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Changes in the classification of carcinogenic chemicals in the work area

Section III of the German List of MAK and BAT Values

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Abstract Carcinogenic chemicals in the work area are currently classified into three categories in section III of the German List of MAK and BAT Values (list of values on maximum workplace concentrations and biological tolerance for occupational exposures). This classification is based on qualitative criteria and reflects essentially the weight of evidence available for judging the carcinogenic potential of the chemicals. It is proposed that these categories – IIIA1, IIIA2, IIIB – be retained as Categories 1, 2, and 3, to correspond with European Union regulations. On the basis of our advancing knowledge of reaction mechanisms and the potency of carcinogens, these three categories are supplemented with two additional categories. The essential feature of substances classified in the new categories is that exposure to these chemicals does not contribute significantly to risk of cancer to man, provided that an appropriate exposure limit (MAK value) is observed. Chemicals known to act typically by nongenotoxic mechanisms and for which information is available that allows evaluation of the effects of low-dose exposures, are classified in Category 4. Genotoxic chemicals for which low carcinogenic potency can be expected on the basis of dose-response relationships and toxicokinetics, and for which risk at low doses can be assessed are classified in Category 5.

The basis for a better differentiation of carcinogens is discussed, the new categories are defined, and possible criteria for classification are described. Examples for Category 4 (1,4-dioxane) and Category 5 (styrene) are presented.

Key words Chemical carcinogens · List of MAK and BAT Values · Cancer risk

Abbreviations *MAK* (Maximale Arbeitsplatz-Konzentration) maximum workplace concentration · *BAT* (biologischer Arbeitsstoff-Toleranzwert) biological tolerance value for occupational exposures · *TRK* (technische Richtkonzentration) technical exposure limits for hazardous substances · *EU* European Union

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Introduction

The system for classification of carcinogens by the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area of the Deutsche Forschungsgemeinschaft (subsequently called the Com-

mission) was developed in the 1970s. In the List of MAK and BAT Values the following sections[1] were established: IIIA1 – carcinogenic to humans, IIIA2 – carcinogenic in animal studies, IIIB – suspected carcinogenic potential. By the year 1997 the Commission had assigned 21 substances to section IIIA1, 106 substances to section IIIA2, and 86 to section IIIB (DFG 1997). This classification, like that established by other international bodies, was based on relatively inflexible criteria. In the meanwhile, however, cancer research has made great progress and carcinogenic substances can now be better differentiated on the basis of their mode of action and potency. It was suggested already in 1988 by one of the Commission's working groups (Bolt et al. 1988) that section IIIB should be subdivided on the basis of whether or not further studies of the substances are necessary. This suggestion has been adopted to a great extent by the EU.

This document presents the classification scheme used to-date by the Commission, together with the new classification scheme which is based on new findings.

Categories used to-date

IIIA1

Substances shown to induce malignant tumours in humans

A substance may only be assigned to section IIIA1 (carcinogenic to humans) if it has been shown in epidemiological studies to cause tumours in man. However, sufficient epidemiological data are available for only a few substances. Frequently the cohorts studied were too small to demonstrate effects unequivocally or there are problems in associating the effects with the substance. Therefore, substances for which carcinogenic effects were demonstrated in humans were substances with marked carcinogenic potency that induced a few cases of rare tumours, or to which a large number of people had been exposed. Epidemiological data that, taken by themselves, would not suffice to justify assignment to section IIIA1 can, however, be used for an assignment to this section if they are supported by data which show that the mode of action of a substance is relevant for humans.

IIIA2

Substances shown to be clearly carcinogenic only in animal studies but under conditions indicative of carcinogenic potential at the workplace

Substances assigned to this section are considered to be carcinogenic for man on principle, and, when handled at the workplace, necessitate the same protective measures as do the substances of section IIIA1. This approach is supported by a number of studies which show that the results obtained with animal studies largely concur both qualitatively and quantitatively with those observed in man.

However, there are also substances which have caused tumours in animal studies, but which are considered not to be relevant for man. The definition used to date requires that such substances be assigned to section IIIA2. This implies a hazard which may not really exist. Using the new classification system, such substances will no longer be classified anymore.

The results of epidemiological studies were only taken into account for the assignment of a substance to section IIIA1. However, in the light of the recent improvement in epidemiological methods, it now seems appropriate to use limited evidence from epidemiological studies also for assignment to IIIA2, if this evidence substantiates a suspicion from animal studies.

The previous limitation of section IIIA2 "under conditions indicative of carcinogenic potential at the workplace" has repeatedly caused problems in the classification of substances. It became evident that administration routes or exposure concentrations in animal experiments which are not comparable with those found at the workplace can indeed demonstrate carcinogenic potential of a substance for man. This situation applied to some man-made mineral fibres which, when administered intraperitoneally or intrapleurally, elicited tumours in animals but did not give rise to tumors when the administration was by inhalation, the exposure route most directly comparable with that at the workplace. In order to avoid inconsistency with the above-mentioned definition of section IIIA2, these man-made mineral fibres were designated "as if IIIA2". Such man-made mineral fibres are classified as Category 2 substances under the new classification system.

IIIB

Substances suspected of having carcinogenic potential.
At present, section IIIB contains quite different types of substances (Bolt et al. 1988), including some which have been studied in detail and for which it is currently not expected that further studies would be able to dispel or confirm the suspicion of carcinogenicity, and others for which clarification of the carcinogenic potential must still be carried out. Therefore, a working group of the Commission (Bolt et al. 1988) suggested that section

[1] Carcinogenic substances in the workplace are assigned to section III "Carcinogenic substances" of the List of MAK and BAT Values and are classified into subsections (previously IIIA1, IIIA2 and IIIB). Factually, these subsections were equivalent to categories although the term category was not used. To avoid confusion with the newly proposed Categories 1–5, these are written with a capital letter, and reference to the previous classification system is made by applying the term section.

IIIB be divided into two groups. This suggestion has already been adopted by the EU in such a way that the EU Category 3 comprises two subcategories defined by the following criteria:

a) Substances which are well-investigated but for which the evidence of a tumour-inducing effect is insufficient for classification in Category 2. Additional experiments would not be expected to yield further relevant information with respect to classification;
b) substances which are insufficiently investigated. The available data are inadequate but they raise concern for man. This classification is provisional; further experiments are necessary before a final decision can be made.

Further differentiation of carcinogens

The classification of carcinogenic substances into the three categories (equivalent to sections IIIA1, IIIA2, and IIIB in the List of MAK and BAT Values) which has been used to date was carried out according to the certainty with which a carcinogenic potential could be established. Mode of action and potency of the substance were either not taken into account, or at best were used as supporting arguments. This purely qualitative approach is also common to other international systems of classification. The progress which has been made in research on the multistage process of tumour development permits, however, a more differentiated approach.

Mode of action

The historical development of risk assessment for carcinogens began with genotoxic substances. However, to an increasing degree, chemicals must be assessed which elicited tumors in long-term animal studies, while exerting only minor genotoxic effects or no genotoxicity at all. The substances defined by the exclusionary term "nongenotoxic substances" include carcinogens which are known to induce cancer or to promote cancer by a large variety of mechanisms. They have been shown, for example, to be capable of amplifying the effects of genotoxic carcinogens in the sense of promotion. Effects on receptor-dependent regulatory processes or cytotoxic effects can play an important role. In some cases nonlinear dose-response relationships are observed; in others it is not possible to distinguish the effects of low doses from variability in the physiological range. In contrast to the irreversible, additive damage caused by genotoxic substances, these effects, especially those occurring in the low dose range, are primarily reversible processes with little potential to cause damage. Even for substances which cause oxidative DNA damage *via* secondary reactions involving activation of oxygen, it is difficult to demonstrate damage at low levels of exposure which exceeds background damage resulting from endogenous processes. For cytotoxic substances it can also be shown that slight changes in biochemical equilibria can be compensated by counter-regulating processes. The cell is not damaged until its adaptation mechanisms are exhausted.

In all the above-mentioned cases, the biochemical parameters may increase linearly with the dose – as applies, for example, to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Therefore the term "threshold", below which no (biochemical) effects occur, should be avoided and, wherever possible, the dose-dependence of the changes in the relevant biochemical parameters should be determined and related to changes associated with physiological activity or background exposures.

Such nongenotoxic chemicals have in common that, after low level exposures, they produce primarily reversible changes in the range of the normal physiological variability. Therefore, the Commission considers it justified to classify them as a group and to define exposure levels at which no significant contribution to cancer risk is to be expected.

Potency of carcinogens

For classification of carcinogens by the Commission or by other relevant international bodies, potency did not play a role so far or was only of subsidiary importance. This is due to controversy regarding how to arrive at cancer risk estimates for man and to the difficulty that such estimates, when deduced with disputed methods, are prone to considerable uncertainty. This is true for risk estimates derived from both epidemiological data and, in particular, from the results of animal studies. In this unsatisfactory situation it is necessary to improve the presently used methods of risk estimation in order to reduce the uncertainty attached to the results, and to clarify whether relative risks could be used as a basis for establishing regulations.

The main difficulties in determining the level of cancer risk for man lie in the estimation of values for a heterogeneous human population on the basis of data obtained from animal studies, in the practical difficulty of determining the uncertainty associated with such a value, and in the fundamental impossibility of testing such a hypothesis once it has been conceived. In practice, the data available are also generally inadequate, in addition. The incidence of tumours in animal studies is frequently found to be increased at only one dose, namely at the highest dose that is within the range of the maximum tolerated dose (MTD), or occasionally at two doses. Such data allow only a rough estimate of the carcinogenic potency in an animal experiment; they do not allow a reliable risk assessment for man. For risk characterization, data on the mode of action, dose-response relationships and exposure are required. For exposure assessment, data on the exogenous and endogenous carcinogen exposure to humans, which together make up the so-called background exposure,

are available to an increasing extent. This holds true for both genotoxic and nongenotoxic substances. Data obtained from biochemical effect monitoring, e.g. in the form of levels of DNA and protein adducts as parameters of strain[2] provide a measure of individual strain caused by genotoxic substances. Therefore, for specific situations, e.g. at the workplace, it is possible to determine whether external exposures lead to an increase of background levels of stress or strain parameters. The decisive advantage of this approach lies in the fact that assessments can be made on the basis of information obtained under real exposure conditions from the affected persons themselves. Thus a quantitative element is introduced into the assessment. It must then be decided what degree of contribution to a strain parameter is to be considered significant.

Extra categories for the classification of carcinogens

From the above-mentioned considerations it follows that additional categories for the classification of carcinogens should be introduced. To achieve this it is necessary to combine scientifically different classification criteria. Therefore, sections IIIA1, IIIA2 and IIIB of the List of MAK and BAT Values are retained as Categories 1, 2 and 3 to correspond with the EU Categories. The certainty with which a carcinogenic potential for man can be established continues to be decisive for the classification of a substance. In the documentation, however, information about the mode of action and the potency should be presented and evaluated. This information can then be taken up in the discussion which precedes the establishment of TRK values (technical exposure limits: limits for concentrations of carcinogenic substances at workplaces in Germany).

In addition, two new Categories are established for substances with carcinogenic potential and for which the carcinogenic potency can be assessed, and a MAK value established, by considering all available evidence. Classification of a substance in Category 4 requires the demonstration that the mode of action is based on nongenotoxic properties resulting in reversible effects at low doses. The main criteria for classification in Category 5 will be low potency and the possibility to control internal exposure, e.g. by measuring biochemical effect markers.

It should thus become possible to re-evaluate substances which have been proven to be carcinogenic for man (section IIIA1 and new Category 1) or carcinogenic for animals (section IIIA2 and new Category 2) for their potency at low exposure concentrations at the workplace, and to reclassify them in the new Categories as carcinogens with MAK values, provided the data justify this procedure. In addition, substances which were classified in section IIIB (new Category 3) due to their weak or undetectable effects, when tested with the usual methods, can be better assessed according to the new criteria. Category 3 will then become a genuine list of suspected carcinogens.

Establishing the new Categories 4 and 5 together with their categorization criteria aims at including both mode of action and carcinogenic potency for evaluation of carcinogens.

The new classification categories

Category 1

Substances which cause cancer in man and which can be assumed to make a significant contribution to cancer risk. Epidemiological studies provide adequate evidence of a positive relationship between the exposure of humans and the occurrence of cancer. Limited epidemiological data can be substantiated by evidence indicating that the substance operates through a relevant mechanism of carcinogenicity in man.

Category 2

Substances which are considered to be carcinogenic for man because sufficient data from long-term animal studies or limited evidence from animal studies substantiated by evidence from epidemiological studies indicate that they can make a significant contribution to cancer risk. Limited data from animal studies can be supported by information suggesting that a substance operates through a mode of action relevant to man, and by results of in vitro tests and short-term animal studies.

Category 3

Substances which cause concern that could be carcinogenic for man, but which cannot be assessed conclusively because of lack of data. In vitro tests or animal studies provide indications of carcinogenicity which, however, are not sufficient to classify the substance in one of the other Categories. The classification in Category 3 is provisional. Further studies are required before a final decision can be made. A MAK value may be established provided no genotoxic effects have been detected.

Category 4

Substances with carcinogenic potential for which genotoxicity plays no or at most a minor role. No significant contribution to human cancer risk is expected, provided that the MAK value is observed. The classification is supported especially by evidence of the mode of action

[2] According to the stress and strain concept (Henschler and Lehnert, 1994) stress represents an impact capable of affecting the individual (exposure), strain the factual changes (effects) that result from this impact depending on the individual properties.

indicating that increases in cellular proliferation or changes in cellular differentiation are important. To characterize the carcinogenic risk, the manifold mechanisms contributing to carcinogenesis and their characteristic dose-time-response relationships are taken into consideration.

Category 5

Substances with carcinogenic and genotoxic potential, the potency of which is considered to be so low that, provided that the MAK value is observed, no significant contribution to human cancer risk is to be expected. The classification is supported by information on the mode of action and dose-dependency, and by toxicokinetic data pertinent to species comparison.

Table 1 presents these new criteria for the classification of carcinogenic chemicals in comparison with those from international bodies.

Possible criteria for classification

For the new Categories 4 and 5, criteria are proposed which can be applied for justifying the classification. They are intended as guidelines but not as a complete check-list. Not all of the criteria of a particular Category must be met; fulfilment of only a single criterion, however, is not sufficient for classification. In a case-to-case approach, the classification decision should be based on a founded and comprehensible combination of criteria.

Category 4

Substances with carcinogenic potential for which genotoxicity plays no or at most a minor role. No significant contribution to human cancer risk is expected, provided that the MAK value is observed.

Table 1 The new DFG/MAK criteria for the classification of carcinogenic chemicals compared to those from international bodies

EU	DFG/MAK	ACGIH/TLV	IARC
1 Substances known to be carcinogenic to man	1 Substances which cause cancer in man	A1 Confirmed human carcinogen	1 The agent is carcinogenic to humans
2 Substances which should be regarded as if they are carcinogenic to man	2 Substances which are considered to be carcinogenic for man	A2 Suspected human carcinogen	2A The agent is probably carcinogenic to humans
3 Substances which cause concern for man owing to possible carcinogenic effects; 3b substances which are insufficiently investigated	3 Substances which cause concern that they could be carcinogenic for man but which cannot be assessed conclusively because of lack of data	A3 Animal carcinogen	2B The agent is possibly carcinogenic to humans
3a substances which are well-investigated	4 Substances with carcinogenic potential for which genotoxicity plays no or at most a minor role. No significant contribution to human cancer risk is expected, provided that the MAK value is observed	A4 Not classifiable as a human carcinogen	3 The agent is not classifiable as to its carcinogenicity to humans
	5 Substances with carcinogenic and genotoxic potential, the potency of which is considered to be so low that, provided that the MAK value is observed, no significant contribution to human cancer risk is to be expected		
		A5 Not suspected as a human carcinogen	4 The agent is probably not carcinogenic to humans

Abbreviations: *DFG/MAK* Deutsche Forschungsgemeinschaft/Maximale Arbeitsplatz-Konzentration (German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area) (DFG 1998), *EU* European Union (EU 1993), *IARC* International Agency for Research on Cancer (IARC 1997), *ACGIH/TLV* American Conference of Governmental Industrial Hygienists/Threshold Limit Values Committee (ACGIH 1997)

Criteria which indicate that genotoxic effects do not play a decisive role

Lack of genotoxicity in in vivo and in vitro tests; the latter were negative even though appropriate activation systems were used; genotoxicity only at cytotoxic concentrations.
Lack of reactive metabolites detectable in metabolism studies or presence of reactive metabolites only when metabolic detoxification systems are saturated.
In vivo DNA binding can not be detected when investigated with sensitive methods, e.g. ^{32}P-postlabelling.

Criteria which indicate tumour-promoting properties

Positive results in two-stage carcinogenesis systems.
Perturbation of gene regulation, e.g. alterations in the expression of genes relevant for carcinogenesis such as oncogenes or tumour suppressor genes.
Hormonal or hormone-like effects, e.g. alteration of hormonal feed-back mechanisms.
Receptor-mediated effects.
Enhanced cell proliferation in the target tissue, e.g. stimulation of growth of initiated cells.
Interference with apoptosis.
Inhibition of intercellular communication.
Positive results using cell transformation tests.
Evidence that regenerative cell proliferation, as a consequence of toxicity, plays an essential role.
Tumour formation in organs exhibiting a high incidence of spontaneous tumours.

Indications of nonlinear dose-effect relationships

Development of tumours, e.g. after administration of doses for which first-order toxicokinetics do not apply (e.g. saturation of metabolism).

Criteria indicating low carcinogenic potency

Tumour incidence is increased only slightly above the control values.
The number of tumours per organ is small.
Tumours are species-specific, strain-specific or sex-specific.
The proposed EU definition of low potency may be adopted (T25 > 100 mg/kg body weight and day).

Category 5

Substances with carcinogenic and genotoxic potential, the potency of which is considered to be so low that, provided that the MAK value is observed, no significant contribution to human cancer risk is to be expected.

Criteria for classification

The substance or a metabolite are mutagenic.
Low carcinogenic potency. The proposed EU definition of low potency may be adopted (T25 > 100 mg/kg body weight and day).
Physiological-toxicokinetic modelling based on experimental data indicates a low cancer risk for man.

Criteria which characterize a non-significant contribution to human cancer risk

Different biochemical or biological endpoints may be used to characterize the contribution to cancer risk. Typically, the contribution is considered not significant if an external exposure at the workplace leads to internal exposures in the range of background levels of a reference population not specifically exposed.
Biochemical effect markers (e.g. DNA or protein adducts) are not increased significantly above backgroud levels under workplace conditions.

Examples

The following section gives examples of reasoning employed to justify the classification of substances in Categories 4 and 5.

Classification of 1,4-dioxane in Category 4

The following current MAK value for 1,4-dioxane is 20 ml/m^3; up to now 1,4-dioxane was assigned to section IIIB in the List of MAK and BAT Values (Greim 1996).

Carcinogenicity

Decisive for the former classification to section IIIB were the results of studies with rats in which 1,4-dioxane was administered in the drinking water and caused the development of tumours in the nasal cavity and the liver. The concentrations administered in the drinking water were 0.01%, 0.1% and 1.0%. Tumours developed in the groups receiving the two higher concentrations, but these concentrations were also hepatotoxic and nephrotoxic. Survival was reduced drastically in the 1.0% group (Kociba et al. 1974). Inhalation studies with non-toxic concentrations (2 years, 111 ml/m^3) yielded negative results. The incidence of spontaneous liver tumours in mice was increased significantly.

Genotoxicity

There are a number of genotoxicity studies with 1,4-dioxane which have mostly yielded negative results (Greim 1996). DNA strand breaks were induced in rat hepatocytes at cytotoxic concentrations; in one of three micronucleus tests a positive result was obtained which could not be reproduced (McFee et al. 1994; Mirkova 1994; Mirkova and Ashby 1989; Tinwell and Ashby 1994). In vitro (Woo et al. 1977) and in vivo studies (Stott et al. 1981) failed to show significant binding of 1,4-dioxane to DNA.

Metabolism and toxicokinetics

1,4-Dioxane was one of the first substances for which nonlinear toxicokinetics were demonstrated experimentally (Gehring and Young 1978). The plasma half-life in the rat increased from 1.1 h after i.v. injection of 3 and 10 mg/kg body weight to 14.2 h after administration of 1000 mg/kg body weight, which was explained by saturation of metabolism. Morphological and biochemical changes were observed only at 1,4-dioxane doses in the range causing saturation of metabolism, i.e. doses which could no longer be eliminated efficiently. The authors concluded that other adverse effects such as tumour formation also only occur within such dose ranges. After long-term administration of high doses, induction of metabolism (Young et al. 1978) and stimulation of proliferation in the rat liver (BASF 1987) could be demonstrated. After inhalation exposure of rats to a 1,4-dioxane concentration of 50 ml/m^3 – corresponding to the old MAK value-the pharmacokinetic constants were not changed, i.e., the elimination was not impeded.

The problem in the assessment of these nonlinear kinetics is that the metabolism of 1,4-dioxane is still not adequately understood. 2-Hydroxyethoxyacetic acid is considered to be the detoxication product and main urinary metabolite, but it is in equilibrium with the lactone *p*-dioxan-2-one. It is conceivable that the activation pathway consists of the direct and inducible *alpha*-oxidation of 1,4-dioxane to *p*-dioxan-2-ol, a hemiacetal which is in equilibrium with a hydroxyaldehyde (Woo et al. 1985). However, this has not been demonstrated unequivocally. To this end it would be necessary to determine the dose-dependence of the production of a metabolite considered to be critical or of a reaction product produced from this metabolite.

Conclusions

In spite of its still incompletely characterized metabolism, 1,4-dioxane can be regarded as a well-studied substance which has carcinogenic potential when administered at high levels in animal studies. The available data suggest that genotoxic properties play little or no role in the carcinogenicity (Ashby 1994). Rather, cytotoxic effects are important in all observed alterations and are subject to nonlinear toxicokinetics. 1,4-Dioxane thus fulfills sufficient criteria required for a classification in Category 4. The current provisional MAK value of 20 ml/m^3 was established to avoid irritant effects on the eyes in man, and its observance is therefore also expected to provide protection from cytotoxic effects. It can be retained for the time being.

Classification of styrene in Category 5

The current MAK value for styrene is 20 ml/m^3 (Henschler 1987).

Carcinogenicity

The epidemiological studies which have been carried out to date on workers in the styrene producing and processing industries (IARC 1994; Kolstad et al. 1995) have not yielded clear evidence of carcinogenic effects. Most frequently, tumours of the lymphatic and haematopoietic systems were recorded. However, the data for an increase in the incidence of these tumours were inconsistent, particularly in the studies of the industrial sectors with the highest exposure to styrene. Furthermore, the observed tumour incidences did not correlate with the cumulative exposure to styrene. In addition, the subjects were exposed to other substances as well (e.g., 1,3-butadiene, ethylbenzene, dyes, benzene) in most studies. The IARC assessed the data as "inadequate evidence" for a carcinogenic effect of styrene in man (IARC 1994).

Animal studies on the carcinogenicity of styrene have yielded unclear results. Increased tumour incidences were found in 3 of 11 long-term studies with rodents: two demonstrated an increase in the incidence of lung tumours in mice and one of mammary tumours in rats. The latter, however, was detected only for the medium dose range. Two other long-term studies have been carried out but have not yet been published (Styrene Information and Research Center, USA). Preliminary information emerging from these studies confirms the findings described above, e.g. an increased incidence of lung tumours in the mouse and no corresponding effects in the rat.

Genotoxicity

Most of the mutagenicity studies in vitro showed that metabolic activation systems was necessary to produce positive results with styrene. Cytogenetic studies with experimental animals and exposed workers have produced both negative and positive results (Henschler 1987; IARC 1994).

Mode of action

Styrene is metabolised in the organism to the epoxide styrene-7,8-oxide, which alkylates macromolecules in vitro and in vivo (IARC 1994; Osterman-Golkar et al. 1995). The substance also has mutagenic effects in vitro and was carcinogenic in an animal study (IARC 1994).

Estimation of internal exposure

Recent studies have been carried out with the specific aim of establishing the quantitative aspects of the dependence of the strain by styrene-7,8-oxide in man, rat and mouse on the administered dose of styrene (Csanády et al. 1994; Kessler et al. 1992; Korn et al. 1994; Morgan et al. 1993 a,b,c; Osterman-Golkar et al. 1995;

Pauwels et al. 1996). The parameters chosen to describe the strain included the concentration of styrene-7,8-oxide in the blood and that of its adducts with haemoglobin and DNA. After the administration of comparable doses of styrene, the strain by styrene-7,8-oxide in the low dose range in mice was two to three times greater than that in rats; it increased more than proportionally in response to increasing doses. The strain by this metabolite in man after exposure to styrene concentrations of up to 100 ml/m^3 was one-fifth to one-twentieth of that in rodents (IARC 1994). In man, the styrene-7,8-oxide concentration in blood was shown to correlate linearly with the styrene concentration in air, thereby exposure to a styrene concentration of 20 ml/m^3 at equilibrium produced a styrene-7,8-oxide concentration in venous blood of 1 µg/l. The detection limit was 0.9 µg/l (Korn et al. 1994).

Estimations of the cancer risk associated with exposure to styrene have been carried out on the basis of the strain by styrene-7,8-oxide or its adducts with haemoglobin and DNA, and by taking into account the results of the long-term studies with experimental animals (Csanády et al. 1995; Filser et al. 1993b). The determination of stress and strain was based on extensive studies of the toxicokinetics of styrene and styrene-7,8-oxide in man, rat and mouse (Csanády et al. 1994; Filser et al. 1993 a). For 40 years of styrene exposure at work (styrene vapour concentration of 20 ml/m^3 air, 8 h/day, 5 days/week, 48 weeks/year) cancer risk was calculated to be in the range between 1.7 and 7.5 per 100 000 exposed persons. This risk value is lower by a factor of 67 to 880 than that estimated for a working life exposure to a benzene vapour concentration of 1 ml/m^3 air (TRK value) under workplace conditions (Henschler 1992). Its risk value is also smaller than that estimated for the unavoidable risk resulting from endogenously formed ethylene oxide (1.2 per 10 000 persons: Greim 1993).

Conclusions

The risk of developing cancer during the course of a lifetime as a result of a 40-year exposure to a styrene concentration of 20 ml/m^3 air at work was calculated to be smaller than the unavoidable risk caused by endogenously formed ethylene oxide, for which a value of about 1×10^{-4} was estimated. Therefore, the risk can be considered to be very low, although styrene can cause cancer by a genotoxic mechanism. Thus, styrene meets the criteria for a classification in category 5. The MAK value of 20 ml/m^3 can be retained. The strain by styrene can be monitored by measuring the levels of haemoglobin adducts.

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