File

American Journal of Industrial Medicine 12:453–473 (1987)

Comparison of Regulations on Occupational Carcinogens in Several Industrialized Countries

F. Carnevale, MD, R. Montesano, MD, PhD, C. Partensky, BSc, and L. Tomatis, MD

Regulations controlling the manufacture and use of carcinogens in the industrial setting of various countries are examined. In addition, the occupational exposure limits (OEL) of chemicals known or suspected to be carcinogenic in humans are listed, and criteria for the establishment of OELs are discussed. It is also stressed that control measures should not be confined to a few developed countries, and it is hoped that attracting attention to their unevenness will contribute to the implementation of a more efficient primary prevention of cancer.

Key words: legislation, occupational carcinogens, OEL (occupational exposure limits)

INTRODUCTION

The occurrence of cancer in workers as a result of exposure to carcinogenic substances through their occupation is a major health problem in many countries. It has been estimated that the percentage of cancers attributable to occupation in the United States of America (USA) is 4%, with a range of 2–8% over the whole population [Doll and Peto, 1981]; higher percentages have been calculated by others for cancers at specific target organs [Cole et al. 1972; Pastorino et al. 1984]. These estimates imply that one of every five cancer cases among occupationally exposed populations is attributable to exposure in the workplace [Saracci, 1985; Tomatis, 1987] and indicate that in countries like France and Italy some 6,000–8,000 cancer deaths occur every year as a result of occupational exposure. The implementation of primary prevention, by identifying carcinogenic agents and subsequently banning them or reducing exposure by regulatory measures, is relatively recent.

A survey of regulatory measures for controlling exposure to occupational carcinogens in several industrialized countries carried out 10 years ago [Montesano and Tomatis, 1977] resulted in the following conclusions: 1) legislation prohibiting the manufacture of chemicals shown to be carcinogenic to humans or known to represent a possible cancer hazard to humans existed in only a limited number of the

Servizio di Prevenzione Igiene e Sicurezza nei Luoghi di Lavoro, Florence, Italy (F.C.).
International Agency for Research on Cancer, Lyon, France (R.M., C.P., L.T.).
Address reprint requests to R. Montesano, M.D., Ph.D., International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France.
Accepted for publication May 21, 1987.

© 1987 Alan R. Liss, Inc.

HWBUI0002036

14 countries considered and did not cover the same chemicals in each country; 2) in only a few of the countries was both the importation and the manufacture of certain chemical carcinogens prohibited; 3) the fact that most countries recognized a limited right to compensation but did not provide adequate legislation for prohibiting or even limiting exposure to carcinogens indicated that these important means of primary prevention were not yet widely accepted; 4) there is no reason for the great disparity in legislation in different countries, since the carcinogenicity of chemicals does not stop or change at national borders; 5) legislation in certain countries that prohibits the manufacture and use but permits the importation of carcinogens allows, and surreptitiously stimulates, their manufacture in countries with less stringent regulations; and 6) the criteria used to label chemicals as possibly hazardous to humans on the basis only of experimental evidence of carcinogenicity were arbitrary and over-exclusive.

During the last decade, regulatory agencies in a few countries have become more receptive to accepting evidence of carcinogenicity in humans and/or in animals for determining measures to control exposure to occupational carcinogens. The present paper analyzes the evolution that has occurred in this context during that time, taking into account the progress that has been made in understanding the carcinogenic process.

The countries considered are all industrialized, as it was easier to obtain reliable information for these than for less developed countries, where, often, specific legislation on occupational cancer risks does not exist. Exclusion of a country from this survey does not imply that legislation or regulations controlling exposure to carcinogens do not exist. The analysis is based on two types of information: regulations and legislation prohibiting or controlling the manufacture, use, or importation of carcinogens, and information on how data on carcinogenicity are used to establish permissible occupational levels.

SOURCES OF INFORMATION

Laws and regulatory standards were obtained from health and labor offices in the various countries. The term "regulation" is used in a broad sense in this paper and includes specific laws. The World Health Organization and the International Labour Office were valuable sources of information. Assistance provided by several colleagues is also acknowledged. A summary of the regulations and legislations for each country considered and the relevant source of information are provided in the footnotes to Tables I and II.

In each country, control concerning occupational exposure to toxic substances is covered by a number of laws or regulatory standards and implemented by different bodies. We have attempted to confine our analysis to legislation and regulations in which the carcinogenic activity of chemicals has been the basis for specific regulations; such information is not always clearly given in the original documents, which might result in some apparent inconsistencies in the tabulations of the data. In this document the terms "occupational exposure limit" (OEL) or "permissible exposure limit" (PEL) are used; these are derived from government authorities devoted to controlling exposure to occupational carcinogens. The term TLV (threshold limit value) applies only to values recommended by the ACGIH (USA); these are recommendations made by a non-governmental organization for use as guidelines in the occupational setting.

HWBUI0002037

LEGISLATION OR REGULATORY STANDARDS PROHIBITING OR CONTROLLING THE MANUFACTURE, USE OR IMPORTATION OF CARCINOGENS

The classical studies of Rehn, published in 1895, and by Case et al. in 1954, showing a high risk of bladder cancer among workers exposed to benzidine, 2-naphthylamine, and other aromatic amines, resulted in the cessation of production of 2-naphthylamine in the 1940s, of 4-aminobiphenyl in 1953, and of benzidine in 1971 in the Federal Republic of Germany (FRG) [Ehrlicher, 1971]; and of 2-naphthyllamine in 1949 and of benzidine in 1962 in the United Kingdom (UK) [Parkes, 1976]. Production of 2-naphthylamine persisted in the USA until 1970 and in Japan until 1972, and benzidine is still manufactured in other parts of the world [Parkes, 1976]. A law prohibiting the manufacture of chemical carcinogens was formally introduced in the UK in 1967; it specifically concerned four carcinogens: 2-naphthylamine, benzidine, 4-aminobiphenyl, and 4-nitrobiphenyl. This measure was taken more than 50 years after the incrimination by the International Labour Office [1921] of certain "amino-compounds", in particular benzidine and 2-naphthylamine, as being responsible for the occurrence of tumors of the bladder among workers in dye factories. By 1977, only four countries had regulated production of these four compounds, although the prohibition was also extended to certain other carcinogens in some countries [Montesano and Tomatis, 1977]. Prohibition of some uses of asbestos, arsenic, benzene, 2-naphthylamine, 4-aminobiphenyl, and 4-nitrobiphenyl was introduced in the FRG in 1975.

At present (see Table I), more countries control occupational exposure to chemical carcinogens by prohibiting their manufacture or use; the number of prohibited carcinogens has increased, particularly in the FRG, Sweden, and Finland, where legislation was introduced in 1975, 1981, and 1983, respectively. In the countries considered in Table I, the four aromatic amines mentioned above are the carcinogens that are most frequently regulated. Prohibition of the processing or fabrication of crocidolite or substances containing crocidolite exists only in the FRG, Sweden, and the Netherlands; in the UK prohibition refers also to amosite. In most of the other countries considered, the prohibition refers solely to the application of asbestos by means of spraying. In the case of benzene, the prohibition applies to solvents containing it at concentrations of more than 0.2% (France), more than 1% (FRG), more than 5% (Japan), or, in some types of exposure, to more than 2% (Italy). In the USA, recent epidemiological evidence [Rinsky et al, 1987] shows that a significant risk of leukemia exists following an exposure to 1 ppm of benzene, a level promulgated by the OSHA in 1978 and subsequently invalidated by the Supreme Court [Ashford, 1987].

The Commission of the European Communities has issued proposals and directives prohibiting the production and use of 2-naphthylamine, 4-aminobiphenyl, 4-nitrobiphenyl, benzidine, and the spraying of materials containing asbestos.

In some countries (e.g., Belgium, FRG, Italy, USA), there is no regulation specifically prohibiting the manufacture and use of carcinogens, but the exposure of workers is controlled by reducing exposure to the lowest achievable levels. The impact of such measures depends upon the availability of valid methods to reduce exposure to zero level and of appropriate structures, which may vary from country to country, to ascertain their proper application. It is realized that controlling workers'

HWBUI0002038

TABLE I. List of Occupational Carcinogens and Countries in Which Specific Legislation or Regulatory Standards Prohibit or Control Their Manufacture and Use

Carcinogen	Belgium[a]	Finland[b]	France[c]	FRG[d]	Ireland[e]	Italy[f]	Japan[g]	Nether-lands[h]	Sweden[i]	UK[e]	USA[j]	USSR[k]	EC[l,m]
2-Acetylaminofluorene		+							+		+		
ortho-Aminoazotoluene												+	
4-Aminobiphenyl		+		+[n]	+		+		+	+	+		+
Asbestos (crocidolite)		+[n]	+[n]	+		+		+	+	+	+		+[n]
Benzene	+[n]		+[n]	+[n]		+[n]	+[n]						
Benzidine		+		+[n]	+		+		+	+	+	+	+
Benzidine-based dyes											+		
Bis(chloromethyl)ether		+		+[n]			+		+		+		
Chloromethyl methyl ether		+		+[n]					+		+		
1,2-Dibromo-3-chloropropane									+				
3,3′-Dichlorobenzidine											+	+	
4-Dimethylaminoazobenzene		+							+		+	+	
Hexamethylphosphoramide				+[n]					+				
20-Methylcholanthrene		+							+				
Mustard gas		+											
1-Naphthylamine											+	+	
2-Naphthylamine		+		+[n]	+		+		+	+	+		+
4-Nitrobiphenyl		+		+[n]	+		+		+	+	+		+
N-Nitroso-N-methylurea		+		+[n]					+				
N-Nitrosodimethylamine											+		
Propane sultone				+[n]				+					
β-Propiolactone		+									+		
2,3,7,8-Tetrachloro dibenzo-para-dioxin		+		+									
ortho-Toluidine												+	
Tris(2,3-dibromopropyl) phosphate		+	+[n]										
Yellow fatty dye												+	

[a]Belgium: The Royal Decree, dated 25 October 1967, prohibits a concentration of benzene higher than 0.25% by volume in hydrocarbon spirits or solvents used for cleaning or degreasing purposes or in photoengraving, adhesives, and paints. For all other uses, the benzene concentration may not exceed 1% (this provision does not apply to engine fuels, petrochemicals, or products for laboratory use). Royal Decree amending Article 394 of the General Labour Protection Regulations. Ministry of Employment and Labour and Ministry of Public Health, Brussels. Dated October 25, 1967. Enforcement date: November 1, 1969. Moniteur Belge, Brussels, November 1, 1967.

HWBUI0002039

[b]Finland: Decree of the Ministry of Social Affairs and Health, December 21, 1983.

[c]France. Decree No. 78-394 of March 20, 1978 prohibits the use of asbestos or products containing more than 1 g of asbestos per 100 g for the spraying of buildings (J. Off., March 23, 1978, p 1279). Decree No. 86-269 of February 13, 1986 (J. Off., February 27, 1986, p 3111) prohibits the use of solvents or diluents containing benzene at more than 0.2% by volume, except in closed systems. An order of June 1, 1978 suspended the manufacture, importation, and marketing of clothing and textiles treated with the flame retardant tris(2,3-dibromopropyl)phosphate (TRIS) (J. Off., June 24, 1979, p 1512).

[d]FRG: Verordnung über gefährliche Stoffe (Gefahrstoffverordnung—GefStoffV) vom August 26, 1986 (BGBl. I S. 1470), Carl Heymanns Verlag KG, Köln, Berlin, Bonn, München (1986).

[e]Ireland, UK: In 1967, specific legislation on carcinogenic chemicals in industries was introduced in the UK (The Carcinogenic Substances Regulations, S.I. No. 879, 1967, London, her Majesty's Stationery Office); similar regulations were introduced in Ireland in 1972 (see Factories, Carcinogenic Substances, Processes Regulation, S.I. No. 242, 1972, Dublin). These regulations, which apply to policies subject to the Factories Act 1961, prohibit the manufacture or use of certain carcinogens, namely, 2-naphthylamine, benzidine, 4-aminobiphenyl, 4-nitrobiphenyl, and their salts, and of any substances containing these compounds. Products containing not more than 1% are, however, excluded from this prohibition, provided the prohibited substance is present solely as a by-product of a chemical reaction. However, benzidine may be manufactured either as its monohydrochloride or dihydrochloride or a mixture of both these salts, if this is done in a totally closed system. These salts of benzidine may only be used outside a closed system, as in the form of a slurry with water, consisting of not less than one part water to two parts benzidine salt. Special exemption from this part of the regulations may be granted by the Chief Inspector of Factories for the production of a prohibited substance that will be used only for the purpose of medical and scientific research.

The same regulations control the employment of persons in factories manufacturing or using 1-naphthylamine, ortho-toluidine, ortho-dianisidine, 3,3'-dichlorobenzidine, and their salts, as well as auramine and magenta. In the case of the latter two substances, the regulations apply only to their manufacture. This control consists of avoidance by all practicable means of any exposure of the worker and of periodical medical examinations, including cytological examination of the urine for abnormal cells every 6 months, during employment in factories subject to the regulations. A register of these employees is kept with particulars of their employment. When they are examined medically and upon termination of employment, the workers are given cautionary cards that recommend continuation of such screening tests and indicate where they may be undertaken. In Ireland, the regulations also require a register of persons employed in the manufacture of the "controlled" substance. This register records the periods of employment in connection with the above-mentioned substances, as well as the monthly medical examinations, and this must be kept available for inspection for at least 20 years from the date of the medical examination.

A separate regulation prohibits the importation into the UK of so-called prohibited carcinogens (The Carcinogenic Substances Regulations [Prohibition of Importation], S.I. No. 1675, 1967, London, Her Majesty's Stationery Office).

The "Mule Spinning (Health) Special Regulations 1953" specifies that for lubrication of mule spindlers, no oil other than "white oil" or oil entirely of animal or vegetable origin or mixed should be used.

Asbestos (Prohibitions) Regulations (Health and Safety Commission Newsletter No. 43, p 3, August 1985) prohibit: 1) the importation of crocidolite and amosite fibre, 2) supplying these minerals and products containing them as an article or substance for use at work, 3) the use of those minerals and products containing them in the manufacture and repair of any other product, 4) asbestos spraying, and 5) installation of new asbestos insulation.

(continued)

HWBUI0002040

TABLE 1. List of Occupational Carcinogens and Countries in Which Specific Legislation or Regulatory Standards Prohibit or Control Their Manufacture and Use (Continued)

[f]Italy: The Act of March 5, 1963 prohibits the use of benzene-based solvents in the following: dry-cleaning, degreasing and spot removal, waterproofing of fabrics, manufacture and repair of waterproof clothing and shoes, painting, varnishing and decorating, paint and varnish remover, and the manufacture of printing inks. In these operations, benzene may occur as an impurity at levels of up to 2% by weight (Law of March 5, 1963, No. 245. Limitazione dell'impiego del benzolo e suoi omologhi nelle attivita lavorative. Enforcement date: March 21, 1963. Gazzetta Ufficiale della Republica Italiana, Rome, March 21, 1963, Vol. 104, No. 77, pp 1450–1451). Ministero della Sanita. Ordinanza 26 June 1986, Gazz. Uff. Republica Italiana no. 157, pp. 19. Cirrolare 1 July 1986, Gazz. Uff. Republica Italiana no. 157, pp. 27–28.

[g]Japan: Industrial Safety and Health Law (Rodo Anzen Eisei Ho) prohibits production, import, transfer, provision or use (except for test or research purposes) of the following: 1) yellow phosphorous matches (no longer used); 2) benzidine and its salts; 3) 4-aminobiphenyl and its salt; 4) 4-nitrobiphenyl and its salts; 5) bis(chloromethyl)ether; 6) 2-naphthylamine and its salts; 7) benzene-containing rubber cement, in which the solvent fraction contains more than 5% benzene by volume; 8) any preparation that contains more than 1% by weight of (2)–(6).

[h]Netherlands: The following are among the principal provisions of the Asbestos Decree (enforcement date: October 1, 1978) (Decree of April 1, 1977, Stb. 269) promulgating general administrative regulations for the implementation of the Silicosis Law of 1951 (Stb. 134) (The Asbestos Decree). (Staatsblad van het Koninkrijk der Nederlanden, 1977). Section 2 prohibits the possession of crocidolite for purposes of sale and the processing or the fabrication of crocidolite or substances or products containing crocidolite. Section 3 prohibits the spraying of asbestos or substances or products containing asbestos. Section 4 prohibits the processing or fabrication of asbestos or substances or products containing asbestos for heat insulation or acoustic, safety, or decorative purposes. Under the provisions of Section 5, the concentration of asbestos substances in the air at work places where asbestos or substances or products containing asbestos are processed or fabricated must be kept to a minimum. Levels of asbestos substances in inhaled air must be kept to a minimum and, with the exception of crocidolite, may not exceed 2 fibers/ml of air (a fiber is defined as any particle with a length exceeding 5 μm and a length:diameter ratio of at least 3:1). Section 6 prescribes that directors of manufacturing plants may not introduce methods of processing or fabricating asbestos or substances or products containing asbestos that have not previously been used in that undertaking. In addition, asbestos or substances or products containing asbestos may be processed or fabricated into a product that has not previously been manufactured in the undertaking, or has previously been manufactured in that undertaking only without using such substances, only if the district administrator has been notified in advance. Under Section 7, the provisions of Sections 2–4 may be waived under special circumstances. Section 8 prescribes that, except where indicated by the Minister of Social Affairs, a Special Advisory Commission established by the Minister must give its views on all such cases. A decree of January 12, 1976 prohibits the use, transformation or processing, conditioning, packaging, transportation, or storage of propane sultone. A commentary on the decree explains the reasons for the prohibition (in particular, the carcinogenicity of this substance) (Decree of January 12, 1976 to issue general regulations of the Workers' Protection Act, 1934 (Besluit van 12 januari 1976 tot vastelling van een algemene maatregel van bestuur ter uitvoering van de Veiligheidswet 1934). Staatsblad van het Koninkrijk der Nederlanden, The Hague, 1976, No. 97, pp 1–4).

HWBUI0002041

[l]Sweden: Ordinance issued by the National Swedish Board of Occupational Safety and Health on Occupational Exposure Limit Values, published May 7, 1984 under the provisions of Section 18 of the Working Environment Ordinance (1977: 1166). In this table are included carcinogenic substances (Group A) that may not be produced, used, or otherwise handled. The same applies to any product containing one or more of such substances as contaminants in a concentration of 0.1% or more by weight. In addition, the substances listed below (Group B) and products containing such substances in a concentration of 1% or more by weight, may not be produced, used or otherwise handled without the permission of the Labour Inspectorate: para-aminoazobenzene; auramine; benzal chloride; benzotrichloride; mustard gas; bis-chloroethylether; β-butyrolactone; 2,4-diaminoanisol; 2,4-diaminotoluene; dianisidine (3,3'-dimethoxybenzidine); diazomethane; 3,3'-dichlorobenzidine; 1,2:3,4-diepoxybutane; diethyl sulphate; dimethyl sulphate; ethyl methanesulphonate; ethylene dibromide; ethylenimine; ethylene thiourea; methylenebis-ortho-chloroaniline (3,3-dichloro-4,4'-diaminodiphenyl methane, MOCA); methylmethanesulfonate; 1-naphthylamine; *N*-nitrosodimethylamine; phenyl-β-naphthylamine; 1,3-propane sultone; β-propiolactone; propylenimine; thioacetamide; thiourea; ortho-tolidine (3,3'-dimethylbenzidine); tris(2,3-dibromopropyl)phosphate; urethane.

[k]USA: No permissible exposure limit (PEL) is given for the compounds listed. Only solid or liquid mixtures containing less than 0.1% of 4-aminobiphenyl, benzidine, 4-nitrobiphenyl, 2-naphthylamine, bis(chloromethyl)ether, and chloromethyl methylether are excluded. The standards also exclude solid or liquid mixtures containing less than 1% of the other carcinogens (American Conference of Governmental Industrial Hygienists (1985): TLVs, Threshold Limit Values and Biological Exposure Indices for 1985-86, Second Printing. Cincinnati, OH, pp 41-42. Morbidity and Mortality Weekly Report Supplement Vol. 35, No. 15, 1986. NIOSH, Centers For Disease Control.

[b]USSR: From International Labour Office (1980) Occupational Exposure Limits for Airborne Toxic Substances, Second (revised) edition. A Tabular Compilation of Values from Selected Countries. Occupational Safety and Health Series, No. 37, Geneva.

[l]EC = European Communities.

[m]Proposal for a Council Directive on the protection of workers by the proscription of specified agents and/or work activities (Off. J. Eur. Commun. C 270, Vol. 27, p 3, October 10, 1984; Amendment of the preceding Directive submitted May 31, 1985). The following are not permitted alone or as intentional constituents of a preparation: 2-naphthylamine and its salts, 4-aminobiphenyl and its salts, 4-nitrobiphenyl, benzidine and its salts. This prescription does not apply if the agents are present in a substance or a preparation in the form of impurities, by-products, or as a constituent of waste products, if their individual concentration is less than 0.1% w/w in the substance. Council Directive of September 19, 1983 (83/477/EEC) on the protection of workers from the risks related to exposure to asbestos at work (Off. J. Eur. Comm. L 263, p 25, September 24, 1983): the application of asbestos by means of the spraying process must be prohibited.

[n]The prohibition is not obsolete and refers to some specific conditions of use; see other footnotes.

HWBU0002042

TABLE II. Occupational Exposure Limits in Various Countries of Industrial Chemicals Shown to Be Carcinogenic in Humans and/or Experimental Animals

Chemical, process or industry[a]	Evidence of carcino-genicity[b]	Occupational exposure limit					
		USA[c]					
		OSHA	(ACGIH)	FRG[d]	Sweden[e]	France[f]	European communities[g]
Acrylonitrile	2A	4.5*		7*	4.5*	4.5*	
ortho-Aminoazotoluene	2B			–*			
4-Aminobiphenyl	1	–*		–*	P[A]	0.007*	P
ortho-Anisidine	2B		(0.5)	0.5			
Arsenic and arsenic compounds	1						
Arsenic and soluble compounds as As			(0.2)	0.2*			
Arsenic and inorganic compounds		0.1		0.2*	0.05*		
Arsenic trioxide production			(–*)			0.2*	
Arsenic trioxide and arsenic pentoxide, arsenous acid, arsenic acid, and their salts				–*			
Arsine		0.2		0.2	0.05	0.2	
Asbestos	1	0.2 fiber/cm^3			0.5 fiber/cm^3*	1 fiber/cm^3*	1 fiber/cm^3*
Amosite			(0.5 fiber/cm^3*)	1 fiber/cm^3*			
Chrysotile			(2 fibers/cm^3*)	1 fiber/cm^3*)			
Crocidolite			(0.2 fiber/cm^3)	0.5 fiber/cm^3*	P[A]	0.5 fiber/cm^3*	0.5 fiber/cm^3*
Other forms			(2 fibers/cm^3)		0.5 fiber/cm^3*		
Fine dust containing asbestos				2*			
Auramine (technical grade)	2B			–*	P[H]	–*	
Manufacture of auramine	1					–*	
Benzene	1	30*		16*	16*	15*	16.25*
Benzidine	1	–*		–*	P[A]	0.008*	P

HWBUI0002043

Benzidine-based dyes	2A	– *					
Direct black 38 (technical grade)						– *	
Direct blue 6 (technical grade)						– *	
Direct brown 95 (technical grade)						– *	
Benzo[a]pyrene	2A		(– *)	– *	0.005*	– *	
Beryllium and beryllium compounds	2A	0.002*			0.002*	0.002*	
Grinding of beryllium metals and alloys				0.005*			
Others				0.002*			
Bis(chloromethyl)ether	1	– *	(0.005*)	– *	P[A]	0.005*	
Chloromethyl methyl ether	1	– *		– *	P[A]	– *	
β-Butyrolactone	2B			– *	P[B]		
Cadmium and cadmium compounds	2A				– *		
Cadmium chloride						– *	
Cadmium dusts and salts as Cd		0.2	(0.05)				
Total dust					0.05*		
Respirable dust					0.02*		
					New installation 0.01*		
Cadmium oxide							
Fume as Cd			(0.05)		0.02*		
Production			(0.05)				
Carbon tetrachloride	2B	30	(30*)	65°	13*	12	
Chlordecone (Kepone)	2B			– °			
α-Chlorinated toluenes	2B						
Benzal chloride				– °	P[B]		
Benzotrichloride				– °	P[B]		
Benzyl chloride		5		5°	5*	5	
Chloroform	2B	240[b]	(50*)	50°	10*	25	

(continued)

HWBUI0002044

TABLE II. Occupational Exposure Limits in Various Countries of Industrial Chemicals Shown to Be Carcinogenic in Humans and/or Experimental Animals (Continued)

Chemical, process or industry[a]	Evidence of carcinogenicity[b]	Occupational exposure limit					
		USA[c]					
		OSHA	(ACGIH)	FRG[d]	Sweden[e]	France[f]	European communities[g]
Chlorophenols	2B				0.5		
Pentachlorophenol			(0.5)	0.5	0.5	0.5	
Trichlorophenol					0.5		
2,4,5-							
2,4,6-							
4-Chloro-ortho-phenylenediamine	2B						
para-Chloro-ortho-toluidine	2B			–*			
Chlorophenoxy herbicides	2B						
2,4-D			(10)	10			
2,4,5-T			(10)	10			
Chromium							
Chromite ore processing (chromate) as Cr			(0.05*)			–*	
Chromium metal	3		(0.5)		0.5 (Cr and compounds)		
Chromium (II) compounds as Cr			(0.5)				
Chromium (III) compounds as Cr	3		(0.5)	0.1* (calculated as Cr VI)			
Chromium (VI) compounds as Cr	1	0.1[h]			0.02*	0.05*	
Water soluble			(0.05)				
Certain water insoluble			(0.05*)				
Chromic acid as Cr		0.1[h]			0.02*	0.05*	

HWBUI0002045

Coal tars and coal tar pitches	1			–*						
Coal tar pitch volatiles, as benzene solubles		0.2	(0.2*)	–*				0.2*		
DDT	2B		1	1						
N,N' Diacetylbenzidine	2B									
2,4 Diaminoanisole	2B			–*		P^B				
4,4' Diaminodiphenyl ether	2B			–[c]						
2,4 Diaminotoluene	2B			–*		P^B				
1,2 Dibromo-3-chloropropane	2B	0.1		–*		P^A		–*		
3,3' Dichlorobenzidine	2B		–*	0.1*		P^B		–*		
3,3' Dichloro-4,4' diaminodiphenyl ether	2B									
1,2 Dichloroethane	2B		(40)	80[c]		4*				
Diepoxybutane	2B					P^B				
Di(2-ethylhexyl) phthalate	2B		5	10		5				
1,2-Diethylhydrazine	2B									
Diethyl sulfate	2A			0.2*		P^B		–*		
3,3'-Dimethoxybenzidine (ortho-Dianisidine)	2B			–*		P^B		–*		
para-Dimethylaminoazobenzene	2B	*				P^A				
3,3'-Dimethylbenzidine (ortho-tolidine)	2B		–*	–*		P^B				
Dimethylcarbamoyl chloride	2A			(–*)	–*			–*		
1,1 Dimethylhydrazine	2B	1		(1*)	–*	0.2*		0.2	–	
1,2 Dimethylhydrazine	2B				–*	0.2*				
Dimethyl sulfate	2A	5		(0.5*)	Production: 0.1* use: 0.2*	P^B		0.5*		
1,4 Dioxane	2B	360			180[c]	90*		35		
Dioxane (technical grade)				(90)						
Epichlorohydrin	2A	19		(10)	12*	1.9*		10[h]		

(continued)

TABLE II. Occupational Exposure Limits in Various Countries of Industrial Chemicals Shown to Be Carcinogenic in Humans and/or Experimental Animals (Continued)

Chemical, process or industry[a]	Evidence of carcino-genicity[b]	Occupational exposure limit					
		USA[c]					
		OSHA	(ACGIH)	FRG[d]	Sweden[e]	France[f]	European communities[g]
Ethylene dibromide	2A	150	(−*)	−*	P[B]	−*	
Ethylene oxide	2A	1.8	(2*)	5*	9*	10	
					New installation 5*		
Ethylene thiourea	2B	−			P[B]	−*	
Ethyl methanesulphonate	2B				P[B]		
Formaldehyde (gas)	2A	4.5	(1.5*)	1.2°	1	3[h]	
Furniture and cabinent making	1						
Wood dust (beech, oak)		1		−°	4*		
Soft wood		5					
Hexachlorobenzene	2B						
Hexamethylphosphoramide	2B	−*		−*	P[A]		
Hydrazine	2B	1.3	(0.1*)	0.13*	0.1*	0.1*	
Indeno[1,2,3-cd]pyrene	2B			−*			
Lead and lead compounds (inorganic)	2B	0.05				0.15	0.15
Lead dusts and fumes (as Pb)			(0.15)	0.1			
Total dust					0.1		
Respirable dust					0.05		
Lead arsenate as $Pb_3(AsO_4)_2$			(0.15)	−*			
Lead chromate as Cr			(0.05*)	−*	0.02*		
Lead compounds (organolead)	3						
Tetraethyllead as Pb			(0.1)	0.075	0.05		
Tetramethyllead as Pb			(0.15)	0.075	0.05		

HWBUI0002047

Manufacture of isopropyl alcohol (strong-acid process)	1						
Isopropyl alcohol	3		980	980	500	980[h]	
4,4'-Methylenebis(2-chloroaniline) (MOCA)	2A	–	(0.22*)	–*	P[B]	0.22*	
4,4'-Methylene bis-(2-methylaniline)	2B			–*			
Methylmethane sulphonate	2B				P[B]		
Mustard gas	1					–*	
1-Naphthylamine	3	–*			P[B]		
2-Naphthylamine	1		–*	–*	P[A]	0.005*	P
Nickel and nickel compounds	1	1					
Metal			(1)		0.5		
Soluble compounds as Ni			(0.1)		0.1*		
As respirable dust and fumes				0.5*			
As respirable droplets				0.05*			
Nickel carbonyl		0.007	(0.35)	0.7*	0.007*		
Nickel sulfide roasting, fume and dust (as Ni)			(1*)			1*	
Nickel compounds, oxide, carbonates (as Ni)				–*	0.1*		
Nickel sulfide				–*			–
Nickel subsulfide (as Ni)				–*	0.01*		
5-Nitroacenaphthene	2B			–*		–*	
4-Nitrobiphenyl (metabolized to 4-aminobiphenyl)	3		–*	–*	P[A]		P
2-Nitropropane	1						
	2B		90	18*	35[h]*	–*	
		Intended changes					
			(35*)				

(continued)

HWBUI0002048

TABLE II. Occupational Exposure Limits in Various Countries of Industrial Chemicals Shown to Be Carcinogenic in Humans and/or Experimental Animals (Continued)

Chemical, process or industry[a]	Evidence of carcino-genicity[b]	Occupational exposure limit					
		USA[c]					
		OSHA	(ACGIH)	FRG[d]	Sweden[e]	France[f]	European communities[g]
N-Phenyl-2-naphthyl-amine	3	–	(–*)	–°	P[B]		
Polychlorinated biphenyls	2A				0.01*		
Chlorobiphenyl							
42% Chlorine			1	1°			
54% Chlorine			0.5	0.5°			
1,3-Propane sultone	2B	–*		–*	P[B]	–	
β-Propiolactone	2B	–*	(1.5*)	–*	P[B]		
Rubber industry	1						
Soots	1				3		
2,3,7,8-Tetrachlorodibenzo-para-dioxin (TCDD)	2B	–		–*		–*	
Thioacetamide	2B				P[B]		
4,4′-Thiodianiline	2B			–*			
Thiourea	2B				P[B]		
ortho-Toluidine	2B		(9*)	–*		9*	
Urethane	2B			–*	P[B]		
Vinyl chloride	1	2	(10*)	Existing installations 8* Others 5*	2.5*	Existing installations 7.5* New 2.5*	7 ppm/8 h

[a]The chemicals listed are those considered in IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vols. 1–42; the evaluation of carcinogenicity to humans is given (Group 1, Group 2A, Group 2B). A few chemicals (analogues of carcinogens, parent compounds of carcinogenic metabolites, and compounds present in carcinogenic mixtures) are also listed, although they belong to Group 3, agents not classifiable as to their carcinogenicity. Occupational exposure limits are given in mg/m^3 unless otherwise specified.

*indicates that evidence of carcinogenicity was taken into account in establishing the occupational exposure limit.

–indicates that an occupational exposure limit has not been established.

P indicates that the chemical is prohibited (see also Table I).

[b]International Agency for Research on Cancer (1987): IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 7, Overall Evaluations of Carcinogenicity: An Update of IARC Monographs, Volumes 1–42, Lyon.

HWBUI0002049

[c]USA: Two limits are given: one is the regulatory standards promulgated by the OSHA (Morbidity and Mortality Weekly Report, Supplement, Vol. 35, No. 15, 1986); the other is the TLV (threshold limit values) for chemical substances in the work environment adopted by the American Conference of Governmental Industrial Hygienists, for 1985–86 Cincinnati, OH. If the limit values are the same, they are given in the middle of the column.

[d]FRG: Maximum Concentrations at the Workplace and Biological Tolerance Values for Working Materials, 1986, Report No. XXII, Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Weinheim, FRG. Compounds considered as suspect of having carcinogenic potential for humans are marked with the sign "°".

[e]Sweden: Occupational Exposure Limit Values. Translation by the Swedish Plastics and Chemicals Suppliers Association (PKL) of Ordinance AFS 1984:5 issued by the National Swedish Board of Occupational Safety and Health, Solna, 1984. P^A refers to substances of Group A and P^B to Group B (see Table I). See also Holm L, Holmberg B (1987) Exposures to carcinogens and consequences of listing of carcinogens in the Swedish working environment. Regulatory Toxicol Pharmacol 7:185–199.

[f]France: Limit values for Concentrations of Dangerous Substances in Air of Working Places. Institut National de Recherche et de Sécurité, ND 1609–125–86, Paris. The OELs for benzyl chloride, chloroform, 1,1-dimethylhydrazine, dioxane, and epichlorohydrin do not take into account the carcinogenicity of these chemicals (see also circulars of May 14, 1985 and November 20, 1986).

Circular of May 10, 1984, completing annex of the Circular of July 19, 1982. Ministère des Affaires Sociales et de l'Emploi, Paris.

Prevention of Occupational Cancers. Institut National de Recherche et de Sécurité, Circular No. 7 of May 12, 1986, Paris.

Circular of May 5, 1986, completing and modifying annex of the Circular of July 19, 1982. Ministère des Affaires Sociales et de l'Emploi, Paris.

Circular of May 14, 1985 related to Prevention of Occupational Cancers, Annexes I and II. Ministère du Travail, de l'Emploi et de la Formation Professionnelle, J. Off., June 6, 1985, Paris.

Circular of November 20, 1986 completing Annex I of the Circular of May 14, 1985. Ministère des Affaires Sociales et de l'Emploi, Paris.

[g]European communities: Amendment to a Council Directive on the Protection of Workers by the Proscription of Specified Agents and/or Work Activities. Commission of the European Communities, COM(85) 262. Brussels, May 31, 1985.

Official Journal of the European Communities. Council Directive of September 19, 1983 on the Protection of Workers from the Risks Related to Exposure to Asbestos at Work (second individual Directive within the meaning of Article 8 of Directive 80/1107/EEC), No. L 263/23–30, September 24, 1983.

Official Journal of the European Communities. Proposal for a Council Directive on the Protection of Workers from the Risks Related to Exposure to Benzene at Work (fifth individual Directive within the meaning of Article 8 of Directive 80/1107/EEC). No. C 349/32–36, December 31, 1985.

Official Journal of the European Communities. Council Directive of June 29, 1978 on the Aproximation of the Laws, Regulations, and Administrative Provisions of the Member States on the Protection of the Health of Workers Exposed to Vinyl Chloride Monomer (78/610/EEC). No. L 197/12–18, July 22, 1978.

Official Journal of the European Communities. Council Directive of July 28, 1982 on the Protection of Workers from the Risks Related to Exposure to Metallic Lead and its Ionic Compounds at Work (first individual Directive within the meaning of Article 8 of Directive 80/1107/EEC). (82/605/EEC), No. L 247/12–21, August 23, 1982.

Official Journal of the European Communities. Council Directive of October 1, 1985 amending for the sixth time (PCBs/PCTs) Directive 76/769/EEC on the approximation of the laws, regulations, and administrative provisions of the member states relating to restrictions on the marketing and use of certain dangerous substances and preparations. No. L 269/56–58, October 11, 1985.

[h]Ceiling value.

HWBU0002050

exposure to carcinogens results from measures originating from various authorities within a given country. Thus, in Table I, for USA, the OSHA regulatory standards for carcinogens are given, noting that prohibition of the manufacture of an occupational carcinogen could result from a decision of the EPA or the FDA. Similar situations exist in other countries. Of the countries listed in Table I, only two—Japan and the UK—have legislation prohibiting the importation of carcinogens (2-naphthylamine, 4-aminobiphenyl, 4-nitrobiphenyl, and benzidine) in addition to the prohibition of production and use within the country. In the UK, regulations prohibiting the import of crocidolite and amosite fibre also exist. In countries where such regulations did not exist, the import of carcinogenic substances can reach consideration proportions. For instance, it was found that within a period of three months in Italy the import of asbestos was of approximately 13.5 million kg, that of benzene 19 million kg, and that of vinyl chloride 13 million kg [see Guariniello, 1985].

REGULATORY MEASURES TO CONTROL EXPOSURE TO INDUSTRIAL CARCINOGENS FOR WHICH THERE IS EVIDENCE OF CARCINOGENICITY TO HUMANS

Table II lists the chemicals and types of occupational exposures that have been evaluated within the *IARC Monographs* program (International Agency for Research on Cancer, 1987a) for carcinogenicity to humans and/or experimental animals. It includes chemicals or types of exposures for which the degree of evidence of carcinogenicity was classified in Group 1 (*the agent is carcinogenic to humans*); Group 2A (*the agent is probably carcinogenic to humans*); or Group 2B (*the agent is possibly carcinogenic to humans*). For each chemical, the occupational exposure limit is given, and there is an indication as to whether evidence for the carcinogenicity of the chemical was taken into account in establishing the occupational exposure level. It should be noted that the countries listed in Table II follow different criteria for determining the occupational exposure levels for chemical carcinogens.

Both the American Conference of Governmental Industrial Hygienists (ACGIH) (USA) and the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (FRG) separate chemical carcinogens for industrial use into two groups, on the basis of evidence of their carcinogenicity in humans or in experimental animals. In neither of these countries is the use and manufacture of chemicals proven to be carcinogenic in humans prohibited, although it is recommended that technical improvements be made so that workers are not exposed. In Sweden, the use and manufacture of at least some proven carcinogens is prohibited (see also Table I). In the ACGIH list, this recommendation is confined to the four aromatic amines mentioned above; in the FRG and Sweden, many more industrial carcinogens are listed, but OELs are not established for them. For others, an OEL or a TRK (Technische Richtkonzentration [technical guiding concentration]) is provided, based on evidence of carcinogenicity. In the FRG, TRKs are established ad hoc. It must be emphasized that the scientific basis for carcinogenesis does not permit the determination of a level below which no cancer risk exists. Thus, the establishment of TRKs is rather arbitrary, based on both technical feasibility to avoid exposure and on socio-economic considerations. The TLVs recommended by the ACGIH (USA) imply instead that the degree of carcinogenic potency of a chemical can be determined and thus that a "safe" threshold value can be determined (see footnotes to Table II).

HWBUI0002051

Discrepancies among the various countries considered are also evident concerning the regulation of carcinogenic aromatic amines (4-aminobiphenyl, 4-nitrobiphenyl, benzidine, and 2-naphthylamine). The use and manufacture of these carcinogens are prohibited in many countries (see Table I), or special protective and surveillance measures are required (e.g., FRG, USA [ACGIH]). In France, an OEL (although low) is given for three of these carcinogens; in Italy, a directive exists for exposures to aromatic amines, which does not, however, include any prohibition or exposure limit value. The use of crocidolite is banned in FRG, Sweden, and The Netherlands, but not in the other countries considered.

These are some of the most apparent inconsistencies in the regulations for exposure to industrial chemicals that were shown to be carcinogenic to humans many decades ago. Even greater differences exist in the weight given to data on carcinogenicity obtained only in experimental animals.

DISCUSSION

The survey of measures taken by certain industrialized countries to reduce exposure of workers to carcinogens indicates that some improvements have taken place during the last two decades and that greater consideration is given to experimental carcinogenicity data, at least in some countries. Data on carcinogenicity in experimental animals are taken into account in the classification but not in the setting of exposure limit values, particularly in the FRG [Henschler, 1987]. In Sweden, the number of carcinogens regulated on the basis of such data is greater, and the permissible level of exposure is, in general, lower than in other countries. In the USA and the UK, carcinogenicity data in animals play a minor role in the establishment of exposure limit values, which are still mainly based on the a posteriori evidence provided by the epidemiological data.

Even in situations where both experimental and epidemiological carcinogenicity data have been conclusive, as for aromatic amines, the time lag for implementing control measures has been long. For example, for four carcinogenic aromatic amines that were prohibited in 1967 in the UK, control measures were introduced in other European countries either only in the last few years or not at all. In some countries, the use or manufacture of these aromatic amines is not prohibited, but technical devices are to be introduced to exclude or reduce exposure to low levels. This approach implies that such techniques are available and that the proper organizational structure exists to ascertain that human exposure does not occur; however, the implementation of such measures and the surveillance of exposures are left to private initiative. As a second example, the use and manufacture of crocidolite are prohibited in the FRG, Sweden, the Netherlands, and the U.K., but not in other countries.

These two examples of different attitudes towards well-established human carcinogens indicate that in some countries factors other than those related to public health (namely economic) are still of considerable importance in regulating human exposure to industrial carcinogens. In addition, evidence of carcinogenicity to animals does not appear to be taken into consideration in establishing regulatory measures for some chemicals. Past experience [Tomatis et al, 1982; Wilbourn et al, 1986] indicates that properly conducted and evaluated carcinogenicity experiments in animals are useful in predicting human cancer risk. It is valid to refer to the much-quoted example of 4-aminobiphenyl that was not introduced in industry in the UK because it was

HWBUI0002052

shown to be carcinogenic in animals [Walpole et al, 1954]. Long-term carcinogenicity tests in animals have been and are still under criticism, but it is worthwhile to note that the results of properly conducted and evaluated carcinogenicity tests provide a valuable basis for assessing the carcinogenic risk of a chemical to humans [International Agency for Research on Cancer, 1987b]. For many chemicals there are no data in humans, and the only carcinogenicity data available are those in experimental animals. This is the case for some 200 chemicals that were evaluated by IARC as having sufficient evidence of carcinogenicity [International Agency for Research on Cancer, 1987a], and occupational exposure exists for some 50–60% of these chemicals.

The carcinogenesis process is known to be composed of various stages (initiation, promotion, progression), and there is some epidemiological and experimental evidence that different carcinogens act at one of these stages predominantly. A classification of carcinogens according to their mechanism of action cannot, on the basis of today's knowledge, be exhaustive or definite, but examples derived from experimental and epidemiological observations can be used to illustrate possible differences among carcinogens.

Direct alkylating agents, such as N-nitroso-N-ethylurea (which has a half-life of a few minutes), induce tumors in vivo in experimental animals after a single dose on the order of a few milligrams per kilogram body weight, while carbon tetrachloride induces tumors of the liver only after high dose levels given over an extended period of time. Exposure to polycyclic aromatic hydrocarbons may result in the occurrence of tumors at various sites, but, at particularly low levels they can lead to increased susceptibility to cancer development after subsequent exposure to a promoting agent. One such example is prenatal exposure to 7,12-dimethylbenz[a]anthracene followed by exposure to 12-O-tetradecanoylphorbol 13-acetate later in life [Yamasaki et al, 1987]. Epidemiological studies indicate that asbestos acts at an early stage in the development of mesothelioma and at a late stage for lung cancer; similar considerations apply for tumors resulting from exposure to nickel, namely, lung cancer at a late stage and nasal cavity cancer at an early stage [Peto et al, 1982; Peto, 1984]. The same observations have been made for the induction in mice of liver and bladder cancer by 2-acetylaminofluorene [Day and Brown, 1980].

Classification of carcinogens into two categories according to whether or not they can induce DNA damage has also been discussed [Williams, 1983]. It was suggested that carcinogens that do not show this activity should be labelled "epige-

TABLE III. Benzidine-Based Dyes Imported to the USA (in pounds) [Samuels (1981)]

Country of origin	Year		
	1974	1976	1979
India	16,193	23,149	47,733
Egypt	None	None	86,641
Poland	3,910	32,684	21,714
Rumania	None	79,365	11,023
France	250	17,750	220,018
Canada	None	440	2,205
Total	20,353	153,388	389,334[a]

[a]The total quantity reported for 1979, including imports from the Benelux countries, was 469,917 pounds.

HWBUI0002053

netic" carcinogens or "promoters," and that regulatory measures for controlling exposure to them should be less stringent than for carcinogens that are "genotoxic" [Weisburger and Williams, 1981]. Although classification of carcinogens according to their mechanism of action could be an important contribution to cancer prevention, present understanding of the mechanisms of carcinogenesis does not justify it. Since the same carcinogen can act as an "initiator" in one tissue and as a "promoter" in another, agents cannot be classified simply as "initiators," "promoters," or "complete carcinogens" [see International Agency for Research on Cancer, 1983, for further discussion]. Moreover, it cannot be excluded that the late stage of carcinogenesis, which is usually called promotion and which often overlaps with the phase of progression (stage of clinical appearance of the tumors), is also due to a mutational event, or at least that a mutational event is involved.

This inability to classify carcinogens according to their mechanism of action at the present state of our understanding of the mechanisms of carcinogenesis leaves open the debate about whether different types of regulations are warranted for chemicals that have been shown to be carcinogenic at levels of exposure that vary by several orders of magnitude.

One unwanted side effect of the adoption of more regulations on the production and use of chemical carcinogens in developed countries has been the transfer of dangerous industrial processes to developing countries, where regulations controlling worker exposure are either nonexistent or much less stringent [Navarro, 1984]. The extent of this practice is only partially documented [Castelman, 1979, 1983]. Table III, showing the rates of importation of benzidine-based dyes to the USA following the introduction in 1974 of strict regulations controlling benzidine manufacture [Samuels, 1981], provides indirect evidence of the size of the phenomenon: it is also of interest that imports increased by approximately 20 times between 1974 and 1979, and, furthermore, that imports came not only from developing countries but also from some developed countries.

International organizations, by their very nature, can be instrumental in ensuring that information on the carcinogenic risk of chemicals is widely disseminated and that effective regulatory measures to control exposure to carcinogens do not remain confined to a few countries. A resolution concerning exchange of information about banned chemicals was issued by the United Nations in 1979 [United Nations, 1982]. Several useful and reliable sources of information are available, including the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* [International agency for Research on Cancer, 1987a]; the *Environmental Health Criteria*, issued by the International Programme for Chemical Safety [1976–1987]; the International Register of Potentially Toxic Chemicals [1985]; and the International Labour Office [1983]. It is hoped that this paper, by attracting attention to the unevenness of the measures that could, all over the world, prevent occupational cancer, will contribute to implementation of a more efficient primary prevention of cancer.

ACKNOWLEDGMENTS

The authors would like to acknowledge the collaboration and valuable comments of the following persons from different countries in collecting and preparing the material discussed in this paper: T. Fletcher, S.S. Fluss, M. Gilbert, D. Habashi, D. Henschler, M. Ikeda, B. Pannett, J.L. Pasquier, M. Reynier, R. Saracci, L. Simon-

HWBUI0002054

oto, A. Tossavainen, H. Vainio, M.T. van der Venne, P. Westerholm, and J. Wilbourn. The editing by Mrs. E. Heseltine is greatly appreciated, and the secretarial assistance of Mrs. E. Perez has been invaluable.

REFERENCES

Ashford NA (1987): New scientific evidence and public health imperatives. N Engl J Med 316:1084–1085.

Case RAM, Hosker ME, McDonald DB, Pearson JT (1954): Tumours of the urinary bladder in workmen engaged in the manufacture and use of certain dyestuff intermediates in the British chemical industry. I. The role of aniline, benzidine, alpha-naphthylamine and beta-naphthylamine. Br J Ind Med 11:75–104.

Castelman BI (1979): The export of hazardous factories to developing nations. Int J Health Serv 9:569–606.

Castelman BI (1983): The double standard in industrial hazards. Int J Health Serv 13:5–14.

Cole P, Hoover SR, Friedell GL (1972): Occupation and cancer of the lower urinary tract. Cancer 29:1250–1260.

Day NE, Brown C (1980): Multistage models and primary prevention of cancer. J Natl Cancer Inst 64:977–989.

Doll R, Peto R (1981): "The Causes of Cancer." Oxford: Oxford University Press.

Ehrlicher H (1971): Krebs als Berufskrankheit. Arbeitsmed Sozialmed Arbeitshyg 6:221–225.

Guariniello R (1985): Se Il Lavoro Uccide. Riflessioni di un Magistrato, Turin: Giulio Ein audi, Nuovo Politechnico 145, p. 163.

Henschler D (1987): Risk assessment and evaluation of chemical carcinogens: Present and future strategies. J Cancer Res Clin Oncol 13:1–7.

International Agency for Research on Cancer (1983): "Approaches to Classifying Chemical Carcinogens According to Mechanism of Action." Lyon: Joint IARC/IPCS/CEC Working Group Report, IARC Internal Technical Report No. 83/001.

International Agency for Research on Cancer (1987a): "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Suppl. 7, Overall Evaluations of Carcinogenicity: An Update of IARC Monographs" Volumes 1–42, Lyon.

International Agency for Research on Cancer (1987b): "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans—Preamble." Lyon: IARC Internal Technical Report 87/001.

International Labour Office (1921): "Cancer of the Bladder Among Workers in Aniline Factories." Geneva: Studies and Reports, Series F, No. 1.

International Labour Office (1983): "Encyclopaedia of Occupational Health and Safety." Geneva: Vols. I and II.

International Programme for Chemical Safety (1976–1987): "Environmental Health Criteria." Geneva: World Health Organization.

International Register of Potentially Toxic Chemicals (1985): "Bans and Severe Restrictions—The role of IRPTC." Geneva: United Nations Environment Programme, IRPTC Bulletin.

Montesano R, Tomatis L (1977): Legislation concerning chemical carcinogens in several industrialized countries. Cancer Res 37:310–316.

Navarro V (1984): Special report: Policies on exportation of hazardous substances in Western developed countries. N Engl J Med 311:546–548.

Parkes HG (1976): The epidemiology of aromatic amine cancers. In Searle CE (Ed): "Chemical Carcinogens." Washington, DC: American Chemical Society, ACS Monograph 173.

Pastorino U, Berrino F, Gervasio A, Pesenti V, Riboli E, Crosignani P (1984): Proportion of lung cancers due to occupational exposure. Int J Cancer 33:231–237.

Peto J (1984): Early- and late-stage carcinogenesis in mouse skin and in man. In Börzsönyi M, Day NE, Lapis K, Yamasaki H (Eds): "Models, Mechanisms and Etiology of Tumour Promotion."Lyon: International Agency for Research on Cancer, IARC Scientific Publication No. 56, pp 359–371.

Peto J, Seidman H, Selikoff IJ (1982): Mesothelioma mortality in asbestos workers: Implications for models of carcinogenesis and risk assessment. Br J Cancer 45:124–135.

Rehn L (1895): Blasengeschwülste bei Anilinarbeitern. Arch Klin Chir 50:588–600.

HWBUI0002055

Rinsky RA, Smith AB, Hornung R, Filloon TG, Young RJ, Okun AH, Landrigan PJ (1987): Benzene and leukemia. N Engl J Med 316:1044–1050.

Samuels SW (1981): The international context of carcinogen regulation: Benzidine. In Peto R, Schneiderman M (Eds): "Quantification of Occupational Cancer." Cold Spring Harbor, NY: CSH Press, Banbury Report 9, pp 497–512.

Saracci R (1985): Occupation. In Vessey MP, Gray M (Eds): "Cancer Risks and Prevention." Oxford: Oxford University Press, pp 99–118.

Tomatis L (1987): The contribution of the IARC Monographs program to the identification of cancer risk factors. Ann NY Acad Sci (in press).

Tomatis L, Breslow NE, Bartsch H (1982): Experimental studies in the assessment of human risk. In Schottenfeld D, Fraumeni JF, Jr (Eds): "Cancer Epidemiology and Prevention." New York: W.B. Saunders, Chapter 4, pp 44–73.

United Nations (1982): UN General Assembly, 37th Session, 109th plenary meeting, December 17, 1982. Assembly Resolution 37/137.

Walpole AL, Williams MHC, Robert DC (1954): Tumours of the urinary bladder in dogs after ingestion of 4-aminodiphenyl. Br J Ind Med 11:105–109.

Weisburger JH, Williams GM (1981): The decision-point approach for systematic carcinogen testing. Food Cosmet Toxicol 19:561–566.

Wilbourn J, Haroun L, Heseltine E, Kaldor J, Partensky C, Vainio H (1986): Response of experimental animals to human carcinogens: An analysis based upon the IARC Monographs programme. Carcinogenesis 7:1853–1863.

Williams GM (1983): Epigenetic effect of liver tumor promoters and implications for health effect. Environ Health Perspect 50:177–183.

Yamasaki H, Hollstein M, Martel N, Cabral JRP, Galendo D, Tomatis L (1987): Transplacental induction of specific mutation in fetal Ha-*ras* and its critical role in postnatal carcinogenesis. Int J Cancer (in press).

HWBUI0002056

Sent 9/14/84 cc JLW AF RLF From JB Clarke Pub

APPENDIX A

CHEMICALS HAVING VARYING DEGREES OF EVIDENCE FOR CARCINOGENICITY

HWBU0002057

TABLE A-1

CHEMICALS FOR WHICH THERE IS SUFFICIENT EVIDENCE OF CARCINOGENICITY IN EXPERIMENTAL ANIMALS

Acrylonitrile*
Actinomycins
Aflatoxins*
ortho-Aminozotoluene
4-Aminobiphenyl*
2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole
Amitrole*
Aramite
Asbestos*
Azaserine

Benz [a] anthracene
Benzidine*
Benzo [b] fluoranthene
Benzo [a] pyrene
Benzyl violet 4B
Beryllium*
Beryllium oxide
Beryllium phosphate
Beryllium sulphate
Bis(chloromethyl)ether*
B-Butyrolactone

Cadmium*
Cadmium chloride
Cadmium oxide
Cadmium sulphate
Cadmium sulphide
Calcium chromate
Carbon tetrachloride*
Chlorambucil*
Chlordecone (Kepone)
Chloroform
Chromium*
Citrus red No. 2
Cycasin
Cyclophosphamide*

Daunomycin
N,N'-Diacetylbenzidine
4,4'-Diaminodiphenyl ether
2,4-Diaminotolvene
Diabenz [a,h] acridine
Diabenz [a,j] acridine
Diabenz [a,h] anthracene
7H-Dibenzo [c,g] carbazole

Table A-1 continued on next page

* As evaluated by IARC, 1979.
** Chemicals with data on cancer in humans.

TABLE A-1 (continued)

CHEMICALS FOR WHICH THERE IS SUFFICIENT EVIDENCE OF CARCINOGENICITY IN EXPERIMENTAL ANIMALS

Dibenzo [a,e] pyrene
Dibenzo [a,h] pyrene
Dibenzo [a,i] pyrene
1,2-Dibromo-3-chloropropane
3,3'-Dichlorobenzidine*
3,3'-Dichloro-4,4'-diaminodiphenyl ether
1,2 Dichloroethane
Diepoxybutane
1,2-Diethylhydrazine
Diethylstibestrol*
Diethyl sulphate
Dihydrosafrole
3,3'-Dimethoxybenzidine (ortho-Dianisidine)
para-Dimethylaminoazobenzene
trans-2[(Dimethylamino)methylimino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole
3,3'-Dimethylbenzidine (ortho-Tolidine)
Dimethylcarbamoyl chloride*
1,1-Dimethylhydrazine

1,2-Dimethylhydrazine
Dimethyl sulphate*
1,4-Dioxane

Ethinyloestradiol
Ethylene dibromide
Ethylenethiourea
Ethyl methanesolphonate

2-(2-Formylhydrazino)-4-(5-nitro-2-furyl) thiazole

Glycidaldehyde

Hexachlorobenzene
Hexamethylphosphoramide
Hydrazine

Indeno[1,2,3-cd] pyrene
Iron dextran*
Isosafrole

Table A-1 continued on next page

* As evaluated by IARC, 1979.
** Chemicals with data on cancer in humans.

HWBUI0002058

TABLE A-1 (continued)

CHEMICALS FOR WHICH THERE IS SUFFICIENT EVIDENCE
OF CARCINOGENICITY IN EXPERIMENTAL ANIMALS

Lasiocarpine
Lead acetate
Lead phosphate
Lead subacetate

Melphalan*
Merphalan
Mestranol
2-Methylaziridine
Methylazoxymethanol acetate
4,4'-Methylene bis(2-chloroaniline)
bis(2-methylaniline) and its Methyl iodide methanesulphonate
N-Methyl-N'-nitro-N-nitrosoguanidine
Methylthiouracil
Mirex
Mitomycin C
Monocrotaline
5-(Morpholinomethyl)-3-[(5-nitrofurfurylidine)-amino]-2 oxazolidinone

2-Naphthylamine*
Nickel*
Nickel subsulphide
Niridazole
5-Nitroacenaphthlene
1-[(5-Nitrofurfurylidene)amino]-2-midazolidinone
N-[4-(5-Nitro-2-furyl)-2-thiazolyl[acetamide]
Nitrogen mustard and its hydrochloride 4,4'-Methylene
Nitrogen mustard N-oxide hydrochloride Methyl
N-Nitrosodi-n-butylamine
N-Nitrosodiethanolamine
N-Nitrosodiethylamine
N-Nitrosodimethylamine
N-Nitrosodi-n-propylamine
N-Nitroso-N-ethylurea
N-Nitrosomethylethylamine
N-Nitroso-N-methylurea
N-Nitroso-N-methylurethane

Table A-1 continued on next page

* As evaluated by IARC, 1979.
** Chemicals with data on cancer in humans.

TABLE A-1 (continued)

CHEMICALS FOR WHICH THERE IS SUFFICIENT EVIDENCE
OF CARCINOGENICITY IN EXPERIMENTAL ANIMALS

N-Nitrosomethylvinylamine
N-Nitrosomorpholine
N-Nitrosonornicotine
N-Nitrosopiperidine
N-Nitrosopyrrolidine
N-Nitrososarcosine

Oestradiol-17B
Oestrone
Oil orange SS

Polychlorinated biphenyls*
Ponceau MX
Ponceau 3R
1,3-Propane sultone
B-Propiolactone
Propylthiouracil

Safrole
Soots, tars and oils*
Sterigmatocystin
Streptozotocin

Testosterone
Thioacetamide
Thiourea
Toxaphene
Tris(aziridinyl)hosphine sulphide (thiotepa)*
Tris(2,3-dibromopropyl)phosphate
Trypan blue (commercial grade)

Uracil mustard
Urethane

Vinylchloride*

* As evaluated by IARC, 1979.
** Chemicals with data on cancer in humans.

HWBUI0002059

TABLE A-2

CHEMICALS WITH VERY STRONG EVIDENCE
FOR CARCINOGENICITY IN TWO ANIMAL SPECIES

3-Amino-9-ethylcarbazole hydrochloride
ortho-Anisidine hydrochloride
Chlordecone
Chldoroform
4-Chloro-ortho-phenylenediamine
para-Cresidine
Cupferron
2,4-Diaminoanisole sulfate
2,4-Diaminotoluene
Dibromochloropropane
1,2-Dichloroethane
1,2-Dichloroethane
1,4-Dioxane
Hydrazobenzene
4,4'-Methylene-bis (N,N-dimethyl)benzenamine
Michler's ketone
1,5-Naphthalenediamine
5-Nitroacenaphthene
Nitrilotriacetic acid, trisodium salt
Nitrilotriacetic acid
Phenzopyridine hydrochloride
Phenoxybenzamine hydrochloride
Procarbazine
Reserpine
Selenium sulfide
Sulfallate
4,4'-Thiodianiline
Thio-TEPA
ortho-Toluidine hydrochloride
2,4,5-Trimethylaniline
Tris(2,3-dibromopropyl)-phosphate

* National Cancer Institute (NCI) data as evaluated by R.A. Griesemer and C. Cueto, Jr., 1980.

TABLE A-3

CHEMICALS WITH VERY STRONG EVIDENCE FOR CARCINOGENICITY IN ONE SPECIES AND SUFFICIENT EVIDENCE IN A SECOND SPECIES

2-Aminoanthraquinone
1-Amino-2-methyl-anthraquinone
5-Nitro-ortho-anisidine
Nitrofen
para-Nitrosodiphenylamine
Phenestrin
2,4,6-Trichlorophenol
Trimethylprosphate

* National Cancer Institute (NCI) data as evaluated by R.A. Griesemer and C. Cueto, Jr., 1980.

HWBUI0002060

TABLE A-4

CHEMICALS WITH VERY STRONG EVIDENCE FOR CARCINOGENICITY IN ONE SPECIES AND NO EVIDENCE IN A SECOND SPECIES

Acronycine
4-Amino-2-nitrophenol
Aniline hydrochloride
Azobenzene
Chlordane
Chlorobenzilate
3-(Chloromethyl)pyridine hydrochloride
5-Chloro-ortho-toluidine
4-Chloro-ortho-toluidine hydrochloride
Chlorothalonil
Cinnamyl-anthranilate
meta-Cresidine
Dapsone
para, para'-DDE
N,N'-Dimethoxybenzidine-4,4'-diisocyanate
Direct dye, blue 6
Direct dye, black 38
Direct dye, brown 95
Heptachlor
Hexachloroethane
Lasiocarpine
2-Methyl-1-nitroanthraquinone
6-Nitrobenzimidazole
N-Nitrosodiphenylamine
5-Nitro-ortho-toluidine
Oestradiol mustard
Pivalolactone
para-Quinone dioxime
1,1,2,2-Tetrachloroethane
Tetrachloroethylene
Toxaphene
Trichloroethyelene
Trifluralin

TABLE A-5

CHEMICALS WITH SUFFICIENT EVIDENCE FOR CARCINOGENICITY IN TWO SPECIES

4-Chloro-meta-phenylenediamine
ICRF-159
Isophosphamide
Nithiazide

* National Cancer Institute (NCI) data as evaluated by R.A. Griesemer and C. Cueto, Jr., 1980.

HWBUI0002061