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Procedures for Health Risk Assessment in Europe

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This report compares cancer classification systems, health risk assessment approaches, and procedures used for establishing occupational exposure limits (OELs), in various European countries and scientific organizations. The objectives were to highlight and compare key aspects of these processes and to identify the basis for differences in cancer classifications and OELs between various scientific organizations and countries. Differences in cancer classification exist in part due to differences in the ultimate purpose of classification and to the relative importance of different types of data (i.e., animal vs human data, mechanistic data, and data from benign vs malignant tumors). In general, the groups surveyed tend to agree on classification of chemicals with good evidence of carcinogenicity in humans, and agree less on classification of chemicals with positive evidence in animals and inadequate or limited evidence in humans. Most entities surveyed distinguish between genotoxic and nongenotoxic chemicals when conducting risk assessments. Although the risk assessment approach used for nongenotoxic chemicals is fairly similar among groups, risk assessment approaches for genotoxic carcinogens vary widely. In addition to risk assessment approaches, other factors which can affect OELs include selection of the critical effect, use of health-based vs technology-based exposure limits, and consideration of technological feasibility and socioeconomic factors.

***Key Words*: cancer classification; risk assessment; occupational exposure limits.**

INTRODUCTION

Carcinogen classification approaches and risk assessment methodologies are key elements to assessing risks from environmental and occupational exposures to chemicals. When approaches differ between countries, risk management decisions, such as setting of occupational exposure limits (OELs), may also vary. In Europe, differences between countries and scientific organizations exist in terms of how chemical carcinogenicity is evaluated, how risk assessments are performed, and how OELs are established for these chemicals. As a result, cancer classification, risk estimates, and OELs can vary widely for the same chemical. Such differences among countries ultimately can affect manufacture, trade, and commerce. Accordingly, our objectives were to review cancer classification schemes, risk assessment approaches, and procedures used for establishing OELs in various European countries and scientific organizations; to highlight and compare key aspects of cancer classification schemes, risk assessment approaches, and establishment of OELs; and to identify the basis for differences between countries and scientific organizations.

Organizations and countries surveyed for this review include the European Union (EU), the International Agency for Research on Cancer (IARC), the United Kingdom, Germany, the Netherlands, Sweden, Norway, Denmark, and Ireland. Selection of these organizations and countries was based in part on their involvement in risk assessment internationally (e.g., IARC), as well as availability of published information. Chemicals evaluated include acrylonitrile, benzene, chromium, ethylene oxide, tetrachloroethylene, trichloroethylene, and vinyl chloride. These chemicals were selected to include both genotoxic and nongenotoxic chemicals, and based on availability of documentation for OELs. We used several sources of information, including official documentation published by individual countries; journal articles in the peer-reviewed literature; and personal communications from scientists in industry, government, and research institutions.

CLASSIFICATION OF CARCINOGENS

Purpose of Classification

Classification of carcinogens serves several purposes, including setting OELs, labeling, and establishing

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product use restrictions (e.g., product deselection). In many European countries, a chemical's classification with respect to carcinogenicity determines how it is regulated in the workplace. For example, carcinogens for which no level of exposure is considered safe (i.e., chemicals that are classified as genotoxic carcinogens) are often regulated with OELs based on technological feasibility for achieving lowest possible exposure levels, rather than on risk calculations. Additionally, OELs for chemicals classified as genotoxic carcinogens tend to be legally binding and cannot be exceeded. In contrast, OELs for nongenotoxic carcinogens and noncarcinogens are sometimes considered as guidance values, which can be exceeded under certain circumstances (Arboraad, 1992; Hunter *et al.*, 1997; Ogden and Topping, 1997).

Criteria Used for Classifying Carcinogens

Several criteria are used for classifying carcinogens, including, strength vs weight-of-evidence considerations, animal vs human carcinogenicity data, mechanistic data, and type of data being evaluated (Table 1). The strength-of-evidence approach considers only positive evidence of carcinogenicity, whereas the weight-of-evidence approach considers all relevant data, including both positive and negative results from epidemiology and animal carcinogenicity studies (Ashby *et al.*, 1990; Whysner and Williams, 1992). Biological mechanisms and relevance of animal findings to risk of cancer in humans may also be considered (Moolenaar, 1994a; Sanner *et al.*, 1996). This may include information on genotoxicity, biotransformation, and toxicokinetics. Use of data from malignant tumors only vs data from both malignant and benign tumors can also affect classification (Moolenaar, 1994a; Neumann *et al.*, 1997). Most European countries and scientific organizations surveyed classify chemicals using a weight-of-evidence approach, consider animal carcinogens as having a carcinogenic risk to humans and allow for the use of mechanistic data. However, subtle, but important differences do exist.

Although most countries and organizations surveyed use a weight-of-evidence approach, Norway uses a strength-of-evidence approach. In the past IARC also used a strength-of-evidence approach; however, recent classifications (e.g., acrylonitrile) indicate use of a weight-of-evidence approach. Germany considers data from malignant tumors only, whereas other countries, such as Norway, consider data from both malignant and benign tumors (Moolenaar, 1994a; Neumann *et al.*, 1997). The Netherlands consider data from chronic bioassays, mutagenicity tests, and other data (e.g., enzyme inhibition or induction) for classifying carcinogens as either genotoxic or non-genotoxic (HCN, 1978, 1988, 1994, 1996; Moolenaar, 1994a; Whysner and Williams, 1992). In Norway, animal carcinogens are assumed to be human carcinogens unless there is a clear indication that the chemical would not cause tumors in humans (Moolenaar, 1994a).

Classification Schemes

Of the entities surveyed, IARC was the first to develop a system for classifying carcinogens, in 1977, as a means to simplify communication of complex human and experimental data on carcinogenicity to other scientists and to the general public (Ashby *et al.*, 1990). Germany's system for classifying chemicals was also developed in the 1970s by the Commission for the Investigation of Health Hazards of Chemical Compounds in the work area (Neumann *et al.*, 1997, 1998). Since that time, independent classification systems have also been established by the EU, the Netherlands, Norway, and Sweden. While communication of carcinogenic potential is a common goal of each system, it is important to note that there are differences in classification schemes between the different countries. Classification schemes for the various entities surveyed are summarized in Table 2.

The classification schemes of IARC, the EU, and Germany are similar in that they classify chemicals according to their carcinogenic potential in humans (EC, 1999; IARC, 1999a; Neumann *et al.*, 1997, 1998). Both IARC and Germany classify carcinogens into five groups (DFG, 1999; IARC, 1999a). The classification scheme used by the EU contains three categories that similarly classify chemicals according to their human carcinogenic potency. The EU's classification scheme also serves as the basis for labeling and establishing use restrictions in Europe (EC, 1999). Products are labeled as toxic if they contain at least 0.1% of a carcinogen in categories 1 and 2, and are labeled as harmful if they contain greater than 1% of a carcinogen in category 3 (Ashby *et al.*, 1990). The Dutch classify carcinogens into two broad categories according to genotoxicity (Moolenaar, 1994a; Whysner and Williams, 1992; HCN 1978, 1988, 1994, 1996). In the past, Sweden's system for classifying carcinogens considered potency and did not distinguish between human and animal carcinogens. Their system included two potency groups: toxic (T) and harmful (Xn) (SNCI, 1997). However, in January 1995, Sweden's classification system became harmonized with that of the EU pursuant to Sweden's entry into the EU (M. Altahir, personal communication; Sanner *et al.*, 1996). Norway has two classification categories. Category I is for chemicals which are carcinogenic in either animals or humans, and Category II is for chemicals with limited carcinogenicity data and is regarded as a holding category until further information is available (Moolenaar, 1994a). Because Norway does not consider animal carcinogens to be less carcinogenic than human carcinogens, their classification

TABLE 1
Comparison of Classification Criteria Used by European Scientific Organizations and Countries

	IARC	European Union	Germany	Netherlands	Norway
Classification basis:	Carcinogenic potential in humans	Carcinogenic potential in humans	Carcinogenic potential in humans	Genotoxicity	Potency
Evidence: strength *vs* weight:	Weight-of-evidence[a]	Weight-of-evidence	Weight-of-evidence	Weight-of-evidence	Strength-of-evidence[b]
Relevance of animal studies:	Animal carcinogens are considered possibly carcinogenic to humans.	Consider relevance of animal and other experimental data in carcinogenic potential in humans.	Animal carcinogens are considered carcinogenic to humans.	Animal carcinogens can be classified as noncarcinogens for humans, if data from biotransformation, toxicokinetic, and mechanistic studies conclusively indicate that carcinogenicity is irrelevant in humans.	Animal carcinogens assumed to be human carcinogens unless there is clear indication that carcinogen would not cause tumors in humans.[c]
Use of mechanistic data:	Relevance of species-specific, but not dose-dependent, differences in mechanisms can influence classfication.	Mechanistic data and relevance of animal and other experimental data are considered.	Chemicals have, in the past, been classified as carcinogenic based on animal studies, even if mechanism is not relevant for humans.[d]	Classification considers mechanism of action.	Genotoxicity, toxicokinetics, and target organ toxicity can influence potency ranking. If tumors occur only at site of administration, need to consider if exposure route is relevant to humans.
Types of data sources:	Benign tumors not considered sufficient evidence. Classification based only on data in open and published literature.	n/a	Only consider data for malignant tumors.	n/a	Classification based on published and unpublished data. Benign and malignant tumors considered equivalent. Classification also considers potency.

Note. n/a, information not available.

Sources. Holmberg and Lundberg, 1989; Moolenaar, 1994a; Neumann *et al.*, 1997, 1998; Sanner *et al.*, 1996; Whysner and Williams, 1992; F. R. Johannsen personal communication 2000.

[a] IARC used a strength-of-evidence approach in the past, but more recent classifications (e.g., acrylonitrile) indicate a weight-of-evidence approach (IARC, 1999a,b).

[b] Importance of positive data is not diminished by negative data from other studies.

[c] In Norway, chemicals which cause kidney tumors in male rats due to complexion of chemical with the α-2μ globulin are not considered carcinogenic to humans (Moolenaar, 1994a).

[d] Neumann *et al.* (1997, 1998) have proposed a new classification system for Germany which would incorporate information on mechanism. Future classifications are expected to incorporate mechanistic considerations (F. Johannsen, personal communication).

TABLE 2
Comparison of Classification Schemes for Carcinogens

IARC	European Union	Germany	Netherlands	Norway	Sweden
1: Carcinogenic to humans[a]	1: Substances known to be carcinogenic to humans[b]	1: Carcinogenic to humans[c]	I: Genotoxic carcinogens[d] Ia: Direct acting Ib: Indirect acting	I-K1: High potency animal and human carcinogens[e]	1: Substances knows to be carcinogenic to humans
2A: Probably carcinogenic to humans[f]	2: Substances which should be regarded as if they are carcinogenic to humans[g]	2: Carcinogenic in animal studies[h]	II: Nongenotoxic carcinogens[i]	I-K2: Medium potency animal and human carcinogens[j]	2: Substances which should be regarded as if they are carcinogenic to humans
2B: Possibly carcinogenic to humans[k]	3: Not classifiable as to carcinogenicity, but is of concern to humans owing to possible carcinogenic effects 3a: Well-investigated[l] 3b: Insufficiently investigated[o]	3: Suspected carcinogenic potential	III: Suspected carcinogens that cannot be classified according to mechanism[m]	I-K3: Low potency animal and human carcinogens[n]	3. Substances which cause concern for humans owing to possible carcinogenic effects, but for which the evidence is not sufficient for category 2
3: Not classifiable as to carcinogenicity in humans[p]		4. Nongenotoxic carcinogens	IV: Carcinogenic chemicals that cannot be classified[q]	II: Limited data available for classification. Considered a holding category	
4: Probably not carcinogenic[r]		5. Weak potency genotoxic carcinogens			

Sources. M. Altahir, personal communication: DFG, 1999; EC, 1999; HCN, 1978, 1996; IARC, 1994, 1997; Moolenaar, 1994a; Neuman *et al.*, 1997; Sanner *et al.*, 1996; Whysener and Williams, 1992; Zeise *et al.*, 1999.

[a] Based on sufficient evidence of carcinogenicity in humans, or limited evidence of carcinogenicity in humans and strong evidence that mechanism is relevant in humans.

[b] Based on epidemiological data.

[c] Shown to induce malignant tumors in humans. Generally potent carcinogens capable of inducing a few cases of rare tumors, or carcinogens with wide exposure potential.

[d] Chronic bioassays and mutagenicity tests both positive.

[e] Carcinogenic in an epidemiological study or in at least one mammalian experiment; TD_x (the lowest dose, in mg/kg-day, from a chronic animal bioassay, which induces a significant increase in tumors) is 1–15 mg/kg-day.

[f] Based on limited evidence of carcinogenicity in humans, sufficient evidence in animals; or inadequate evidence in humans and strong evidence that mechanism is relevant in humans.

[g] Based either on positive evidence from two animal species or on clear positve evidence from one species along with supporting genotoxicity data, metabolic or biochemical studies, structure–activity relationships, or suggestive epidemiological data.

[h] Cause tumors in animals, under conditions indicative of carcinogenic potential in the workplace. Chemicals in this category also considered carcinogenic to humans.

[i] Chronic bioassays positive, mutagenicity tests negative. Nongenotoxic mechanisms include hormonal alterations, nonspecific stimulation, and either suppression or overstimulation of the immune system.

[j] Same as for K1, but Td_x is between 1–15 and 600 mg/kg-day.

[k] Based on limited evidence in humans and less than sufficient evidence in animals; or inadequate evidence in humans, sufficient evidence in animals.

[l] Substances for which additional experiments would not likely yield further relevant information regarding classification.

[m] Either chronic bioassays or mutagenicity tests are positive; further tests are usually necessary. However, the Health Council of the Netherlands discourages use of this category (HCN, 1988).

[n] Same as for K1, but TD_x is greater than 600 mg/kg-day and evidence that chemical is not genotoxic.

[o] Substances for which further experiments are necessary for a definitive classification.

[p] Based on inadequate evidence in humans and inadequate/limited evidence in animals; or exceptionally, inadequate evidence in humans, sufficient evidence in animals, and strong evidence that mechanism is not relevant in humans.

[q] Chronic bioassays are positive, but no information on mechanism. However, the Health Council of the Netherlands discourages use of this category (HCN, 1988).

[r] Based on negative studies in humans and at least two negative animal studies.

system does not distinguish between animal and human carcinogens (Sanner *et al.*, 1996).

Both the EU and Sweden additionally distinguish between T and Xn carcinogens. Carcinogens in categories 1 and 2 are considered toxic substances with medium or high carcinogenic capacity, based on epidemiology studies, appropriate animal studies, and other relevant information. Carcinogens in category 3 are considered harmful substances with low carcinogenic capacity, based on appropriate animal studies, and other relevant information (EC, 2001; SNCI, 1997). Another unique feature of the classification system used in the EU and Sweden is that it considers carcinogenicity in terms of exposure route. Carcinogens in categories 1 and 2 are additionally classified with the risk phrase "may cause cancer" (R45) or "may cause cancer by inhalation" (R49). Carcinogens in category 3 are additionally classified with the risk phrase "limited evidence of carcinogenic effect" (R40), effective in 2001 (EC, 2001; M. Altahir, personal communication; SNCI, 1997).

The Dutch classification system is particularly informative, as it specifies which dose-extrapolation procedure should be used in the risk assessment process and what additional studies are needed for modification of classification. In the Netherlands, carcinogens in Category I are considered genotoxic carcinogens, capable of inducing irreversible DNA damage, based on positive results from both chronic bioassays and mutagenicity tests (HCN, 1978; Moolenaar, 1994a; Whysner and Williams, 1992). Category I carcinogens have recently been divided into two subcategories. Category Ia carcinogens act via stochastic processes (i.e., they or one of their metabolites can bind directly to DNA) and are not believed to have thresholds. Examples of 1a carcinogens are vinyl chloride, benzo[a]pyrene, 1,2-dichloroethane, and chromium VI compounds. Category Ib carcinogens induce DNA damage via nonstochastic, indirect processes (i.e., inhibition of DNA repair enzymes, elevation of endogenous free radicals) and are assumed to have thresholds for genotoxicity (HCN, 1996). Examples of 1b carcinogens are arsenic, cadmium compounds, and crystalline silica (HCN, 1996, 1998a). Classification of carcinogens as nongenotoxic is based on positive results from chronic bioassays, negative results from mutagenicity studies, and further proof that the carcinogen acts via a nongenotoxic mechanism (HCN, 1978, 1988, 1994, 1996). Nongenotoxic carcinogens may operate through a range of mechanisms, which can stimulate either cell growth or gene expression, resulting in expression of DNA damage caused by genotoxic carcinogens (Whysner and Williams, 1992).

Norway divides Category I carcinogens into three potency groups, K1, K2, and K3, with different labeling requirements and potential use restrictions (Sanner *et al.*, 1996). Selection of potency class is based on epidemiology data, TD_x values[2] dose–response relationships, and mechanistic information such as genotoxicity and toxicokinetics (Sanner *et al.*, 1996). Ranking carcinogens according to potency may more accurately reflect a chemical's inherent hazard than a system which does not consider potency. However, it is also possible that carcinogenic potency in animals does not accurately reflect carcinogenic potency in humans (Moolenaar, 1994a; Sanner *et al.*, 1996). Revisions to Norway's national guidelines on carcinogens stipulate that future classification of carcinogens should incorporate more understanding of the relevance of animal studies for human exposures, considering carcinogenic mechanisms as well as dose- and species-dependent differences in toxicokinetics (Sanner *et al.*, 1996).

Cancer Classification for Specific Chemicals

Differences in classification can arise due to differences in scientific understanding and differences in the intended purpose of the classification. While most countries classify chemicals to estimate risks and set OELs, Norway classifies chemicals primarily for labeling purposes. Differences can also arise due to consideration of mechanistic data, as well as data on biotransformation and toxicokinetics. Variations in classification of carcinogens may also arise due to selection of data sets. Some countries and agencies, such as IARC, rely solely on published data, whereas other countries, such as Norway, review all available data, including unpublished data. The date of the classification or its update can also influence the classification.

The list of chemicals considered carcinogenic in any mammalian species (humans or animals) is similar between different European organizations and countries, although there can be significant differences in how carcinogens are classified (Sanner *et al.*, 1996). Table 3 compares carcinogen classifications for specific chemicals used by IARC, the EU, Germany, the Netherlands, Sweden, and Norway. These specific chemicals were selected to represent both genotoxic and nongenotoxic carcinogens. There is general agreement on carcinogen classifications based mostly on human data; examples include asbestos, benzene, and vinyl chloride. There is less agreement when classification is based mostly on animal data; examples include 1,2-dichloroethylene, tetrachloroethylene, and trichloroethylene. For the chemicals reviewed there is a concordance in classification between the EU, Germany, and Sweden. IARC, whose classification system is similar to that of the EU (as well as Germany and Sweden), is more likely to classify chemicals as having a greater carcinogenic potential in humans

[2] TD_x is the lowest dose, from a chronic animal bioassay, which induces a significant increase in tumors. The potency groups, based on the TD_x value, are as follows: K1, TD_x < 1–15 mg/kg-day; K2, 1–15 < TD_x < 150–600 mg/kg-day; and K3, TD_x > 150–600 mg/kg-day.

TABLE 3
Classifications for Specific Carcinogens in Various Countries and Scientific Organizations

Chemical	IARC	European Union	Germany	Netherlands	Sweden	Norway
Acrylonitrile	2B	n.c.	2	I	n.c.	K2
Asbestos	1	1	1	I	1	K2
Benzene	1	1	1	I	1	K2
Benzo[*a*]pyrene	2A	2	2	I	2	K1
Cadmium	1	2	2	II	2	II
Chloroform	2B	3	3	II	3	K3
Chromium (VI)	1	2	2	I	1	K1
1,2-Dichloroethylene	2B	n.c.	2	I	n.c.	K2
Ethylene oxide	1	2	2	I	2	K1
Methylene chloride	2B	3	3	II	3	K3
Propylene oxide	2B	2	2	I	2	K2
Tetrachloroethylene	2A	3	3	II	3	K2
Trichloroethylene	2A	3	3	II	3	K3
Vinyl chloride	1	1	1	I	1	K2

Note. n.c., not classified. Acetonitrile and 1,2-dichloroethylene are classified as dangerous, but not carcinogenic, by the EU and Sweden.

Source. ACGIH, 1996; M. Altahir, personal communication, DFG, 1999; IARC, 1999a,b; Moolenaar, 1994a; SNCI, 1999.

(e.g., for cadmium, chromium (VI), ethylene oxide, tetrachloroethylene, and trichloroethylene). This is possibly due to IARCs historical use of a strength-of-evidence approach for classifying carcinogens.

RISK ASSESSMENT APPROACHES

Process and Methodologies

Risk assessment involves an evaluation of hazards associated with exposure to chemicals, an understanding of relationships between dose and an adverse effect, extrapolation of effects from high experimental doses to low doses associated with actual exposures, and extrapolation from effects observed in animals to effects expected in humans. Countries in Europe perform risk assessment for different purposes, such as setting acceptable exposure levels, determining disease incidence under realistic exposure conditions, or, in the case of Norway, for classifying carcinogens according to potency. IARC currently does not quantify risks to humans, although IARC has been discussing whether quantitative risk assessments should be incorporated into their monograph program (Moolenaar, 1994a; Sanner *et al.*, 1996). Risk assessment approaches used in the EU, the UK, the Netherlands, Norway, and Denmark are presented in Table 4.

Several elements of the risk assessment process can affect the outcome. These elements include choice of study on which to base the critical effect; consideration of mechanisms; and procedures used to extrapolate from experimental doses in animal studies to low doses typically occurring under actual exposure conditions for humans. Methodologies used for conducting risk assessments vary among countries and organizations. While the EU and other countries surveyed acknowledge that it is preferable to use data from good epidemiological studies, availability of such data for most chemicals is limited, and thus countries typically rely on animal data for conducting risk assessments.

Many European countries surveyed, as well as the EU, use different extrapolation procedures for genotoxic and nongenotoxic carcinogens. For nongenotoxic carcinogens, the EU, the UK, the Netherlands, and Sweden identify NOAELs or LOAELs which are converted to safe doses through use of safety or uncertainty factors (Moolenaar, 1994a; Zeise *et al.*, 1999). Denmark does not use a NOAEL/LOAEL approach to estimate risks for nongenotoxic carcinogens, but rather uses either a simplified multistage model, the Mantel–Bryan model, or a linear model, depending on available data and mechanism of growth promotion (Moolenaar, 1994a). Norway bases potency determinations on an evaluation of all data sets, with no distinction between benign and malignant tumors, or between human and animal carcinogens, although potency determinations can be influenced by consideration of genotoxicity and target organ toxicity (Moolenaar, 1994a; Sanner *et al.*, 1996). Norway does not extrapolate from high doses to low doses, but rather uses the TD_x approach to separate Category I carcinogenic chemicals into three potency subclasses, as discussed above (Moolenaar, 1994a; Sanner *et al.*, 1996).

Extrapolation procedures for genotoxic carcinogens can vary widely among countries. The EU defines acceptable risk levels as being at least 1000 times lower than the T25, which is the chronic daily dose,

in mg/kg-day, at which 25% of animals develop tumors, accounting for incidence of background tumors (Dybing *et al.*, 1997; W. F. ten Berge, personal communication). For genotoxic carcinogens without a threshold (*i.e.*, carcinogens in subcategory Ia) the Netherlands use the multistage model to extrapolate linearly from the lowest dose showing excess tumors in animals or humans (HCN, 1978, 1994, 1996; Moolenaar, 1994a; Zeise *et al.*, 1999). The rationale for extrapolating from the lowest dose is that at higher doses the shape of the dose–response curve could be affected by overt toxicity. Other extrapolation procedures can be used for genotoxic carcinogens without a threshold, if there are substantial supplementary data which suggest in a convincing way that such a different approach is more appropriate, as is the case with benzene (DECOS, 1989; HCN, 1988, 1995, 1997; Zeise *et al.*, 1999). In the Netherlands, risk levels for subcategory Ia carcinogens are calculated by scientific advisory groups, and acceptable risk levels are determined by policy (HCN, 1988). For genotoxic carcinogens with thresholds (those in subcategory Ib), the Netherlands use the same approach as for nongenotoxic carcinogens. In those (exceptional) cases where the available data on carcinogenicity and mutagenicity do not allow classification, but a quantitative cancer risk assessment is nevertheless deemed desirable, precautionally such a substance is treated as if it were a 1a carcinogen. An example is wood dust (HCN, 2000). In Denmark, the maximum likelihood estimate from one-and two-hit models, as well as the 99% upper confidence limit, are calculated for genotoxic carcinogens, considering data from multiple studies. Judgment regarding likely risk to humans considers results from all studies (Moolenaar, 1994a,b).

Risk assessment of genotoxic carcinogens in the UK differs from that used by other countries in that it is done on a case-by-case basis, without use of an established quantitative procedure (Moolenaar, 1994a). Furthermore, unlike many other countries, the UK does not use models for extrapolating from high doses in animal studies to low doses in humans (Zeise *et al.*, 1999). Instead of using models, experts representing employers, labor, and other interested parties review the available data and arrive at a consensus judgment on the type of low-dose effects expected at actual exposure levels (Ogden and Topping, 1997).

Currently, there are no environmental exposure standards for genotoxic carcinogens in Sweden. However, the Institute of Environmental Medicine at The Karolinska Institute has proposed some recommended exposure limits, on an ad hoc basis, and some of these (e.g., for benzene, ethylene, PAHs) have been incorporated in proposed environmental goals. These recommended exposure limits are calculated to correspond to an estimated life time cancer risk of 1×10^{-5} (G. Johanson, personal communication).

OCCUPATIONAL EXPOSURE LIMITS

Process and Methodologies

Most of the European countries surveyed, as well as the EU, use separate committees for evaluating scientific data and technological and socioeconomic considerations. Table 5 lists the key committees involved in setting OELs for the organizations and countries surveyed. The composition of the committees, especially the committees responsible for evaluating the scientific data, varies between countries. It is plausible that the composition of the committees can impact the ultimate value of the OEL, for example, through differences in consideration of relative importance of economic and technological issues vs health considerations. In the EU, Germany, and Sweden, the committees which review the scientific data consist of independent scientific experts, whereas the committee in the UK consists of scientists representing employers, labor, and other trade organizations (Hogberg *et al.*, 2000; Hunter *et al.*, 1997; Ogden and Topping, 1997; Zielhuis *et al.*, 1991). The committee in the Netherlands is appointed by the Health Council of the Netherlands, which is an independent advisory board to both the government and parliament (Feron *et al.*, 1994). In Denmark and Norway, the committees are appointed by the government (Holmberg and Lundberg, 1989; Zielhuis *et al.*, 1991). With the exception of Norway, all countries surveyed and the EU, prepare documents which summarize health aspects; with the exception of Sweden, these documents include a recommendation for an OEL (Feron *et al.*, 1994; Holmberg and Lundberg, 1989; Hunter *et al.*, 1997; Ogden and Topping, 1997; Zielhuis *et al.*, 1991). Documentation prepared by Norway is not available to the public (AIHA, 1996).

Basic procedures for establishing OELs are listed in Table 6. In most countries, the first step for establishing an OEL for a given chemical involves a committee of scientific experts that reviews scientific data and prepares a criteria document, which may or may not include a recommendation for an OEL. In the second step, information in the criteria document, along with socioeconomic considerations and technological feasibility, is considered for setting an operational OEL. In the EU, the UK, the Netherlands, and Denmark, an additional committee reviews the OEL before it is finally promulgated (Cross *et al.*, 1997; Feron *et al.*, 1994; Holmberg and Lundberg, 1989; Hunter *et al.*, 1997; Ogden and Topping, 1997; Zielhuis *et al.*, 1991).

Specific approaches for establishing OELs can differ considerably between countries. Differences in approach exist with regard to extrapolation procedures, such as models to estimate risk levels, and use of uncertainty factors; use of acceptable risk levels vs technological constraints or economic importance of a chemical;

TABLE 4
Comparison of Methodologies Used for Conducting Risk Assessments

	European Union	United Kingdom	Netherlands	Norway	Denmark	Sweden
Key purpose of risk assessment:	Describe actual incidence of disease expected under defined exposure conditions.	Determine likelihood or magnitude of carcinogenicity that may occur under actual exposure conditions.	Derive acceptable exposure levels, for both the general public and occupational settings.	Estimate potency for purposes of carcinogen classification and labeling.	Determine best estimate of human risk under actual exposure conditions, along with an uncertainty estimate. Presented as a virtually safe dose corresponding to a 1 in a million risk in the human population.	Predict effects of carcinogens on humans at low exposure levels.
Studies used:	n/a	Decided on a case-by-case basis from the entire data set using scientific judgment.	Studies showing highest risk are used. Data for both malignant tumors and benign tumors capable of transforming to malignant tumors are used.[a] Preference for studies with relevant exposure routes. Preference for oral or inhalation lifetime studies, in mammals.	Determination of potency based on evaluation of all available data. Benign and malignant tumors considered equivalent.	Data from all available studies are used.	n/a
Use of animal *vs* human data:	n/a	Preference for estimates based on adequate human data, rather than animal data.	Although good epidemiology studies are preferred, animal studies are mainly used due to lack of availability of epidemiology studies.	Negative epidemiological studies do not serve as proof that chemical is not carcinogenic. Animal and human carcinogens considered equivalent.	Preference for estimates based on adequate human data, rather than animal data. Animal doses considered-equivalent to human doses in terms of mg/kg-day.	n/a

Mechanistic considerations:	Distinguish between genotoxic and nongenotoxic carcinogens.	Distinction between genotoxic and nongenotoxic carcinogens.	Distinction betwween genotoxic and nongenotoxic carcinogens. Biological mechanisms, functional effects, and chemical structure are considered.	Genotoxicity and target organ toxicity can be used to influence potency ranking, but does not affect determination of TD_x^b value.	Risk assessment differs depending on whether chemical is genotoxic or acts as a promoter. Assessment of mechanism can incorporate consideration of target organ toxicity.	Different procedures used for genotoxic and non-genotoxic carcinogens.
Extrapolation procedures used:	T25 approach used for genotoxic carcinogens.[c] NOAELs or LOAELs identified for nongenotoxic carcinogens.	Mathematical models not used. For quantitative estimates of low-dose risk for genotoxic carcinogens, safe exposure levels are determined by scientific experts. NOAELs or LOAELs identified for nongenotoxic carcinogens.	For nonthreshold genotoxic carcinogens, extrapolate linearly from lowest dose showing excess tumors, based on the multistage, one-hit model of carcinogenesis.[d] NOAELs or LOAELs identified for nongenotoxic carcinogens.	No extrapolation to low doses.[e] Potency based in part on TD_x value.	Different nonthreshold low-dose extrapolation models used for genotoxic carcinogens and promoters, on a case-by-case basis. Dose levels associated with promotion not used. Multiple extrapolations usually performed; estimate of virtually safe dose based on results from all extrapolations.[f]	For genotoxic carcinogens, acceptable cancer risks are established at 1×10^{-5},[g] NOAELs or LOAELs identified for nongenotoxic carcinogens.

Note. n/a, information not available.

Sources. HCN, 1994, 1988a,b; Moolenaar, 1994a,b; Paustenbach, 1995; Whysner and Williams, 1992; Zeise *et al.*, 1999.

[a] Data for benign tumors are used only when malignant tumors of the same type occur at equivalent and/or higher exposure levels.

[b] TD_x is the lowest dose, in mg/kg-day, from a chronic animal bioassay, which induces a significant increase in tumors.

[c] T25 is the chronic daily dose (mg/kg-day) at which 25% of animals develop tumors.

[d] Alternate extrapolation procedures can be used for nonthreshold genotoxic carcinogens, if data indicate that this is appropriate (i.e., for benzene).

[e] Although as a rule Norway does not extrapolate risks at low doses, Norway has estimated risk of leukemia due to benzene exposure while filling gas tanks and risks associated with exposure to acrylamide in cosmetics.

[f] For genotoxic carcinogens, Denmark uses maximum likelihood estimate from one- and two-hit models, as well as the 99% upper confidence limit for multiple data sets. For nongenotoxic carcinogens Denmark uses biologically based (simplified multistage) model of Thorslund *et al.*, the Mantel–Bryan model, or a linear model (Moolenaar, 1994a).

[g] In Sweden, recommended environmental exposure limits are proposed on an ad hoc basis by the Institute of Environmental Medicine at the Karolinska Institute.

TABLE 5
Key Committees for Establishing OELs

European Union
- SCOEL—Scientific Committee on Occupation Exposure Limits: Committee of independent scientific experts
- ACSHH—Advisory Committee for Safety, Hygiene, and Health Protection at Work: So-called Tripartite Committee with six representative (two each from the government, employers' organizations, and trade unions) per country

United Kingdom
- WATCH—Working Group on the Assessment of Toxic Chemicals: Technical experts nominated by employers, labor, and independent parties
- ACTS—Advisory Committee on Toxic Substances: Expert committee with representatives from employees and employers organizations, trade unions, and other interested parties

Germany
- MAK Commission—Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area: Scientists appointed *ad personam* in their capacity as authoritative experts
- Committee on Dangerous Compounds (AGS): Committee of representatives from trade organizations, government organizations, and scientists

Netherlands
- DECOS—Dutch Expert Committee on Occupational Standards: Expert advisory committee appointed by Health Council of the Netherlands
- Subcommittee on MAC Values of the Social Economic Council: Representatives of employers organizations, trade unions, and governmental departments

Sweden
- SCG—Swedish Criteria Group: An expert committee at the Swedish National Institute for Working Life (NIWL) consisting of about 20 scientists from within the NIWL, and from universities, representing various areas in toxicology and occupational medicine. Observers from the Swedish National Board of Safety and Health and trade unions also participate in the SCG.
- Committee of the Swedish Work Environment Authority (SWEA):[a] Composed of independent scientists

Denmark
- Limit Value Committee
- Committee on Substances and Materials

Norway
- Committee: Established by Labor Inspection (Inspection), with representatives from government, employees, and employers

[a] The Swedish name for SWEA is Arbetsmiljoverket, formerly (prior to January 2001) called the Swedish National Board of Occupational Safety and Health (SNBOSH) (G. Johannson, personal communication).

TABLE 6
Comparison of Basic Procedures for Establishing OELs

European Union
1. SCOEL:
   a. Advises the European Commission on setting OELs: either indicative limit values (ILVs) or binding limit values (BLVs);
   b. Reviews all relevant toxicological data;
   c. Prepares short summary document, including underlying scientific basis for identifying critical effect and for recommending either an ILV (for nongenotoxic chemicals) or a degree of cancer risk at specific exposure levels (for genotoxic chemicals);
   d. Incorporates public comments;
   e. Finalizes summary document, which is published by the Office for Official Publications of the European Communities (OPOCE), in Luxembourg.
2. ACSHH recommends final OEL to the European Commission; considers technical and socioeconomic factors.

United Kingdom
1. WATCH prepares scientific criteria documents, including recommendation for occupational exposure standard (OES) or for setting maximum exposure limits (MEL).
2. ACTS considers recommended OES, along with technical issues (e.g., manufacture and use data, exposure and control levels), cost–benefit considerations, and social acceptability of residual risk of a MEL.
3. MELs further scrutinized by British parliament, including additional formal cost–benefit analysis.

TABLE 6—*Continued*

Germany
1. MAK Commission:
   a. Evaluates all literature and data;
   b. Prepares scientific document, including recommended health-based OEL. Economic and technological feasibility not considered for recommended OEL.
2. Proposed OEL evaluated by AGS as committee of representatives from industry, consumer organizations, trade unions, and trade organizations. Committee may occasionally consider practical criteria (e.g., working procedures, exposure patterns) for establishing OEL.

Netherlands
1. DECOS:
   a. Critically evaluates all relevant toxicological data;
   b. Oversees preparation of criteria document (CD), including proposal for health-based recommended OEL (HBR-OEL) for chemicals with thresholds, including nongenotoxic carcinogens and subcategory Ib carcinogens, or a health-based calculated-occupational cancer risk value (HBC-OCRV) for genotoxic carcinogens without thresholds (subcategory Ia carcinogens);
   c. Considers comments from experts worldwide;
   d. Finalizers CD for publication by the Health Council of the Netherlands. For Ia carcinogens, presents air concentrations associated with excess lifetime cancer mortality risks of 4×10^{-3} and 4×10^{-5}.
2. Subcommittee on MAC values of the Social Economic Council:
   a. Consults with supporting organizations regarding the HBR-OEL;
   b. Discusses and evaluates technical/socioeconomic feasibility of HBR-OEL;
   c. Recommends operational MAC to Minister of Social Affairs and Employment;
   d. Specifically notes whether recommended MAC is identical to HBR-OEL and, if not, identifies reason for the difference. Aim is to have all MAC values identical to HBR-OEL, if not immediately feasible, then as soon as possible.
3. Final maximum accepted concentration (MAC) set by Minister of Social Affairs and Employment.

Sweden
1. SCG:
   a. Gathers and evaluates data on health effects[a]
   b. Reviews criteria documents and OELs of other countries/organizations (e.g., the Nordic Expert Group, ACGIH);
   c. Prepares consensus report summarizing toxicological and medical data from peer-reviewed medical journals. Report presents dose–response relationships, defines critical effect for occupational exposures, and identifies a NOAEL or LOAEL, but does not include proposed OEL.
2. SWEA Committee:
   a. Considers technical feasibility and health effect;
   b. Performs cost–benefit analysis;
   c. Analyzes consequences of a change in the OEL;
   d. Proposes an OEL;
   e. Prepares a draft ordinance which is sent to the labor-market parties, branch organizations, and other relevant authorities (e.g., the Chemical Inspectorate, the Swedish Environmental Protection Agency, the National Institute for Working Life, etc.) for comments.
3. Final standard promulgated by Layman Board of SWEA.

Denmark
1. Danish Working Environment Service (DWES)[b] prepares scientific documentation for proposed OEL, based on information from other countries/organizations (e.g., Nordic Expert Group, ACGIH), and experiences from Danish workplaces.
2. Limit Value Committee reviews proposed OEL and evaluates health aspects/control techniques for proposed OEL.
3. Committee on Substances and Materials evaluates economic/technological aspects of OEL, including cost–benefit analysis, submits evaluation to director of DWES.
4. The National Labour Inspection considers OELs in countries comparable to Denmark, to ensure that Danish OEL will not be stricter than OELs in other comparable countries. Changes in OEL which would involve considerable extra costs must be weighed against any health benefits documented in the medical literature[c]

Norway
1. Committee proposes OEL based on health, technology, and economics. Scientific documentation (i.e., criteria documents) not published; instead use documentation of Nordic Expert Group, ACGIH, U.S. National Institute of Safety and Health, and Norwegian workplace experiences.
2. Proposed OEL sent for review and comments to labor unions/employers organizations.
3. Committee submits final recommendation for OEL to the director of Labor Inspection (Inspection), based on comments from labor unions and employers organizations.
4. Inspection assesses and publishes OELs.

[a] Selection of irritation as critical effect more likely in Sweden/other Scandinavian countries than in mainland Europe (Holmberg and Lundberg, 1989; Lundberg, 1991).

[b] DWES is an administrative department under the Ministry of Labor, consisting of a Central Directorate, an Occupational Health Institute, and 14 local inspection districts.

[c] For chemicals involving a particular risk, DWES can circumvent the standard procedure (AIHA, 1996; Zielhuis *et al.*, 1991).

TABLE 7
Comparison of Approaches for Establishing OELs[a]

European Union	United Kingdom	Germany	Netherlands	Sweden
Regulation of threshold chemicals[b]				
Indicative limit value (ILV): For chemicals for which a clear threshold can be identified (i.e., nongenotoxic chemicals) Based on NOAEL/LOAEL and uncertainty factor, such that no adverse health effects expected to occur	Occupational exposure standard (OES): For nongenotoxic chemicals with a threshold Based on NOAEL/LOAEL and uncertainty factor, such that risks expected to be minimal	Maximale Arbeitsplatz-Konzentration (MAK) or maximum concentration in the workplace: For nongenotoxic chemicals Primarily based on NOAEL/LOAEL; partical criteria such as working procedures/exposure patterns considered when possible	Maximum accepted concentration values (MAC values): For nongenotoxic chemicals and genotoxic chemicals with threshold[c] Based on NOAEL/LOAEL and uncertainty factors	OELs for noncarcinogens identified using NOAEL/LOAEL with consideration for technological/socioeconomic constraints
Regulation of nonthreshold chemicals				
Binding limit value (BLV): For chemicals without thresholds (i.e., genotoxic carcinogens, sensitizers), for which compliance with proposed limit is not technically feasible, or for which consensus on proposed level not achieved Based on acceptable risk level of T25/1000[d] and socioeconomic and technical constraints	Maximum exposure limit (MEL): For chemicals without thresholds (i.e., genotoxic carcinogens, primary respiratory sensitizers) or for which achievement of OES is considered impractical Based on technical feasibility, socioeconomics, cost–benefit analysis[e]	Technische Richtkonzentration (TRK) or technical guidance concentration: For chemicals with evidence of carcinogenicity or mutagenicity observable only after several decades Based on minimum possible level that can be achieved with current technology	Health-based calculated occupational cancer risk values (HBR-OCRVs): For genotoxic chemicals without thresholds (subcategory Ia carcinogens) Based on a maximum accepted lifetime cancer risk level of 4×10^{-3}, as a higher reference cancer risk value[f] Risk estimated using multistage model of carcinogenesis, unless data justify use of other extrapolation procedure	OELs for carcinogens based on health and technological feasibility
Use of uncertainty factors				
Species-specific factors for interspecies variability[g] Intraspecies variability[h] Biological sigificance of adverse effect Adequacy of database Exposure duration Slope of the dose–response curve	Species studied[i] Exposure route Amount and quality of data Severity of critical effect[j]	n/a	Intraspecies factor for human data, especially if studies involve intentional exposure of young, healthy volunteers and were short-term in duration	n/a

Consideration of socioeconomic/technical issues[k]

Socioeconomic issues considered for establishing BLVs	Socioeconomic, technical issues considered for OES and MEL Cost–benifit analyses considered for OES; required for MEL	Technological and socioeconomic issues considered in all cases for TRKs and occasionally for MAKs	HBR-OEL evaluated with respect to socioeconomic and technical considerations	Socioeconomic and technological feasibility considered for noncarcinogens Technological feasibility considered for carcinogen

Legal status of occupational exposure levels[l]

BLVs considered legally binding ILVs serve as recommendations	Both OES and MEL are legally enforceable	Both MAKs and TRKs must be adhered to	MACs have legal status, provided that they are set according the Netherlands three-step procedure	OELs are legally binding

Sources. AIHA, 1996; Arboraad, 1992; Carnevale *et al.*, 1987; DFG, 1992; Fairhurst, 1995; HCN, 1995; Hogberg *et al.*, 2000; Holmberg and Lundberg, 1997; Hunter *et al.*, 1997; MVROM/MSZW, 1990; Ogden and Topping, 1997; SCOEL, 1998; Stijkel *et al.*, 1996; Van Leeuwen *et al.* 1996; Zielhuis *et al.*, 1991.

[a] Information on chemical regulation and uncertainty factors not readily available for Denmark and Norway; therefore, these countries not presented in table.

[b] Chemicals for which carcinogenic activity is considered secondary to tissue damage (e.g., chloroform, carbon tetrachloride).

[c] Genotoxic carcinogens with thresholds act via nonstochastic, indirect mechanisms, such as inhibition of DNA repair enzymes or generation of DNA-reactive compounds. (e.g., arsenic, cadmium, crystalline silica).

[d] T25 is chronic daily dose, in mg/kg-day, at which 25% of animals develop tumors.

[e] For assessing benefits, cancer risk of employee exposed at the MEL assumed to be half the cancer risk of same employee previously exposed above the MEL.

[f] HRCRV, a maximum tolerable cancer risk level, equivalent to overall background risk in Dutch industry of one serious accident per 10,000 workers per year, for a 40-year occupational duration. Legal obligation to take all possible measures to meet the ALARA principle (i.e., exposure should be as low as reasonably achievable).

[g] UFs of 7, 4, and 1.4 used for mice, rats, and dogs, respectively, to account for differences in caloric demands, and an additional factor of 3 for residual uncertainty.

[h] Default value of 3 used for differences within an occupational population; default value of 10 used for teratogenic/embryotoxic effects which are of concern to the general population.

[i] UFs generally not applied to human data; UFs generally range between 4 and 10 for animal data.

[j] i.e., an uncertainty factor of 1 may be used for a chemical with sufficient and reliable data and which causes sensory irritation (not considered a serious effect). In contrast, an uncertainty factor of 50 may be used for chemicals which are teratogenic in animals (Ogden and Topping, 1997).

[k] Denmark—health considerations balanced with control techniques and economics; Norway—economic/technical aspects are considered.

[l] Denmark—OELs have legal status; Norway—OELs considered as legal norms and do not have legal status.

and point of departure value which is affected by choice of critical endpoint and study. The frequency at which OELs are updated can also differ among countries, according to priorities set based on patterns of use and exposure (Zielhuis *et al.*, 1991). The frequency at which an OEL is updated can influence its value due to inclusion of more recent data. Table 7 shows specific approaches for establishing OELs in the EU, the UK, Germany, the Netherlands, and Sweden.

Many of the European countries surveyed use separate criteria for setting OELs for genotoxic and nongenotoxic carcinogens. OELs for threshold (i.e., nongenotoxic) chemicals tend to be primarily based on NOAELs or LOAELs, while OELs for genotoxic carcinogens are based, to a large extent, on technological feasibility for achieving the lowest possible exposure level, as it is generally considered that no level of exposure to a carcinogen is safe (Cross *et al.*, 1997; HCN, 1995; Hunter *et al.*, 1997; Ogden and Topping, 1997; SCOEL, 1999). In both the EU and the UK OELs for respiratory sensitizers, particularly those acting via immunological mechanisms, are also based on technological feasibility. This is consistent with the belief that such respiratory sensitizers are not likely to have a threshold of exposure below which sensitization would not occur (Ogden and Topping, 1997; SCOEL, 1999). The EU and the Netherlands constitute exceptions, in that OELs for genotoxic carcinogens are based on risk levels considered acceptable by society (HCN, 1988, 1998b; Neumeier, 1993). The Netherlands makes an additional distinction between genotoxic carcinogens with and without thresholds. Genotoxic carcinogens with thresholds are regulated as nongenotoxic carcinogens in the Netherlands, using NOAELs or LOAELs (HCN, 1994, 1996, 1998b).

Use of uncertainty factors (UFs) in setting OELs can differ among countries and organizations. For example, species-specific uncertainty factors, or scaling factors, are used for interspecies variability in the EU, whereas other countries do not explicitly differentiate between species when applying UFs (Fairhurst, 1995; Stijkel *et al.*, 1996; Van Leeuwen *et al.*, 1996). Another application unique to the EU is the use of uncertainty factors to account for the nature of the dose–response relationship (SCOEL, 1999). For intraspecies variability, the EU and the Netherlands are more likely than the UK to apply uncertainty factors when using human data (Fairhurst, 1995; Stijkel *et al.*, 1996; Van Leeuwen *et al.*, 1996). Both the EU and the UK consider adequacy of the database as well as the nature of the adverse health effect when selecting uncertainty factors. For example, the EU considers biological significance of the adverse effect, and the UK considers severity of the effect (Fairhurst, 1995; SCOEL, 1999; Van Leeuwen *et al.*, 1996).

Occupational Exposure Limits for Specific Chemicals

Table 8 lists OELs for specific chemicals in the EU, the UK, Germany, the Netherlands, Ireland, Sweden, and Denmark. Our analysis indicates that OELs can vary significantly among countries. For some chemicals, such as acrylonitrile, OELs are comparable among different countries (between 2 and 4 ppm); for other chemicals, such as benzene and trichloroethylene, OELs can vary by as much as 10-fold. There are several reasons for these differences. As noted above, differences in OELs among European countries and organizations can be due to methodological factors as well as differences in national policies and priorities and consideration of technical and socioeconomic issues. Some of the factors that contribute to differences in OELs are highlighted below.

Even when using the same study, countries may consider different critical effects. For example, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (DFG, 1999) (MAK[3] Commission) considered epidemiology studies with ethylene oxide (ETO) as providing supplementary evidence of carcinogenicity (DFG, 1993), whereas the UK determined that the epidemiological studies provided evidence of spontaneous abortions and fetal deaths, rather than carcinogenicity (HSE, 1998). Despite using the same study of ETO in rats, the UK determined that ETO caused dose-related increases in leukemia and testicular cancer, while the German MAK Commission determined that ETO induced dose-dependent increases in brain tumors in addition to leukemia and testicular cancer (DFG, 1993; HSE, 1998). Although the German MAK Commission and the UK considered different critical effects, the OELs for ETO in both countries are based on technological feasibility, as ETO is considered a human carcinogen by the German MAK Commission and a potential human carcinogen by the UK. However, the OEL is higher in the UK (5 vs 1 ppm) possibly due to different cost–benefit considerations. These are separately taken into account within the procedure of OEL settings in the UK. In Germany, the MAK Commission does not propose health-based MAK values for carcinogens, and the socioeconomic and feasibility assessment is a subsequent task of the tripartite Committee on Dangerous Chemicals (“Ausschuss für Gefahrstoffe”—AGS). In this case of ethylene oxide, the AGS has arrived at a “technical guidance concentration” (TRK) of 1 ppm.

Differences in OELs can occur as a consequence of selection of the critical effect. For example, Nordic countries are more likely than other countries to use irritation as a critical effect (Holmberg and Lundberg,

[3] Maximale arbeitsplatz-konzentration (maximum accepted workplace concentration).

TABLE 8
Occupational Exposure Limits for Specific Chemicals

	Acrylonitrile	Benzene	Chromium compounds[a]	Ethylene oxide	Tetrachloroethylene	Trichloroethylene	Vinyl chloride
European Union	n/a	0.5 ppm[b]	n/a	n/a	n/a	n/a	7 ppm
United Kingdom	2 ppm	5 ppm	0.05 mg/m^3	5 ppm	50 ppm	100 ppm	3 ppm
Germany	3 ppm	5 ppm	0.05 mg/m^3	1 ppm	50 ppm	50 ppm	1 ppm
Netherlands[c]	0.7 ppm[d] (1.52 mg/m^3)	1 ppm (3.25 mg/m^3)	0.025 mg/m^3	0.5 ppm (0.84 mg/m^3)	35 ppm (240 mg/m^3)	35 ppm (190 mg/m^3)	3 ppm (7.7 mg/m^3)
Sweden	2 ppm	0.5 ppm	0.02 mg/m^3	1 ppm	10 ppm	10 ppm	1 ppm
Denmark	2 ppm	5 ppm	0.02 mg/m^3	1 ppm	30 ppm	30 ppm	1 ppm
Ireland[e]	2 ppm	3 ppm	0.05 mg/m^3	5 ppm	50 ppm	100 ppm	5 ppm

Note. n/a, not available.
Sources. ACGIH, 1996; Cross *et al.*, 1997; DECOS, 1989; 1992; DFG, 1992; DGA, 1989: DGL, 1992; MSZW, 1999, 2000; NAOSE, 1999; SNBOSH, 1996.
[a] Expressed as mg/m^3 Cr (except for Germany, expressed as mg/m^3 as CrO_3) for chromium VI (UK, Germany), soluble chromium compounds (Netherlands), chromic acid and chromates (Sweden, Denmark), or Cr VI for Ireland.
[b] Recommended 8h TWA, based on risk assessment.
[c] OELs in the Netherlands are reported in mg/m^3; OELs in the table are listed in ppm for purposes of comparison.
[d] OEL for acrylonitrile is an unofficial draft recommendation.
[e] Ireland develops very few of its own OELs; majority based on American Council of Government and Industrial Hygienists—threshold limit values (ACGIH-TLVs) or UK's OES and MEL values.

1989; Lundberg, 1991). Since irritation tends to occur at lower levels than more adverse effects, such as lung function decreases, choice of irritation as a critical effect is likely to yield a more restrictive OEL. For example, there is a 10-fold variation in the OEL for trichloroethylene, from 10 ppm in Sweden to 100 ppm in the UK and Ireland. In general, selection of irritation instead of CNS effects for noncarcinogens may result in lower OELs for solvents (e.g., tetrachloroethylene and trichloroethylene in Sweden).

Another country-specific approach which could also contribute to differences in OELs is use of technological constraints vs acceptable risk for regulating chemicals without thresholds, such as genotoxic chemicals and sensitizers. For example, both the EU and the Netherlands use acceptable risk levels for establishing OELs for genotoxic carcinogens. This is in contrast to other countries surveyed which base OELs for genotoxic carcinogens on technological feasibility and socioeconomic considerations. The use of acceptable risk levels by the EU and the Netherlands could account for the lower OELs for acrylonitrile and ethylene oxide in the Netherlands and for benzene in the EU and the Netherlands.

Since setting of OELs is a national responsibility, the relative importance of various socioeconomic considerations may differ among countries, for example, depending on whether a chemical is associated with an industry of particular economic importance in a given country. Therefore, in addition to the factors already mentioned above, OELs may also differ due to national priorities and policies.

CONCLUSIONS

This review compared cancer classification, health risk assessment approaches, and procedures used for establishing OELs in various European countries and organizations. An important function of cancer classification is to facilitate labeling, for establishing use restrictions. Most European countries and organizations surveyed classify carcinogens according to a weight-of-evidence approach which considers all relevant data, including both positive and negative results from epidemiology and animal carcinogenicity studies, as well as mechanistic data. However, classification schemes differ among the various countries and organizations. IARC, which was the first organization to develop a classification scheme, classifies chemicals according to their carcinogenic potential in humans. This approach was adopted by both the EU and the Germany. In contrast, the Netherlands and Norway do not explicitly differentiate between animal and human carcinogens. Rather, the approach used in the Netherlands is based on genotoxicity and is directly relevant to how risk is evaluated and how the OEL is determined. In Norway carcinogens are classified according to potency, expressly for labeling and establishing use restrictions. A comparison of classification of specific carcinogens among IARC, the EU, and Germany, who have comparable classification schemes, revealed that there is good agreement when classification is based mostly on human data, such as for asbestos, benzene, and vinyl chloride; there is less agreement when classification is based mostly on animal data.

There are also country- and organization-specific procedures for estimating risks. Risk estimation procedures for nongenotoxic chemicals are fairly comparable among the various governing organizations and are based on a NOAEL or LOAEL and an uncertainty factor. However, there are country-specific differences, especially with respect to use of uncertainty factors. There is more variability in risk estimation procedures for genotoxic carcinogens. Whereas both the Netherlands and Denmark use linear extrapolation procedures, the EU uses a margin of exposure type of approach. Extrapolation procedures are decided on a case-by-case basis in the UK. Norway does not use extrapolation procedures at all, but rather bases their potency classifications on actual experimental doses.

Inasmuch as OELs are based on risk estimates, differences in risk estimates carry over into differences in derivation of OELs. Although OELs for nongenotoxic chemicals are based on NOAELs or LOAELs and uncertainty factors, as a rule, the consideration of socioeconomic factors and technological constraints varies among the governing organizations surveyed; with the UK, the Netherlands, and Sweden giving greater consideration to these issues than the EU or Germany. OELs for genotoxic carcinogens are regulated either according to technical feasibility, as in the UK and Germany, or according to acceptable risk levels, as for the EU and the Netherlands.

A comparison among the various governing organizations for several chemicals revealed several trends with respect to OELs. These were as follows: (1) risk-based OELs were lower than OELs based on socioeconomic factors and technological feasibility, for genotoxic carcinogens (e.g., for acrylonitrile, benzene, and ethylene oxide, in the EU and the Netherlands); (2) cost–benefit considerations may result in higher OELs (e.g., for ethylene oxide and trichloroethylene, in the UK); and (3) selection of irritation instead of CNS effects for noncarcinogenic chemicals may result in lower OELs for solvents (e.g., for tetrachloroethylene and trichloroethylene, in Sweden). Whether these trends would be borne out with a greater number of chemicals remains to be determined. What is certain is that there will inevitably be differences in OELs among various governing organizations, in part due to differences in risk assessment procedures and in part due to differences in risk management decisions.

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