WORKBOOK FOR USER WORKSHOP

— —

EPA GUIDELINES

FOR

HEALTH RISK ASSESSMENT

OF

CHEMICAL MIXTURES

— —

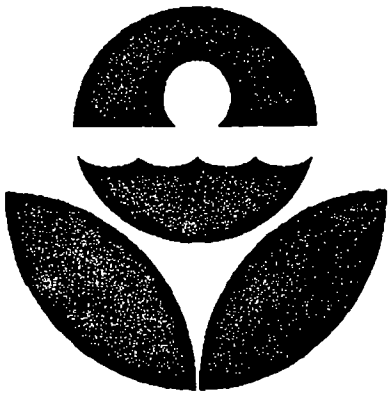
DENVER, REGION VIII

MAY 3, 1988

#348

GUIDELINE-SPECIFIC BRIEFING SLIDES

RISK ASSESSMENT GUIDELINES: *Chemical Mixtures*



EPA

Environmental
Protection Agency

EPA CHEMICAL MIXTURES GUIDELINES

Hazard Identification	Characterizing toxicity of mixture, similar mixture, or components
Dose-Response Assessment	Evaluating dose-response data for mixture, similar mixture, or components
Exposure Assessment	Refer to exposure assessment guidelines
Risk Characterization	Estimating risk using all appropriate methods

WHY ARE MIXTURES IMPORTANT?

Mixtures, rather than single compounds, are often found in:

- Landfill leachate
- Pollutants in ambient air
- Purification byproducts in drinking water

WHAT IS NEW?

Framework for working within data constraints

Criteria for judging quality of risk assessment data

Emphasis on flexibility, judgment, a clear articulation of assumptions

Option not to quantify the risk

ASSESSMENT OF DATA QUALITY

Information on Interactions

Actual Data ⟷ **Insufficient Data**

Health Effects Information (Dose-Response)

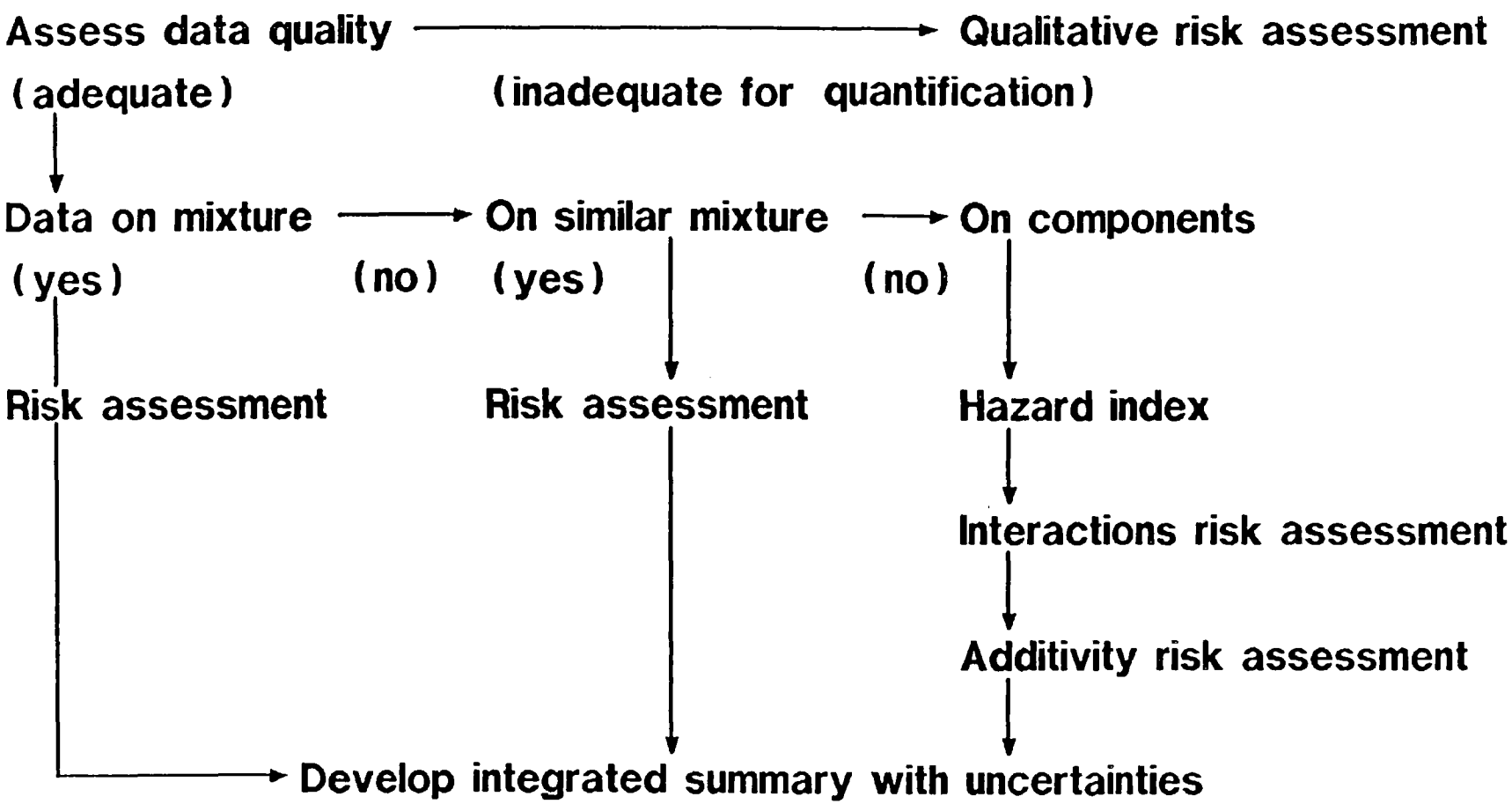
Full Health Effects Data ⟷ **Insufficient Data**

Exposure Information

Monitoring Data ⟷ **Insufficient Data**

Without adequate information, no quantitative assessment is made!

OPTIONS FOR MIXTURE ASSESSMENTS



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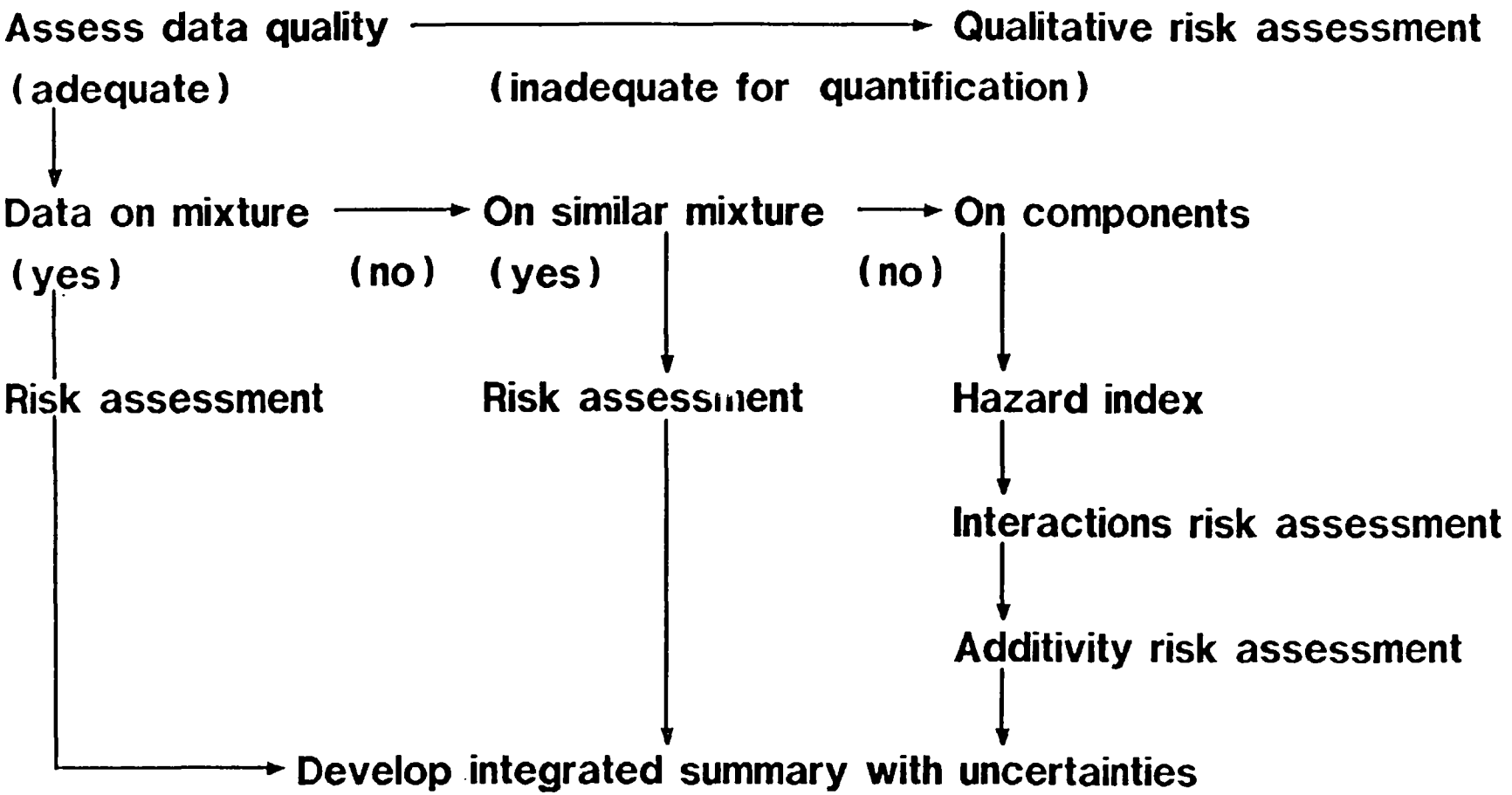

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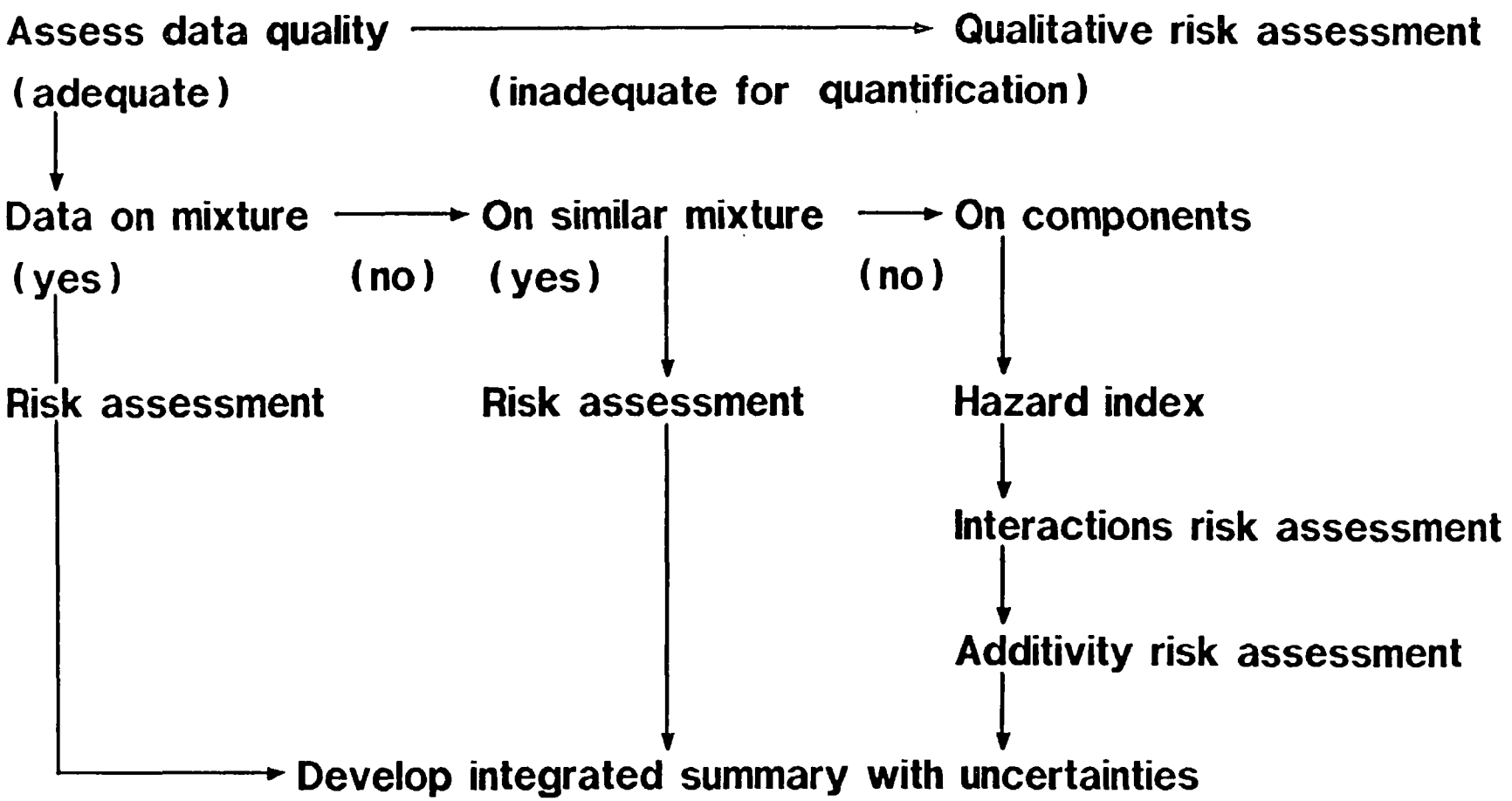
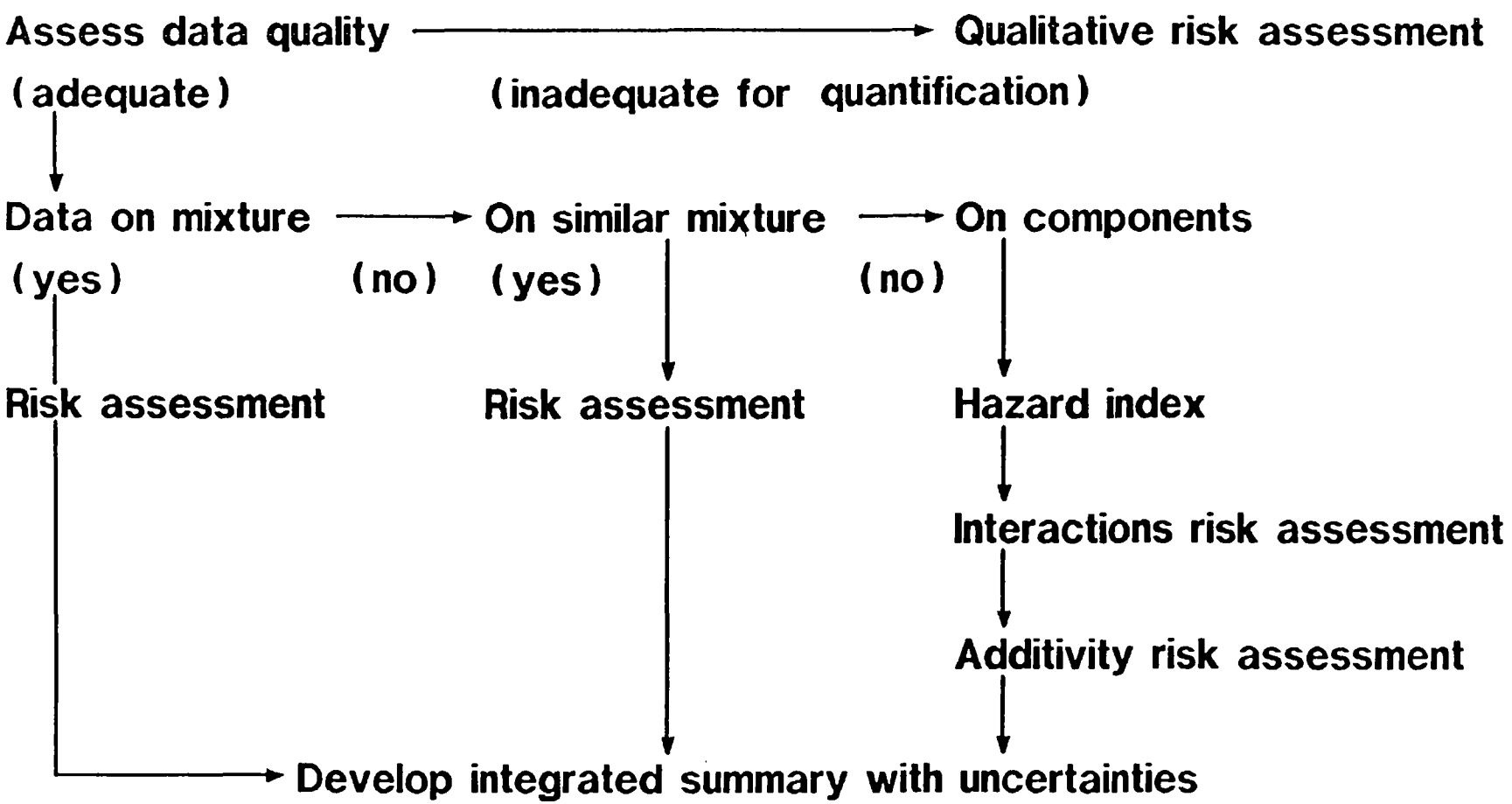


OPTIONS FOR MIXTURE ASSESSMENTS



UNCERTAINTIES

Evaluate and express uncertainties in:

- Composition

  Interactions

  Health effects

  Exposure

ASSUMPTIONS AND LIMITATIONS

Discuss information such as:

- Interactions
- Modeling assumptions
- Data limitations

SUMMARY - MIXTURE ASSESSMENT

- Science and art
- Judgment must be exercised
- Divergence of situations requires flexibility in approach
- Assessor must pass on assumptions, judgments, and uncertainties to the decision maker (risk characterization)

CASE STUDIES

MIXTURE CASE STUDY 1

PARTICIPANT'S OVERVIEW
MIXTURES ASSESSMENT
CASE STUDY 1

- The following pages contain a case study that should guide you through the mixture assessment guidelines and give you an opportunity to do some straight forward calculations for both systemic and cancer health risks.

- As noted in the case, the goals of the exercise are to familiarize the students with the specifics of the mixtures guideline and also to provide the student with hands-on experience in working through the guidelines.

- As well as responses to the specific questions raised in the problem, you should discuss the extent to which the stated goals of the guidelines -- to encourage consistency and scientific quality in risk assessments -- have or have not been demonstrated.

- Be sure to make extensive use of the Guidelines and provide, whenever appropriate, specific page and column numbers from the Guidelines in your responses.

MIXTURES ASSESSMENT TRAINING
CASE STUDY # 1
ESTIMATION OF RISK FOR POLLUTED GROUNDWATER

The Situation

Ground-water contamination is one of the nation's more common pollution problems and one of the most difficult to address in terms of identifying human health risk. Too often, monitoring data are incomplete making an adequate assessment impossible.

As the groundwater risk assessor for your office, you have been asked to analyze the situation confronting the public health officials of Mudville: five chemicals have been found in their drinking water wells! In addition to examining the specifics of the applications of the Guidelines to the risk assessment process, this case study will emphasize the need to identify and evaluate the uncertainties inherent in the assessment.

Concentrations of five chemicals (benzene, bromoform, carbon tetrachloride, 1,1-dichloroethylene and toluene) have been measured in four drinking water wells in Mudville. The pollutants, all of which were measured above their respective detection limits, are generally assumed to have originated in and leached from a landfill near the wells. The landfill has been capped with clay so that the only present exposure route of the chemicals to the citizens of Mudville is through the drinking water. Moreover, during the past three years, the contaminant levels in the wells have declined about ten percent. The results of the most recent monitoring tests are shown in Table 1.

In this exercise, you are asked to assess the human health risk posed by the contaminant mixture in the wells, and to be prepared, if necessary, to brief the Regional Administrator on these risks. Using data provided in the tables at the end of this handout and the Agency's Guidelines for the Health Risk Assessment of Chemical Mixtures, you will be guided by a series of tasks through the risk assessment process.

SUMMARY OF DATA TABLES (ATTACHED)

Table 1 shows the most recent monitoring data for the 5 chemicals in four Mudville drinking water wells. Notice that "maximum" levels are also identified. In order to simplify this exercise, we suggest you use these maximum values in your calculations. In at least one of the exercises you will need to discuss the implications of this simplification. Moreover, we

suggest you consult the Exposure Assessment Guidelines to decide how you might deal with data in the "real" world.

Tables 2 and 3 respectively show the systemic toxicity and carcinogenicity information available for the well pollutants.

Table 2 (column 3) shows the Reference Dose (RfD) for each compound. The RfD is an estimate, with uncertainty spanning an order of magnitude, of the amount of a substance thought to be without adverse effect in humans, even if exposure at this level occurs for a lifetime. Column 6 shows the "allowable" concentration in drinking water, estimated from the RfD, assuming daily consumption of 2L of water by a person weighing 70 kg. (The word "allowable" should not be understood to connote safety. Among Agency risk assessors this concentration, since it is based on the risk reference dose, is now more commonly referred to as a "reference" level.)

Table 4 provides data on the cancer risk estimates for the individual wells. Data on toxic interactions (which is very important in mixture risk assessment) are shown in Table 5.

Task A: Given the data in hand, and using the rating schemes (Table 2 of the Guidelines), decide whether a quantitative risk assessment (QRA) can be performed. If your answer is affirmative, which of the procedures (whole mixture, similar mixture, etc.) should be used?

Suggestions: In performing this evaluation, you will want to consider, among other things, the following:

1. the 'preferred' type of data that would be used in an assessment;

2. the nature and extent of interactions of all types among the mixture components;

3. the availability of health effects and exposure information on the well water or its components;

4. the extent to which professional judgement enters into this evaluation

Task B: Table 5 summarizes the available data on toxic interactions of the chemicals found in the wellfield; benzene and toluene, and carbon tetrachloride and toluene. The data are not sufficient to determine whether there are long-term interactions between the chemicals present in the wells.

What use can be made of these data in the risk assessment?

Suggestions: Consider the following:

1. the various types of interactions that can take place, and their temporality;

2. the effects of synergistic or antagonistic interactions on a mixture risk assessment;

3. the effect such interactions can have on exposure, the hazard index, or the cancer risk assessment;

4. the conclusions, from the data in Table 5, for the risk assessment conducted for Mudville's drinking water.

Task C: Using information on actual and "allowable" reference levels of exposure to a compound(s), the guidelines recommend the development of a "hazard index" (HI) as a rough measure of the degree of toxicity of a mixture.

Use the data available in the tables and the information provided in the guidelines to perform such an evaluation for non-cancer effects. Decide whether there is cause for concern for the non-carcinogenic effects of this mixture.

Suggestions: Among the factors you will need to consider are the following:

1. similarity of action of the components (are any data provided to enable you to judge this?);

2. the use of the formula given for the HI in the guidelines;

3. the extent to which additivity in response or dose can be applied to the components of the well water;

4. the confidence in the RfD, and the uncertainty factors used in its estimation;

5 the extent to which the HI provides a quantitative estimate of hazard;

6. the significance of the differences in toxic endpoints for the mixture components.

Task D: The excess cancer risk (R) from a lifetime exposure to the mixture is calculated using the following formula:

R= U1 x E1 + U2 x E2 +.....Un x En

Un = unit risk estimate (risk from 1 ug/L) of the nth toxicant
En = monitored level in the well (ug/L) of the nth toxicant

Using the above formula, and the data in Table 1, calculate the excess cancer risk from a lifetime exposure to the mixture for well 1. Insert your answer in column 1 of Table 4.

Please discuss the differences between the excess risk determined using the "maximum levels" and the risks calculated for the individual wells. Also, please discuss the reasons for the two overall cancer risk estimates shown in Table 4.

Suggestions: In your review, you should consider the following:

1. the applicability of the formula at various exposure levels;

2. the extent to which additivity can be applied to the cancer data for the components of the well water;

3. the similarities and differences between this formula and that used to describe the potential systemic toxicity;

4. the influence of weight of evidence of carcinogenicity in the overall risk assessment.

Task E (Part 1): The evaluation of uncertainty and the presentation of the uncertainties, assumptions, and limitations of the assessment is an important part of risk assessment.

Discuss the major points of uncertainty in the assessment of risk of the sampled drinking water wells of Mudville.

Suggestions: You should, at a minimum, discuss the uncertainties in the interaction data, in the exposure information, and in hazard estimates done in the assessments. In so doing you should consider the following:

1. data on interactions;

2. the precision of the RfDs and the effect of this precision on the uncertainty of the mixture assessment;

3. the implications of the use of "maximum" exposure levels (do the Exposure Assessment Guidelines help?);
4. the lack of uniformity in the cancer data;

5. the absence of data on other exposure routes or on individuals who do not fit EPA's assumptions (e.g., children, individuals drinking more or less than 2L per day, persons who may be exposed at work, with lower body weights or other special considerations).

Task E (Part 2): Summarize the most important "overall" conclusions of the risk assessment?

Suggestions: You should consider the following in your review:

1. your conclusion of the cancer and non-cancer risk to a person drinking water from the wells;

2. your summary of the quality of the available data and the uncertainties of the assessment;

3. the extent to which this exercise demonstrated (or failed to adequately bring out) the stated goals of the guidelines - to promote quality and consistency in risk assessment.

TABLE 1. MONITORING DATA

CHEMICAL	CONCENTRATIONS IN WELLS (ug/l)[a]				
	Well 1	Well 2	Well 3	Well 4	Maximum Level
Benzene	22.	17.	10.	30.	30.
Bromoform	82.	30.	34.	42.	82.
Carbon tetrachloride	20.	21.	14.	20.	21.
1,1-Dichloroethylene	33.	27.	41.	22.	41.
Toluene	540.	470.	600.	520.	600.

[a] All concentrations are above the detection limits. These are the latest measurements, but the concentrations seem to be decreasing over time.

TABLE 2. SYSTEMIC TOXICITY INFORMATION FOR THE EXAMPLE SITE ASSESSMENT

CHEMICAL	MAXIMUM CONC'N[a] (ug/l)	REFERENCE DOSE[b]			REFERENCE LEVEL (RL)[c] (ug/l)	E/RL	CRITICAL TARGET ORGAN
		RfD (mg/kg-d)	CONFIDENCE IN RfD	UF USED FOR RfD			
Benzene	30	.0007[e]	---	1000	25.	1.2	blood
Bromoform	82	.006[f]	low	10	210.	.39	liver
Carbon tetra-chloride	21	.0007	medium		25.	.86	liver
1,1-DCE	41	.009	medium		320.	.13	liver
Toluene	600	.3	medium		11000.	.057	blood

Hazard Index (liver) = 1.4
Hazard Index (blood) = 1.3

a: Maximum monitored level (See Table 1).

b: An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population, including sensitive subgroups, that is likely to be without appreciable risk of deleterious effects even if exposure occurs during a lifetime.

RfDs are estimated to one significant digit. RLs and the E/RL ratio are carried with two digits since they are calculated intermediate values. The Hazard Index is only given to one digit to reflect the precision of the RfD.

c: RfDs are converted to RLs assuming daily consumption of 2 L of water by a 70 kg person, and the application of a factor of 1000 to convert mg to ug.

d: The target organ affected in the critical study, i.e., in a series of studies, the study showing an adverse effect at the lowest dose level (see Appendix to IRIS).

e: No reference dose has been established for non-cancer effects of benzene. This value was derived by EPA's Office of Drinking Water, U.S. EPA 1985.

f: No reference dose has been established for bromoform. The value reported here is fictitious, as are the uncertainty factor and level of confidence in the fictitious RfD.

TABLE 3. CARCINOGENICITY INFORMATION FOR THE EXAMPLE SITE ASSESSMENT

CHEMICAL	MAXIMUM CONC'N. (ug/l)[a]	UNIT RISK[b] (/ug/L)	EXCESS RISK[c]	WEIGHT OF EVIDENCE[d]
Benzene	30	8.2×10^{-7}	2.5×10^{-5}	A
Carbon Tetrachloride	21	3.7×10^{-6}	7.8×10^{-5}	B2
1,1-DCE	41	1.7×10^{-5}	7.0×10^{-4}	C

Mixture cancer risk (without DCE) = 1×10^{-4}

Mixture cancer risk (including DCE)= 8×10^{-4}

[a] Maximum monitored levels (See Table 1).

[b] Upper bound of the estimated excess cancer risk from lifetime exposure to 1.0 ug/l in drinking water, assuming consumption of 2 L water per day by a 70 kg person. The actual risks are not likely to be greater, and could be significantly smaller than this estimate.

Note that this value (and the excess risk) are not rounded because they are intermediate values in the risk assessment

[c] Upper bound of the estimated excess cancer risk from lifetime exposure at the maximum monitored concentration.

[d] See the cancer risk assessment guidelines (US EPA, 1986b).

TABLE 4. CANCER RISK ESTIMATES FOR INDIVIDUAL WELLS[a]

CHEMICAL	EXCESS CANCER RISK WELL 1	WELL 2	WELL 3	WELL 4
Benzene		1.4×10^{-5}	8.2×10^{-6}	2.5×10^{-5}
Carbon tetrachl.		7.8×10^{-5}	5.2×10^{-5}	7.4×10^{-5}
1,1-DCE		4.6×10^{-4}	7.0×10^{-4}	3.7×10^{-4}
Mixture risk				
without DCE		9×10^{-4}	6×10^{-5}	1×10^{-4}
including DCE		6×10^{-4}	8×10^{-4}	5×10^{-4}

a. For assumptions and interpretations see footnotes Table 3.

TABLE 5

DATA ON TOXIC INTERACTIONS FOR WELL WATER CHEMICALS

COMPOUNDS	ROUTE[a]	DURATION	SPECIES	EFFECT/ORGAN	INTERACTION[b]	# STUDIES
toluene/	inhal	acute	human	excretion/lung	inhibition	1
benzene	inhal	acute	human	elimin./blood	none	1
	inhal	acute	human	metabolism/body	none	1
	i.p.	acute	rat	excretion/body	inhibition	3
	i.p.	acute	rat	elimin./blood	inhibition	1
	i.p.	acute	rat	metabolism/body	inhibition	3
	i.p.	acute	rat	metabolism/liver	inhibition	1
	s.c.	acute	rat	excretion/body	inhibition	1
	s.c.	acute	mouse	function/marrow	inhibition	1
toluene/	i.p.	acute	mouse	mortality/body	potentiation	1
carbon tet.	i.p.	acute	mouse	depression/cns	potentiation	1

a: inhal= inhalation, i.p.= intraperitoneal injection, s.c.= subcutaneous injection.

b: listed process is lower rate or less severity than expected (if inhibition); or is higher rate or greater severity (if potentiation).

MIXTURE CASE STUDY 2

MIXTURE ASSESSMENT TRAINING
CASE STUDY # 2

The Situation:

You are the Senior Science Advisor to the Regional Administrator. On your way to work one morning, you are greeted with the following headline:

DEADLY DIOXIN DELUGES DOWNTOWN
EPA Officials Hold Breath.....And Are Silent

"Sources close to the Regional Administrator of EPA (RA) have informed the Gazette that the Agency has obtained 'high tech data' showing that the city's new $100 M recycling energy-from-waste municipal waste combustor (MWC) is emitting dioxin, which--according to EPA -- is 'the most toxic man-made chemical'. In addition, EPA documents state in reference to dioxin that 'there is no safe level for exposure to such a compound. The recommended level of exposure for humans is zero.'

"These air emissions daily form a plume which casts a deadly pall over the center of the city, with a maximum impact on the grounds of our beloved Wilma Wilder's Shelter for Widows and Waifs. (Ms. Wilder was recently recognized by her admiring fellow citizens when the Mayor's mother presented her with the coveted 'Octagenarian of the '80s' award.) When interviewed in connection with this story Ms. Wilder confessed to 'not feeling as good as I used to.'

"Contacted at his home in the suburbs, 30 miles upwind from the MWC facility, the RA pleaded ignorance of details of the problem, but said he remembers not discussing the matter with his aides -- particulary his Senior Science Adviser. However, he promised this reporter that the latter would report to him by 2 pm this afternoon and that the RA would be available to the media in the Press Room (inexplicably called the Lion's Den) at a press conference later in the afternoon. At that time, the RA intends to discuss the MWC emission data and its implications."

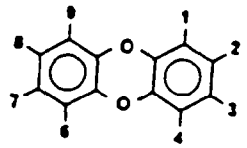
Your eagerness to greet the new day having been blunted, you arrive at work and set about gathering data from recent MWC tests as well as other background information on dioxins in general, on the materials being emitted from the MWC, and on the proper conduct of a risk assessment on a mixture.

After reviewing this material, you should proceed through the tasks that are set forth in this handout. Please make extensive use, where appropriate, of the guidelines.

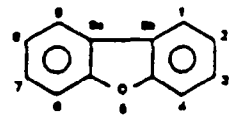
BACKGROUND INFORMATION

A. General Information

The "dioxin" that was referred to in the newspaper stories, as being emitted from the MWC is not a single chemical. Rather, the emissions are a mixture of chemically related chlorinated dibenzo-p-dioxins and -dibenzofurans (CDDs and CDFs), as well as many other components (for which no data are shown). The 75 CDDs and 125 CDFs comprise a "family" of structurally related compounds:



DIBENZODIOXIN



DIBENZOFURAN

Each of the CDDs or CDFs is described as a congener. The CDDs having the same number of chlorine atoms belong to the same homologous group (the same is true for the CDFs). Therefore there are eight CDD homologues (i.e., each having one to eight chlorine atoms). Chemically distinct members of a homologous group are called isomers. For example, there are 22 isomers in the tetra-homologous group of CDDs (the TCDDs). One of these 22 isomers is 2,3,7,8-TCDD.

Most toxicity information is available for 2,3,7,8-TCDD and two HxCDDs. Some information is available for 2,3,7,8-TCDF. While much less is known about the toxic potential of the other congeners, this information is sufficient to assess their relative toxicity. In general, congeners with chlorine substituents at positions 2,3,7, and 8 are significantly more toxic than isomers not so substituted (see Appendix B).

B. Data Available on MWC emissions

Data pertaining to the MWC and its emissions are provided on several attachments. Table 1 shows the relative toxicity (the Toxic Equivalence Factor or TEF; see below) of the 15 most toxic congeners. We will shortly review how these TEFs are used in the risk assessment.

Table 2 shows the results from recent sampling of the MWC stack and the average concentrations of the various homologues and selected congeners (the most toxic ones, those having chlorine atoms at the 2,3,7, and 8 positions) found in the emissions.

Tables 3 and 4 respectively show exposure information and hazard information on 2,3,7,8-TCDD which will be used to estimate the risk posed by the emissions.

C. The TEF Procedure

Most ambient exposures to these compounds involve mixtures of CDDs and CDFs, and in almost all cases there is no information on the toxicity of the mixture in question. Therefore, in an attempt to deal with the uncertainty presented by the absence of data on the mixture, EPA has adopted an interim procedure (the TEF procedure) based on dioxin toxicity equivalence factors (TEFs) for estimating the risks from exposure to CDD/CDF mixtures.[1]

The following is a brief description of the TEF procedure. In the TEF approach, the exposure level of each CDD and CDF congener or homologous class is replaced by the concentration of 2,3,7,8-TCDD that is estimated to potentially cause the same health effect as the CDD\CDF in question. These exposure levels (now in terms of TCDD equivalents) are used in the risk assessment. The TEF procedure involves the following steps:

1. Analytically determine the CDDs and CDFs in the sample, preferably determining both the total and 2,3,7,8-substituted congeneric concentration.

2. Determine the appropriate values for the TEFs. These are shown in Table 2.

3. Multiply the congener concentrations in the sample by the TEFs in Table 2. This expresses the measured concentrations in common terms, i.e., in terms of 2378-TCDD equivalents. For example, the average concentration of 2378-PeCDD of 650 ng/dscm (see Table 3) multiplied by its TEF of 0.5 (Table 2), gives the 2378-TCDD equivalent value (TEQ) for this congener as 325 ng/dscm.

4. Sum the TEQs to obtain the total concentration of 2378-TCDD equivalents in the mixture.

   Thus, in cases in which the concentrations of the 15 2378-substituted congeners listed in Table 2 are known:

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[1]Interim procedures for estimating risks associated with exposures to mixtures of chlorinated dibenzo-p-dioxins and -dibenzoforans (CDDs and CDFs) EPA/625/3-87/012, March 1987.

2378-TCDD Equivalents = (TEF of each 2,3,7,8-CDD or CDF congener X the concentration of that congener)

5. This latter value, in combination with exposure and toxicity information (tables 4 and 5), allows the assessor to estimate the risks associated with the mixture.

D. Risk Calculations

Although this is not a course on how to perform a risk assessment, you need to know how to estimate exposure and risk in order to work through the following material.

1. Estimation of exposure

Table 2 contains data on measured stack emissions from the MWC. The emissions contain an average concentration of 120 ng 2378 HxCDDs/dscm. The exposure information presented in Table 4 indicates that a reasonable estimate for ground level concentration at 1 km downwind is approximately 10^5 to 10^6 fold dilution of the stack emissions (for purposes of illustration we will use only the latter value in these calculations). The estimate for ground level concentration at 1 km is therefore approximately:

120×10^{-6} ng 2378-HxCDDs/m^3 air.

Table 1 shows that EPA has assigned a TEF value of 0.04 to the 2378-HxCDDs. Therefore, the estimated exposures is:

$0.04 \times 120 \times 10^{-6} = 4.8 \times 10^{-6}$ ng TCDD/m^3 air.

Information available in Table 3 indicates that approximately 75% of an inhaled dose is absorbed in the lung. Accordingly, the estimate of the absorbed dose is:

3.6×10^{-6} ng TCDD/m^3, or 3.6×10^{-3} pg TCDD/m^3 air.

2. Estimation of cancer risk

The estimate of the upper limit of the cancer risk resulting from a lifetime exposure = dose x unit risk for carcinogenicity (see Table 3) = $(3.6 \times 10^{-3}$ pq/$m^3) \times (3.3 \times 10^{-5}$/pg/$m^3) =$ $= 10^{-7}$[B2].

Now let's get on with the exercise!

Task A: Focusing on Figure 1 of the Mixture Guidelines, and using the data provided in the Tables for this exercise, decide whether the preferred approach can be used, and, if so, why. If the preferred approach is not possible, determine which approach can be used.

Task B: Use Table 2 to evaluate the quality of the data on interaction, health effects and exposure. Does this evaluation change the determination you made in Task A?

Suggestion: Consider the quality of the data on interactions, health effects and exposure.

Task C: Discuss the appropriateness of using the TEF procedure with the data available in this case.

Suggestions: You will need to consider the following:

1. the assumptions that must be made about the components of the mixture to make this approach defensible;

2. whether there are differences in justification for use of this approach with respect to cancer or systemic toxicity;

3. the role of judgment and professional opinion in determining the applicability of this approach.

Task D: Using the data presented in the Tables and the examples shown at the beginning of the case, estimate the cancer and the teratogenic risk to the exposed population posed by this mixture for isomer-specific data.

1. Estimate the average exposure and the absorbed dose (in pg TCDD eqts./m^3 of air) for a person living 1 km downwind from the MWC (you may wish to consult the sample calculation provided above).

2. Estimate the upper limit of excess cancer risk from this exposure to an individual (use the material in D1 as an example).

3. Estimate the risk for teratogenic effects for a woman living 1 km downwind from the MWC.

4. What additional exposure sites might be considered?

Task E: In our review of Case Study #1, we discussed the importance of the evaluation and presentation of uncertainties and limitations of a risk assessment. For this task, please discuss the major uncertainties in the risk estimation of this mixture.

Suggestions: You should consider the following points:

1. the uncertainties associated with the analytical data and the data on interactions, health effects, and exposure;

2. uncertainty associated with the assumptions necessary to use of the TEF procedure;

3. why it is important to discuss uncertainties;

4. how representative are the stack emission data? Can you quantify the uncertainty in the use of the average concentration and isomer distribution data;

5. the uncertainties and limitations resulting from the fact that only CDDs and CDFs in the emissions were used for the risk assessment.

Task F: Prepare a short briefing on the risks posed by the MWC emissions for the RA. Be sure to include a description of the way the mixture (and other) guidelines were used to develop the risk assessment.

Be sure to include information on the following:

1. characterization of the cancer risk; of the teratogenic risk;

2. assumptions and uncertainties limiting those assessments;

3. ideas on what could be done to limit some of the uncertainty; (e.g., how could a better assessment be developed?)

4. the extent to which the guidelines bolster or limit the evaluation.

TABLE 1

CDD/CDF ISOMERS OF MOST TOXIC CONCERN[a]

Dioxin		Dibenzofuran	
Isomer	TEF[b]	Isomer	TEF[b]
2,3,7,8-TCDD	1	2,3,7,8-TCDF	0.1
1,2,3,7,8-PeCDD	0.5	1,2,3,7,8-PeCDF	0.1
		2,3,4,7,8-PeCDF	0.1
1,2,3,4,7,8-HxCDD	0.04	1,2,3,4,7,8-HxCDF	0.01
1,2,3,7,8,9-HxCDD	0.04	1,2,3,7,8,9-HxCDF	0.01
1,2,3,6,7,8-HxCDD	0.04	1,2,3,6,7,8-HxCDF	0.01
		2,3,4,6,7,8-HxCDF	0.01
1,2,3,4,6,7,8-HpCDD	0.001	1,2,3,4,6,7,8-HpCDF	0.001
		1,2,3,4,7,8,9-HpCDF	0.001

[a] In each homologous group, the relative toxicity factor for the isomers not listed above is 1/100 of the value listed above.

[b] TEF = Toxicity Equivalence Factor = relative toxicity assigned. These factors are utilized in the "TEF Procedure": the concentration of each CDD/F isomer (or homologue, if isomer-specific data is lacking) is multiplied by the appropriate TEF factor listed above, resulting in an estimate of the TCDD equivalents for that isomer.

TABLE 2

STACK EMISSION DATA*
(ng/dscm)

Compound	Average Concentration	Range
MonoCDD	7.4	ND - 13**
DCDDs	39	ND - 130
TrCDDS	45	ND - 140
TCDDs : total	230	42 - 450
: 2378	100	21 - 200
PeCDDs: total	1200	270 - 2800
: 2378	650	510 - 940
HxCDDs: total	510	140 - 1500
: 2378	120	100 - 570
HpCDDs: total	160	120 - 390
2378	110	90 - 240
OCDD	41	33 - 110
MonoCDF	19	8 - 55
DICDFs	66	48 - 98
TrCDFs	80	34 - 120
TCDFs : total	75	49 - 87
: 2378	30	22 - 76
PeCDFs: total	250	130 - 540
: 2378	130	100 - 280
HxCDFs: total	900	640 - 1200
: 2378	620	440 - 820
HpCDFs: total	200	160 - 260
: 2378	120	90 - 180
OCDF	6	ND - 20

* Averages and ranges derived from monitoring measurements made on five successive days.

** ND: <0.5 ng/dscm.

TABLE 3

EXPOSURE INFORMATION DATA

EPA'S USUAL EXPOSURE ASSUMPTIONS

I. ASSUMPTIONS ON THE EXPOSED INDIVIDUAL

Lifespan: 70 years

Bodyweight:

Adult: 70 kg

Child: 10 kg

Breathing rate

Adult: 20 m^3/day

II. ASSUMPTIONS ON BIOAVAILABILITY FOLLOWING INHALATION:

- 2,3,7,8-TCDD (and other CDDs and CDFs) in the emissions are adsorbed onto particulate matter
- about 75% of inhaled particulates are retained in the lung.
- all the 2,3,7,8-TCDD on the particulates is biologically available .

III. AIR DISPERSION MODEL NEEDS:

Stack exit temperature
Flow rate
Stack diameter
Stack height
Ambient temperature
Data assumptions about local climate
Residential pattern

IV. RULE OF THUMB AIR DISPERSION RESULT:

"ballpark" estimate is about 10^5 to 10^6 fold dilution of stack emissions at the point of maximum annual concentration.

TABLE 4

HAZARD INFORMATION DATA

FOR

2,3,7,8-TCDD

- Slope factor for carcinogenic response = 1.6×10^5 per mg/kg/day, derived from feeding study in rats. B2 carcinogen.

- Unit risk number (inhalation) (upper limit estimate of incremental cancer risk for continuous lifetime exposure to 1 pg/m^3 of 2,3,7,8-TCDD in ambient air) = 3.3×10^{-5} . This estimate takes into account the fact that 25% of the inhaled material is exhaled, and 75% is retained and absorbed.

- RfD (based on teratogenic effects) = 1 pg/kg/day.

TABLE A

MIXTURE GUIDELINE EXAMPLE

CDD/CDF INCINERATOR EMISSIONS

ESTIMATION OF RISK

1. HOMOLOGUE-SPECIFIC ESTIMATION OF TCDD EQUIVALENTS

Compound	Concentration (ng/dscm)	TEF	TCDD Equivalents (ng/dscm)
Mono CDD	7.4	0	
DCDDs	39	0	
TriCDDs	45	0	
TCDDs	230	1	
PeCDDs	1200	0.5	
HxCDDs	510	0.04	
HpCDDs	160	0.001	
OCDD	41	0	
Mono CDF	19	0	
DCDFs	66	0	
TrCDFs	80	0	
TCDFs	75	0.1	
PeCDFs	250	0.1	
HxCDFs	900	0.01	
HpCDFs	200	0.001	
OCDF	6	0	
		TOTAL	

* Rounded to 1 significant figure.

TABLE B

MIXTURE GUIDELINE EXAMPLE

CDD/CDF INCINERATOR EMISSIONS

ESTIMATION OF RISK

2. ISOMER-SPECIFIC ESTIMATION OF TCDD EQUIVALENTS

Compound	Concentration (ng/dscm)	TEF	TCDD Equivalents (ng/dscm)
2378-TCDD	100	1	100
other TCDDs			
2378-PeCDDs			
other PeCDDs			
2378-HxCDDs			
other HxCDDs			
2378-HpCDDs			
other HpCDDs			
OCDD			
2378-TCDF			
other TCDFs			
2378-PeCDFs			
other PeCDFs			
2378-HxCDFs			
other HxCDFs			
2378-HpCDFs			
other HpCDFs			
OCDF			

TOTAL _____

Rounded to 1 sign. fig. _____

TABLE C

MIXTURE GUIDELINE EXAMPLE

CDD/CDF INCINERATOR EMISSIONS

ESTIMATION OF RISKS

ESTIMATE OF EXPOSURE AND RISK

APPENDIX A

EXPLANATION OF DOSE AND RESPONSE ADDITION MODELS FOR USE IN CHEMICAL MIXTURE RISK ASSESSMENT

DOSE ADDITION

Dose addition is one method for estimating the potential toxic effects of a mixture of chemicals. This procedure involves the addition of the effective dose of each component, i.e., the ratio of the exposure dose and the RfD for that chemical. This is illustrated in the following table.

	RfD	Potency (1/RfD)	Exposure Dose	Effective Dose*
Chemical 1	10	0.1	100	1
Chemical 2	2	0.5	20	10
			Hazard Index:	11

* Exposure dose / RfD

This example illustrates that the effective dose of the mixture, in effect, accounts for the relative toxic potencies of the individual chemicals of the mixture.

The best justification for dose addition is knowledge that the mixture components act by the same mechanism, on the same target organ, in the same species. In practice these conditions rarely obtain.

1. Data on mechanism of action is seldom available.

2. Target organ specificity of the RfD must be evaluated. RfDs are based on the "critical effect", i.e., in a series of studies, the effect observed at the lowest dose. The organ system affected by the critical effect is the "critical" target organ. At higher doses other effects may be observed, or different target organs may be affected.

In general, only RfDs based on the same critical target organ should be combined in the Hazard Index calculation. Dose addition combining RfDs that are based on different critical target organs, may overestimate the true mixture toxicity.

3. The species basis of RfDs varies. A Hazard Index using RfDs based from different species introduces errors of unknown magnitude.

Information on the critical target organ (and some indication of target organs affected at higher doses) may be obtained from EPA's IRIS data base, or from toxicology references Judicious consideration of such dose-response information may enable the application of dose addition even when the data providing the best justification (data in the same species and target organ, toxicants acting by the same mechanism) are not available.

The following examples illustrate the problems discussed above, and their pragmatic resolution. Example 1 illustrates a Hazard Index that is fairly well justified by the available toxicity data. Example 2 illustrates Hazard Index estimates that might be judged too uncertain to be used.

EXAMPLE 1

GOOD JUSTIFICATION FOR SIMILAR TOXIC ACTION ASSUMPTION

Component	Crit. Target Organ	Species	RfD	Exposure Dose	Exposure RfD
Chemical 1	blood	rat	5	90	18
Chemical 2	blood	rat	1	35	35
Chemical 3	blood	rat	0.1	10	100
				Hazard Index:	153 (=200)

EXAMPLE 2

POOR JUSTIFICATION FOR SIMILAR TOXIC ACTION ASSUMPTION

Component	Crit. Target Organ	Species
Chemical 1	liver	human
Chemical 2	blood*	rat
Chemical 3	blood	monkey

* The liver is affected at slightly higher doses. Therefore one might be justified in estimating a hazard index for chemicals 1 and 2. However, such an index would be an uncertain estimate, since it involves two disparate species.

RESPONSE ADDITION

In response addition, the component risks (response rates) are summed, and the probabilities of simultaneous risks are

subtracted from this summation. This is illustrated in the following example, using cancer as the response:

Chemical	Risk
1	0.001
2	0.003

Mixture risk = [Probability of cancer due to chemical 1] +
[Probability of cancer due to chemical 2] -
[Probability of cancer due to both chemicals]
= 0.001 + 0.003 - (0.001)*(0.003) = 0.003997
= 0.004

This example shows that if the true case is independence of toxic action, response addition is sufficiently accurate even at the fairly high cancer risks of 0.001 and 0.003. There are reasonable theoretical arguments[a] supporting the judgment that even if synergism is observed in a bioassay (i.e., at relatively high doses), the response addition risk estimate for the (much lower) ambient exposures would not be significantly increased by interaction terms. Although these arguments do not consider synergism in biological factors such as pharmacokinetics or physiological transport, they support the use of simple response addition at low doses.

In the case of systemic toxicants, considerations arguing against detectable synergism at low doses may not be justified since there are data[b,c] showing synergism at component doses which individually are "no-effect" levels.

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[a]Thorslund, T.W. and G. Charnley. 1986 Use of the multistage model to predict the carcinogenic response associated with time-dependent exposures to multiple agents. ASA/EPA Conference on interpretation of environmental data: Current assessment of combined toxicant effects. Washington, DC., May 5-6.

[b]Charbonneau, M., et al. 1986. Acetone potentiation of rat liver injury induced by trichloroethylene-carbon tetrachloride mixtures. Fund. Appl. Toxicol. 6 654-661.

[c]Eastmond, D.A., et al. 1987. An interaction of benzene metabolites reproduces the myelotoxicity observed with benzene exposure. Toxicol. Appl. Pharmacol. 91:85-96.

APPENDIX B

Potencies of Dioxins Relative to 2,3,7,8-TCDD

Chemical	Guinea pig LD_{50}	Carcino-genicity	Reproductive/ teratogenic effects	Receptor binding	Enzyme Induction: AHH: Animal cells	Enzyme Induction: AHH: Human cells	Enzyme Induction: EROD	Cell keratin.	Flat (XB) cell assay	Immuno-toxicity in vitro
CDDs:										
Mono thru tri	$<10^{-4}$	--	--	.001-.01	<.001	--	--	.01	--	.005
2378-TCDD	1	1	1	1	1	1	1	1	1	1
TCDDs	<.001	--	<.001	<.01-.16	<.001-.02	--	--	<.001-.01	--	--
2378-PeCDD	.67	--	--	1	.02-.2	--	--	.5	--	--
PeCDDs	.002	--	--	--	<.001	--	--	--	--	--
2378-HxCDDs	.03	.04	.01	.05	.001-.1	--	--	.005	--	--
HxCDDs	--	--	--	--	<.001	--	--	--	--	--
2378-HpCDDs	.004	--	--	--	.002-.004	--	--	--	--	--
HpCDDs	.002	--	--	--	<.001	--	--	--	--	--
OCDD	--	--	<.00001	--	<.001	--	--	--	--	--
CDFs:										
Mono thru tri	--	--	--	≤.001-.02	<.001	<.001	--	.001	--	--
2378-TCDF	.28; .5	--	.03-.13	.3 ; .24 ; .4	.01-.4	.4	.1	.05	.1	.1 , 1
TCDFs	--	--	--	.001-.05	≤.001 ; .04	.4	≤.005	--	--	--
2378-PeCDF	--	--	--	.13 ; .7 ; .6	<.3 ; .4	.8	.1	--	--	--
12467-PeCDF	--	--	--	.15	.002	--	<.001	--	--	--
PeCDFs	--	--	--	.001-.1	≤.001-2	.6	≤.001	--	--	--
2378-HxCDFs	.017	--	--	.04-.5	.05-.2	.9	.1-.5	--	--	--
HxCDFs	--	--	--	.001	.001 ;.002	--	.006	--	--	--
2378-HpCDFs	--	--	--	--	.004	--	--	--	--	--
HpCDFs	--	--	--	<.001	<.001	--	--	--	--	--

Memo to Facilitator Trainees Attending the Mixtures Session

During the discussion of applications of the Mixture Guidelines, you may wish to use examples from your own experiences in risk assessment. Please consider the following during your preparation for this discussion:

1. Describe a situation where you had to evaluate (qualitatively or quantitatively) the health risk from an existing mixture. How did you judge the adequacy of the toxicology and exposure data? How did you present your findings?

2. If you were to perform a risk assessment of a mixture now, what would you change from your previous procedures? Which of the changes would make more use of the Agency Mixture Guidelines? Do the Guidelines assist you in describing the uncertainties in the mixture risk assessment?

CASE STUDY

Scenario

Data Tables and Summary (or both)

Tasks for Trainees

Guidance for Facilitators