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Discrepancy among acute guideline levels for emergency response

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ABSTRACT

Acute guidance values are tools for public health risk assessment and management during planning, preparedness and response related to sudden airborne release of hazardous chemicals. The two most frequently used values, i.e. Acute Exposure Guidance Levels (AEGL) and Emergency Response Planning Guideline (ERPG), were compared in qualitative and quantitative terms. There was no significant difference between the general level of AEGL and ERPG values, suggesting the two systems are equally precautious. However, the guidance values diverged by a factor of 3 or more for almost 40% of the substances, including many of high production volume. These deviations could be explained by differences in selection of critical effect or critical study and in a few cases differences in interpretation of the same critical study. Diverging guidance values may hamper proper risk communication and risk management. Key factors for broad international acceptance of harmonized values include transparency of the decision process, agreement on definition of toxicological tiers, and a target population including sensitive groups of the general population. In addition, development of purely health based values is encouraged. Risk management issues, such as land use and emergency response planning should be treated separately, as these rely on national legislation and considerations.

1. Introduction

The need for control of major chemical releases has burgeoned in recent years related to globalization of the chemical market and stricter safety regulations, increased fear for terrorist acts and increased international collaboration during civil and military missions. Chemical release may be a consequence of fires, industrial and transportation accidents, natural accidents such as tornadoes, earthquakes and flooding, chemical spills, terrorism and chemical warfare. Depending on the nature of such releases, individuals or large groups may be acutely exposed to hazardous substances at levels ranging from lethal or life threatening to harmless.

During emergencies there is an urgent need for society to quickly decide which actions to take. In such situations, acute guidance values are very helpful. Acute guidance values are developed for once-in-a-lifetime, short term exposure to airborne substances. Being based on thorough toxicological health risk assessments, the guidance values give a rapid indication of potential health consequences of specific chemical exposures in the population. The acute guidance values are intended to give decision support during planning, preparedness and response on potential human health consequences of chemical releases [1–6]. Among those who use acute guidance values are: Community emergency planners, Emergency responders, Air dispersion modelers, Industrial process safety engineers, Local Emergency Planning Coordinators, State Emergency Response Commission, Industrial hygienists and toxicologists, Transportation safety engineers, Fire protection specialists, Civil and military government agencies, Risk assessors and risk managers, Resource Conservation and Recovery managers.

At present, several sets of acute guidance values are available in the global arena. However, there are no internationally accepted set of values and comparative analyses of the alternatives are absent. Furthermore, it has been argued that individual efforts by different countries may not be adequate to fill the gaps for several reasons: extensive resource requirement of having separate approaches, communication problems and practical difficulties associated with having numerous different ways of evaluating exposures to acutely toxic chemicals [4,7]. The lack of national and international harmonization thus hampers risk management and communication between stakeholders e.g. during national cooperation during large chemical accidents or during international collaboration in case of cross-national releases or at international civil or military missions. Seveso II is a European Council directive (96/82/EC) concerning the control of major-accident hazards involving dangerous substances. The lack of harmonization was illustrated in a survey of Seveso II competent authorities in 15 European countries [8]. The survey revealed that a variety of different types of acute exposure values are used for Seveso II applications and highlight an opportunity

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for greater collaboration on scientific inputs to application of the Directive in Europe.

The two internationally most frequently used guidance values are the Acute Exposure Guideline Levels (AEGL), developed by the U.S. National Advisory Committee for the Development of Acute Exposure Guideline Levels for Hazardous Substances (AEGL Committee) and the Emergency Response Planning Guidelines (ERPG) developed by the Emergency Response Planning Committee of the American Industrial Hygiene Association (AIHA) [1,2,9–11]. The AEGL and the ERPG systems are similar in that they have three comparable threshold levels (Tiers). Thus, inhalable exposure above the Tier 1 level causes slight, reversible effects such as discomfort and/or irritation. Notably, ERPG but not AEGL includes odor as a Tier 1 effect. When the exposure exceeds Tier 2 the health effects are disabling. The effects may be non-reversible and/or impair the ability to escape but they are still non-fatal. Exposure above Tier 3 is deemed to be life threatening or fatal.

The aim of the present study was to compare, in qualitative and quantitative terms, the AEGL and ERPG values. The analysis of the magnitude of divergence between the two sets of values and the evaluation of the underlying rationales for the divergence, was performed in order to elucidate the need for international harmonization.

2. Methods

2.1. The database

The following data were compiled in a database: Chemical name in English as named by AEGL and ERPG, Chemical Abstracts Service (CAS) number, AEGL guidance values for all three Tiers and for all exposure durations, ERPG guidance values for all three Tiers, point of departures (POD), critical studies, interspecies and intraspecies uncertainty factors (UF) and their rationales, modifying and adjustment factors and their rationales. In addition, risk phrases regarding acute inhalatory exposure and corrosion to the eyes were taken from the European Commission Directive 67/548/EEC. All information published until January 2009 was entered.

All available AEGL and ERPG guidance values were incorporated in the database. In some cases the committees did not recommend a value (a) because of insufficient data to derive a value or (b) because the derived AEGL or ERPG value was higher than the concentration derived for the next Tier. In some cases, as described below, the different sources for AEGL values and documents were unavailable or incongruous. The AEGL values for dimethylformamide and toluene were published on the internet, but the corresponding Technical Support Documents (TSD) were not available. AEGL values derived for the nitrogen mustards were contradictory in that three different sets of values were published (a) on the internet, (b) in the paragraph in the TSD were the AEGL values are derived and (c) in the summary of the TSD [1]. In addition, no specific interspecies or intraspecies UF were given to n-hexane (AEGL-2), 1,3-butadiene (AEGL-3) and butane (AEGL-2 and -3). The AEGL-1 values of monomethylamine and ethylamine and the AEGL-2 value of 1,4-dioxane were based on two different key studies and therefore added as two separate sets of data in the database.

2.2. Statistical analysis

The AEGL and ERPG values were compared at all three Tiers for all substances that appeared in both lists. Only the 1-h values were considered since this is the only exposure duration for which ERPG values are given. To facilitate comparisons, AEGL/ERPG quotients were calculated for each substance at each Tier. Normality was tested by Kolmogorov-Smirnov test and found to be non-significant. The overall comparison of guidance value quotients was performed using a Wilcoxon Signed Rank Test comparing medians with a hypothetical value of 1.0.

Table 1
Number of chemicals with available guidance values in January 2009.

Tier	AEGL	ERPG	AEGL or ERPG	AEGL and ERPG
1	142	105	187	60
2	224	138	274	88
3	218	137	268	87
Any Tier	226	138	279	88
All three Tiers	136	105	173	59

2.3. Qualitative comparisons

The major sources of information for qualitative comparisons are the standing operating procedures for AEGL and the Handbook for ERPG, respectively [2,11]. These documents were primarily used to analyze the transparency of the process, definition of Tiers and specification of target groups. The risk assessment documents of 34 compounds with AEGL/ERPG quotients above 3.0 or below 0.33 were studied in more detail in order to identify the reasons for divergence and to compare the completeness and transparency of the rationales for setting guidance values. The main reasons were classified in four categories; (1) Selection of critical effect or definition of Tiers, (2) Selection of critical studies, (3) Interpretation of data, and (4) Missing data.

3. Results

3.1. Quantitative comparisons

In January 2009, there were 226 compounds with final or interim AEGL values in at least one Tier (Table 1). The corresponding number of ERPG values was 138. The database contained 274 substances that either had an AEGL or an ERPG value in any Tier. However, only about 30% of the substances were assigned both an AEGL and an ERPG value.

The concordance between the AEGL and ERPG values is shown in Fig. 1. For majority of the chemicals the difference between the two systems was small, with AEGL/ERPG quotients falling within 0.33 and 3.0. Both the median (tested by Wilcoxon signed rank test) and the geometric means were close to unity. The latter were 1.26 (95% confidence interval 0.82–1.96) for tier 1, 1.03 (0.86–1.24) for tier 2, and 0.96 (0.81–1.15) for tier 3. This suggests that the two

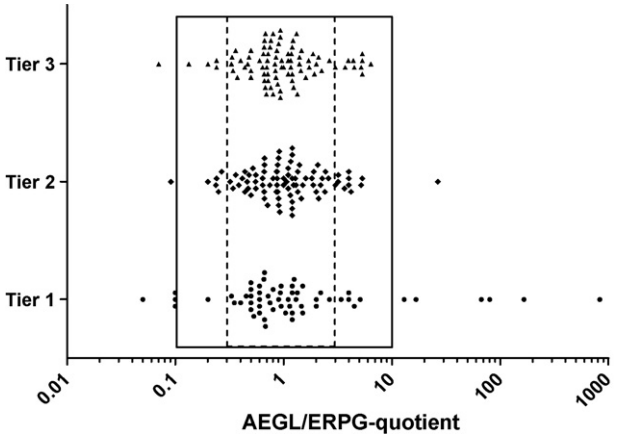

Fig. 1. AEGL/ERPG quotient for Tier 1 (●, notable discomfort), Tier 2 (⧫, severe effects and/or impaired ability to escape) and Tier 3 (▲, life threatening). The boxes mark quotients at the ranges 0.3–3 (dashed) and 1–10 (full), respectively.

Table 2
Substances with deviating AEGL and ERPG values (AEGL/ERPG quotient above 3.0 or below 0.33).

Chemical name	CAS No.	HPV	Risk phrases	AEGL/ERPG quotient		
				Tier 1	Tier 2	Tier 3
Acetaldehyde	75-07-0	Yes	37	4.5	–	–
Butadiene, 1,3-	106-99-0	Yes	–	67	27	–
Acrylic acid	79-10-7	Yes	20	–	–	0.24
Benzene	71-43-2	Yes	–	–	5.3	4.0
Carbon disulfide	75-15-0	Yes	63	13	3.2	–
Carbon monoxide	630-08-0	Yes	23, 61	–	0.24	–
Chloroacetyl chloride	79-04-9	Yes	23	–	3.2	5.2
Chloromethyl methyl ether	107-30-2	Yes	20	–	–	0.2
Chlorosulfonic acid	7790-94-5	–	37	5.0	–	–
Dimethylamine	124-40-3	Yes	20, 37, 41	17	–	–
Ethylacrylate	140-88-5	Yes	20, 37	830	–	–
Fluorine	7782-41-4	–	26	3.4	–	–
Hexafluoroacetone	684-16-2	–	23	–	0.2	–
Hexafluoropropylene	116-15-4	Yes	20, 37	4.0	–	–
Hydrazine	302-01-2	–	23	0.2	–	–
Hydrogen selenide	7783-07-5	–	23	–	3.7	–
Hydrogen sulfide	7783-06-4	–	26	5.1	–	–
Methyl bromide	74-83-9	Yes	23, 37	–	4.2	3.7
Methyl chloride	74-87-3	Yes	–	–	–	3.0
Methyl isocyanate	624-83-9	Yes	23, 37, 41, 63	–	0.27	0.13
Butyl acrylate, n-	141-32-2	Yes	37	166	5.2	–
Nitric acid	7697-37-2	–	–	–	4.0	–
Oleum[a]	8014-95-7	–	37	0.1	–	5.3
Phosphine	7803-51-2	–	26	–	4.0	–
Stibine	7803-52-3	–	20	–	3.0	6.4
Sulfur dioxide	7446-09-5	–	23	–	0.25	–
Sulfur trioxide/sulfuric acid[a]	7446-11-9	–	23	0.1	–	5.3
Tetramethoxysilane	681-84-5	Yes	26, 37, 41	–	0.09	0.07
Toluene	108-88-3	Yes	63	4.0	4.0	4.5
Trimethylamine	75-50-3	Yes	20	80	–	–
Vinyl chloride	75-01-4	Yes	–	–	0.24	0.24

HPV = High Production Volume chemical.
Risk phrases: 20 = harmful by inhalation, R23 = toxic by inhalation, R26 = very toxic by inhalation, R37 = irritating to respiratory system, R41 = risk of serious damage to eyes, R61 = may cause harm to the unborn child, R63 = possible risk of harm to the unborn child.
[a] For all practical purposes, the toxicology of oleum and sulfur trioxide in air is equivalent to sulfuric acid mist. The three compounds are therefore assessed together by both the ERPG and the AEGL committee.

systems are similarly precautious. However, about 40% of the substances have diverging values by more than three-fold in at least one tier. About 20% of the values show larger than threefold deviation and about 5% of the values deviate more than tenfold. For two substances the deviation even exceeds two orders of magnitude.

Thirty four out of 88 (39%) of the substances with both an AEGL and an ERPG value diverged by more than a factor of three in least at one of the three Tiers (Table 2s). The chemicals with diverging guidance values include 20 compounds classified as High Volume Products (HVP) according to the EPA list of 1990 [12] and 13 compounds that are classified as toxic or very toxic by inhalation (R23, R26). Out of these, 5 compounds are both HPV and classified as toxic/very toxic by inhalation (Table 2).

3.2. Qualitative comparisons

At Tier 1, there are 15 compounds with diverging guidance values (Table 3). For nine of the 15 substances, a main reason for divergence relates to the selection of the critical effect. The ERPG committee, in contrast to the AEGL committee, considers clearly defined objectionable odor or other sensory awareness as a critical effect at Tier-1. This discrepancy results in substantially lower ERPG values for seven compounds.

For two chemicals, *chlorosulfonic acid* and *methyl isocyanate*, the reason for divergence seems to be a combination of selection of critical effect and interpretation of data. Thus, in the assessment of *chlorosulfonic acid* both committees use their previous risk assessment for sulfuric acid as a basis for the POD. However, whereas the AEGL committee applies a modifying factor of 2, considering that chlorosulfonic acid splits into sulfuric and hydrochloric acid, the ERPG committee modifies the value by calculating the concentration of formed sulfuric and hydrochloric acid, yielding a slightly different result. Finally, the two committees base their values on different critical effects, namely respiratory irritation and sensory awareness. In their assessment of *methyl isocyanate*, the AEGL committee states that no Tier-1 value can be given since the threshold for severe systemic effects in sensitive groups may lie below the threshold for irritation in the general population. In contrast, irritation is the critical effect used by ERPG to set the Tier 1 value.

In two cases (*acetaldehyde* and *hexafluoropropylene*) the reason for divergence between the two committees was identified as the selection of different critical studies. For *acetaldehyde*, the critical study chosen by the ERPG committee (Silverman et al., 1946) was regarded to be of too low quality by the AEGL committee. ERPG, on the other hand, states that the critical study selected by the AEGL committee (Sim and Pattle, 1957) relates to higher exposure and is therefore not considered as critical. As critical study for *hexafluoropropylene*, AEGL used an acute toxicity study (Du Pont, 1960), whereas ERPG used a subacute study (Stadler et al., 1990). The reason not to use the Du Point study, although referred to in the bibliography, is not explained in the ERPG document.

In three cases; *fluorine*, *hydrazine* and *oleum/sulfur trioxide/sulfuric acid*, ERPG and AEGL use the same critical study but interpret the result differently and derive markedly different guidance levels. The critical study for *fluorine* (Keplinger, 1968) show no irritation among five human subjects at the lowest dose tested (10 ppm for 15 min), whereas eye irritation was evident at slightly higher dose (25 ppm for 5 min). AEGL applies a total UF of six to

Table 3
Chemicals with diverging guidance values (ERPG/AEGL quotient above 3.0 or below 0.33) at Tier 1 and reasons inferred from the technical support documents.

Chemical name	AEGL (ppm)	ERPG (ppm)	Reasons for divergence	
			AEGL	ERPG
Acetaldehyde	45	10	Critical study: Sim and Pattle (1957) Comment by AEGL: The study by Silverman et al (1946) are limited in design, exposure methods were poorly described and actual concentrations were not determined.	Critical study: Silverman et al. (1946) Comment by ERPG: Sim and Pattle (1957) relates to higher exposure than Silverman et al (1946) and are therefore not considered as critical
Butadiene, 1,3-	670	10	Critical effect: Slight smarting of the eyes and difficulty in focusing	Critical effect: Odor
Butylacrylate, n-	8.3	0.05	Critical effect: Decreased maternal body weight, clinical signs of irritation, reduced number of live fetuses and increased resorptions	Critical effect: Odor
Carbon disulfide	13	1	Critical effect: Increase in blood acetaldehyde in humans with moderate intake of alcohol	Critical effect: Odor
Chlorosulfonic acid (CSA)	0.021	0.42	Critical effect: Respiratory irritation Comment by AEGL: CSA considered to be approximately twice as toxic as H_2SO_4, since one molecule of CSA yields one molecule of H_2SO_4 and molecule of HCl.	Critical effect: Sensory awareness Comment by ERPG: 2 mg/m^3 CSA yields 1.6 mg/m^3 $H_2SO_4$and 0.6 mg/m^3 HCl, which is close to or below the limit for sensory awareness.
Dimethylamine	10	0.6	Critical effect: Sensory irritation	Critical effect: Odor
Ethylacrylate	8.3	0.01	Critical effect: Lesions in the olfactory epithelium.	Critical effect: Odor
Fluorine	1.7	0.5	Critical effect: Sensory irritation Critical study: Keplinger et al, (1968) UF: 6	Critical effect: Sensory irritation and odor Critical studies: Keplinger et al, (1968), Ricca (1970), and Lyon (1962) UF: implicit factors of 20 (sensory irritation) or 0.4 (odor)
Hexafluoropropylene	40	10	Critical study: Du Pont (1960), an acute inhalation toxicity study	Critical study: Stadler et al (1990), a subacute inhalation toxicity study
Hydrazine	0.1	0.5	Critical study: US Air force (1964) Comment by AEGL: Mild irritation observed at 0.4 ppm	Critical study: US Air force (1964) Comment by ERPG: No effects observed at 0.8 ppm
Hydrogen sulfide	0.51	0.1	Critical effect: Headache	Critical effect: Odor
Methyl isocyanate	ND	0.025	Comment by AEGL: Developmental toxicity may occur at threshold for irritation	Critical effect: Irritation
Oleum, Sulfur trioxide or Sulfuric acid	0.2 mg/m^3	2 mg/m^3	Comment by AEGL: Some respiratory irritation are shown in many human volunteer studies at concentrations higher than 0.2 mg/m^3	Comment by ERPG: Decrease in forced expiratory volume without symptoms among asthmatics and throat irritation, dryness and cough are evident at 1 mg/m^3 but are considered as very mild.
Toluene	200	50	TSD not available	–
Trimethylamine	8	0.1	Critical effect: Respiratory irritation	Critical effect: Odor

UF = Uncertainty factor; ND = Not determined.

account for intraspecies variation and a limited database. In contrast, the ERPG value is 20 times below the identified NOAEL of 10 ppm, implying that an UF has been applied. The risk assessment for *hydrazine* is based on a study by the US Air Force (1964). Whereas AEGL gave a thorough description of the study and noted mild irritation at 0.4 ppm, ERPG briefly stated that no effect was seen at 0.8 ppm. *Oleum, sulfur trioxide and sulfuric acid* are assumed by both committees to have the same potency as sulfuric acid mist. The reason for divergence is not clearly identified in that ERPG states in their rationale that no significant discomfort occurs below 2 mg/m^3. However, in the hazard identification ERPG states that 1 mg/m^3 causes irritation and cough and that asthmatics experience decreased airway conductance at this level with reference to Utell et al. (1982).

The AEGL document on *toluene* is not available at the AEGL home page, therefore the reasons for divergence at Tier 1 could not be evaluated.

At Tier 2, there are 17 compounds with different guidance values (Table 4). In four cases (*n-butyl acrylate, methyl isocyanate, phosphine* and *vinyl chloride*) the reason for divergence relates to the selection of critical effects. Both committees mention the reproductive effects of *n-butyl acrylate*, but the AEGL document considers it as a basis for a Tier 1 rather than a Tier 2 value. In the assessment of *methyl isocyanate*, the AEGL refers to fetotoxicity and cardiac arrhythmias. In contrast, the ERPG document uses respiratory depression in rodents Respiratory depression by 50% (RD50) as a POD for the guidance value. Also in the assessment of *phosphine*, the selection of critical effect differs. AEGL refers to red mucoid nasal discharge to define a protective threshold for Tier 2, whereas ERPG base its conclusion on respiratory and CNS effects reported from occupational settings. In the risk assessments of *vinyl chloride*, both committees refer essentially to the same key reference (Lester et al., 1963), however, the PODs are different. ERPG departs from the NOAEL of 6000 ppm for irritation in humans, while AEGL base their guidance value on the NOAEL of 12,000 ppm for dizziness.

In seven cases the reason for divergence is related to the selection of critical studies. In four of these cases (*benzene, chloroacetyl chloride, hydrogen selenide* and *methyl bromide*) the key reference used by ERPG is rated as being of low quality by the AEGL committee. In the assessment of *methyl bromide* as well as in one additional case (*sulfur dioxide*) the key reference used by AEGL is missing in the ERPG document. The opposite, namely a missing ERPG key reference in the AEGL document is also evident in one case (*nitric acid*). In the assessments of carbon disulfide, the two committees use dif-

Table 4
Chemicals with diverging guidance values (ERPG/AEGL quotient above 3.0 or below 0.33) at Tier 2 and reasons inferred from the technical support documents.

Name	AEGL (ppm)	ERPG (ppm)	Reasons for divergence	
			AEGL	ERPG
Benzene	800	150	Critical study: Molnar et al. (1986) Comments by AEGL: Decrease in locomotor activity among male rats at doses above 4000 ppm for 4 h. Greenburg (1926) was not considered since no details about the analytical procedure were provided	Critical study: Greenburg (1926) Comment by ERPG: Occupational exposures to 10–150 ppm for 5 h was associated with headache, lassitude and general weakness
Butadiene, 1,3-	5300	200	Critical effect: General NOAEL in humans Comment by ERPG: The study by Irvine (1981) was not considered due to minor fetotoxicity together with maternal toxicity	Critical effect: Fetotoxicity Comment by ERPG: Fetotoxicity was observed in rats after repeated exposure to 1000 ppm but not 200 ppm. (Irvine et al., 1981)
Butyl acrylate, n-	130	25	Critical effect: clinical signs, lesions on nasal mucosa Critical study: Klimisch (1978) Comment: Reproductive effects was considered as base for Tier 1	Critical effect: reproductive and developmental effects Critical study: Merkle (1983) Comment: Klimish (1978) is missing in reference list
Carbon disulfide	160	50	Critical study: Goldberg (1964) Comment by AEGL: Inhibition to escape observed in rats at doses above 1000 ppm for 4 h	Critical study: Vigliani (1954) Comment by ERPG: Paralysis and psycosis observed among workers at doses above 500–1000 ppm
Carbon monoxide	83	350	Critical effect: COHb 4% Comment by AEGL: The COHb should be protective also for patients with coronary artery disease	Critcal effect: COHb 10–12%
Chloroacetyl chloride	1.6	0.5	Critical study: Dow (1986) Critical effect: Impaired ability to escape in rats due to lacrimation and eye squinting Comment by AEGL: Duration was not reported by Vaccaro (1988)	Critical study: Vaccaro (1988) Critical effect: painful eye irritation in humans
Hexafluoroacetone	0.2	1	Critical study: Du Pont (1989) Critical effect: Developmental toxicity from 1 ppm Comment by AEGL: Absence of maternal toxicity reported	Critical study: Morrison (year not given) Critical effect: Clinical signs in rats after 100 ppm for 4 h Comment: Maternal toxicity reported in a study (Mullin, 1990) that seems to be the same as Du Pont (1989)
Hydrogen selenide	0.73	0.2	Critical study: Zwart (1989) Critical effect: 1/3 of AEGL-3 (lethality) Comment by AEGL: AEGL rate the study by Dudler and Miller (1941) as limited but supportive.	Critical study: Dudley and Miller (1941) Critical effect by ERPG: Severe irritation of eye and nose at 1.5 ppm but tolerable at 0.3 ppm
Methyl bromide	210	50	Critical studies: Several Critical effect: Neurotoxicity Comments by AEGL: the quality of the study by Irish (1940) is low and the study by Russo et al (1984) was negative.	Critical studies: Irish et al. (1940) and Russo et al. (1984) Critical effects: Irritation and CNS dysfunction Comment: The critical studies used by AEGL are missing in the ERPG report
Methyl isocyanate	0.067	0.25	Critical studies: Varma (1987) and Tepper et al. (1987) Critical effects: Reduced fetal body weight and increased cardiac arrhythmias in rats and mice	Critical study: Alarie et al. (1987) Critical effects: RD50 Comment: Tepper et al. (1987) and experimental data from Varma (1987) is missing
Nitric acid	24	6	Critical study: Du Pont (1987) Critical effect: partially closed eyes, lung noise and gasping Comment: von Nieding et al. (1980) is missing	Critical study: von Nieding et al. (1980) Critical effect: Certain chronic bronchitis patients exposed to 5 ppm for 5 min reacted with increased airway resistance.
Phosphine	2.0	0.5	Critical study: Newton et al. (1993) Critical effect: red mucoid nasal discharge Comment: The highest dose tested (10 ppm for 6 h) that resulted in only red mucoid nasal discharge was used and considered protective.	Critical study: Misra et al. (1988) Critical effect: Mild to moderate self reported respiratory and CNS effects among workers exposed to levels of approx. 1 ppm for 1–3 h.
Stibine	1.5	0.5	Critical study: Price (1979) Critical effect: Depressed activity, renal tubule dilation, pulmonary inflammation, eye irritation and closure in rats Comment by AEGL: The relatively brief time to death following acute exposure is consistent with death as a consequence of pulmonary edema rather than death from renal failure subsequent to hemolysis.	Critical study: AIHA (1999) Critical effect: Hemolysis in analogy with arsine

Table 4 (*Continued*)

Name	AEGL (ppm)	ERPG (ppm)	Reasons for divergence	
			AEGL	ERPG
Sulfur dioxide	0.75	3	Critical study: Hackney et al. (1984) and Schacter et al. (1984) Critical effect: Moderate bronchoconstriction in exercising asthmatics	Critical study: Sheppard et al. 1980 Critical effect: Bronchconstriction that required therapy among asthmatics Comment: Hacknet et al. (1984) and Schacter et al. (1984) are missing
Tetramethoxy silane	0.91	10	Comments by AEGL: 15 ppm was the no-effect level for irreversible effects according to Kolesar et al. (1989) and a UF of 30 was applied.	Comment by ERPG: Threshold for respiratory irritation from 15 ppm according to Kolesar et al. (1989).
Toluene	1200	300	Comment: TSD not available	–
Vinyl chloride	1200	5000	Critical study: Lester et al. (1963) Critical effect: Dizziness above 12 000 ppm for 5 min	Critical study: Millner (personal communication, 2003), Patty et al. (1930), and Lester et al. (1963) Critical effect: No irritation among humans exposed to 6000 ppm. Anesthesia in guinea pigs at 25 000 ppm for 90 min.

COHb = Carboxy hemoglobin; TSD = Technical Support Document; UF = Uncertainty Factor; RD50 = Respiratory depression by 50%; CNS = Central nervous system.

ferent key critical studies. None of them explains the choice of key study.

The reason for divergence is clearly related to interpretation of data in five cases. In two of these cases (*1,3-butadiene* and *hexafluoroacetone*) one committee used fetal toxicity as critical effect, while the other did not consider this effect due to maternal toxicity observed in the same study. The comparison of the rationales for guidance values on *hexafluoroacetone* further showed that the AEGL and ERPG committees seem to use the same critical data but with reference to two different publications. According to the TSD from the AEGL committee, the study by Du Pont (1989) shows no maternal toxicity and the developmental effects are considered as critical. However, in the (same?) study by Morrison (year not given) cited by ERPG, maternal toxicity is reported and therefore developmental effect is not considered as being the critical one. In the assessment of *carbon monoxide*, both committees use carboxyhemoglobin (COHb) as a biomarker of toxicity. ERPG refers to 10–12% COHb as the critical exposure level for the whole population, including sensitive subpopulations (people with heart disease), whereas AEGL refers to 4% as a protective threshold for the more sensitive group. *Stibine* is a compound that partly shares the mechanism of toxicity with arsine. The ERPG value for stibine is based on hemolysis in analogy with arsine. AEGL, however, comments that the rapid lethal effect observed after acute exposure to stibine is likely to be related to pulmonary edema rather than the more slowly occurring renal failure resulting from hemolysis. In one case (*tetramethoxy silane*), the same key study (Kolesar et al., 1989) and POD (15 ppm) are used as basis for the guidance values, however, whereas AEGL applies an UF of 30, ERPG implicitly uses a factor of 1.5.

As for Tier 1, we were unable to retrieve the AEGL document on toluene.

At Tier 3, there are 13 compounds with diverging guidance values (Table 5). Although lethality is per definition the critical effect of Tier 3, there are two compounds for which the AEGL and ERPG committees base their conclusions on different critical effects. In the case of *chloromethyl methyl ether*, although based on the same critical study, AEGL departs from the lower 95th confidence limit of the concentration causing a 5% increase in response (BMCL05) for lethality while ERPG uses the NOAEL for pulmonary edema. In the assessment of *methyl isocyanate*, AEGL, but not ERPG, uses pup mortality as a basis for Tier 3.

In four cases the discrepancy relates mainly to selection of critical study. In two of these cases (*methyl bromide* and *oleum/sulfur trioxide/sulfuric acid*) it relates to missing reference in the ERPG document. In the TSD for *methyl chloride* the AEGL committee comments on the key references used by ERPG as being of insufficient quality. The assessment of *vinyl chloride* is partly based on the same key studies, however, AEGL use the lower of the two reported EC50 values for cardiac sensitization from Clark-studies (1973), whereas ERPG related to the higher value from a later publication (Clark et al., 1982).

For six chemicals the AEGL and ERPG select the same or similar critical studies for Tier 3, but nevertheless derive different guidance values. For two of these (*acrylic acid* and *tetramethoxy silane*), similar PODs were used, but when AEGL used uncertainty factors of 10 and 30, ERPG implicitly used 2.5 and 1.5, for acrylic acid and tetramethoxy silane, respectively. In another case (*Chloroacetyl chloride*), ERPG states that the critical study (Dow, 1986) show labored breathing at 32 ppm, whereas AEGL states that the same study labored breathing is reported at 522 ppm, which also are NOAEL for lethality. In two cases (*benzene* and *1,3-butadiene*) the quantitative elaboration of dose–response data seem to make a difference in the suggested values. AEGL used NOAEL and LC01, for benzene and butadiene, respectively, rather than the LC50 used by ERPG for both substances. ERPG assessed *stibine* as being analoguous to arsine and hemolysis was deemed as being the critical effect. As for Tier 2, the AEGL committee comments that the relatively brief time to death following acute exposure is consistent with pulmonary edema rather than hemolysis.

Finally, as for Tier 1 and 2, we could not retrieve the AEGL document on *toluene*.

4. Discussion

In January 2009, the number of substances that have either an AEGL or an ERPG value was 279 (Table 1). The overlap between the two sets of values is rather low and AEGL and ERPG values are therefore used as complementary sets, e.g. as a basis for Protective Action Criteria (PAC) by the U.S. Office for Health Safety and Security [13] or for setting Dutch Intervention values [3]. It is likely that the low overlap reflects differences in the selection processes between the two systems. The AEGL program develops guidance values for chemicals "...that could potentially cause dangerous inhalation exposures to persons through accidental releases to air or by means of a terrorist action." [1]. The AEGL priorities were developed by combining nominations by several stakeholders. In this way, the chemicals of highest concern and interest for a variety of scenarios, including industrial application, transportation, and chemical remediation accidents as well as potential malicious release, became AEGL candidates. Thus, the AEGL program seems to focus primarily on public health concerns. The first and second AEGL Chemical Priority List appeared in the Federal Register on May

Table 5
Chemicals with diverging guidance values (ERPG/AEGL quotient above 3.0 or below 0.33) at Tier 3 and reasons inferred from the technical support documents.

Name	AEGL (ppm)	ERPG (ppm)	Reasons for divergence	
			AEGL	ERPG
Acrylic acid	180	750	Critical study: Hagan and Emmons (1988) Critical effect: MLE01 = 1806 ppm Comment by AEGL: UF = 10	Critical study: Hagan (personal com.) Critical effect: LC01 = 2180 ppm Comment: An apparent use of UF = 2.5
Benzene	4000[a]	1000	Critical study: Molnar (1986) Critical effect: NOAEL (lethality) = 5940 ppm for 4 h Comment by AEGL: the levels are supported by historic knowledge on occupational exposure without acute mortality	Critical study: Several Critical effect: LC50 (rodents) = 10,000 ppm Comment by ERPG: Reported tolerated dose for humans >1000 ppm
Butadiene, 1,3-	22,000[b]	5000	Critical study: Shugaev (1969) Critical effect: LC01 = 41,000 ppm Comment: AEGL calculated LC01	Critical study: Shugaev (1969) Critical effect: LC50 = 130,000 ppm
Chloroacetyl chloride	52	10	Critical study: Dow (1986) Critical effect: NOAEL (lethality) = 522 ppm Comment by AEGL: labored breathing in animals reported at doses higher than 522 ppm	Critical study: Dow (1986) and others Critical effect: NOAEL = 522 ppm. After repeated exposure = 1 ppm Comment by ERPG: labored breathing in animals reported at 32 ppm
Chloromethyl methyl ether	2	10	Critical study: Drew et al. (1975) Critical effect: BMCL05 (lethality) = 18 ppm Comment by AEGL: UF = 17	Critical study: Drew et al. (1975) Critical effect: NOAEL (pulmonary edema) = 12.5 ppm Comment: No apparent use of UF:s
Methyl bromide	740	200	Critical study: Kato et al. (1986) Critical effect: BMCL05 = 701 ppm for 4 h	Critical study: not given Critical effect: lethality observed at doses above 250 ppm Comment: Kato et al. (1986) is missing
Methyl chloride	3000	1000	Critical study: Morgan et al. (1982) and Chellman et al. (1986) Critical effect: Threshold for lethality on day 1 at repeated exposure of 5000 ppm Comment by AEGL: The study by von Oettingen (1955) was stated to be insufficient and the methodology not to meet current standards and White et al. (1982) is only an abstract.	Critical study: von Oettingen (1955) and White et al. (1982) Critical effect: LC50 = 2500 ppm
Methyl isocyanate	0.2	1.5	Critical study: Schwetz et al. (1987) Critical effect: NOAEL pup mortality = 1 ppm for 6 h	Critical study: Several Critical effect: Threshold for lethality on adult animals Comment: ERPG does not seem to consider pup mortality as a Tier-3 effect
Oleum, Sulfur trioxide or Sulfuric acid	160 mg/m^3	30 mg/m^3	Critical study: Runckle and Hahn (1976) Critical effect: LC01	Critical study: Several Critical effect: Lethality Comment: Runckle and Hahn (1976) is missing
Stibine	9.6	1.5	Critical study: Price et al. (1979) Critical effect: NOAEL = 191 ppm for 30 min Comment by AEGL: The relatively brief time to death following acute exposure is consistent with death as a consequence of pulmonary edema rather than death from renal failure subsequent to hemolysis.	Critical effect: Life threatening rate of hemolysis in analogy with arsine.
Tetramethoxy silane	1.4	20	Critical study: Dow 1992 Critical effect: BMCL05 of 26 ppm Comment by AEGL: UF = 30	Critical study: Dow (1992) Critical effect: NOAEL = 31 ppm Comment: An apparent UF of 1.5
Toluene	4500[a]	1000	Comment: AEGL document not available	–
Vinyl chloride	4800[a]	20,000	Critical study: Clark and Tiston (1973) Critical effect: cardiac sensitization EC50 = 50,000 ppm after 5 min exposure Comment: AEGL use the lower of the reported EC50, i.e. 50,000 i.s.o. 71,000 ppm	Critical study: Prodan et al. (1975), Lester et al. (1963) and Clark et al. (1982) Critical effect: NOAEL = 100,000 ppm and cardiac sensitization EC50 = 71,000 ppm

a ≥ 10% Lower Explosive Limit (LEL), b ≥ 100% LEL; MLE50 = Maximum Likelyhood Estimate of 1% lethality; BMCL05 = the lower 95th confidence limit of the concentration causing a 5% increase in response; LC01 = Lethal concentration 1%; EC50 = Effect concentration 50%.

21, 1997, and May 31, 2002, respectively. In total, 471 chemicals have been given priority by AEGL. In slight contrast to the AEGLs, the ERPGs are "...designed as a tool to assist environmental, health and safety professionals in the development of emergency response strategies for protecting workers and general public..." [2]. According to the process for developing ERPG, any person, company or organization may select a compound and prepare a document to be discussed and adopted by the ERPG committee. The ERPG work is

Table 6
Summary of major reason for divergent AEGL and ERPG guidance values.

	No. of divergent values	Choice of critical effect	Choice of key study	Interpretation of key study including use of UF	Unclear
Tier 1	15	9	2	3	1
Tier 2	17	4	7	5	1
Tier 3	13	2	4	6	1

therefore primarily driven by those stakeholders that have the need and resources to develop values for specific compounds within their own field of interest and responsibility. The focus on workers' protection and occupational safety is underlined by the ERPGs being developed by the American Industrial Hygiene Association.

Overall, there is no marked difference between the magnitudes of the AEGL and ERPG guidance values (Fig. 1). However, substantial differences are seen for individual compounds. One out of five values diverges by more than three-fold, and one out of twenty by more than a factor ten. Such discrepancies may cause interpretation and communication problems in the risk management that may have practical implications, e.g. during cross-national releases or other big releases with many parties involved. Major discrepancies may also affect the communication and trust between diverse actors – think tanks, experts, journalists, politicians, and governmental officials – engaged in the process of establishing a legitimate definition of risk.

The observed discrepancy between the two sets of guidance values remains also when the comparisons are restricted to HPV or to toxic/very toxic chemicals (Table 2). The HPV chemicals are of special concern, since they are produced, transported and used in high quantities, thereby increasing the risk of accidental or deliberate mass exposure at the global arena. The HPV chemicals with deviating values include some that are classified as harmful to the unborn. These substances may cause substantial worry in a mass exposure situation including pregnant women, especially since the information about developmental toxicity is often vague and imprecise.

The reasons for divergence were classified in three major categories, plus a fourth class of unclear reason due to missing TSD. These three categories relate to major steps, although not fully exclusive, in the process of determining the numerical acute guidance value: (1) selection of a critical effect as a part of the hazard identification, (2), selection of critical study and identification of POD, and (3) qualitative evaluations and interpretation of the data, including management of uncertainty and e.g. models for time extrapolations.

The present study shows that there are different major reasons for the discrepancy between the three Tiers (Table 6). It seems that the discrepancies at Tier 1 are predominantly explained by the selection of critical effect (especially the inclusion of odor recognition, as discussed below), while discrepancies at Tier 2 and Tier 3 to a higher extent relate to the identification of the critical study and interpretation of the data.

There is a larger discrepancy between AEGL and ERPG at Tier 1 as compared to Tiers 2 and 3 (Fig. 1). The dominant reason for divergence at Tier 1 relates to the different Tier definitions. The AEGL standing operating procedure definition says: "AEGL-1 is the airborne concentration... of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure." The ERPG Tier 1 definition is slightly different: "The maximum airborne concentration below which most individuals could be exposed for up to one hour without experiencing anything other than mild transient adverse health effects or perceiving a clearly defined objectionable odor." As shown in the present study, the interpretation of "perceiving objectional odor" within the ERPG does not meet the criteria "notable discomfort", although some odor may lead to discomfort of certain individuals. On the other hand, the information about odor thresholds is important for emergency response and planning. For example, smell reported by the public may be used to detect, track and identify chemical releases. In addition, it may also define a part of the population that are exposed to non-toxic levels but may request information or health consultation. If the practical use of Tier 1 guidance values aims for this kind of interventions it may be justified to include odor. However, in single cases the AEGL and ERPG, Tier 1 values differ by nearly three orders of magnitude. Such huge discrepancies may still result in communication problems, and certainly so in cases where the AEGL and ERPG guidance values are considered as being practically equivalent and/or reported as stand-alone values without explanation of the underlying rationales.

At the Tier 2 level, we identified a few cases of missing references in both the ERPG and the AEGL documents. A more pronounced difference relates to transparency, i.e. how well the qualities and shortcoming of the candidate critical studies are described during the selection process. Thus, for several compounds the AEGL committee chooses not to use the same critical study as ERPG and explains the rationale for that decision, for example by pointing out limitations of the exposure measurements, low analytical quality, lack of data on exposure duration etc. The process of selection of critical study/studies is not transparently described in the ERPG documents. Differences in choice of critical study may also relate to data availability. This may be the case when the critical data are quite old and/or when there are few studies. A closer international collaboration would lead to increased sharing and availability of data across borders and thereby improve the basis for selection of the appropriate POD.

The definition of Tier 3, life threatening or fatal effects, is narrower and one might think that both the critical effect and the critical study are easily identified. Nevertheless, for two compounds the critical effects differ between the two systems. The Tier-3 values for chloromethyl methyl ether are both based on the same study (Drew et al., 1975). Using the benchmark dose approach, the AEGL committee calculated the BMCL05 for lethality and applied UFs, while the ERPG Tier 3 value is based on the NOAEL for pulmonary edema. Both Tier 3 values for methyl isocyanate are based on lethality, but the pup mortality used by AEGL is not considered by ERPG. Again, as with Tier 2, the selection of critical studies is more transparent in the AEGL documents in that the reasons for excluding of a study are often given. However, most of the discrepancies seen at Tier 3 are related to differences in the interpretation of the same study. In a few cases there are even conflicting statements in the description of the same critical study. For example, the AEGL document on chloroacethyl chloride states that the critical study shows labored breathing in animals above 552 ppm, while ERPG states that the same study reports this effect already at 32 ppm. It is beyond the scope of the present study to determine the correctness of such statements, yet the two interpretations are clearly divergent. Even in those cases where the AEGL and ERPG committees base their decisions on the same (or very similar) POD, the use of different UFs may affect the final value. The ERPG Committee states that uncertainty or safety factors may be used when appropriate and when the data are sufficient [2]. However, there is no standard procedure for their use and the technical support

documents [14] give no further insight. This contrasts the AEGL technical support documents which are clear with respect to the applied UFs. In the AIHA 2008 handbook an analysis was made of the UFs applied in the past, however, the analysis was very short and only performed for ERPG-3 values [2]. We therefore calculated implicit ERPG UFs, by comparing the suggested value with the identified threshold level, e.g. NOAEL, of the critical study [15]. Four compounds were identified where the use of UF or implicit UF clearly influenced the level of divergence between AEGL and ERPG; Fluorine (Tier 1), and acrylic acid, chloromethyl methyl ether, tetramethoxy silane (Tier 3). In general, ERPG seem to apply lower implicit UFs in the range 1–2.5, as compared with AEGL (10–30). In the case of fluorine, the ERPG use an implicit UF for sensory irritation of 20, but also support the final value with data related to odor. Another cause of divergence, mainly evident during interpretation of data for tier 3, relate to the use of dose–response models to calculate reference points. For three compounds (1,3-butadiene, tetramethoxy silane and chloromethyl methyl ether) the AEGL committee based their Tier 3 guidance values on LC01 and the lower 95th confidence limit of the concentration causing a 5% increase in response (BMCL05), while the ERPG utilized a more traditional and less model-dependent approach with LC50, and NOAEL. If this difference reflects the policies of AEGL and ERPG remains unclear. However, the SOP of AEGL clearly states that "The preferred approach will be to use the BMC approach to identify the highest exposure at which the toxicological effects used to define an AEGL tier were not observed. If the data are insufficient for a meaningful statistical analysis to use that approach, then the level will be determined empirically from experimental data." A similar statement regarding dose response modeling could not be found in the ERPG handbook.

The present study provides a toxicologically founded base for understanding the causes of discrepancy between sets of guidance values for acute exposure. It also points toward a need for international harmonization. This need has previously been indicated in terms of implementation of the European Seveso II directive [8]. In general quantitative terms, the AEGL and ERPG values are seemingly equally protective. However, about one third of the individual values differ more than three-fold and a few differ by up to two or even three orders of magnitude. Similar results have been reported by others [16]. The compounds with diverging values include several HPV chemicals as well as chemicals labeled as highly toxic. Based on the great impact of inclusion of odor as a base for Tier 1 we suggest first, that any international set of guidance values should focus sole on risk assessment and avoid involvement of risk management. Information about odor threshold gives important information for certain responders. However, this information can easily be found in other information sources and should be regarded as additional rather than a base for toxicity guidance. The separation between health risks and risk management is important to receive acceptance, since most stakeholders within the field of emergency planning, preparedness and response are locally organized and may want to use these figures for a variety of different purposes. Some organizations may want to develop their own values based on the AEGL values. This is currently the process in the Netherlands, where so-called intervention values are developed based on existing AEGL values. Secondly, we suggest that the process should be made transparent in order to enable a critical discussion over time. A thorough up-to-date literature review is the basis for the deduction of both AEGL and ERPG values. Concentration–effect or dose–effect relationships are described for every ERPG Tier but in a form of summary of the critical studies. Based on the published ERPG information it is not transparent how an ERPG value is derived since (1) the key study is not clearly defined but rather a group of supporting references, (2) the manner of time extrapolation is not explained (3) UF seem to be applied but are not explicitly described. As a basis for international harmonization, the Standard Operating Procedure developed by the AEGL committee [1] could form a conceptual base. Further, with respect to transparency of the toxicological rationales within a document, it is also important to declare who has taken part in the preparement of documents, committee meetings and any conflicting interests of the participants. Recently, the AEGL committee was identified in a Government Accounting Office survey of EPA advisory committees as being a highly scientific/technical advisory committee. As such, they have to comply with standard conflict of interest ethics requirements [17]. It is important that an internationally harmonized system of guidance values for acute exposure of airborne hazardous compounds reaches sustainability and are able to cover both chemicals currently prioritized under AEGL and ERPG as well as new chemicals that may be registered on the market in the future. In addition, the process must include a procedure for revision and this will certainly benefit from a transparent documentation of all rationales.

In conclusion, there is a significant discrepancy for individual compounds among guidance values for hazardous chemicals, including many HPV and highly toxic chemicals. This may interfere with trustful and efficient communication during preparedness and response to sudden chemical releases. A transparent process and rationales as well as a clear separation between risk assessment and risk management is important to form an internationally harmonized set of guidance values. Such values are also needed to handle new chemicals and for revision of previously assessed.

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