 must all be considered in making an assessment of mutagenicity. In addition, certain responses in tests that do not measure well-defined mutagenic end points (e.g., SCE induction in mammalian germ cells) or germ-cell tests in higher eukaryotes (e.g., Drosophila tests) may provide a basis for raising the weight of evidence from one category to another.

Sufficient evidence for potential human germ-cell mutagenicity would include cases in which positive responses are demonstrated in a mammalian germ-cell test. Also, in general, sufficient evidence exists when there is confirmed mutagenic activity in other test systems (positive responses in at least two different test systems, at least one of which is in mammalian cells), and there is sufficient evidence for germ-cell interaction as defined above.

Suggestive evidence encompasses a weight-of-evidence category between sufficient and limited that includes cases in which there is some evidence for mutagenic activity and for interaction with germ cells.

Limited evidence for potential human germ-cell mutagenicity exists when evidence is available only for mutagenicity tests (other than mammalian germ cells) or only for chemical interactions in the gonad.

Table 1.—Classification of Weight of Evidence for Potential Human Germ-Cell Mutagenicity [a]

1. *Sufficient* evidence exists when positive responses are demonstrated in:
   a. at least one *in vivo* mammalian germ-cell mutation test, or
   b. at least two point mutation tests (at least one in mammalian cells) plus sufficient evidence that the chemical interacts with mammalian germ cells, or
   c. least two structural chromosome aberration tests (at least one in mammalian cells) plus sufficient evidence that the chemical interacts with mammalian germ cells, or
   d. one gene mutation assay in mammalian cells and one structural chromosome aberration test in mammalian cells and sufficient evidence for chemical interaction with mammalian germ cells.

2. *Suggestive* evidence exists in those cases in which there are positive data for both mutagenic activity and evidence for chemical interactions in the gonad, but the evidence is less than sufficient. This category is potentially large and heterogeneous in nature and ranges from almost sufficient to essentially limited.

3. *Limited* evidence denotes a situation in which the evidence is limited to information on mutagenic activity or to evidence of chemical reactivity in the target.

[a] Takes into consideration the extent, quality, and consistency of responses bearing on an agent's ability to product mutagenic events and to interact with the mammalian gonadal target. Nonmutagenic test responses (e.g., SCE in germ cells) may help to elevate evidence of mutegenicity from one category to another.

Designation of evidence as limited does not preclude the use of such information to set priorities for further testing or to support a case for potential carcinogenicity.

Although definitive proof of nonmutagenicity is not possible, it seems appropriate that a chemical could be classified operationally as not a human germ-cell mutagen, if it gives negative responses in those test systems that together fulfill the criteria (i.e., all relevant end points) for sufficient evidence of a potential human germ-cell mutagen, providing that all assays have been properly performed. Test systems used to define a negative should be capable of detecting weak responses (adequate statistical power) and should be appropriate for the chemical or class of chemicals under investigation.

Negative evidence of chemical interaction in the gonad in the presence of evidence of mutagenic activity may still signal some concern in regard to somatic effects(*10*). Other combinations of relevant information will most likely require case-by-case evaluation. It may also be possible to operationally define a chemical as not being a human germ-cell mutagen based on negative results from other assays which provide information about mutagenicity and/or interaction with germ-cell chromatin.

C. Quantitative Assessment

The preceding section addressed primarily the processes of hazard identification, i.e., the determination of whether a substance is a potential germ-cell mutagen. Often, no further data will be available, and judgments will need to be based on mainly qualitative criteria. For quantitative risk assessment, further information is required, namely, determination of the heritable effect per unit of exposure (dose-response) and the relationship between mutation rate and disease incidence. Dose-response information is combined with anticipated levels and patterns of human exposure in order to derive a quantitative assessment (risk characterization).

1. Dose-Response

Two approaches to obtaining dose-response data are available. One approach requires experimental data on germinal mutations induced in intact mammals. Several test systems may provide such information, e.g., the mouse heritable translocation, dominant skeletal, dominant cataract, and specific-locus tests. Although the dominant skeletal and cataract assays have the advantage of measuring dominant mutations, the heritability of observed effects has not been clearly demonstrated. The experimental data on induced mutation frequency are usually obtained at exposure levels much higher than those that will be experienced by human beings. An assessment of human risk is obtained by extrapolating the induced mutation frequency or the observed phenotypic effect downward to the approximate level of anticipated human exposure.

The Agency will strive to use the most appropriate extrapolation models for risk analysis and will be guided by the available data and mechanistic considerations in this selection. However, it is anticipated that for tests involving germ cells of whole mammals, few dose points will be available to define dose-response functions. In these situations certain theoretical considerations will apply(*20*). For point mutations, linear extrapolations with no threshold may be used as a conservative approximation, provided the results allow one to rule out major germ-cell selection. For structural chromosome rearrangements such as heritable translocations, linear extrapolation of the experimental data is thought to overestimate the risks at low levels of exposure and use of a multiple-hit model is more appropriate.

The second experimental approach for quantitative assessment of genetic risk uses molecular dosimetry data from intact mammals in conjunction with mutagenicity and dosimetry data from other validated test systems(*21*). The intact mammal is used primarily for relating the exposure level for a given route of administration of a chemical to germ-cell dose, i.e., the level of mutagen-DNA interactions. This information is then used in conjunction with results obtained from mutagenicity test systems in which the relationship between the induction of mutations and chemical interactions with DNA can be derived.

Using mutagen-DNA interactions as the common denominator, a relationship can be constructed between mammalian exposure and the induced mutation frequency. The amount of DNA binding induced by a particular chemical agent may often be determined at levels of anticipated human exposure. This approach is still experimental and its application involves many unknowns, such as possible differences between mammalian germ cells and cells of the reference system with regard to types of genetic damage induced and magnitude of repair.

For some mutagenic events, DNA may not necessarily be the critical target. Interaction of chemicals with other macromolecules, such as tubulin, which is involved in the separation of chromosomes during nuclear division, can lead to chromosomal nondisjunction. At present, general approaches are not available for dose-response assessments for these types of mutations. Ongoing research should provide the means to make future assessments on chemicals causing aneuploidy.

2. Exposure Assessment

The exposure assessment identifies populations exposed to toxic chemicals, describes their composition and size, and presents the types, magnitudes, frequencies, and durations of exposure to the chemicals. This component is developed independently of the other components of the mutagenicity assessment(9).

3. Risk Characterization

In performing mutagenicity risk assessments, it is important to consider each genetic end point individually. For example, although certain chemical substances that interact with DNA may cause both point and chromosomal mutations, it is expected that the ratio of these events may differ for individual chemicals and between doses for a given chemical. Furthermore, transmissible chromosomal aberrations appear to be inducible with higher frequencies in meiotic and postmeiotic germ-cell stages, which have a brief life span, than in spermatogonial stem cells, which can accumulate genetic damage throughout the reproductive life of an individual. For these reasons, when data are available, the Agency, to the best extent possible, will assess risks associated with all genetic end points.

Any risk assessment should clearly delineate the strengths and weaknesses of the data, the assumptions made, the uncertainties in the methodology, and the rationale used in reaching the conclusions, e.g., similar or different routes of exposure and metabolic differences between humans and test animals. When possible, quantitative risk assessments should be expressed in terms of the estimated increase of genetic disease per generation or per lifetime, or the fractional increase in the assumed background spontaneous mutation rate of humans(5). Examples of quantitative risk estimates have been published (6, 22); these examples may be of use in performing quantitative risk assessments for mutagens.

IV. References

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Part X

Environmental Protection Agency

Proposed Guidelines for the Health Assessment of Suspect Developmental Toxicants and Request for Comments

ENVIRONMENTAL PROTECTION AGENCY

[PRL-2765-7]

Proposed Guidelines for the Health Assessment of Suspect Developmental Toxicants

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed Guidelines for the Health Assessment of Suspect Developmental Toxicants and Request for Comments.

SUMMARY: The U.S. Environmental Protection Agency is proposing Guidelines for the Health Assessment of Suspect Developmental Toxicants (Guidelines). These Guidelines are proposed for use within the policy and procedural framework provided by the various statutes that EPA administers to guide Agency analysis of developmental toxicity data. We solicit public comment and will take public comment into account in revising these Guidelines. The Guidelines will be reviewed by the Science Advisory Board in meetings now tentatively scheduled for April 1985.

These proposed Guidelines were developed as part of a broad guidelines development program under the auspices of the Office of Health and Environmental Assessment (OHEA), located inthe Agency's Office of Research and Development. Consonant with the role of OHEA's Reproductive Effects Assessment Group (REAG) as the Agency's senior health committee for developmental toxicity assessment, the Guidelines were developed by an Agency-wide working group chaired by the REAG.

DATE: Comments must be postmarked by January 22, 1985.

ADDRESSES: Comments may be mailed or delivered to: Dr. Carole A. Kimmel, Reproductive Effects Assessment Group (RD-689), Office of Health and Environmental Assessment, U.S. Environmental Protection Agency, 401 M Street, SW., Washington, DC 20460.

FOR FURTHER INFORMATION CONTACT: Dr. Carole A. Kimmel, telephone: 202-382-7331.

SUPPLEMENTARY INFORMATION: A preliminary draft of the Guidelines was sent for review to approximately 20 scientists in the field of developmental toxicology within government, universities in the United States, and the private sector. Comments received from these reviewers, generally favorable, were taken into account in developing the Guidelines proposed here.

References and supporting documents used in the preparation of these Guidelines as well as comments received are available for inspection and copying at the Public Information Reference Unit (202-382-5926), EPA Headquarters Library, 401 M Street, SW., Washington, DC, between the hours of 8:00 a.m. and 4:30 p.m.

Dated: November 9, 1984.

William D. Ruckelshaus,

Administrator.

Contents

I. Introduction

These Guidelines describe the procedures that the U.S. Environmental Protection Agency will follow in evaluating potential developmental toxicity associated with human exposure to environmental toxicants. In the past, the Agency has sponsored conferences and issued publications which addressed issues related to such evaluations(*1, 2, 3*). These publications provided some of the scientific basis for these risk assessment Guidelines, and testing guidelines have provided protocols designed to determine the potential of a test substance to induce structural and/or other abnormalities in the developing conceptus. The Agency's authority to regulate substances that have the potential to interfere adversely with human development is derived from a number of statutes which are implemented through multiple offices within the Agency. Because many different offices evaluate developmental toxicity, there is a need for intra-agency consistency in the approach to assess these types of effects. The procedures described here will promote consistency in the Agency's assessment of developmental toxic effects.

Approximately 50% of human conceptuses fail to reach term(*3, 4*); approximately 3% of newborn children are found to have one or more significant congenital malformations at birth, and, by the end of the first postnatal year, about 3% more are found to have serious developmental defects (*5, 6*). It is estimated that 20% of human congenital malformations are caused by mutations, 10% are attributable to known environmental factors, and the remainder result from unknown causes (*7*).

Numerous agents have been shown to be developmental toxicants in animal test systems(*8*). Several of them have also been shown to be the cause of adverse developmental effects in humans, including alcohol, aminopterin, busulfan, chlorobiphenyls, diethylstilbestrol, isotretinoin, organic mercury, thalidomide, and valproic acid (*9, 10, 11, 12*). Exposure to agents affecting development generally results in multiple manifestations (malformation, functional impairment, altered growth, and/or lethality). Therefore, assessment efforts should encompass a wide array of adverse developmental end points such as spontaneous abortions, stillbirths, malformations, and other adverse functional physical changes that occur postnatally.

The developmental toxicity assessments prepared pursuant to these Guidelines will be utilized within the requirements and constraints of the applicable statutes to arrive at regulatory decisions concerning developmental toxicity. These Guidelines provide a general format for analyzing and organizing the available data for conducting risk assessments. The Guidelines do not change any statutory or regulatory prescribed standards for the type of data necessary for regulatory action. Moreover, risk assessment is just one component of the regulatory process and defines the adverse health consequences of exposure to a toxic agent. The other component, risk management, combines risk assessment with the directives of the enabling regulatory legislation together with socio-economic, technical, political, and other considerations to reach a decision as to whether or how much to control future exposure to the suspected toxic agent. The issue of risk management will not be addressed in these Guidelines.

The National Research Council(*13*) has defined risk assessment as being comprised of some or all of the following

components: hazard identification, dose-response assessment, exposure assessment, and risk characterization. In general, the process of assessing the risk of human developmental toxicity may be adapted to this format. However, due to special considerations in assessing developmental toxicity, which will be discussed later in these Guidelines, it is not always appropriate to follow the exact standards as defined for each component.

Hazard identification is the qualitative risk assessment in which all available experimental animal and human data are used to determine if an agent is likely to cause developmental toxicity. In considering developmental toxicity, these Guidelines will address not only malformations, but also fetal wastage, growth alteration, and functional abnormalities that may result from developmental exposure to environmental agents.

The dose-response assessment defines the relationship of the dose of an agent and the occurrence of developmental toxic effects. According to the National Research Council(*13*), this component would usually include the results of an extrapolation from high doses administered to experimental animals or noted in epidemiologic studies to the low exposure levels expected for human contact with the agent in the environment. However, since at present there is no mathematical extrapolation model that is generally accepted for developmental toxicity, the Agency, for the most part, continues to use safety factors and margins of safety, which will be discussed in these Guidelines.

The exposure assessment identifies populations exposed to the agents, describes their composition and size, and presents the types, magnitudes, frequencies, and durations of exposure to the agent.

In risk characterization, the exposure assessment and the dose-response assessment are combined to estimate some measure of the risk of developmental toxicity. As part of risk characterization, a summary of the strengths and weaknesses in each component of the assessment are presented along with major assumptions, scientific judgments, and, to the extent possible, estimates of the uncertainties.

II. Definitions and Terminology

The Agency recognizes that there are differences in the use of terms in the field of developmental toxicology. For the purposes of these Guidelines the following definitions and terminology will be used.

Developmental Toxicology—The field dealing with the induction of adverse effects on the developing organism occurring up to the time of puberty. The manifestations of developmental toxicity include: (1) Death of the developing organism, (2) structural abnormality (teratogenicity), (3) altered growth, and (4) functional deficiency.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure; the distinguishing feature between the terms is the period during which the insult occurred. The terms, as used here, include malformation, altered growth, and *in utero* death.

Altered Growth—A significant alteration in fetal or neonatal organ or body weight. Body weight may or may not be accompanied by a change in crown-rump length and/or in skeletal ossification. Altered growth can be induced at any stage of development, may be reversible, or may result in a permanent change.

Functional Teratology—The field dealing with the causes, mechanisms, and manifestations of alterations or delays in functional competence of the organism or organ system following exposure to an agent during critical periods of development either pre- or postnatally.

Malformations and Variations—A malfunction is usually defined as a permanent structural deviation which generally is incompatible with or severely detrimental to normal postnatal survival or development. A variation is usually defined as a divergence beyond the usual range of structural constitution but which may not have as severe an effect on survival or health as a malformation. Distinguishing between variations and malformations is difficult since there exists a continuum of responses from the normal to the extreme deviant. There is no generally accepted classification of malformations and variations. Other terminology that is often used but no better defined, includes anomalies, deformations, and aberrations.

III. Qualitative Assessment (Hazard Identification of Developmental Toxicants)

Developmental toxicity studies provide a number of end points that are useful for evaluating the potential of an agent to produce adverse outcomes of pregnancy. The four types of effects on the conceptus that may be produced by *in utero* exposure to toxicants include death, structural abnormality, altered growth, and functional deficits. Of these, the first three effects are measured in the conventional developmental toxicity (teratogenicity) protocol (discussed below), while functional deficits are seldom evaluated in routine assessments of environmental agents. This section will discuss the format and analysis of conventional studies as well as the use of data from other types of studies, including functional studies, short-term tests, and pharmacokinetics.

A. Conventional Developmental Toxicology Protocols: End Points and Their Interpretation

The most commonly used protocol for assessing developmental toxicity involves the administration of a test substance to pregnant animals (usually mice, rats, or rabbits) during the period of major organogenesis, evaluation of maternal responses throughout pregnancy, and examination of the dam and the uterine contents just prior to term(*2, 3, 14, 15*). Other protocols may use exposure periods of one to a few days to investigate periods of particular sensitivity for induction of anomalies in specific organs or organ systems(*16*). Fetuses alive at maternal sacrifice are thoroughly evaluated for alterations in morphological development. Because the relationship of maternal and fetal toxicity is important in assessing the developmental toxicity of an agent, dose-response data are important. Ideally, study designs should include a high dose, which produces some maternal toxicity (i.e., a level that produces marginal but significantly reduced body weight or weight gain during pregnancy up to a level that produces no more than 10% maternal mortality), a low dose, which demonstrates a no-observed-effect level (NOEL) for maternal and/or fetal effects, and at least one intermediate dose level. Test animals should be selected based on considerations of species, strain, age, weight, and health status, and should be randomized to dose groups in order to reduce bias and provide a basis for performing valid statistical tests. Replication of the study is desirable and strengthens the confidence of data interpretation.

The next two sections discuss individual end points of maternal and developmental toxicity, respectively, as measured in the conventional developmental toxicity study. The third section deals with the integrated evaluation of all data, including the relative effects of exposure on maternal animals and their offspring.

1. End Points of Maternal Toxicity

A number of end points that may be observed as indicators of maternal toxicity are listed in Table 1. Maternal

mortality is an obvious end point of maternal toxicity; however, a number of other end points can be observed which may give an indication of the subtle effects of the agent. For example, in well-conducted studies the end point, percent pregnant, indicates the general fertility rate of the animal stock used and is an important indicator of toxic effects if treatment begins prior to implantation.

Table 1.—End Points of Maternal Toxicity

- Mortality
- Percent Pregnant (Includes all litters with implants)
- Body Weight
  - Treatment days (at least first, middle, and last treatment days) Secrifice day
- Body Weight Change
  - Throughout Gestation
  - During treatment (including increments of time within treatment period)
  - Post-treatment to sacrifice
  - Corrected maternal (body weight change throughout gestation minus gravid uterine weight or litter weight at sacrifice)
- Organ Weights (in cases of suspected specific organ toxicity)
  - Absolute
  - Relative to body weight
- Food and Water Consumption (where relevant)
- Clinical Signs (on days of treatment and at sacrifice)
  - Daily weight changes during treatment
  - Types and incidence of clinical signs

Body weight and the change in body weight are viewed collectively as indicators of maternal toxicity for most species, although these end points may not be as useful in rabbits, because body weight changes in rabbits are not good indicators of pregnancy status. Body weight changes may provide more information than a daily body weight measured during treatment or during gestation. Changes in weight during treatment could occur that would not be reflected in the overall weight change throughout gestation, because of compensatory weight gain that may occur following treatment but before sacrifice. For this reason, changes in weight during treatment can be examined as another indicator of maternal toxicity.

Changes in maternal body weight corrected for gravid uterine weight at sacrifice may indicate whether the effect is primarily maternal or fetal. For example, there may be a signficant reduction in weight gain throughout gestation and in gravid uterine weight, but no change in corrected maternal weight gain which would indicate primarily an intrauterine effect. Conversely, a change in corrected weight gain and no change in gravid uterine weight suggests primarily maternal toxicity and little or no intrauterine effect. An alternate estimate of maternal weight change during gestation can be obtained by subtracting the sum of the weights of the fetuses. However, this weight does not include the uterine tissue, placental tissue, or the amniotic fluid.

Changes in other end points should also be determined. For example, changes in relative and absolute organ weights may be signs of maternal effect when an agent is suspected of causing specific organ toxicity. Food and water consumption data are useful, especially if the agent is administered in the diet or drinking water. The amount ingested (total and relative to body weight) and the dose of the agent (relative to body weight) can then be calculated, and changes in food and water consumption with treatment can be evaluated along with changes in body weight and body weight gain. Consumatory data are also useful when an agent is suspected of affecting appetite, water intake, or excretory function. Clinical signs of toxicity may also be used as indicators of maternal toxicity. Daily body weight changes during treatment along with clinical observations may be useful in describing the profile of maternal toxicity.

2. End Points of Developmental Toxicity

Because the maternal animal and not the conceptus is the individual treated during gestation, statistical analysis of the data should consider both the individual fetus and the litter. Table 2 indicates the way in which fetal and litter end points can be expressed.

Table 2.—End Points of Developmental Toxicity

All litters

- No. implantation sites/dam
- No. corpora lutea (CL)/dam*
- Percent Preimplantation loss
- No. and percent live fetuses/litter
- No. and percent resorptions/litter
- No. and percent litters with resorptions
- No. and percent late fetal deaths/litter
- No. and percent nonlive (late fetal deaths + resorptions) implants/litter
- No. and percent litters with nonlife implants
- No. and percent affected (nonlive + malformed) implants/litter
- No. and percent with affected implants
- No. and percent litters with total resorptions

Litters with live fetuses

- No. and percent litters with live fetuses
- No. and percent live fetuses/litter
- No. males/litter
- No. females/litter
- No. ratio/litter
- Mean (x̄) fetal body weight/litter
- Mean (x̄) male body weight/litter
- Mean (x̄) female body weight/litter
- No. and percent externally malformed fetuses/litter
- No. and percent viscerally malformed fetuses/litter
- No. and percent skelatally malformed fetuses/litter
- No. and percent malformed fetuses/litter
- No. and percent litters with malformed fetuses
- No. and percent malformed males/litter
- No. and percent malformed females/litter
- No. and percent fetuses with variations/litter
- No. and percent litters having fetuses with variations
- Types and incidence of individual malformations
- Types and incidence of individual variations
- Individual fetuses and their malformations and variations (grouped according to litter and dose)

* Only when treatment begins prior to implantation. May be difficult in mice.

When treatment begins prior to implantation, an increase in preimplatation loss could indicate an adverse effect either on the developing blastocyst or on the process of implantation itself. Further studies would be necessary to determine the cause and extent of this type of effect.

The number of live fetuses per litter, based on all litters, includes any litters that have no live implants. On the other hand, total nonlive implants (postimplantation loss), is a combination of the end points, resorptions, and late fetal deaths. An increased incidence per litter for any of the end points indicating postimplantation loss would be considered a significant toxic effect to the conceptus. The number of litters showing an increased incidence for these end points is less useful than incidence per litter, because a litter is counted whether it has one or all resorbed, dead, or nonlive implants.

A statistically significant increase in postimplantation loss following exposure to an agent is a severe form of developmental toxicity, but there is considerable interlitter variability in the incidence of postimplantation loss(*17*). If a statistically significant increase is found after exposure to an agent, the data may be compared not only with concurrent controls, but also with recent historical control data. If a given study control group exhibits an unusually high or low incidence of postimplantation loss compared to historical controls, then scientific judgment would have to be used to determine the adequacy of the studies for risk assessment purposes.

The end point for affected implants (i.e., the combination of nonlive and

malformed conceptuses) given an indication of the total intrauterine response to an agent and sometimes reflects a better dose-response relationship than each taken individually. This is especially true at the high end of the dose-response curve in cases where most implants die *in utero*. In such cases, the malformation rate may appear to decrease because only unaffected fetuses have survived to term. If the incidences of prenatal death or malformation is unchanged, then the incidence of affected implants will not provide any additional information.

The number of live fetuses per litter, based on those litters that have one or more live fetuses, may be unchanged even though the incidence of nonlive in all litters is increased. This could occur either by an increase in the number of litters with no live fetuses or by an increase in the number of implants per litter. A decrease in the number of live fetuses per litter should be accompanied by an increase in the incidence of nonlive implants per litter, unless the implant numbers differ among dose groups.

The sex ratio per litter, as well as the body weights of males and females, can be examined to determine whether or not one sex is preferentially affected by the agent. However, this is an unusual occurrence.

A change in fetal body weight is a sensitive indicator of developmental toxicity, in part because it is a continuous variable. In some cases, fetal weight reduction may be the only indicator of developmental toxicity; if so, there is always a question remaining as to whether weight reduction is a permanent or transitory effect. When fetal weight reduction is the only indicator of developmental toxicity, data from the two-generation reproduction study(3) may be useful for evaluating these parameters. Ideally, follow-up studies to evaluate postnatal viability, growth, and survival through weaning should be conducted. There are other factors that should be considered in the evaluation of fetal weight changes. For example, in polytocous animals, fetal weight is usually inversely correlated with litter size, and the upper end of the dose-response curve may be confounded by smaller litters and increased fetal weight. Additionally, the average body weight of male fetuses is greater than that of female fetuses in the more commonly used laboratory animals.

Live fetuses should be examined for external, visceral, and skeletal malformations. If only a portion of the litter is examined, then it is preferable that those to be examined be selected on a random basis from each litter. The incidence of individual types of malformations and variations gives an indication of the types of developmental deviations produced by a particular agent. A listing of individual malformations and variations by fetus gives an indication of the pattern of developmental deviations. The incidence of external, visceral, and skeletal malformations gives an indication of which systems may be specifically affected. A significant increase in the incidence of particular malformations or of the total number of fetuses malformed per treated litter as compared with controls indicates a teratogenic effect. If variations are significantly increased in a dose-related manner, these should also be evaluated as a possible indication of developmental toxicity. The Interagency Regulatory Liaison Group noted that dose-related increases in spontaneously occurring defects are as relevant as dose-related increases in any other developmental toxicity end points(18). The number and percentage of litters with malformed fetuses are more reliable indicators of developmental toxicity than the number of litters with resorptions, since malformations do not occur frequently in controls. The data on the incidence of individual types of malformations and variations should be examined for significant changes which may be masked if the data on all malformations and variations are pooled. This information can also be used for comparison with historical control data. Appropriate historical control data are helpful in interpretation of major malformations, especially those that normally occur at a low incidence when seen in an individual study apparently unrelated to dose.

3. Overall Evaluation of Maternal and Developmental Toxicity

As discussed previously, individual end points are evaluated in developmental toxicity studies, but an integrated evaluation must be done considering all maternal and developmental end points in order to interpret the data fully. The overall interpretation usually consists of the evaluation of maternal toxicity and the dose levels at which it occurs, then the evaluation of developmental toxicity and the levels at which these end points occur. In general, an agent that produces changes in any of the four major classes of developmental toxicity at a dose that is minimally toxic or not toxic to the maternal animal is considered to have selective developmental effects. However, when effects are produced at maternally toxic doses by agents to which adult human exposure may occur at toxic levels (e.g., smoking, alcohol, solvents), these developmental effects should no be ignored.

Approaches for ranking agents for their selective developmental toxicity are being developed. Schardein(9) has reviewed several of these. Of current interest are approaches that develop ratios relating an adult toxic dose to a developmental toxic dose(19, 20, 21). Ratios near unity indicate that developmental toxicity occurs only at doses producing maternal toxicity; as the ratio increases, there is a greater likelihood of developmental effects occurring without maternal manifestations. Although further exploration and validation are necessary, such approaches may ultimately help in identifying those agents that pose the greatest threat and should be given priority for further testing(22).

B. Functional teratology

Developmental effects, which are inducible by exogenous agents, are not limited to death, structural abnormalities, and altered growth. Rather, it has been demonstrated in a number of instances that subtle alterations in the functional competence of an organ or a variety of organ systems may result from exposure during critical developmental periods that may occur between conception and puberty. Often, these functional defects are observed at dose levels below those at which gross malformations are evident(23). Much of the early work in this field was related to behavioral evaluations, and the term "behavioral teratology" became prominent in the mid 1970s. Less work has been done on other functional systems, but sufficient data have accumulated to indicate that the cardiopulmonary, immune, endocrine, digestive, urinary, and reproductive systems are subject to alterations in functional competence. Hence the term "functional teratology" has been applied to this general area.

The variety of systems and end points that may be evaluated is too extensive to discuss here(24), (25). At present no standard testing procedures are routinely used, and this has led to apparent discrepancies in the outcome of certain studies. Some attempts to standardize and evaluate procedures are being made(26). The determination of functional competence often involves highly specialized training and equipment and is not generally practical for routine test procedures. Therefore, these approaches may have their greatest application in determining the nature of a suspected alteration in term-

of its biological significance and dose-response relationship.

The means for appropriate interpretation of data from functional teratology studies is not always clear due to the lack of knowledge about the toxicological significance of specific functional alterations. However, several general concepts have arisen from the research to date which may be useful in designing studies and evaluating data.

1. Several aspects of study design are similar to those used in standard developmental toxicity studies (e.g., a dose-response approach with the highest dose producing minimal overt maternal or fetal toxicity, number of litters large enough for adequate statistical power, randomization of animals to dose groups, litter generally considered the statistical unit, etc.).

2. Replication of a study strengthens the confidence of data interpretation.

3. Use of a pharmacological challenge may aid in evaluating function and "unmasking" effects not otherwise detectable, particularly in the case of organ systems that are endowed with a reasonable degree of functional reserve capacity.

4. Choice of functional tests with a moderate degree of background variability may be more useful in detecting effects of agent exposure than tests based on functional systems with low variability that may be impossible to disrupt without being life-threatening. Butcher et al.(*27*) have discussed this with relation to behavioral end points.

5. A battery of functional tests is often necessary to evaluate fully the functional competence of any given system; these tests may need to be conducted at several ages to account for maturational changes.

6. Critical periods for the disruption of functional competence may include both the prenatal period to the time of puberty, and the effect is likely to vary depending on the time of exposure.

Although interpretation of functional data may be difficult at present, there are at least two days in which the data from these studies may be useful for risk assessment purposes. First, these studies can be used to indicate whether or not an agent has the potential to cause functional alterations, and whether these effects occur at doses lower than those that produce other forms of toxicity. Second, if the agent in question is already in the environment, the functional data may be used for focusing on organ systems to evaluate in exposed human populations.

C. Short-Term Testing in Development Toxicity

The need for developmental toxicity screens has arisen from the large number of agents in or entering the environment and the increased interest in reducing the number of animals used in and the expense of testing. Currently, two approaches are being considered for their applicability in the overall testing process: an *in vivo* mammalian screen and a variety of *in vitro* systems. Neither approach is seen at this time as replacing current *in vivo* developmental toxicity testing. Rather, they are being considered for their usefulness in assigning priorities for further, more extensive testing.

1. *In Vivo* Mammalian Teratology Screen

An *in vivo* approach developed by Chernoff and Kavlock(*28*) uses the pregnant mouse and it designed to reduce the resources required for preliminary indication of developmental toxicity. This approach is based on the hypothesis that a prenatal insult, which results in altered development, will be manifested postnatally as reduced viability and/or impaired growth. In general, the test substance is administered over the period of major organogenesis at a single dose level that will elicit some degree of maternal toxicity. After birth, the pups are counted and weighed on days 1 and 3. End points that are considered in the evaluation include: general maternal toxicity (including survival and weight gain), litter size, viability and weight of the offspring, and gross malformations. Basic priority categories for further testing have also been suggested: (1) Agents that induce perinatal death should receive highest priority, (2) agents inducing perinatal weight changes should be ranked lower in priority, and (3) agents inducing no effect should receive the lowest priority(*28*). The major goal of this test is to predict the potential for developmental toxicity of an agent in the species utilized. It does not increase the ability to extrapolate risk to other species, including humans. Additional studies to evaluate the validity of this approach as a screen for developmental toxicity are currently being carried out, and a system for giving a numerical ranking to the results has been suggested to prioritize agents for further testing(*29, 30*).

2. *In Vitro* Teratology Screens

Test systems that fall under the general heading of "*in vitro*" include any system that employs a test subject other than the intact pregnant mammal. These systems have long been used to assess events associated with normal and abnormal development, but only recently have they been considered for their potential as screens in testing (*31, 32, 33*). Many of these systems are now being evaluated for their ability to predict the developmental toxicity of various agents. This validation process requires certain considerations in study design, including defined end points for toxicity and an understanding of the system's ability to handle various test agents(*32, 34*). A list of agents for use in these validation studies has been developed(*35*).

3. Application

When the validity of a screening system is established, it may be used to set priorities for further, more comprehensive *in vivo* testing. In many cases, a battery of two or more screening systems may be needed, employing tests with end points that collectively represent several embryologic processes. In addition, many of these systems can be applied in an attempt to answer specific questions of a dose-response, target-organ, or mechanistic nature. *In vitro* approaches may aid in establishing the effective dose that reaches the target tissue. Either the *in vivo* or *in vitro* short-term approaches may be useful in addressing structure-activity relationships and the synergistic-antagonistic potential of chemical interactions. Thus, pertinent information can be derived from these approaches and may be useful in the assessment of potential risk.

D. Pharmacokinetics

Extrapolation of data between species can be aided considerably by the availability of data on the pharmacokinetics of a particular agent in the species tested and, if possible, in humans. Information on half-lives, placental metabolism and transfer, and concentrations of the parent compound and metabolites in the maternal animal and conceptus may be useful in predicting risk for developmental toxicity. Such data may also be helpful in defining the dose-response curve, developing a more accurate comparison of species sensitivity including that of humans (*36, 37*), determining dosimetry at target sites, and comparing pharmacokinetic profiles for various dosing regimens or routes of exposure.

Pharmacokinetic studies in developmental toxicology are most useful once a developmental toxic effect has been produced in a give species with a particular agent. Pharmacokinetic

data for risk assessment in developmental toxicology ideally should be derived from pregnant females at the stage when developmental insults occur. Often the only data available are from males, nonpregnant females, or from pregnant females at a time unrelated to the event of interest (e.g., pharmacokinetic analyses done during the fetal period when malformations were induced early in organogenesis). The correlation of pharmacokinetic and developmental toxicity data may be useful in determining the contribution of specific pharmacokinetic parameters to the effects observed (*38*).

E. Human Studies

Because of the ethical considerations involved, little human testing has been or is likely to be done. Therefore, dose-effect developmental toxicity data from humans are generally not available. Human epidemiologic studies may provide the best information for assessing human risk and would reduce the problems in species-to-species extrapolation. However, interpretation of epidemiologic data must account for confounding factors, such as maternal age, parity, multiple exposures to environmental agents, difficulty in obtaining accurate estimates of exposure levels in the environment, insufficient data on background incidence of certain developmental end points, etc. When human data are available, they can be used with other supporting animal data to assess human risk.

F. Comparisons of Molecular Structure

Comparisons of the chemical or physical properties of an agent with those of known developmental toxicants may provide some indication of a potential for developmental toxicity. Such information may be useful in priority-setting of Agents for testing or for further evaluation when only minimal data are available.

G. Weight-of-Evidence Determination

Information available from studies discussed previously, whether indicative of potential concern or not, must be evaluated and factored into the assessment. The types of data may vary from chemical to chemical, and certain types of data may be more relevant than other types of data in performing developmental toxicity assessments. Therefore, all data pertinent to developmental toxicity should be examined in the determination of a chemical's potential to cause developmental toxicity in humans. Whatever evidence may exist from humans must also be factored into the assessment.

IV. Quantitative Assessment

Risk assessment involves the description of the nature and often the magnitude of potential human risk, including a description of any attendant uncertainty. In the final phase of the risk assessment, the outputs of the qualitative evaluation, the dose-response, and the exposure data are combined to give qualitative and/or quantitative estimates of the developmental toxicity risk. As part of the risk assessment, a summary of the strengths and weaknesses of the hazard identification, dose-response assessment, exposure assessment, and the risk characterization are presented. Major assumptions, scientific judgments, and, to the extent possible, estimates of the uncertainties in the assessment are also presented.

A. Dose-Response Assessment

Because human dose-effect data usually are not available, other methods have been used in developmental toxicology for estimating exposure levels that are unlikely to produce adverse effects in humans. The dose-response assessment is usually based upon the evaluation of tests performed in laboratory animals. Two approaches frequently employed involve the use of safety factors and margins of safety, which in some respects are conceptually similar. However, they are computed differently and are often used in different regulatory situations. The choice of approach is dependent upon many factors, including the statute involved, the situation being addressed, the data base used, and the needs of the decision-maker.

The safety factor approach is intended to derive a calculated exposure level that is unlikely to cause any developmental toxic responses in humans. The size of the safety factor will vary from agent to agent and will require the exercise of scientific judgment(*3, 39*), taking into account interspecies differences, the nature and extent of human exposure, the slope of the dose-response curve, and the severity of the developmental effects observed at exposure levels below maternal toxicity in the test species. The safety factor selected is then divided into the NOEL obtained from the most appropriate and/or sensitive mammalian species examined to obtain an acceptable exposure level. Currently, there is no one laboratory animal species that can be considered most appropriate for predicting risk to humans(*9*). Each agent should be considered on a case-by-case basis.

The margin of safety approach derives a ratio of the NOEL from the most sensitive species to the estimated human exposure level from all potential sources(*40*). The adequacy of the margin of safety is then considered, based upon the weight of evidence, including quality of data, number of species affected, dose-response relationships, and other factors such as benefits of the agent.

As discussed earlier, the preferred study design for a developmental toxicity study includes a minimum of three doses: a high dose that produces minimal maternal toxicity, at least one intermediate dose, and a low dose that demonstrates a NOEL. Nevertheless, there may be circumstances in that there is a need to perform a risk assessment based on the results of a study in which a NOEL could not be identified, but, rather, in which the lowest dose administered caused some marginally significant effect(s). This lowest dose could be identified as the lowest observed effect level (LOEL). In circumstances where a LOEL can be identified, it may be appropriate to apply an additional safety factor. The magnitude of this additional factor is dependent upon scientific judgment. In some instances, additional studies may be needed to strengthen the confidence in this additional safety factor.

B. Exposure Assessment

The results of the dose-response assessment are combined with an estimate of human exposure in order to obtain a quantitative estimate of risk. The proposed Guidelines for Exposure assessment are being developed separately and will not be discussed in any detail here. In general, the exposure assessment describes the magnitude, duration, schedule, and route of exposure. This information is developed from monitoring data and from estimates based on modeling of environmental exposures. Unique considerations relevant to developmental toxicity are duration and period of exposure as related to stage of gestation (i.e., critical periods), and the fact that a single exposure may be sufficient to produce adverse developmental effects (i.e., chronic exposure is not necessary for developmental toxicity to be manifested).

C. Risk Characterization

There are numerous uncertainties associated with the toxicological and exposure components of risk assessment that in the past have often not been

readily apparent or consistently presented. The presentation of any qualitative or quantitative risk assessment for developmental toxicity should be accompanied by statements concerning the quality of the data, resolving power of the studies, number of end points examined, selection of doses, replication of the data, the number of species examined, pharmacokinetic considerations, and any other factors that affect the quality and precision of the assessment. The presentation of any numerical estimate should be sufficiently qualified as to the assumptions used and the accuracy of the estimates.

In the assessment of developmental toxicity, statistical considerations require special attention. For example, the power of a study (i.e., the ability to demonstrate an effect), is limited by the sample size used in the study, the background incidence of the end point observed, and the variability in the incidence of the end point. As an example, Nelson and Holson(41) have shown that the number of litters needed to detect a 5 or 10 percent change was dramatically lower for fetal weight (a continuous variable with low variability) than for resorptions (a binomial response with high variability). With the current recommendation in testing protocol being 20 rodents per dose group(1, 3), it is possible to detect an increased incidence of malformations in the range of 5 to 12 times above control levels, an increase of 3 to 6 times the *in utero* death rate, and a decrease of 0.15 to 0.25 times the fetal weight. Thus, even within the same study, the ability to detect a change in fetal weight is much greater than for the other end points measured. Consequently, for statistical reasons only, changes in fetal weight are often observable at doses below those producing other signs of developmental toxicity.

At present, there is no mathematical model that is generally used for estimating developmental toxicity responses below the applied dose range. This is due primarily to the lack of understanding of the biological mechanisms underlying developmental toxicity, intra/interspecies differences in the types of developmental events, the influence of maternal effects on the dose-response curve, and whether or not a threshold exists below which no effect will be produced by an agent. The assumption of a threshold is based largely on the biological rationale that the embryo is known to have some capacity for repair of the damage or insult(42), and that most developmental deviations are probably multifactorial in nature(43). However, the existence of a no effect level cannot be proven statistically.

Discussions of risk extrapolation procedures have noted that further work is needed to improve mathematical tools for developing estimates of potential human developmental risk(32, 44). Gaylor(45) has suggested an approach for controlling risk that combines the use of mathematical models for low-dose estimation of risk with the application of a safety factor based on a preselected level of allowable risk. This approach is similar to approaches proposed for carcinogenesis, but does not preclude the possibility of a threshold, and may provide a more quantitative approach to controlling risk. For the present, the Agency will continue to use safety factors and margins of safety as described above, where applicable. However, more appropriate models will be sought and applied if considered acceptable.

These Guidelines summarize the procedures that the U.S. Environmental Protection Agency will follow in evaluating the potential for agents to cause developmental toxicity. These Guidelines will be reviewed and updated as advances are made in the field, since it is evident that our ability to evaluate and predict human developmental toxicity is imprecise. Further studies that delineate the mechanisms of developmental toxicity and pathogenesis, provide comparative pharmacokinetic data, and elucidate the functional modalities that may be altered by exposure to toxic agents will aid in the interpretation of data and interspecies extrapolation. These types of studies, along with further evaluation of the relationship between maternal and fetal toxicity and the concept of a threshold in developmental toxicity, will provide for the development of improved mathematical models to more precisely assess risk.

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