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Recommended Default Methodology for Analysis of Airborne Exposures to Mixtures of Chemicals in Emergencies*

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Emergency planning and hazard assessment of Department of Energy (DOE) facilities require consideration of potential exposures to mixtures of chemicals released to the atmosphere. Exposure to chemical mixtures may lead to additive, synergistic, or antagonistic health effects. In the past, the consequences of exposures to each chemical have been analyzed separately. This approach may not adequately protect the health of persons exposed to mixtures. This article presents default recommendations for use in emergency management and safety analysis within the DOE complex where potential exists for releases of mixtures of chemicals. These recommendations were developed by the DOE Subcommittee on Consequence Assessment and Protective Actions (SCAPA). It is recommended that hazard indices (e.g., $HI_i = C_i/Limit_i$, where C_i is the concentration of chemical "i") be calculated for each chemical, and unless sufficient toxicological knowledge is available to indicate otherwise, that they be summed, that is, $\sum_{i=1}^{n} HI_i = HI_1 + HI_2 + \ldots + HI_n$. A sum of 1.0 or less means the limits have not been exceeded. To facilitate application of these recommendations for analysis of exposures to specific mixtures, chemicals are classified according to their toxic consequences. This is done using health code numbers describing toxic effects by target organ for each chemical. This methodology has been applied to several potential releases of chemicals to compare the resulting hazard indices of a chemical mixture with those obtained when each chemical is treated independently. The methodology used and results obtained from analysis of one mixture are presented in this article. This article also demonstrates how health code numbers can be used to sum hazard indices only for those chemicals that have the same toxic consequence.

Keywords Chemical Mixtures, Exposures, Health Effects, Health Code Numbers

Emergency planning, hazard assessment, and safety analysis for U.S. Department of Energy (DOE) facilities require consideration of potential exposures of people and the environment to chemical substances released to the atmosphere. These potential exposures may be to pure substances or to mixtures. Exposure to mixtures of chemicals may lead to additive, synergistic, or antagonistic effects. In the past, the consequences of exposure to each chemical component have been analyzed and compared with guideline values separately. It has not been established that this approach is conservative.

This article presents default recommendations for assessing exposures to mixtures for use in emergency planning and other emergency management applications, and safety analysis within the DOE complex. It also describes the preparation of a matrix of chemicals versus health effects and target organs for implementation of this default mixture methodology. The proposed default methodology is needed because there is seldom enough toxicity information available for a sophisticated analysis of the effects of exposure to mixtures of materials likely to be involved in accidental releases from DOE facilities.

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The calculated concentrations at the receptor point(s) of interest are compared with the Emergency Response Planning Guidelines (ERPGs)[1] or other legally mandated or advisory limit to obtain hazard indices (HIs) for each chemical. ERPGs are being developed by the American Industrial Hygiene Association (AIHA) Emergency Response Planning (ERP) committee for accidental chemical exposures to the public. ERPG values have been approved for eighty-seven (87) chemicals to date (January 1999). Because there are no ERPGs for many chemicals, DOE's Subcommittee on Consequence Assessment and Protective Actions (SCAPA) has developed a hierarchy of concentration-limit parameters for deriving temporary emergency exposure limits (TEELs).[2]

ERPGs or TEELs are used in the simplified emergency planning sequence described in this article. It is recommended that, unless chemicals are known to display significant interactive effects (superadditivity or subadditivity) or proven to be nonadditive, hazard indices (e.g., $HI_i = C_i/Limit_i$, where C_i is the concentration of chemical "i") for chemicals should be added for each specific target organ and/or mode of action (i.e., $\sum HI_{i(p)}$, where "p" represents a specific target organ and/or mode of action).

Application of these recommendations involves preparation of a matrix of the chemicals in a mixture and their toxicological classification using health code numbers (Table I).[3] This allows for evaluation of consequences in terms of modes of action (e.g., acute effects versus cumulative or chronic effects) and toxic endpoints (e.g., by target organ, Table II) for each chemical. The hazard indices are calculated for each chemical, and then summed for those chemicals having the same toxic consequences (i.e., the same health code number series). Patty[3] gives a table of these codes for approximately 600 chemicals, and codes have been derived from the safety profiles in SAX[4] for about 100 additional chemicals. Some health code numbers have been expanded (Table II) to facilitate classification of chemicals by target organ when this information is available.

This methodology has been applied to specific mixtures of chemicals at DOE facilities. Chemicals are sorted by health code numbers, which determine those chemical-specific hazard indices that should be added and those that can be treated independently. Application to a 14-component mixture of chemicals at one DOE facility is presented as an example.

PRELIMINARY CONSIDERATIONS

Source Term Determination

The first step in the analysis of specific accident scenarios is the determination of the nature and quantities of materials

TABLE I
Health code number key for toxicological classification of chemicals

Health code number	Health effect
1	Cancer—currently regulated by OSHA as carcinogens
2	Chronic (cumulative) toxicity—Suspect carcinogen or mutagen
3	Chronic (cumulative) toxicity—Long-term organ toxicity other than nervous, respiratory, hematological or reproductive
4	Acute toxicity—Short-term high hazards effects
5	Reproductive hazards—Fertility impairment or teratogenesis
6	Nervous system disturbances—Cholinesterase inhibition
7	Nervous system disturbances—Nervous system effects except narcosis
8	Nervous system disturbances—Narcosis
9	Respiratory effects other than irritation—Respiratory sensitization (asthma)
10	Respiratory effects other than irritation—Cumulative lung damage
11	Respiratory effects - Acute lung damage/edema
12	Hematological (blood) disturbances—Anemias
13	Hematological (blood) disturbances—Methemoglobinemia
14	Irritation - eye, nose, throat, skin—Marked
15	Irritation - eye, nose, throat, skin—Moderate
16	Irritation - eye, nose, throat, skin—Mild
17	Asphyxiants, anoxiants
18	Explosive, flammable, safety (No adverse effects encountered when good housekeeping practices are followed)
19	Generally low risk health effects—Nuisance particulates, vapors, or gases
20	Generally low risk health effects—Odor

Note: (see *Patty's Industrial Hygiene and Toxicology*, 2nd ed., vol. 3A, p. 157. John Wiley & Sons, New York (1985).)

present and at risk, as well as the time profile of concentrations at the receptor point(s) of interest. Any accident scenario involving an explosion or other violent chemical reaction could result in the dispersion of chemicals unchanged. However, new chemical compounds may be created (e.g., phosgene from combustion of carbon tetrachloride, nitrogen dioxide from nitric acid reactions with organic material), and the form of the chemical may be changed (e.g., from a liquid to a vapor).

Exposure Duration

For release durations of 15 minutes or more, concentrations for comparison with the appropriate guidelines should be calculated as the peak 15-minute time-weighted average (TWA) at the receptor points of interest.[2] For release durations of less than 15 minutes, concentrations for comparison with guideline values may be calculated over a shorter time period but, as a practical lower time limit, not less than 1 minute.

For many chemicals of interest, toxic effects are concentration-dependent. For the present purpose, this by definition includes all chemicals having either Occupational Safety and Health Administration (OSHA)[5] or American Conference of Governmental Industrial Hygienists (ACGIH®)[6] short-term exposure limit (PEL-STEL, TLV-STEL) or ceiling limit values (PEL-C, TLV-C), where PEL = permissible exposure limit, and TLV = Threshold Limit Value, and other chemicals known to cause concentration-dependent toxic responses when inhaled.

For these chemicals, exposure duration may not be the prime consideration. For practical reasons (e.g., limitations of instantaneous concentration monitoring for many chemicals), the peak 15-minute TWA concentration at the receptor point of interest may be used except for those substances that may cause immediate irritation or severe toxicity when exposures are short[6] (e.g., hydrogen sulfide, sulfur dioxide). In such cases, if the release scenario being analyzed gives rise to peak concentrations significantly higher than the peak 15-minute TWA concentration, then a shorter averaging time corresponding to the release duration (not less than 1 minute) should be used.

Other chemicals have toxic effects that are dose-dependent, that is, the severity of the effect increases as the total quantity of absorbed chemical increases. For these chemicals only, the average exposure concentration over a longer period (up to one hour) may be used.[2] Few exposures are likely to exceed one hour.

These categories are not mutually exclusive. There are chemicals that elicit concentration-dependent responses at high

TABLE II
Health code numbers used to classify toxic effects by target organ

HCN	Target organ	HCN	Target organ
1.00	OSHA carcinogen (29 CFR 1910.1000)	5.00	Reproductive toxin
1.01	Bladder carcinogen	6.00	Cholinesterase toxin
1.02	Liver carcinogen	7.00	Nervous system toxin
2.00	Suspect carcinogen or mutagen	7.01	Central nervous system
2.01	Kidney carcinogen	8.00	Narcotic
2.02	Liver carcinogen	9.00	Respiratory sensitizer
3.00	Chronic systemic toxin	10.00	Chronic respiratory toxin
3.01	Bladder	11.00	Acute respiratory toxin
3.02	Unspecified hematological effects	12.00	Blood toxin - anemia
3.03	Bone	13.00	Blood toxin - methemoglobinemia
3.04	Bone marrow	14.00	Severe irritant
3.05	Brain	14.01	Eye irritant - severe
3.06	Eye (chronic ocular)	14.02	Skin irritant - severe
3.07	Gastrointestinal tract	15.00	Moderate irritant
3.08	Heart	15.01	Eye irritant - moderate
3.09	Kidney	15.02	Skin irritant - moderate
3.10	Liver	16.00	Mild irritant
3.11	Skin	16.01	Eye irritant - mild
3.12	Skin perforation	16.02	Skin irritant - mild
4.00	Acute systemic toxin - Short-term high hazard effects	17.00	Asphyxiants, anoxiants
4.01	Eye (acute, other than irritation)	18.00	Explosive, flammable safety (no adverse effects with good housekeeping)
4.02	Nose	19.00	Generally low-risk health effects—nuisance particles, vapors or gases
		20.00	Generally low-risk health effects—odor

Note: (see *Patty's Industrial Hygiene and Toxicology*, 2nd ed., vol. 3A, p. 157. John Wiley & Sons, New York (1985).)

concentrations that also produce dose-related responses at lower doses. For example, acute exposure to high concentrations of benzene can affect the central nervous system, and exposures at lower levels causes hematopoietic effects and leukemia. Also, chemicals such as beryllium, chloroform, ethylene oxide, and formaldehyde exert chronic, dose-dependent effects at low concentrations and display acute toxicity at high concentrations.

Exposure to Multiple Chemicals with Independent Effects

When simultaneous or consecutive exposure to more than one chemical occurs, the toxicological consequences depend upon the target organ(s) of each chemical at the concentration or exposure-dose (concentration x exposure time) of interest, and any interactive effects among these chemicals. If it can be shown that (a) there are no interactive effects (e.g., superadditivity, subadditivity, synergism, antagonism), (b) the target organ(s) are not the same, and (c) the modes of toxicological action are not the same, then the consequences of exposure to multiple chemicals may be considered independent rather than additive.

The exposure concentration (C_i) should be compared with the appropriate guideline concentration (e.g., ERPG) to evaluate acceptability of that exposure as in equations (1) and (2). The ratio of concentration to guideline gives the hazard index (HI_i) for chemical "i":

$$HI_i = \frac{C_i}{ERPG_i} \quad [1]$$

where

$$HI_i \leq 1 \quad [2]$$

means the guideline has not been exceeded.

Exposure to Multiple Chemicals with Combined Effects

In the absence of data supporting the independence of health effects of chemicals in a mixture, the conservative approach (considering the consequences of exposure to be additive)[7] should be taken. The rationale for this additive approach is that treatment of simultaneous exposure to multiple chemicals as independent could allow a greater potential exposure to occur. Consequently, the burden of proof should lie with the decision to treat these kinds of exposures as independent, rather than with the decision to conservatively treat them as additive. This is consistent with the approach recommended by both the Environmental Protection Agency (EPA)[8] and ACGIH[6] and is discussed in some detail in chapter 1 of Hayes.[7]

A more accurate approach is possible if the exposure-response curves[9] are known for all components of the chemical mixture and all the toxic endpoints of interest for the accident scenario being analyzed. Here, "exposure" is represented by concentration or dose, depending upon the chemicals and their toxic endpoints. Unfortunately, these exposure-response curves are known for only a limited number of chemicals.

RECOMMENDED METHODOLOGY

Assessment of Exposures to Chemical Mixtures

Calculate the peak 15-minute TWA concentration, and when applicable for dose dependent chemicals, the peak 60-minute TWA concentration (C_i) for each chemical component "i" at each receptor point. If the release duration is less than 15 minutes, the peak concentration may be averaged over a shorter period (not less than 1 minute). For dose-dependent chemicals only, the concentration at the receptor point of interest may be calculated as the peak 60-minute TWA concentration if the peak 15-minute TWA value is too restrictive (e.g., HI $\geq$ 1.0).

Calculate the ratio of concentration (C_i) to the relevant concentration-limit guideline (e.g., $ERPG_i$, using equation 1)[10] for each chemical to obtain the hazard index, HI_i, for that chemical. Guidelines depend upon the specific application (e.g., emergency classification, see Table III). The release could be considered acceptable if the hazard indices for each receptor point of interest are equal to or less than unity for independently acting chemicals. Unless chemicals are known to display significant interactive

TABLE III
Concentration-limit guidelines for emergency planning[10]

Receptor point	Emergency class		
	Alert	Site	General
Within facility (or 30 m)[A]	≥ERPG-2		
Facility boundary (or 200 m from facility structure)[B]		≥ERPG-2	
Site boundary (or on-site location accessible to public)[C]			≥ERPG-2

Notes:
[A]Default distance for concentration within a facility (see Hazard Categorization of DOE Facilities, DOE-STD-1027-92: Hazard Categorization and Accident Analysis Techniques for Compliance with DOE Order 5480.23 Nuclear Safety Analysis Reports, December 1992).
[B]Default distance to be used if no clearly defined facility structure or boundary can be identified.[10]
[C]This would apply to public roads traversing DOE sites, cafeterias, libraries, etc., to which the public has uncontrolled access, and from which they cannot be evacuated within 30 minutes.

effects (superadditive or subadditive) or are proven to be non-additive, hazard indices for chemicals should be added:[7]

$$\sum_{i=1}^{n} HI_i = HI_1 + HI_2 + \ldots + HI_n \quad [3]$$

As a first approximation, this sum of the hazard indices for chemicals exerting combined effects must be less than or equal to one to be acceptable:

$$\sum_{i=1}^{n} HI_i \leq 1 \quad [4]$$

Toxic Effects Matrix

If assuming additivity of all the chemicals involved in an exposure produces an unacceptable analytical result (i.e., HI $\gg$ 1.0), a matrix of chemicals, their target organs, and/or mode of action should be prepared. Other options for categorizing toxic chemicals may be used instead (e.g., by toxic agent, chemical category). The categorization options are neither all-inclusive nor mutually exclusive. It might be desirable to further subdivide or combine categories of chemicals in specific cases (e.g., gases and vapors, nonvolatile liquids, and solids, or combining corrosives, vesicants, and irritants). A discussion of a suggested approach for implementation of this methodology follows.

Required input includes a list of all chemicals in the mixture (the Chemical Abstract Service Registry Number [CASRN] ensures positive identification), the airborne concentration (C_i), and the applicable concentration-limit (L_i) for each receptor point of interest. Requirements for implementation of the mixture methodology include the chemical category (Table IV, which is modified from Patty, p. 156),[3] and the toxicological classification of each chemical in the mixture, starting with the health code numbers in Patty (pp. 158–185).[3] The category gives the concentration-limit classification used to determine whether the toxicological consequences of exposure to a chemical are concentration-dependent, dose-dependent, or both.[2] Health code numbers for chemicals not listed in Patty are derived from the "Safety Profile" in SAX,[4] three or more health code numbers being determined for each chemical (Table V).

Chemicals can be sorted by name or CASRN. The expanded health code numbers for health effects caused by exposure to each chemical are entered in the matrix. This allows health effect target organs to be included in the toxicological sorting of chemical mixtures. If the SAX safety profile did not list a target organ for a chemical, toxicity was assumed to be systemic (i.e., health code numbers 3.00 for chronic, or 4.00 for acute). Unless chemicals are known to display significant interactive effects (superadditivity or subadditivity), hazard indices for chemicals (e.g., Table VI) are added for each specific target organ and/or mode of action (i.e., $\sum HI_{i(p)}$, where "p" represents a specific target organ and/or mode of action). A non-specific or systemic health code for a chemical should be included in summation of consequences for the primary health code number (e.g., hazard indices for chemicals having health code number 3.00 should be added to the hazard indices for chemicals having health code numbers 3.10, 3.11, etc.). To be acceptable, the sum of the hazard indices must be less than or equal to unity (i.e., $\sum HI_{i(p)} \leq 1.0$).

TABLE IV
Chemical category, concentration-limit classification, and exposure duration treatment

Category[A]	Concentration-limit classification[A]	Exposure duration treatment[B]
1A	Ceiling standard	Concentration-dependent[D]
1B	Irritants	Concentration-dependent[D]
1C	Technological feasibility[C]	Concentration-dependent[D]
2	Acute toxicants	Dose-dependent[E] (exposure limits for 8 hours/day)
3	Cumulative toxicants	Dose-dependent[E] (exposure limits for 40 hours/wk)
4	Both acute and cumulative	Dose-dependent[E] (exposure limits for 8 hours/day and/or 40 hours/week)

Notes:
[A]These categories (column 1) and classifications (column 2) are taken directly from Table 6.7, *Patty's Industrial Hygiene and Toxicology*, 2nd ed., vol. 3A, p. 156. John Wiley & Sons, New York (1985).
[B]For release durations less than 15 minutes, concentrations may be calculated over a shorter time period, but not less than 1 minute if the chemical is known to exert immediate toxic effects.
[C]Permissible exposure limits (PELs) for substances in this category have been set (by OSHA) either by technological feasibility or good hygiene practices, and no adjustments should be made based on the length of exposure, that is, these PELs are treated as ceiling limits.[3]
[D]For concentration-dependent chemicals, the concentration at the receptor point of interest is calculated as the peak 15-minute time-weighted average (TWA) concentration.
[E]For dose-dependent chemicals, the concentration at the receptor point of interest may be calculated as the peak 60-minute TWA concentration.

TABLE V
Target organ health code numbers and concentration-limit classification for chemicals in mixture

No.	Chemical name	CASRN	Health code numbers 1	2	3	4	5	Category
1	Acetone	67-64-1	16.00	8.00				1B
2	Benzene	71-43-2	2.00	12.00	3.00	14.01	14.02	1C
3	Biphenyl	92-52-4	15.00					1B
4	Carbon tetrachloride	56-23-5	3.10	2.00	5.00			1A
5	Chlorobenzene	108-90-7	3.00	8.00	5.00			4
6	Diphenylamine	122-39-4	3.10	3.09	3.01	5.00		3
7	Ethylene glycol	107-21-1	15.00	3.00	7.00			1B
8	Methyl ethyl ketone	78-93-3	15.00	8.00	3.00			1B
9	Methylene chloride	75-09-2	17.00	3.10	8.00			4
10	Phenol	108-95-2	14.00	4.00	2.00			1B
11	Tetrachloroethylene	127-18-4	3.10	7.01	8.00	2.00		1A
12	Toluene	108-88-3	15.00	8.00	7.01			2
13	Trichloroethane, 1,1,1-	71-55-6	16.00	8.00	3.00			1B
14	Xylene	1330-20-7	15.00	8.00	5.00			2

Chemicals in a 14-component mixture, identified as being "at risk" in one accident scenario at a DOE facility, their CAS numbers, health code numbers, and concentration-limit classifications, are presented in Table V. A few concentration-limit classifications given in Patty have been changed, based on SAX safety profile indications that a chemical was an irritant. When irritation is the toxic endpoint, the hazard indices are adjusted by a conservatively chosen factor, depending upon whether the chemical is a marked (severe), moderate, or mild irritant. The health code numbers for chemicals whose HIs should be added for a particular toxic endpoint are shown in bold print in the examples shown in Tables VII, VIII, and IX.

TABLE VI
Concentrations, concentration-limits, and hazard indices for chemicals in mixture

No.	Chemical name	C@30m mg/m^3	C@100m mg/m^3	TEEL-2 mg/m^3	TEEL-3 mg/m^3	HI (T-2) @ 30 m	HI (T-3) @ 30 m	HI (T-2) @ 100 m	HI (T-3) @ 100 m
1	Acetone	5770	544	20100	20100	0.287	0.287	0.0271	0.0271
2	Benzene	417	43.2	479	3190	0.870	0.131	0.0901	0.0135
3	Biphenyl (Diphenyl)	50.1	4.72	7.00	100	**7.160**	0.501	0.674	0.0472
4	Carbon tetrachloride	69.8	6.57	629	4720	0.111	0.0148	0.0104	0.00139
5	Chlorobenzene	206	19.4	920	4600	0.224	0.0448	0.0211	0.00422
6	Diphenylamine	34.1	3.21	50.0	500	0.682	0.0682	0.0642	0.00642
7	Ethylene glycol	24.8	2.34	102	152	0.243	0.163	0.0229	0.0154
8	Methyl ethyl ketone	3780	356	2950	8850	**1.280**	0.427	0.121	0.0402
9	Methylene chloride	1220	115	2600	13900	0.469	0.0878	0.0442	0.00827
10	Phenol	7.37	0.693	193	770	0.0382	0.00957	0.00359	0.00090
11	Tetrachloroethylene	122	11.5	1360	6780	0.0897	0.0180	0.00846	0.00170
12	Toluene	901	84.8	1130	3760	0.797	0.240	0.0750	0.0226
13	Trichloroethane, 1,1,1-	887	83.5	5450	16400	0.163	0.054	0.0153	0.00509
14	Xylene	520	48.9	868	3910	0.599	0.133	0.0563	0.0125
Summation of hazard indices for all chemicals						**13.0**	**2.18**	**1.23**	0.206

Notes: T-2 or T-3 = TEEL-2 or TEEL-3, where TEEL = temporary emergency exposure limit, or ERPGs if available. Hazard indices exceeding unity are bolded.

TABLE VII

Summation of hazard indices for chemicals in mixture having the same toxic consequences: chronic (cumulative) toxic effects (i.e., health code numbers 3.xy)

No.	Chemical name	Health code numbers 1	2	3	4	5	HI for T-2 @ 30 m	HI for T-3 @ 30 m	HI for T-2 @ 100 m	HI for T-3 @ 100 m
2	Benzene	2.00	12.00	**3.00**	14.01	14.02	0.870	0.131	0.0901	0.0135
4	Carbon tetrachloride	**3.10**	2.00	5.00			0.111	0.0148	0.0104	0.00139
5	Chlorobenzene	**3.00**	8.00	5.00			0.224	0.0448	0.0211	0.00422
6	Diphenylamine	**3.10**	**3.09**	**3.01**	5.00		0.682	0.0682	0.0642	0.00642
7	Ethylene glycol	15.00	**3.00**	7.00			0.243	0.163	0.0229	0.0154
8	Methyl ethyl ketone	15.00	8.00	**3.00**			**1.28**	0.427	0.121	0.0402
9	Methylene chloride	17.00	**3.10**	8.00			0.469	0.0878	0.0442	0.00827
11	Tetrachloroethylene	**3.10**	7.01	8.00	2.00		0.0897	0.0180	0.00846	0.00170
13	Trichloroethane, 1,1,1-	16.00	8.00	**3.00**			0.163	0.0541	0.0153	0.00509
Sum of hazard indices for chemicals with chronic (cumulative) toxic effects							**4.13**	**1.01**	0.397	0.0962

Note: Hazard indices exceeding unity are bolded.

RESULTS

Concentrations and hazard indices for two concentration limits (i.e., ERPG or TEEL levels 2 and 3) at two receptor points are given in Table VI for all chemicals in the mixture. These receptor points are at distances of 30 meters (within facility) and 100 meters (outside the facility) from the release. The concentrations were provided by the facility, and were based on inventories, assumed release fractions, and atmospheric dispersion calculations. The sums of the hazard indices for each receptor point and each concentration limit are also presented in Table VI. These represent the opposite extreme from consideration of each hazard index separately, which is the current practice at many DOE facilities. For example, the concentration for each chemical in the mixture at 100 meters from the point of release is given in column 4. The concentration limit (ERPG-2, or TEEL-2 if there are no ERPGs for the chemical)* is given in column 5. The hazard index ($HI_i = C_i/TEEL\text{-}2_i$) is given in column 9. All the individual hazard indices are less than 1.00, but their sum ($\sum HI_i$) is 1.23, greater than 1.00.

Tables VII, VIII, and IX present results for summation of the hazard indices for all chemicals in the mixture with the same toxic consequences: cumulative toxic effects (Table VII),

TABLE VIII

Summation of hazard indices for chemicals in mixture having the same toxic consequences: narcosis (i.e., health code number 8.00)

No.	Chemical name	Health code numbers 1	2	3	4	5	HI for T-2 @ 30 m	HI for T-3 @ 30 m	HI for T-2 @ 100 m	HI for T-3 @ 100 m
1	Acetone	16.00	**8.00**				0.287	0.287	0.0271	0.0271
5	Chlorobenzene	3.00	**8.00**	5.00			0.224	0.0448	0.0211	0.00422
8	Methyl ethyl ketone	15.00	**8.00**	3.00			**1.28**	0.427	0.121	0.0402
9	Methylene chloride	17.00	3.10	8.00			0.469	0.0878	0.0442	0.00827
11	Tetrachloroethylene	3.10	7.01	**8.00**	2.00		0.0897	0.0180	0.00846	0.00170
12	Toluene	15.00	**8.00**				0.797	0.240	0.0750	0.0226
13	Trichloroethane, 1,1,1-	16.00	**8.00**	3.00			0.163	0.0541	0.0153	0.00509
14	Xylene	15.00	**8.00**	5.00			0.599	0.133	0.563	0.125
Sum of hazard indices for chemicals causing narcosis							**3.91**	**1.29**	0.368	0.122

Note: Hazard indices exceeding unity are bolded.

*Temporary Emergency Exposure Limits (TEELs) have been developed for over 1250 chemicals to date. The latest list (Rev. 15) is available on DOE-EH's home page, http://tis-hq.eh.doe.gov/web/chem_safety/doe_reg.html.

narcosis (Table VIII), and irritation (Table IX). All sums of hazard indices greater than 1.00, indicating the need to take some protective action (e.g., reduce inventory of one or more of the chemicals), are presented in bold type.

DISCUSSION

This methodology is *default* methodology; if specific pharmacokinetic or other biological information for the mixture being analyzed is available, the analyst should use that information. It is not biological effects that are being added, but, rather, hazard indices. Obviously, some gross simplifying assumptions are made in recommending simple addition of the hazard indices, in the absence of knowledge about synergistic or antagonistic effects. However, there is much support for this simplistic approach.[6–8]

Beck, Calabrese, and Anderson, in the first chapter of Hayes,[7] "The Use of Toxicology in the Regulatory Process," stated, following a discussion of the available experimental evidence, ". . . most interactions should be considered additive until proven otherwise." They point out many of the complicating factors involved.

This methodology permits the analyst to at least identify chemicals that have the same target organ, or similar modes of action. The health code number system also lends itself to greater sophistication than is presented in this article. For example, another digit could be added for specific modes of action in the same target organ if such information is available for more than one component of a mixture (e.g., 3.10.1 and 3.10.2 for toxins causing chronic liver toxicity by two independent pathways). No attempt is made to classify the relative importance of target organ effects. For this default methodology, the simplifying assumption is made that, if more than one chemical in a mixture causes narcosis, for example, these chemicals' hazard indices should be added. The most limiting of the hazard index summations (i.e., the one that yields the largest value) should be used for evaluation of the release scenario at a particular receptor point. For example, for a concentration limit at 30 meters of ERPG-2 (or TEEL-2), the sums of the hazard indices are 4.13 for chronic toxic effects (Table VII), 3.91 for narcosis (Table VIII), and 6.10 for irritation (Table IX). Thus, although all exceed 1.00, irritation is the limiting effect. The chemicals contributing most to this are biphenyl (HI = 3.60), benzene (HI = 0.870), and methyl ethyl ketone (HI = 0.641), so reduction of inventories or attempts to improve containment of these chemicals is indicated.

Examination of the individual hazard indices in the example (Table VI) shows that there are a few values that exceed unity (bolded numbers). These indicate unacceptable conditions, irrespective of how mixtures are being treated, and would demand mitigative action such as inventory reduction or engineering controls. Whenever the hazard index at a receptor location exceeds unity for any single chemical in a mixture, exposure to that mixture will be unacceptable.

The example illustrates that even though all the individual hazard indices are less than one, the sum of all the hazard indices can be more than one (Table VI). Table VII gives results of applying the recommended mixture methodology for all chemicals in the example mixture that result in cumulative systemic effects, and Table VIII gives results for chemicals that cause narcosis. Even though the individual hazard indices at 30 meters for chemicals with cumulative toxic effects and narcosis (Table VIII) are less than unity, their sum is greater than unity for a concentration limit of TEEL-3. Consequently, some mitigative action to reduce the potential concentration of one or more of these chemicals would be required.

For irritants in the example (Table IX), the sum of the adjusted hazard indices exceeds unity only at 30 meters if the limit is TEEL-2, although it is barely less than one if the limit is

TABLE IX

Summation of hazard indices for chemicals in mixture having the same toxic consequences: irritation (i.e., health code numbers 14.xy, 15.xy, and 16.xy)

No.	Chemical name	Health code numbers 1	2	3	4	5	Adj. factor	HI for T-2 @ 30 m	HI for T-3 @ 30 m	HI for T-2 @ 100 m	HI for T-3 @ 100 m
1	Acetone	**16.00**	8.00				0.25	0.0718	0.0718	0.00677	0.00677
2	Benzene	2.00	12.00	3.00	**14.01**	**14.02**	1.00	0.870	0.131	0.0901	0.0135
3	Biphenyl	**15.00**					0.50	**3.60**	0.251	0.337	0.0236
7	Ethylene glycol	**15.00**	3.00	7.00			0.50	0.122	0.0816	0.0115	0.00770
8	Methyl ethyl ketone	**15.00**	8.00	3.00			0.50	0.641	0.214	0.0603	0.0201
10	Phenol	**14.00**	4.00	2.00			1.00	0.0382	0.00957	0.00359	0.000900
12	Toluene	**15.00**	8.00				0.50	0.399	0.120	0.0375	0.0113
13	Trichloroethane, 1,1,1-	**16.00**	8.00	3.00			0.25	0.0407	0.0135	0.00383	0.00127
14	Xylene	**15.00**	8.00	5.00			0.50	0.300	0.0665	0.0282	0.00625
Summation of hazard indices for respiratory irritants								**6.10**	0.957	0.579	0.0914

Note: Adjustment factors (Adj. factor) of 1.0 for "severe" (code 14), 0.5 for "moderate" (code 15), and 0.25 for "mild" (code 16) have been applied to the hazard indices. Hazard indices exceeding unity are bolded.

TEEL-3. Some mitigative action would be required in the first case, and desirable in the second. With respect to irritants, questions have arisen as to whether the response (K) should not be equated with concentration (C) to some power greater than unity (i.e., $K = C^nT$, where T is exposure time and $n \geq 1$).[11] However, the recommended methodology depends upon the calculation of hazard indices that compare concentrations at the point of interest with the concentration limit at that point. If $HI > 1$ for an individual chemical, then mitigative action must be taken regardless of whether or not consequences increase more rapidly than the concentration. If $HI < 1$ and $n > 1$, consequences decrease more rapidly than concentration, so the proposed methodology will err on the conservative side.

CONCLUSIONS

A default methodology has been recommended for use in emergency planning, hazard assessments, and other applications that pertain to emergency management and safety analysis within the DOE complex. This methodology conservatively addresses voids in methods being used for evaluating exposures to multiple chemicals. To facilitate application of the methodology, a matrix of chemicals and target-organ toxicities, in terms of health code numbers, is presented for an example mixture of 14 chemicals. The matrix approach can be used to decide which chemical-specific hazard indices must be added, and which can be treated separately.

It is recommended that hazard indices ($HI_i = \frac{C_i}{ERPG_i}$) be calculated for each chemical, and unless contraindicated by experimental data or empirical toxicological knowledge for each chemical, these hazard indices should be summed (equation (3)):

$$\sum_{i=1}^{n} HI_i = HI_1 + HI_2 + \ldots + HI_n$$

This sum is subjected to the test (equation (4))

$$\sum_{i=1}^{n} HI_i \leq 1$$

to determine acceptability of the scenario being evaluated, and whether protective actions or administrative controls should be applied. To be acceptable, individual hazard indices, and if appropriate, $\sum HI_i$s, must be ≤ 1.00. It is concluded that the recommended methodology is much superior to the practice of treating exposures to each chemical as independent, and better than the practice of simply adding the hazard indices for all chemicals in any given mixture.

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