Scientific Criteria Used for the Development of Occupational Exposure Limits for Metals and Other Mining-Related Chemicals

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The scientific approaches employed by selected internationally recognized organizations in developing occupational exposure limits (OELs) for metals and other mining-related chemicals were surveyed, and differences and commonalties were identified. The analysis identified an overriding need to increase transparency in current OEL documentation. OEL documentation should adhere to good risk characterization principles and should identify (1) the methodology used and scientific judgments made; (2) the data used as the basis for the OEL calculation; and (3) the uncertainties and overall confidence in the OEL derivation. At least within a single organization, a consistent approach should be used to derive OELs. Opportunities for harmonization of scientific criteria were noted, including (1) consideration of severity in identification of the point of departure; (2) definition of the minimum data set; (3) approaches for interspecies extrapolation; (4) identification of default uncertainty factors for developing OELs; and (5) approaches for consideration of speciation and essentiality of metals. Potential research approaches to provide the fundamental data needed to address each individual scientific criterion are described. Increased harmonization of scientific criteria will ultimately lead to OEL derivation approaches rooted in the best science and will facilitate greater pooling of resources among organizations that establish OELs and improved protection of worker health. © 2002 Elsevier Science (USA)

Key Words: occupational exposure limit; harmonization; metals.**

INTRODUCTION

Little disagreement exists that occupational exposure limits (OELs)[2] provide health and safety professionals with an important tool for protecting worker health (discussed in Paustenbach, 1990; Paustenbach, 1994). The importance of OELs is highlighted by the fact that many organizations around the world develop them. However, despite the general agreement on the need for OELs, significant disparities can exist in the specific OEL values established by different organizations and in the methods used to derive them.

The general approach used by most organizations includes a review of the epidemiology and toxicology information to identify potential hazards, selection of critical effects, and dose–response estimation to determine suitable exposure levels. Although this overall framework is generally shared among organizations that derive OELs, there is significant disparity in the methods used. Some of this diversity reflects risk management decisions, such as determining the appropriate levels of residual risk to the exposed population or weighing health-based limits with technical feasibility or economic impact. The approaches that are used for OEL derivation are often chosen to fit the unique needs of the constituencies involved and the mission of the organization. These science policy issues are outside the

[2] Abbreviations used: ACGIH, American Conference of Governmental Industrial Hygienists; AOEL, acceptable operator exposure level; BEI, biological exposure indices; BMD, benchmark dose; CNS, central nervous system; CSAF, chemical specific adjustment factor; CSTEE, Scientific Committee for Toxicity, Ecotoxicity, and the Environment; DECOS, Dutch Expert Committee on Occupational Standards; DFG, Deutsche Forschungsgemeinschaft; ESADDI, estimated safe and adequate daily dietary intake; EU, European Union; FAIR, Food, Agriculture and Fisheries Programme; HCN, Health Council of the Netherlands; ICNCM, International Committee on Nickel Carcinogenesis in Man; IDLH, immediately dangerous to life or health; IPCS, International Programme on Chemical Safety; LOAEL, lowest observed adverse effect level; MAK, maximale arbeitsplatz-konzentrationen; MMAD, mass median aerodynamic diameter; MOAEL, minimal observed adverse effect level; NOAEL, no observed adverse effect level; NOC, not otherwise classified; NRC, National Research Council; NTP, National Toxicology Program; OEL(s), occupational exposure limit(s); OSHA, United States Occupational Safety and Health Administration; PBPK, physiologically based pharmacokinetics; POD, point of departure; RDA, recommended daily allowance; RfC, reference concentration; SCOEL, Scientific Committee on Occupational Exposure Limits; TLV-TWA, threshold limit value—time weighted average; TNO, Netherlands Organization for Applied Scientific Research; UF, uncertainty factors; U.S. EPA, United States Environmental Protection Agency; WHO, World Health Organization.

scope of this review. However, some of the diversity in approaches reflects issues that have not been fully evaluated scientifically and the absence of well-documented methods for OEL derivation. It is in these areas that increased communication and transparency regarding the scientific basis for setting OEL values can serve to enhance the usefulness of OELs in occupational hygiene practice.

The potential value of harmonizing approaches for derivation of OELs is being increasingly recognized through trends toward workforce globalization and collaboration among standard-setting bodies. Harmonization encourages understanding of methods used by different organizations, increasing the acceptance of assessments derived by these various approaches, and, when appropriate, working toward convergence of scientific criteria. It is important to note that the concept of harmonization is distinct from standardization and does not imply that identical approaches be used among organizations (Sonich-Mullin, 1997). It does, however, imply clear communication of the methods used by an organization to aid in sharing of information (with associated time and cost savings). This would mean that differences between approaches of different organizations would reflect clearly defined scientific policy differences or differences in scientific judgment, and be identifiable as such.

A strong argument for harmonization of OEL methodologies can be made for many reasons, as summarized in Table 1. In light of these considerations, it is encouraging that the field of occupational risk assessment is already moving toward increased harmonization. Probably the clearest example of efforts in this direction is the development of standard approaches for setting OELs within Europe. The Scientific Committee on Occupational Exposure Limits (SCOEL, 1999) has published its methodology for deriving OELs within the European Union (EU). Another recent EU-sponsored effort has focused on criteria for establishing OELs for workers exposed to pesticides (FAIR, 2000). Recent

TABLE 1
Potential Benefits of Harmonization in Setting OELs

Increase the transparency of health-based OELs, making clear to the occupational health practitioner the uses and limitations of a particular OEL.

Enhance the degree of confidence in the process used to derive the OELs by emphasizing the communication of key scientific criteria that are used to derive them.

Facilitate the pooling of resources among bodies that set OELs to increase the coverage of OELs for the thousands of substances for which no guidance exists, and to decrease the time it takes to update OELs as new data become available.

Increase the provision for similar levels of worker health protection in different parts of the world, by increasing the consistency in the scientific criteria used as the basis for deriving OELs.

efforts to define aerodynamic diameter fractions for coordinating OEL derivation with workplace exposure assessment for particles exemplifies how success in harmonizing scientific criteria for OELs can be achieved (Vincent, 1999).

As an effort to evaluate the degree to which harmonization of approaches is taking place and to facilitate communication on scientific criteria for deriving OELs, this study evaluated science-based issues related to deriving OELs for metals, metal compounds, and other substances associated with mining-related industries. The currently published OELs were evaluated for a small sample of compounds (including silica and compounds of chromium, copper, lead, and manganese) as a means of highlighting opportunities for greater harmonization or even standardization of approaches and to emphasize areas in which scientific criteria need further development. Metals provide a good class of compounds for this effort because they are common in industrial processes. Metals also present some unique challenges, such as consideration of speciation and essentiality, in addition to the occupational risk assessment considerations faced in evaluating other classes of chemicals.

METHODS

Since OELs are established by many organizations throughout the world, a case study approach was used to highlight similarities and differences, as well as the strengths of different approaches to OEL derivation used by diverse groups. The case study chemicals were selected based on importance (production volume, potential for exposure, inherent toxicity), as well as readily apparent differences in the current OEL values published by several internationally recognized organizations.

After finalizing case study selection, the OEL documentation for each chemical was critically analyzed. OELs established based on toxicological considerations rather than economic or technical feasibility (i.e., health-based OELs) were the focus of the analysis. OELs that were included in the review were the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit values (TLVs), the Dutch Expert Committee on Occupational Standards (DECOS) health-based OELs (a committee of the Health Council of the Netherlands), and the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area of the Deutsche Forschungsgemeinschaft (DFG) maximale Arbeitsplatz-Konzentrationen (MAKs). Note that some health-based OELs (e.g., the MAKs and the values set by the DECOS) may be further modified based on technical or economic feasibility considerations in establishing final published limits. These organizations were selected as examples of OEL-setting bodies that receive a

large degree of international attention and that establish OELs based on health rather than risk management considerations. A second reason for the choice of study organizations was that each group has published OELs for some, if not all, of the case study chemicals. Although the primary purpose in this study was to review a small sampling of compounds and organizations to highlight opportunities for harmonization in scientific criteria for OEL development, methods for a number of other organizations in the analysis of the scientific issues involved are also cited.

RESULTS

Case Study Summaries

Table 2 provides the current OEL values for the five case study chemicals for the ACGIH, DECOS, and the DFG (MAK values); Table 3 provides the basis for the OELs for metals for the case study chemicals for which English-language documentation was available from more than one organization. Because the valence of the chromium (Cr) ion is important in determining chromium biology and toxicology, the OELs for chromium differ greatly according to chemical speciation. OELs have been developed for Cr metal, Cr (III), Cr (IV), and Cr (VI) species. The TLV-TWA for Cr metal dust was adopted in 1981 (as described in ACGIH, 1996). In a reevaluation in 1996, ACGIH concluded that it was appropriate to retain the current value, since exposure over the previous 10 years did not yield reports of adverse health effects (ACGIH, 1996). In support of this decision, the chosen value was supported by a NOAEL of 3.1 mg/m^3 (the highest exposure level) in a 4-week inhalation study in rabbits (Johansson *et al.*, 1980). DECOS reviewed the data for Cr metal and concluded that the data were not sufficient to derive a health-based OEL, but did not disagree with the continued use of the 0.5 mg/m^3 limit in force at the time of the reevaluation (DECOS, 1998a). No MAK value has been established for Cr metal, based on the assigned cancer classification for chromium and compounds. DFG's policy is not to develop MAK values for nonthreshold carcinogens (DFG, 2001).

The TLV-TWA for Cr (III) was based on the absence of changes of pathophysiological significance at exposures to Cr (III) salts below 0.5 mg/m^3 in epidemiology or animal studies, and the lack of an association between Cr (III) salts and cancer (ACGIH, 1996). Therefore, the previous TLV-TWA value was retained (ACGIH, 1996). The DECOS (1998a) relied on similar studies, but used two animal studies (Johansson *et al.*, 1986a, 1986b) to quantitatively derive the OEL. These two reports of the same subacute inhalation study in rabbits exposed to soluble Cr (III) compounds noted abnormal macrophages (oblong, smooth) in alveoli at 0.6 mg/m^3. This exposure concentration was selected as a MOAEL

TABLE 2
Occupational Exposure Values for Case Study Chemicals[a]

Compound	ACGIH	DECOS	MAK
Chromium			
Metal	0.5	ND[b]	Ca[c]
Cr (III)	0.5	0.06	Ca
Cr (IV)	—[d]	0.05	—
Cr (VI) (soluble)	0.05	Ca	Ca
Cr (VI) (insoluble)	0.01	Ca	Ca
Copper			
Inorganic dust	1	—	1 (I)[e]
Fume	0.2	—	0.1 (R)[f]
Lead			
And its inorganic compounds	0.05	—	0.1 (I)
Manganese			
Inorganic	0.2	—	0.5 (I)
Silica			
Amorphous diatomaceous earth calcined	—	—	0.3 (R)
Amorphous diatomaceous earth uncalcined	10 (I); 3 (R)	—	4 (I)
Amorphous fume	2 (R)	—	0.3 (R)
Amorphous fused	0.1 (R)	—	0.3 (R)
Amorphous gel	10	—	4 (I)
Amorphous precipitated	10	—	4 (I)
Amorphous pyrogenic	—	—	4 (I)
Amorphous quartz glass	0.1 (R)[g]	—	0.3 (R)
Crystalline Cristobalite	0.05 (R)	0.075	Ca
Crystalline Quartz	0.05 (R)	0.075	Ca
Crystalline Tridymite	0.05 (R)	0.075	Ca
Crystalline Tripoli, as quartz	0.1 (R)	—	—

[a] All values are in mg/m^3.
[b] ND indicates that the data were evaluated but no OEL was derived.
[c] Ca indicates that no OEL was established based on the cancer classification.
[d] —indicates that no documentation exists.
[e] (I) indicates that the OEL is based on the inhalable fraction.
[f] (R) indicates that the OEL is based on the respirable fraction.
[g] The ACGIH TLV-TWA includes quartz glass under silica, amorphous-fused.

(minimal observed adverse effect level). To derive the OEL for soluble Cr (III), the MOAEL was adjusted by a factor of 3 for extrapolation from a MOAEL to a NOAEL (no observed adverse effect level), and by a factor of 3 for interspecies extrapolation, resulting in a composite uncertainty factor of 10.[3] For insoluble Cr (III) compounds, the data were regarded as insufficient to derive an OEL, but DECOS did not disagree with the continued use of the 0.5 mg/m^3 limit in force at the time of the reevaluation (DECOS, 1998a). Based on the assigned cancer classification for chromium and chromium compounds, no MAK value has been established for Cr (III). Thus, in contrast to ACGIH and DECOS, which

[3] The values of 3 shown here actually represent the square root of 10 (3.16, or 1/2 of 10 on a log scale), rounded to one significant figure. This leads to the confusing result that $3 \times 3 = 10$.

TABLE 3
Derivation of OEL for Case Study Metals

Compound, organization	OEL basis	POD mg/m^3	OEL mg/m^3	UF[a]
Cr metal, ACGIH	Experience with TLV	NS[b]	0.5	1[c]
Cr (III), ACGIH	Absence of effects at less than 0.5	NS	0.5	1[c]
Cr (III), DECOS	Animal minimal LOAEL	0.6	0.05	10[d]
Cr (IV), DECOS	Animal LOAEL	0.5	0.05	10[d]
Cr (VI) (sol.), ACGIH	Experience with TLV	NS	0.05	1[c]
Cr (VI) (ins.), ACGIH	Chemical analogy	NS	0.01	
Cu, ACGIH	Human NOAEL	0.4	0.2	2
Pb, ACGIH	Human NOAEL for blood lead	NA	0.05	3[e]
Mn, ACGIH	Human LOAEL	1	0.2	5
Mn, MAK	Human minimal LOAEL	0.25	0.5 (I)	1[f]

[a] The apparent UF was calculated by dividing the POD by the OEL. MAK values for copper and lead are not shown in this table, even though the OELs are shown in Table 2, because no English documentation was available. See the text for further details.

[b] NS, a single point of departure estimate was not noted in the OEL documentation; NA, not applicable.

[c] Derived assuming the current TLV is considered as a Human NOAEL.

[d] The composite factor of 10 included subfactors of 3 to account for extrapolation from a LOAEL and 3 for extrapolation from an animal study.

[e] The UF of 3 represents the difference between the target blood lead level of 30 μg/dL and the blood lead level of 9.5 μg/dL anticipated to result from exposure to the TLV-TWA.

[f] Due to differences in measurement techniques the OEL of 0.5 mg/m^3 as total dust was described as being roughly equivalent to the minimal LOAEL from the critical study.

did not consider Cr (III) a human carcinogen, the DFG (1992, 2001) based the MAK for Cr (III) on the value for Cr (VI) (a Category 2 carcinogen, considered to be carcinogenic in humans based on animal studies substantiated by epidemiological studies). Comparison of the documentation for the OELs derived by these three organizations does not specifically indicate the reason for the apparent discrepancy in the carcinogenicity assessments. However, it appears that ACGIH (1996) and DECOS (1998a) weighed the negative findings in epidemiology studies more heavily, while the DFG (1992) may have considered the epidemiology data less conclusive, after taking into account positive findings in intratracheal instillation studies with Cr (III).

The DECOS (1998a) is the only one of the three organizations studied that developed an OEL for Cr (IV). The OEL was based on a LOAEL (lowest observed adverse effect level) of 0.5 mg/m^3 for effects on the lung in a chronic study in rats (Lee *et al.*, 1989). An uncertainty factor of 3 for extrapolation from a LOAEL to a NOAEL and an uncertainty factor of 3 for interspecies

differences resulted in a composite uncertainty factor of 10.

The approaches used for developing OELs for hexavalent chromium compounds also differed substantially among the three organizations. ACGIH (1996) derived different TLV-TWA values for soluble and insoluble forms of Cr (VI), not otherwise classified (NOC). Separate TLV values have also been developed for a number of specific chromates. The 1996 ACGIH documentation for water soluble Cr (VI) (NOC) noted that the "TLV for soluble chromates will be maintained at current value of 0.05 mg/m^3 until an in-depth review is completed by the committee." Cr (VI) (NOC) was classified as a confirmed human carcinogen (A1). No other supporting data were provided. For insoluble Cr (VI) compounds, the same TLV-TWA was recommended as for zinc chromate until more dose–response information becomes available. DECOS (1998a) considered Cr (VI) compounds carcinogenic to humans and assumed a genotoxic mode of action. Consistent with its methodology, DECOS (1998a) calculated cancer risk estimates, but no health-based OEL was recommended. Based on an evaluation of the carcinogenicity of Cr (VI), no MAK values have been derived for hexavalent chromium compounds (DFG, 1992). The OELs for Cr (VI) highlight a clear difference in approaches used by different organizations for setting OELs for compounds of known carcinogenic potential, even when similar conclusions regarding the carcinogenic potential of a chemical are reached (see further discussion of this issue in Seeley *et al.*, 2001).

In summary, ACGIH, DECOS, and DFG considered a similar array of data, but used widely varying approaches to develop markedly different OELs for chromium and chromium compounds.

The TLV-TWA for copper was derived to protect from irritation and systemic effects, and is based largely on epidemiological data (ACGIH, 1991). Based on the chronology presented in the 1991 documentation, a reevaluation in 1973 resulted in ACGIH increasing the TLV-TWA for copper fume from 0.1 to 0.2 mg/m^3, based on a letter reporting that employees exposed to copper fumes at levels up to 0.4 mg/m^3 experienced no ill effects (Luxon, 1972) and supported by other epidemiology studies. The ACGIH documentation did not provide any other information on the exposure conditions, cohort size, or endpoints evaluated. Considering this letter to identify a human NOAEL of 0.4 mg/m^3, the current TLV provides a margin of exposure of 2 from a human NOAEL for copper fume. The TLV for copper dusts and mists is 1 mg/m^3, a value that the documentation considered "should provide similar protection against adverse health effects." The strength of the database and the rationale for the copper dust/mist TLV-TWA is less clear than for copper fume. Irritation is the critical endpoint for copper dust, but details were not provided on the degree of irritation observed at specific exposure

levels. Copper is currently listed on ACGIH's "Chemical Substances Under Study" list (ACGIH, 2001). The MAK for copper and compounds is 1 mg/m^3 inhalable dust. According to the DFG methodology (DFG, 2001) the inhalable fraction is to be measured when the MAK is based on total dust. The MAK for copper fume is 0.1 mg/m^3 respirable. (The respirable fraction is to be measured when the MAK value is based on adverse effects associated with the level of fine dust.) No published documentation in English on the MAK value was available for review. Copper is currently on the working program for DECOS (personal communication from DECOS, 2001).

For lead, only the ACGIH TLV-TWA documentation was available for review (ACGIH, 1996). The TLV-TWA was back-calculated from a blood lead level of 9.5 μg/dL. This blood lead concentration was selected to protect against developmental effects such as depressed intellectual development in children exposed to lead during gestation. As discussed in the ACGIH documentation, the threshold for this effect remains uncertain. ACGIH concluded that blood lead levels of 30 μg/dL would not affect a woman's ability to bear children who would subsequently develop normally. However it was noted that the TLV committee would reevaluate the value of 30 μg/dL as new data become available. Based on the ratio of the calculated blood lead concentration resulting from exposure at the level of the TLV (9.5 μg/dL) and the biological exposure index (BEI) of 30 μg/dL, the TLV affords an approximate margin of safety of 3-fold. The lower blood lead level associated with the TLV as compared to the BEI allows for other nonoccupational exposures to occur without increasing blood lead levels above 30 μg/dL. Although a MAK value has been developed for lead (DFG, 2001), no English version of the documentation of this value was available for review. Lead is currently on the working program for DECOS (personal communication from DECOS, 2001).

The TLV-TWA (ACGIH, 1996) for elemental and inorganic manganese compounds is based on human epidemiological studies that indicate the potential for lung and central nervous system effects (Roels *et al.*, 1987), and male reproductive effects at around 1 mg/m^3 (Lauwerys *et al.*, 1985). A TLV-TWA of 0.2 mg/m^3 was recommended from these studies, since the threshold for effects on the CNS and the lungs is not known definitively and due to the progressive nature of these effects. Manganese is currently listed on the ACGIH's "Chemical Substances Under Study" list. The MAK value (DFG, 1999) was based on the lowest average manganese concentration (approximately 0.25 mg/m^3) shown to cause slight neurotoxic symptoms in exposed workers (Iregren, 1990). The MAK documentation (DFG, 1999) noted that, at the time of the Iregren (1990) study, the sampling equipment typically used in Germany led to concentration measurements approximately twice those that would be measured under identical conditions with the equipment generally used in the United States and Sweden. (See also Vincent, 1999, for a discussion of this issue.) So, 0.25 mg/m^3, measured in Sweden in the study by Iregren (1990), is equivalent to 0.5 mg/m^3 in total dust measured in Germany. Therefore, a MAK value of 0.5 mg/m^3 was recommended. Since the effects at this level were minimal, did not develop in all exposed persons, and were not dose-dependent, this concentration was used as a basis for the MAK, without application of uncertainty factors. Manganese is currently on the working program for DECOS (personal communication from DECOS, 2001). The scientific bases for the manganese OELs of the different organizations were very different, although the resulting values of the OEL do not vary greatly.

In addition to metal compounds, a variety of other substances are often associated with industrial processes related to metal mining, manufacturing, or processing. Differences in the derivation for OELs for nonmetal compounds were also noted; the OEL values for silica were used as a case study. All three organizations included in this study differentiate among a variety of forms of silica on the basis of the degree to which amorphous versus crystalline silica is present.

The ACGIH has derived TLV-TWA values for multiple types of amorphous silica (ACGIH, 1991, 1996). The TLV-TWAs for uncalcined amorphous diatomaceous and amorphous precipitated silica were based on the default values for inert dusts, presumably due to the apparent low intrinsic toxicity of these forms of silica. For calcined diatomaceous earth (which is formed in a process that generates crystalline silica), ACGIH recommended that exposure be gauged against exposure limits for the three crystalline forms of silica, reflecting greater concern for crystalline forms. A TLV-TWA has also been established for amorphous silica fume. This value was based on studies that found abnormal X-ray findings in workers exposed to high (but unmeasured) concentrations of silica fume. The single study that included exposure measurements did not provide sufficient data to identify a no-effect level. In this study, Corsi and Piazza (1970) reported that less than 1% of workers exposed for less than 5 years, and 14% of workers exposed for 10 or more years, had abnormal X-ray findings. Based on silica content, respirable silica exposure in this study was estimated as 1.6 mg/m^3. A TLV-TWA value of 2 mg/m^3 was recommended for silica fume in accordance with recommendations of several independent groups that had evaluated the same data. For fused amorphous silica, few data exist except for several intratracheal instillation studies, which demonstrate that fused silica can induce effects similar to those seen with crystalline silica (as described below), although to a lesser degree. Due to evidence that fused silica can induce fibrosis, a TLV of 0.1 mg/m^3 was recommended. Precipitated silica (amorphous gel) did not increase fibrosis in chronic inhalation studies in several

species. No adverse effects were observed in a cohort of workers exposed to precipitated silica (exposure concentration not reported). Therefore, a TLV of 10 mg/m^3 was recommended, based on the default TLV for "particulates not otherwise specified."

The MAK values for amorphous silicas (DFG, 1991), including quartz glass, fused silica, silica fume, and calcined diatomaceous earth, were established based on evidence that these forms of silica have some potential for inducing a fibrogenic effect, although generally to a lesser degree than for crystalline silica. Based on these findings, a MAK value of 0.3 mg/m^3 respirable dust was derived. For other amorphous forms, a NOAEL of 1 mg/m^3 and a LOAEL of 6 mg/m^3 were identified in a rat inhalation study of pyrogenic silicas (Reuzel *et al.*, 1987). An increase in "focal interstitial fibrosis" was noted, although the effect was reversible. This value was supported by the absence of effects in humans exposed to amorphous silicas (exposure levels and endpoints evaluated not reported) and an inhalation study in monkeys in which 15 mg/m^3 of pyrogenic silica, but not silica gel or precipitated silica, induced some lung changes (Groth *et al.*, 1979). Based on a LOAEL in rats of 6 mg/m^3 for effects of questionable significance, a MAK value of 4 mg/m^3 as total dust was recommended for pyrogenic silica, precipitated silica, silica gel, and diatomaceous earth.

All three organizations included in this study recommended OEL values for crystalline forms of silica that were markedly different from the OELs for amorphous forms. Separate TLV-TWA values have been developed for four crystalline silica polymorphs, quartz, cristobalite, tridymite, and tripoli (as quartz). For quartz, the TLV-TWA was lowered by a factor of 2 to 0.05 mg/m^3 from the previous value of 0.1 mg/m^3 (respirable) (ACGIH, 2000). This change was based on recent evidence that the incidence of silicosis in workers who were exposed at or near the level of the previous TLV-TWA was higher than previously thought. The TLV Committee noted that these studies did not report functional changes at the prior TLV-TWA. However, based on uncertainties in the epidemiology data and questions on the relationship between silicosis and lung cancer, it was recommended "to use available means to keep the exposures well below the TLV-TWA." The current TLV-TWA documentation for cristobalite indicates that animal studies suggest that this silica polymorph is more potent than quartz (ACGIH, 1991). Therefore ACGIH adopted a TLV-TWA for cristobalite of half the value recommended for quartz at that time. A similar rationale was used in deriving the TLV-TWA for tridymite (ACGIH, 1991). However, with the more recent update (ACGIH, 2000) of the quartz TLV-TWA, this rationale is no longer consistent with the current TLV-TWA values, which are the same for all three crystalline forms. For tripoli, a microcrystalline form of quartz, the TLV-TWA is 0.1 mg/m^3 in accordance with the TLV for quartz

at the time that the TLV for tripoli was established (ACGIH, 1991). This TLV-TWA has not yet been updated to reflect the changes in the quartz TLV-TWA. It is noteworthy that cristobalite, tridymite, and tripoli are listed on the "Chemicals Under Study List" (ACGIH, 2001), although they have not yet appeared on the notice of intended changes.

The DECOS developed a health-based OEL for the crystalline silica polymorph, quartz (DECOS, 1992). In a recent review of the carcinogenicity of crystalline silica (DECOS, 1998b), it was concluded that "crystalline silica inhaled in the form of quartz or cristobalite from occupational sources is carcinogenic to humans (Group 1)." The most well-supported mode of action for tumorigenic responses observed in animal studies was considered to be epithelial proliferation associated with persistent inflammation; however, direct genotoxicity or genotoxicity due to generation of reactive oxidants was not ruled out. Based on this analysis, it seems likely that no OEL would be developed if the DECOS were to re-evaluate crystalline silica in light of the 1998 review, since a potential genotoxic mode of action has not been ruled out. Based on its carcinogenic potential, no MAK values have been derived for the crystalline forms of silica (DFG, 2001).

These case studies demonstrate that even for "health-based" OELs, which presumably are not dependent on risk management considerations, there are large differences in both the OEL values and the basis for those values. A similar observation was made in a recent review of European OELs for a variety of carcinogenic compounds (Seeley *et al.*, 2001). Based on the case studies, a central commonality and a number of differences among the approaches used by the different organizations were identified. All of the organizations developed OELs by first conducting a critical evaluation of the exposure, epidemiology, and toxicology data and determining the effects associated with the exposure of interest. All of the organizations also identified a critical effect level (also known as a point of departure, or POD) to the extent feasible based on the data and then extrapolated from that value to the OEL. Sometimes the supporting documentation explicitly identified the POD and the study in which it was identified, while other organizations presented the supporting data, but used a significant amount of professional judgment in determining the POD. In some of the latter cases, the documentation was sufficiently complex that even an experienced toxicologist–risk assessor found it challenging to identify the quantitative basis for the OEL. The organizations also differed markedly in their approach to extrapolating from the POD to the OEL. Some organizations (e.g., DECOS for Cr (III)) applied specific uncertainty factors to perform this extrapolation, while others did not explicitly state the reason for the magnitude of the difference between the POD and the recommended OEL. There was also a clear difference in the

approach used for carcinogenic compounds (see Seeley *et al.*, 2001, for a more in-depth discussion of this area). The rest of this paper considers in detail these commonalties and differences in the approaches used for the development of OELs.

Database Considerations

When available, well-documented human studies of the appropriate duration will nearly always be preferred for OEL derivation. This is likely to be particularly true for metals and other substances used in the metal or mining-related industries, since long human experience with these industrial processes increases the likelihood for tracking of effects in exposed workers. For the case studies reviewed here, epidemiology data played a key role in deriving the OELs for copper, lead, manganese, and crystalline silica. Occupational epidemiology data can be particularly useful for the development of OELs, because the duration and conditions of exposure and the study population are similar to that for the population of interest.

Human data can be obtained from epidemiology studies, case studies, or, in some cases, ethically conducted clinical exposures. Peer-reviewed studies are preferred. If a company report that has not been peer reviewed is considered, evidence that the data have been validated (e.g., a quality assurance audit statement) is desirable. There are no hard-and-fast rules for determining whether data are of adequate quality to include in OEL development. Considerable professional judgment applies, although higher standards would tend to be applied to a study used as the basis for an OEL than a study used as supporting data. It would be desirable to apply higher standards to studies used to derive internationally recognized OELs, while a screening level or preliminary OEL might require less rigorous documentation. Guides have been developed to aid in the collection of epidemiology data related to metals and their species (e.g., ICME, 1999; NiPERA, 2001).

Although epidemiology data can provide useful information, these data need to be evaluated carefully to determine whether the data are sufficient to establish causality. Criteria for judging the adequacy of epidemiological studies are well recognized (Hill, 1965; U.S. EPA, 1994; WHO, 2000). All of these criteria need to be evaluated in considering whether a chemical caused an effect; no one factor alone can definitively show causality, and the reader is referred to the cited documents for a more detailed discussion.

An issue related to database considerations that is often faced in setting OELs is how to use so-called gray literature, consisting of unpublished data. For example, the TLV-TWA value for copper fume was based in part on a letter reporting no adverse effects at exposures up to 0.4 mg/m^3, and ACGIH maintained the Cr (III) TLV-TWA in its 1996 review based on the absence of reported adverse effects at the previous TLV-TWA. Developing OELs based on this type of data has the advantage of making maximal use of the available human data, but it has the disadvantage of lack of transparency. Other scientists reviewing the documentation cannot independently evaluate the conclusions, because minimal or no information is provided on the number of people exposed, endpoints evaluated, and exposure conditions (length of time exposed, type of monitoring done, range of exposure levels). At a minimum, organizations deriving OELs and using such gray literature should provide basic documentation of these elements and should weigh the quality of the data against standard criteria (see Table 4) when determining the confidence they will put in that data.

Gray literature, if it is of sufficient quality, can be a useful data source that is currently being used only minimally. If companies are already doing health monitoring of employees and exposure monitoring, much of the data for improving OEL development may already exist in an unanalyzed form. Presumably the two major impediments to publishing such data are the cost of a thorough statistical analysis as part of an epidemiology study and the lingering reluctance of some journals to publish negative studies. This suggests that it would be useful to work with industrial hygiene and risk assessment journals in order to facilitate publication of industrial hygiene reports in which no effects were noted. The goal would be to ensure that more of the source data reach the open literature. Web-based publication of data without statistical analyses may also be a means for getting the data into the open literature at a low cost to the companies collecting the data. The public availability of such data would increase the credibility of OELs that are based on minimally documented industry reports concluding that experience with a certain exposure level indicates that exposure to this concentration is safe.

In the absence of adequate human data, the choice of the best study(s) to use as the basis for an OEL becomes less clear. OELs are routinely established for substances that vary greatly in the strength of the underlying database, which may range from strong epidemiology studies supported by animal studies to only

TABLE 4
Considerations in Evaluating Epidemiology Data[a]

Elements of a Well-Reported Study

A description of the objectives and research design

A description of selection procedures for the study population and comparison group, population characteristics, sources of the exposure data, and the methods of data collection

A discussion of major confounding factors and data analysis methods

The criteria used for interpreting results

[a] Adapted and expanded from U.S. EPA, 1994 and WHO, 2000.

a few case reports or a single animal study. Many organizations do not define a minimal database for establishing a risk value. Rather, a description of the types of data and their potential utility is more commonly provided. Similarly, most organizations do not define a rigid hierarchy for selecting the type of study to use in determining the POD. Rather, it is more common for organizations to use a weight of evidence approach that looks at all of the data together (e.g., SCOEL, 1999). In some settings, a clear data hierarchy provides the benefit of enhancing consistency and transparency in the OEL derivation process. For example, the methodology for setting IDLH (immediately dangerous to life or health) values (NIOSH, 2001) provides an example of a clearly defined data hierarchy system. On the other hand, this level of rigidity may not be necessary as long as the OEL documentation clearly describes the extent of the database and provides a well-reasoned rationale for selecting a particular subset of the data as the basis for the OEL. Some organizations do have a minimum database requirement. For example, the method used by the Committee on Updating Occupational Exposure Limits of the Health Council of the Netherlands (HCN, 2000) outlines minimum data requirements. According to this method, data on acute toxicity and repeated-dose toxicity are required. As a minimum, a multidose study in a relevant species using a relevant route of administration and evaluating an array of endpoints should be available. The U.S. EPA methodology (1994) defines the minimum database for deriving an inhalation reference concentration (RfC) as an adequate human study or a well-conducted subchronic animal inhalation study that includes evaluation of the respiratory tract.

The rationale for a minimum data requirement is that any value derived from fewer data would be too uncertain to provide meaningful guidance. On the other hand, the absence of any OEL, even one based on limited data, provides a severe handicap to the occupational health practitioner who often must make a decision in the field. It could be argued that the OEL documentation itself provides the means to assess the degree of confidence one should place on an OEL. However, current approaches to OEL documentation might benefit from application of more direct strategies for communicating the strength of the database to the occupational health practitioner. For example, the extent of the database supporting the OELs for the five case study compounds reviewed varied greatly from fairly robust epidemiology data for inorganic lead, manganese, and crystalline silica (as quartz) to limited human and animal data for noncarcinogenic chromium compounds and amorphous silica. Yet none of the OEL values provided explicit information on the degree of uncertainty in the OEL value resulting from the inability of the available studies to detect potential adverse health effects. Possibilities for addressing this issue include the use of well-defined uncertainty factors

for adequacy of the database or the use of confidence ratings (e.g., Dourson *et al.*, 1992; U.S. EPA, 1994). Confidence ratings provide a means for characterizing the strengths of the key study(s), as well as the strengths and weaknesses of the entire database, and can be supplemented with a narrative describing such strengths and weaknesses in more detail. Feron *et al.* (1994), in a summary of OEL methods in the Netherlands, noted that organizations should clearly state when the data are inadequate to derive an OEL. The use of an uncertainty factor approach has been incorporated into some of the proposed OEL methods and has been standard practice in human health risk assessment for environmental exposures (reviewed in Dourson *et al.*, 1996; Haber *et al.*, 2001) (described in more detail below in the Uncertainty Factor Section).

Point of Departure

As noted above, all of the OEL approaches evaluated the overall database in order to determine a POD for development of the OEL. For this analysis we refer to the POD as the concentration to which uncertainty factors (explicit or implicit) are applied to derive the OEL. None of the case study organizations defined the appropriate basis for this POD, but this issue was addressed by SCOEL (1999), in the European Union documentation for acceptable operator exposure levels (AOELs) (FAIR, 2000), and by HCN (2000). These latter groups prefer to base OELs on a NOAEL. When a NOAEL is not available, a LOAEL can be used, taking into account the additional extrapolation needed. The U.S. EPA's IRIS defines a NOAEL as "the highest exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control" (U.S. EPA, 2001). The International Programme on Chemical Safety (IPCS, 1999) defines the NOAEL based on there being "no detectable adverse alteration of morphology, functional capacity, growth, development or life span of the target." Note that the NOAEL can be defined by changes that are statistically or biologically significant, and that increases in frequency and severity of an effect are considered. One definition of adversity, used in the environmental context, is available from the U.S. EPA (2001): "A biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge." In the occupational arena, the SCOEL (1999) developed a severity scale for evaluating systemic and irritant effects (Table 5). Using this scale, the SCOEL defined adversity as beginning at concentrations that induce effects between severity levels 2 and 3. While other approaches might differ in some details, the approach developed by SCOEL is an important step toward enhancing

TABLE 5
Adversity Definitions Used by SCOEL[a]

Systemic effects	Irritant effects
1. No effects observed	1. No effects observed; no awareness of exposure
2. Compensatory effect or early effect of dubious significance without adverse health consequences	2. Very slight effects; awareness of exposure
3. Early health impairment (clear adverse effects)	3. Slight irritant effects or nuisance (e.g. smell); easily tolerable
4. Overt disease, possibly death	4. Significant irritation/nuisance, overt health effects; barely tolerable
	5. Serious health effects (e.g. pulmonary edema); intolerable

[a] Adapted from SCOEL (1999).

transparency and consistency by defining the effects considered adverse for occupational risk assessment.

A relatively recent innovation in risk assessment for determining the POD is the use of the benchmark dose (BMD) approach, which fits a flexible mathematical curve to the experimental data to determine a dose corresponding to a predetermined response level (Crump, 1984; Dourson *et al.*, 1985). A significant advantage of the BMD approach is that a BMD can be determined even if an experimental study did not identify a NOAEL. In addition, the POD determined using this approach is not confined to the tested dose levels. The mathematical modeling approaches used are similar to those used throughout the world for cancer modeling. Although none of the organizations included in the case studies we evaluated specifically mentioned use of the BMD approach, recent guidelines for AOELs for pesticides (FAIR, 2000) do refer to this method. This sort of modeling approach was also used by the U.S. Occupational Safety and Health Administration (OSHA) in evaluating the risk of kidney dysfunction as part of the development of its cadmium standard (OSHA, 1993). BMD modeling may be particularly valuable for the evaluation of epidemiology data in the development of OELs, because it allows the use of individual exposure data, rather than "binning" of exposure levels. Unlike animal studies in which an exposure group represents animals all exposed to the same concentration of chemical, each worker typically has a slightly different exposure history, resulting in a continuous range of exposures. Traditional risk assessment addresses this issue by grouping workers with similar exposure levels (e.g., 0–200, 201–400, 401–600, and 601–800 ppm/years) and using the midpoint of the ranges to determine NOAELs and LOAELs. A problem with this approach, however, is that the NOAELs and LOAELs are an artifact of the grouping, and different values could be obtained by different grouping (e.g., 0–300, 301–600, 601–

900 ppm/years). Conducting dose–response modeling of the individual data removes such artifacts by considering each individual's exposure and response.

Although many OELs for metals have been developed from epidemiology data, some (e.g., the OELs for Cr (III)) are based on a POD derived from animal data. In such cases, it is necessary to extrapolate exposure levels from animals to humans. Ideally, such extrapolation takes into account interspecies differences in the breathing rate and respiratory tract structure of experimental animals and humans. Several different approaches can be used for conducting such extrapolations. All of the case study organizations used the animal exposure level directly in developing the OEL. The AOEL methodology (FAIR, 2000) states that extrapolation from an animal exposure concentration directly to a human exposure concentration uses an implicit allometric scaling based on $bw^{0.75}$. This is because alveolar ventilation rate scales across species using the 0.75 power of body weight. Allometric scaling assumes that the parent compound is the form responsible for a chemical's toxicity and that biotransformation detoxifies the chemical rather than activating it. Allometric scaling may therefore be a reasonable initial approach for metals, which generally are not metabolized and for which clearance is the primary means of removal from the body, and thus a key determinant of tissue dose.

However, there are several other factors that do not scale directly with body weight, but which also affect the tissue dose from inhalation exposure. The lung deposition of inhaled particles (and therefore the dose to the lung) depends on the particle size and on the respiratory tract structure. Differences in particle size can be important if the particle size in the animal study is much smaller than that found under occupational conditions. For example, the NTP (1996a, 1996b, 1996c) studies of nickel carcinogenesis used particle size distributions with mass median aerodynamic diameters (MMADs) of 2–2.5 μm. By contrast, the limited data on occupational exposures to nickel compounds in refineries indicate that less that 10% of the mass is respirable, and the MMAD for those particles is on the order of 4 μm (discussed in greater detail in Haber *et al.*, 2000). This means that, for a given concentration in air, a much larger dose was delivered to the lung in the animal study than would be delivered under occupational exposure conditions. Differences in particle size are addressed to some degree by differentiating between OELs for respirable and inhalable fractions, as was done for the MAK OELs for copper, lead, manganese, and silica, and the ACGIH values for silica (see Table 2). However, the precision of such an approach is low. The low precision (and potential lack of transparency) is evident in the development of the MAK OEL for manganese. Because the sampling equipment used in Germany yields concentration measurements twice

those measured at identical workplaces with the equipment generally used in Sweden (where the study that is the basis for the POD was conducted), the MAK OEL is twice the minimal severity LOAEL used as the POD. Thus, the OEL was derived using an uncertainty factor of 1, even though it appears at first glance that a factor of 0.5 was used.

The structure of the respiratory tract is also important in determining interspecies differences in the respiratory tract tissue dose. For example, the rat nasal passages are much more convoluted than those of humans, and rats are obligate nose-breathers, resulting in higher upper respiratory tract deposition in rats than in humans. The U.S. EPA (1994) has developed a particle dosimetry model to aid in extrapolation from animals to humans. The implications of the differences in particle deposition in animals and humans can be observed using the Johansson *et al.* (1986a, 1986b) studies that were the basis for the Cr (III) OELs developed by DECOS. DECOS used the exposure concentration at the MOAEL of 0.6 mg/m^3 as the POD, but dosimetric considerations conducted according to the U.S. EPA methodology result in a MOAEL (human equivalent concentration) of 0.07 mg/m^3 for this effect on the pulmonary region of the lung. Details of this calculation are shown in Appendix A. The U.S. EPA (1994) methodology also provides methods for calculating the human equivalent concentration for gases, taking into account whether the chemical acts at the portal of entry, systemically, or both.

Other scientists have developed more sophisticated methods for extrapolating from animals to humans, although they are more time-intensive and require specialized expertise. For example, the U.S. EPA (1994) particle dosimetry model cannot account for differences in clearance from the lung, but Oberdorster and colleagues (e.g., Hsieh *et al.*, 1999; Yu *et al.*, 2001) have included particle clearance in a model for inhaled nickel dosimetry and have applied it to occupational scenarios. Physiologically based pharmacokinetic (PBPK) models can also be used to improve animal to human extrapolation (reviewed in Clewell and Andersen, 1994).

Extrapolations from Other Routes and from Biological Indices

For some chemicals, there are insufficient data from the inhalation route to derive an OEL, or the oral data may be of much higher quality. In such cases, it may be appropriate to conduct a route-to-route extrapolation. The key issue in doing such extrapolation is consideration of whether there are portal of entry effects. For example, route-to-route extrapolation is not appropriate if a chemical causes respiratory effects from inhalation exposure, gastrointestinal effects from oral exposure, or is subject to first-pass metabolism in the liver from

oral exposure. Therefore, for developing an OEL from oral data, sufficient inhalation data must be available to show that the critical effect does not occur in the respiratory tract. Route-to-route extrapolation can be appropriately performed in situations where the critical effect is a systemic one, such as neurological effects or kidney effects. Biological exposure indices can be particularly useful for doing route-to-route extrapolation, since they allow exposure from different routes to be expressed in consistent units. For example, the ACGIH TLV-TWA for lead is based on blood lead levels, and the acceptable concentration was determined in studies where both inhalation and oral exposure may have occurred. Use of the biological exposure index allows the integration of total dose from all sources. Thus, biological indices are useful for some chemicals as a measure of internal doses to workers. As a result, organizations such as the ACGIH (2001) and DFG (2001) derive levels for assessing internal exposures to some chemicals. For example, the ACGIH (2001) has recommended biological exposure indices (BEIs) for water-soluble Cr (VI) and for lead, as well as for a variety of other metals.

Application of Uncertainty Factors

Uncertainty factors (UF) are used routinely (either explicitly or implied as part of a margin of safety) in establishing OELs, as a means to account for uncertainty in extrapolating from the selected POD. However, despite their wide application, the rationale for their use, areas of uncertainty considered, and the recommended default values differ by organization. In addition, the degree to which UFs are explicitly defined in OEL documentation varies widely. Table 6 provides examples of UF approaches proposed for occupational risk assessment. None of the three organizations included in our evaluation of the case study chemicals applies a defined set of default uncertainty factors, although DECOS uses the TNO (1996) recommendations as a general guide (personal communication from DECOS). Although the ACGIH and MAK likely make adjustments to OELs based on similar considerations, a systematic approach for accomplishing this is not explicit in their OEL documentations. As a means of comparing occupational and environmental health risk assessment approaches, default values used by U.S. EPA have also been included in Table 6.

Harmonization efforts in occupational risk assessment have not yielded specific recommended default values for uncertainty factors, even within an individual organization. Instead, recognition has evolved that the selection of uncertainty factors will be done on a case-by-case basis (SCOEL, 1999). This represents a step forward in the development of scientific criteria, by indicating that, although the value of uncertainty factors will be chemical-specific, the magnitude and rationale for the UF should be described in the OEL

TABLE 6
Proposed Default Uncertainty Factors
for OEL Derivation

Area of uncertainty	TNO	Naumann	Zielhuis and van der Kreek	U.S. EPA[a] RfC
			Default uncertainty factor values	
Interspecies	3	1[b]	1–10	3[c]
Intraspecies	3	10	1–3	10
Duration of exposure[d]	1–10	3	5–10	10
LOAEL to NOAEL	—[e]	3	2–4	10
Type of critical effect[f]	1	—	—	—
Dose–response curve[g]	1	—	—	—
Database	1	1	—	10
Maximum default	100	100	1200	3000[h]

[a] U.S. EPA RfC value was included as a comparison for occupational and nonoccupational human health risk values. These default values are modified as appropriate based on the available data.

[b] The default value of 1 assumes appropriate allometry has been applied.

[c] Assuming appropriate dosimetric adjustments have been conducted.

[d] Refers to extrapolation from subacute to subchronic or subchronic to chronic studies.

[e] A dash indicates that a default value is not specified for this area of uncertainty.

[f] This factor accounts for the biological significance of the observed effect.

[g] The steeper the dose–response curve the smaller the factor can be.

[h] The maximum default value is 3000 in recognition of the overlap in coverage of the factors when four full areas of uncertainty exist. If five full areas of uncertainty exist, an RfC is not derived.

documentation. Adopting this principle would increase the transparency of currently available OELs.

The scientific basis for selection of default uncertainty factor values has been discussed in detail elsewhere for occupational risk assessment (FAIR, 2000, Haber *et al.*, 2001; Naumann *et al.*, 1995; Zielhuis and van der Kreek, 1979), and therefore is not repeated in detail here. Newer developments, such as the current effort by the IPCS for deriving chemical-specific adjustment factors (CSAF) (IPCS, 2001; Meek *et al.*, 2001) for human health risk assessment for environmental exposures, maximize the use of chemical-specific data, when available. Similar concepts would enhance the use of chemical-specific data to derive UFs for OELs. Indeed, Naumann *et al.* (1997) proposed a similar approach for OEL development for pharmaceuticals, and Sweeney *et al.* (2001) recently used a PBPK approach, coupled with Monte Carlo analysis, to derive composite UFs for ethylene glycol ether OELs. Thus, sophisticated approaches are being used in the occupational arena and should continue to be used, to the degree the data allow, for derivation of new OELs.

Although much of the scientific development in the application of UFs in the environmental area appears to be directly applicable to occupational risk assessment, extrapolation for human variability does differ for occupational and environmental risk assessment. It has been argued that the default value for this factor should be lower for the occupational setting, since the population of interest is composed of healthy working adults and excludes potentially sensitive segments of the population such as children or the elderly. As an example, in its recommended process for deriving health-based OELs, TNO (1996) recommended a default value of 3 for human variability, instead of the factor of 10 that has been used traditionally for nonoccupational human health risk assessment (for example, in U.S. EPA, 1994). The TNO (1996) methodology further notes that this argument would not apply to occupational exposures that induce developmental toxicity. It also stands to reason that if factors other than age or "general health" drive differences in susceptibility, then a reduction in the factor to cover human variability may not be appropriate. For example, if nonoccupational exposures (such as alcohol or smoking) or genetic predisposition induce greater susceptibility, then reducing the default uncertainty factor based on age differences would not capture the range of variability of the occupationally exposed population. Overall, a reduction in the uncertainty factor for human variability seems reasonable for most cases, but the exceptions we note make a strong case for using chemical-specific data to identify potential populations at increased risk.

An argument related to decreasing the magnitude of the UF for human variability for metals has also recently been discussed in the context of nickel (CSTEE, 2001). According to this argument, human variability for some metals (inorganic nickel in this case) may be less than for nonmetal chemicals, because inorganic metal compounds are generally less likely to be dependent on metabolism. However, as noted in the discussion of the UF for nickel in this document (CSTEE, 2001), metabolism reflects only a subset of the factors that influence toxicokinetics. In light of this possibility, the data were not judged to be sufficient to support a reduction of the UF. This evaluation of nickel highlights the utility of the CSAF approach for determining the appropriate value of UFs, since the CSAF approach provides a framework for evaluating the degree to which the data for any particular metal would support movement away from default UF values.

Although movement toward refining the rationale for UF selection in occupational risk assessment is encouraging, evaluation of the case studies highlights current differences in the routine application of UFs (Table 3). Our review represents just a small sampling of the OEL values for metals derived by organizations around the world, but it appears sufficient to highlight key points. For many of the OELs, the POD was not explicitly described, making it difficult to determine the magnitude of any UFs that were considered. Even in cases where the POD was discernable, no explicit description of the basis and rationale for the magnitude of the

composite uncertainty factor was generally given. The exception was the Cr (III) and Cr (IV) OELs recommended by DECOS (1998a), which applied a factor of 3 for extrapolation from a MOAEL or LOAEL and a factor of 3 for interspecies extrapolation.

It also appears that there are differences in the use of UFs to account for intraspecies (human) variability. For example, an apparent UF of 2 was used for the TLV-TWA for copper, while an apparent factor of 3 was used for lead when the critical effect was based on a human NOAEL. The UF values used for the copper and lead TLV-TWAs are generally consistent with intraspecies factors used in a series of health-based OELs in the United Kingdom as described by Fairhurst (1995) and are similar to the value of 3 recommended by HCN (2000) and TNO (1996). It is noteworthy that for chemicals such as lead, for which developmental toxicity is the critical endpoint, exposure of pregnant workers would result in exposure of the sensitive population (fetuses), which is the same sensitive population as has been identified for general population exposure (FAIR, 2000; TNO, 1996). For other OELs based on a POD from animal data, such as the DECOS (1998a) OELs for Cr (III) and Cr (IV), there was no explicit notation of a factor to account for human variability. For manganese, the total UF for the TLV-TWA was a factor of 5, but the document authors did not identify which portion of this factor was intended to cover human variability and which portion was intended to cover extrapolation from a LOAEL. The MAK value for manganese was based on a minimal human LOAEL and apparently did not incorporate a factor to account for human variability. Based on this limited analysis, increased harmonization in the application of UFs and better communication of the rationale for their use is clearly needed.

OELs for Carcinogens

While a generally consistent paradigm is used by most organizations for setting OELs for noncarcinogens, dramatic differences are apparent in the approaches used for carcinogens. Some organizations (e.g., ACGIH) routinely establish quantitative OELs for carcinogens, while others (e.g, DECOS, DFG) do not derive health-based OELs for nonthreshold carcinogens, although they do derive health-based OELs for carcinogens with thresholds. In addition, carcinogen classification schemes vary widely among organizations that establish OELs.

All of the case study organizations consider mode of action to some degree in setting OELs for carcinogens. For example, all of the organizations evaluate whether the tumors induced by the chemical in animals are relevant to human carcinogenicity. All of the organizations also consider whether the chemical causes tumors by a genotoxic (by causing gene mutations) mode of action or a nongenotoxic one. Examples of nongenotoxic modes of action include cytotoxicity followed by regenerative cell division and hormonally related events. Organizations such as DECOS (1998a) and DFG (2001) consider direct-acting genotoxic carcinogens to have no threshold for carcinogenicity, while nongenotoxic (or indirect genotoxic) modes of action would result in a threshold or a very shallow slope in the low-dose region. For example, if a chemical acts via cytotoxicity and regenerative cell division, doses below those causing cytotoxicity would presumably not cause cancer. Some organizations (FAIR, 2000) also distinguish direct DNA reactivity (forming DNA adducts) from indirect effects on DNA, such as chromosome aberrations resulting from interaction with the proteins that drive cell division.

Although metals with positive results in genotoxicity assays are typically considered nonthreshold genotoxic carcinogens, further research is needed in this area. Metals can induce genotoxicity through diverse mechanisms, including through direct DNA reactivity or indirect mechanisms, such as inhibition of DNA repair, or via the formation of reactive oxygen species leading to DNA damage (Chang, 1996). The degree to which these alternative pathways can be demonstrated for a particular metal will affect the type of dose–response model (e.g. threshold or nonthreshold) used in deriving the OEL.

Additional Issues of Specific Importance for Metals

An area of specific importance to metals is in determining the degree to which data are available to develop OEL recommendations for different forms of the metal. Issues of speciation include determining the degree to which toxicological differences result from differences in physical form (e.g., copper dust vs fume deposition), chemical form (e.g., the bioavailability of Cr (III) versus Cr (VI)), or other unique toxicological properties of the compound (amorphous versus crystalline silica).

Figure 1 provides an example of a decision process for determining the degree to which an OEL can be developed for different forms of metals. This framework can also be used to improve the documentation for the rationale for applying an OEL for one form of a metal to another form, or choosing not to apply the OEL. This analysis includes an evaluation as to whether multiple forms exist and if the potential health hazards are likely to differ on this basis. If the initial hazard identification does not suggest that speciation is an important factor, then an evaluation of the adequacy of the available data for the form (or forms) is made, followed by a decision to collect data or derive an OEL from the existing data set. In the event that sufficient data are available for all relevant forms, separate OELs can be developed. It is more common, however, that sufficient data would be available for only a subset of the forms. Two alternatives for dealing with this situation include (1) collecting additional data for each form of interest and (2) assuming
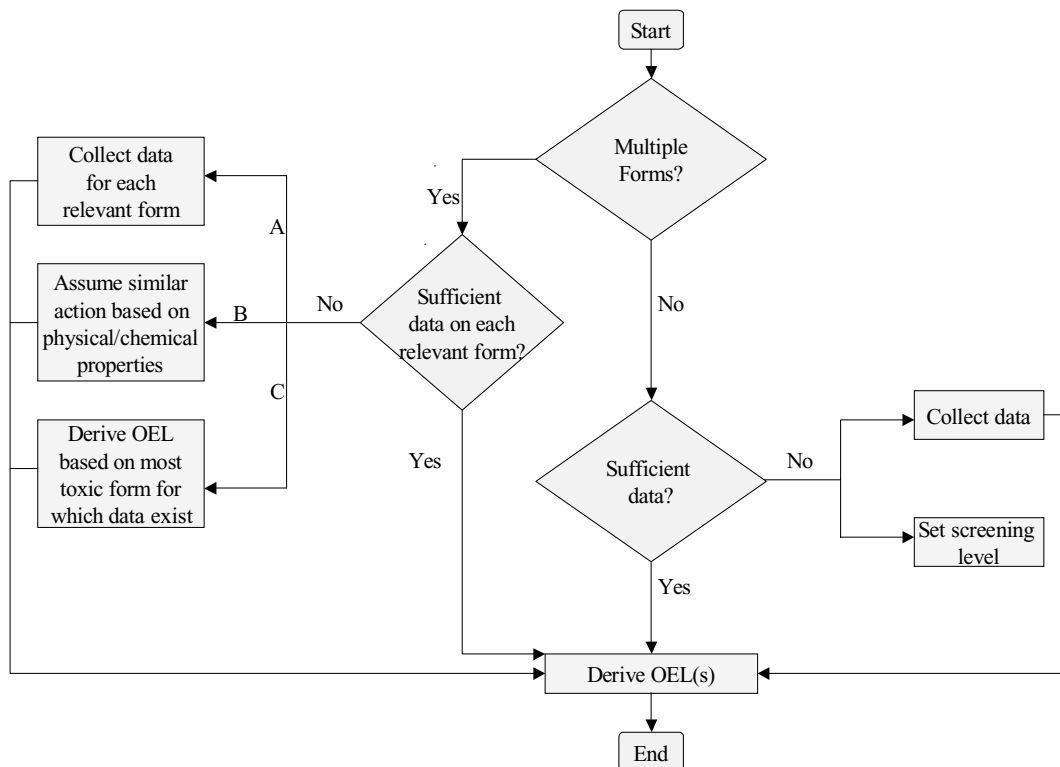
FIG. 1. Decision process for considering speciation in deriving OELs.

similar toxicology based on a physical or chemical characteristic of interest (e.g., degree of crystallinity of silica or the solubility of nickel compounds). If the latter approach is followed, careful consideration needs to be made of the characteristics of interest, to ensure that the surrogate choice is appropriate. A health-protective approach in the absence of data is to assume that all compounds are as toxic as the most toxic form.

Overall, this process is consistent with current approaches, and the case studies suggested that the role of speciation has typically been considered, at least to some degree. However, it is critical that the evaluation be sufficiently described to communicate the degree to which the occupational hygiene practitioner can rely on an OEL for specific compounds of interest in the work area.

Another special challenge for the derivation of OELs for metals and minerals is the issue of essentiality. For a number of metals, such as selenium, zinc, and Cr (III), toxic effects can result from exposure to high doses, but adverse health consequences can also result from insufficient intake. This means that the net dose–response curve is the sum of the downward sloping dose–response curve for essentiality in the low-dose region and the upward sloping dose–response curve for toxicity at higher doses (see Fig. 2). In such cases, the choice of uncertainty factor needs to consider the lower portion of the dose–response curve.

The U.S. EPA RfD for Cr (III) is an example of the appropriate consideration of essentiality in the establishment of oral risk values (U.S. EPA, 2001). A similar concept would apply for OEL derivation, subject to the caveats in the following paragraphs. Cr (III) acts as a cofactor for insulin and is required for maintaining normal glucose levels. The dietary requirement for Cr (III) is not known, but an Estimated Safe and Adequate Daily Dietary Intake (ESADDI) of 50–200 μg/day has been established (NRC, 1989). The RfD for Cr (III) is 1.5 mg/kg-day, corresponding to 105,000 μg/day for
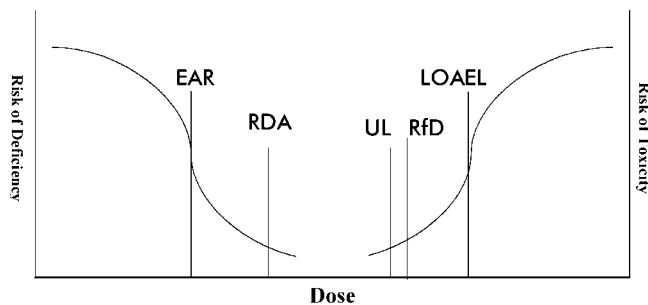

FIG. 2. Assessment for essential elements. Hypothetical example of the impact of uncertainty factor selection on the probability of an adverse response for an essential metal. EAR, estimated average requirement; RDA, recommended dietary allowance; UL, tolerable upper level intake; RfD, reference dose; LOAEL, lowest observed adverse effect level.

a 70-kg human. This RfD is higher than the ESADDI, and is consistent with the ESADDI, since doses *below the ESADDI* may be of concern, while exposure to levels *above the RfD* may also be of concern.

Two major caveats are important in applying the essentiality concept to OEL development. First, essentiality refers to the *systemic* dose, not the dose to the portal of entry, the respiratory tract. Inhalation exposure to a metal fume or particulate could lead to respiratory effects at atmospheric concentrations below those that would lead to systemic doses in the essentiality range. For example, the OELs established for water-soluble Cr (III) by ACGIH (1996) and DECOS (1998a) are 0.5 and 0.06 mg/m^3, respectively, based on lung effects. Using the default air intake for occupational exposure of 10 m^3/day and assuming the entire lung dose is absorbed, these OELs correspond to systemic doses of 5000 and 600 μg/day. Because the systemic dose at the DECOS OEL is close to the ESADDI, careful evaluation of the appropriateness of that OEL would be needed *if* the OEL were based on a systemic effect. However, since the OEL is based on a lung effect, a low systemic dose at the OEL is still consistent with the biology of Cr (III).

The second major caveat is that essentiality refers to the total dose from all sources. The development of an OEL based on systemic effects of an essential element would be a three-step process. First, the safe total systemic dose is determined. Second, nonoccupational exposure from sources such as the diet, drinking water, and ambient air is evaluated to determine the background dose from these sources. Finally, the difference between the safe systemic dose and the total systemic background dose is determined in order to identify the OEL. In other words, occupational exposure should be considered to be on top of normal dietary intake (and other background intake) of the metal. This may pose particular challenges if a narrow window exists between essentiality (e.g., the recommended daily allowance or RDA) and doses that begin to cause toxic effects.

In summary, the key issue regarding essential metals is that it is nonsensical to derive a safe exposure level based on systemic effects that are below the nutritional requirement. OEL development needs to take into account both the total safe dose of essential metals and the daily intake from dietary and other sources. However, these issues only apply when the most sensitive endpoint is a systemic effect.

RECOMMENDATIONS AND CONCLUSIONS

A case study approach has been used to identify similarities and differences in OEL derivation for metals, metal compounds, and other chemicals related to mining operations, as well as general issues related to the development and documentation of OELs. The overriding theme in this analysis was the need to increase the degree to which the selected approach was described in the OEL documentation. Consistent with good risk characterization principles, OEL documentation should (1) be transparent with regard to methodology and scientific judgments; (2) clearly identify the data used as the basis for the OEL calculation; (3) discuss the strengths and weaknesses in the OEL derivation; and (4) use scientific approaches consistent with those for other OELs (at least within an organization). It will become increasingly important to adhere to these principles of risk characterization as the field of occupational risk assessment moves away from default approaches and adopts tools that use chemical-specific data to the maximum extent possible. For example, application of BMD modeling, dosimetric adjustments, CSAFs, and cancer mode of action summaries will require renewed effort to make clear the scientific weighing of evidence that was used in making decisions.

Recommendations are summarized in Table 7. The first four recommendations can be implemented without additional research; the primary barriers to implementation are limited resources (for the development of improved documentation, or for developing manuscripts on negative studies) and institutional inertia. This report found that even when organizations review similar data sets, differences in the resulting health-based OELs can occur. This situation raises a significant problem for practicing occupational hygienists, who must often choose the appropriate OEL based on limited or poor documentation of the scientific rationale underlying the recommended value. Although some differences in OELs can be explained by differences in science policy (e.g., different approaches for setting limits for carcinogens), other differences can be addressed through increased information. The last five recommendations in Table 7 list specific areas where both harmonization and additional research would be beneficial. The first step in this harmonization

TABLE 7
Recommendations on Scientific Criteria for OELs

Improve transparency and completeness of OEL documentation, including identification of strengths and weaknesses of the analysis

Provide greater accessibility to "gray literature"

Increase dissemination and publication of occupational studies that evaluate several endpoints, but observe no effect

Develop approaches for characterizing the overall confidence in OELs

Harmonize the consideration of severity in the identification of the point of departure

Harmonize the definition of a minimum data set for the development of an OEL

Harmonize the approach for interspecies extrapolation

Harmonize the default uncertainty factors used in developing OELs

Harmonize the approach for consideration of speciation and essentiality of metals

is clearer communication of the process used in addressing these issues while deriving OELs. It is envisioned that clear documentation of the approach used will help crystallize similarities and differences in OEL development. This can help to focus research addressing the latter five points in the table and ultimately perhaps lead to a greater scientific consensus.

In many cases, there were scientifically defensible alternative approaches to address issues that were explored, such as defining a minimum database, selecting a point of departure, or making uncertainty factor decisions. For these areas, the primary barriers to harmonization are in validation of alternative approaches, education of the scientists who develop OELs, and additional resources needed to implement some of these approaches. The next few paragraphs briefly lay out possible approaches to research addressing some of these remaining issues.

Database considerations: Defining a minimum data set. A component of evaluating the adequacy of human data is to ascertain the minimum database needed to place high confidence in an OEL. A workable research approach would be to compile published human data for metals and metal compounds having datasets rich in various study types. To test the impact of using only certain study types (e.g., case studies, full epidemiology reports), one could develop preliminary OEL values based on selected subsets of the data. By comparing OELs derived using various study types, it would be possible to evaluate the level of data sophistication needed to derive a high quality OEL. The results of this research approach would provide a further scientific basis for determining minimum database requirements.

Interspecies extrapolation: Using state of the science methods. Dosimetric adjustment methods capture important interspecies differences in dose that are not directly accounted for in current OELs. An ongoing interagency effort led by the EPA is developing dosimetry for the oral, inhalation, and dermal routes, with particular attention to the portal of entry. Implementation of such methods will require validation of the approach, dissemination of the approach, and dedication of resources for the increased consideration of mode of action and more time-intensive calculations needed to implement the approach.

Uncertainty factors (UFs): Defining defaults. Research approaches used to validate default UF values for application in the environmental arena (e.g., Dourson *et al.*, 1992) could be used successfully for the occupational arena. One approach that has been used to develop quantitative UF defaults is to determine the ratio between the value of interest (e.g., the animal NOAEL) and the surrogate value (e.g., the human NOAEL) for a reasonably large group of sample chemicals. This sample is then used to characterize the distribution of that ratio, and the UF needed to cover a specified proportion of this variability is then determined. This approach could be optimized for OEL derivation by examining distributions of data for routes of exposure and effects common to workplace environments. As one example, the distribution of animal/human NOAEL ratios for inhalation studies for metals and metal compounds could be used to derive the default UF for animal-to-human extrapolation. This general research approach could be used to derive default UFs to account for many areas of uncertainty relevant to OEL derivation.

Overall, it is apparent that the potential value of harmonization of scientific methods for deriving OELs is being increasingly recognized. This is viewed as a favorable trend for two specific reasons. First, increased harmonization of default scientific approaches will improve the transparency in OEL derivation. Second, harmonization of approaches will tend to highlight the strengths of methods used by diverse groups and thus will favor the application of approaches viewed by a wide audience of occupational risk assessors as being rooted in the best science. This commonality in approach might ultimately minimize the differences observed in health-based OELs and perhaps decrease potential confusion for occupational health practitioners responsible for worker health on a global basis. Increased harmonization would also open the door to sharing of the resulting analyses. Pooling of resources is a critical goal, because decreased redundancy of work would allow for the use of resources to expand the coverage of OELs for substances for which no OEL guidance is currently available.

APPENDIX A. CALCULATION OF THE HUMAN EQUIVALENT CONCENTRATION

The DECOS OEL is based on the observation of abnormal macrophages (oblong, smooth) in alveoli at 0.6 mg/m^3 in a subacute inhalation study in rabbits (Johansson *et al.*, 1986a, 1986b). This effect in the alveoli is considered a pulmonary effect. The study authors reported a mass median aerodynamic diameter (MMAD) of 1 μm, but did not provide any measure of the breadth of the distribution, such as a geometric standard deviation (GSD). Information on the particle generation protocol can aid in the estimation of the breadth of the distribution, but this information was not reported. Therefore, a sensitivity analysis was conducted using a range of GSD values. GSD values ranging from 1 to 5 μm were considered in the calculation, based on typical GSD values reported in experimental animal studies, particularly those reporting an MMAD of 1 μm. The regional deposited dose ratio (RDDR) was calculated using the RDDR program provided by the U.S. EPA (1994). The RDDR represents the ratio between the dose deposited in a given region of the

respiratory tract when animals are exposed to a given concentration of the particle in air and the dose to the same respiratory tract region received by humans exposed to the same air concentration. The RDDR is normalized by regional surface area. (Other dosimetry methods, such as that used by Oberdorster and colleagues, normalize based on tissue weight.) In addition to the particle size distribution, inputs to the calculation of the RDDR include the animal and human body weight, the surface area of the respiratory tract region of interest, and the minute volume[4]. Using this approach, RDDR values for the pulmonary region of 0.123 to 0.134 were calculated for male rabbits exposed to a particle size distribution of with an MMAD of 1 μm and a GSD of 1–5 μm, indicating that the uncertainty in the GSD had a minimal impact for this set of conditions. An RDDR of 0.12 was chosen for this calculation. The human equivalent concentration is calculated by multiplying the RDDR and the NOAEL, LOAEL, or MOAEL, resulting in a MOAEL (HEC) of 0.072 mg/m^3.

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