GENERAL REMARKS ON THE SUBSTANCES CONSIDERED

This fiftieth volume of the *IARC Monographs* comprises monographs on five antineoplastic agents, four antimicrobial agents, two diuretics, ciclosporin (an immunosuppressant), cimetidine (used in the treatment of gastric and duodenal ulcers), paracetamol (a popular analgesic and antipyretic drug) and dantron (a laxative). Many pharmaceutical drugs were evaluated in previous *IARC Monographs* (see Table 1), including some of those covered in this volume. Azacitidine and trichlormethine—both antineoplastic agents—and nitrofural—an antibacterial drug—were re-evaluated because new data on carcinogenicity in experimental animals had been published since the earlier evaluations; thiotepa and chloramphenicol were re-evaluated largely because of new data on carcinogenicity in humans.

Table 1. Pharmaceutical agents evaluated in the *IARC Monographs*

Agent	Vol. no.	Year	Evaluation[a]		
			Human	Animal	Overall
Anaesthetics					
Anaesthetics (unspecified mixtures)	Suppl. 7	1987	I	-	3
Chloroform	Suppl. 7	1987	I	S	2B
Cyclopropane	Suppl. 7	1987	I	ND	3
Diethyl ether	Suppl. 7	1987	I	ND	3
Divinyl ether	Suppl. 7	1987	I	ND	3
Enflurane	Suppl. 7	1987	I	I	3
Fluroxene	Suppl. 7	1987	I	ND	3
Halothane	Suppl. 7	1987	I	I	3
Isoflurane	Suppl. 7	1987	I	I	3
Methoxyflurane	Suppl. 7	1987	I	I	3
Nitrous oxide	Suppl. 7	1987	I	I	3
Trichloroethylene	Suppl. 7	1987	I	L	3
Analgesics and anti-inflammatory agents					
Aurothioglucose	13	1977	ND	L	3
Oxyphenbutazone	13	1977	ND	ND	3

Table 1 (contd)

Agent	Vol. no.	Year	Evaluation[a]		
			Human	Animal	Overall
Analgesics and anti-inflammatory agents (contd)					
Paracetamol (Acetaminophen)	50	1990	I	L	3
Phenacetin	Suppl. 7	1987	L	S	2A
Analgesic mixtures containing phenacetin	Suppl. 7	1987	S	L	1
Phenazopyridine hydrochloride	Suppl. 7	1987	I	S	2B
Phenylbutazone	Suppl. 7	1987	I	ND	3
Antibacterial drugs					
Ampicillin	50	1990	I	L	3
Chloramphenicol	50	1990	L	I	2A
Chrysoidine	Suppl. 7	1987	I	L	3
Dapsone	Suppl. 7	1987	I	L	3
Dihydroxymethylfuratrizine	24	1980	ND	I	3
Ethionamide	13	1977	ND	L	3
Isoniazid (Isonicotinic acid hydrazide)	Suppl. 7	1987	I	L	3
Nitrofural (Nitrofurazone)	50	1990	I	L	3
Nitrofurantoin	50	1990	I	L	3
1-[(5-Nitrofurfurylidene)amino]-2-imidazolidinone (Nifuradene)	7	1974	ND	S	2B
N-[4-(5-Nitro-2-furyl)-2-thiazolyl]acetamide (Furothiazole)	7	1974	ND	S	2B
Panfuran S (a formulation with dihydroxymethylfuratrizine and several other compounds)	24	1980	ND	S	2B
Penicillic acid	10	1976	ND	L	3
Rifampicin	24	1980	ND	L	3
Sulfafurazole (Sulphisoxazole)	Suppl. 7	1987	I	I	3
Sulfamethoxazole	Suppl. 7	1987	I	L	3
Antineoplastic drugs					
Actinomycin D (Dactinomycin)	Suppl. 7	1987	I	L	3
Adriamycin (Doxorubicin)	Suppl. 7	1987	I	S	2A
Azacitidine (5-Azacytidine)	50	1990	ND	S	2A
Azaserine	10	1976	ND	S	2B
N,N-Bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine)	Suppl. 7	1987	S	L	1
Bischloroethyl nitrosourea (BCNU)	Suppl. 7	1987	L	S	2A
Bleomycins	Suppl. 7	1987	I	L	2B
1,4-Butanediol dimethanesulfonate (Myleran)	Suppl. 7	1987	S	L	1
Chlorambucil	Suppl. 7	1987	S	S	1

Table 1 (contd)

Agent	Vol. no.	Year	Evaluation[a]		
			Human	Animal	Overall
Antineoplastic drugs (contd)					
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) (Lomustine)	Suppl. 7	1987	I	S	2A
1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (Methyl-CCNU)	Suppl. 7	1987	S	L	1
Chlorotrianisene (*see* Hormones)					
Chlorozotocin	50	1990	ND	S	2A
Cisplatin	Suppl. 7	1987	I	S	2A
Cyclophosphamide	Suppl. 7	1987	S	S	1
Dacarbazine	Suppl. 7	1987	I	S	2B
Daunomycin (Daunorubicin)	10	1976	ND	S	2B
Diethylstilboestrol (*see* Hormones)					
Ethynodiol diacetate (*see* Hormones)					
5-Fluorouracil	Suppl. 7	1987	I	I	3
17α-Hydroxyprogesterone caproate (*see* Hormones)					
Isophosphamide	26	1981	ND	L	3
Mannomustine	9	1975	ND	L	3
Medphalan	9	1975	ND	I	3
Megestrol acetate (*see* Hormones)					
Melphalan	Suppl. 7	1987	S	S	1
6-Mercaptopurine	Suppl. 7	1987	I	I	3
Merphalan	9	1975	ND	S	2B
Methotrexate	Suppl. 7	1987	I	I	3
Mitomycin C	10	1976	ND	S	2B
MOPP[b] and other combined chemotherapy including alkylating agents	Suppl. 7	1987	S	I	1
Nitrogen mustard	Suppl. 7	1987	L	S	2A
Nitrogen mustard *N*-oxide	9	1975	ND	S	2B
Norethisterone (*see* Hormones)					
Prednimustine	50	1990	ND	I	3
Prednisone (*see* Hormones)					
Procarbazine hydrochloride	Suppl. 7	1987	I	S	2A
Streptozotocin (Streptozocin)	17	1978	ND	S	2B
Treosulphan	Suppl. 7	1987	S	ND	1
Trichlormethine (Trimustine hydrochloride)	50	1990	ND	S	2B
Triethylene glycol diglycidyl ether (Ethoglucid)	11	1976	ND	L	3
Tris(aziridinyl)-*para*-benzoquinone (Triaziquone)	Suppl. 7	1987	I	L	3

Table 1 (contd)

Agent	Vol. no.	Year	Evaluation[a]		
			Human	Animal	Overall
Antineoplastic drugs (contd)					
Tris(1-aziridinyl)phosphine sulphide (Thiotepa)	50	1990	S	S	1
2,4,6-Tris(1-aziridinyl)-*s*-triazine	9	1975	ND	L	3
Uracil mustard (Uramustine)	Suppl. 7	1987	I	S	2B
Vinblastine sulphate	Suppl. 7	1987	I	I	3
Vincristine sulphate	Suppl. 7	1987	I	I	3
Antifungal, antiprotozoan and antiparasitic agents					
Chloroquine	13	1977	ND	I	3
DDT (Clofenotane)	Suppl. 7	1987	I	S	2B
Furazolidone (*also antibacterial*)	31	1983	ND	I	3
Griseofulvin	Suppl. 7	1987	ND	S	2B
γ-Hexachlorocyclohexane (Lindane)	Suppl. 7	1987	I	L	2B
Hycanthone mesylate	13	1977	ND	I	3
Metronidazole (*also antibacterial*)	Suppl. 7	1987	I	S	2B
Niridazole	13	1977	ND	S	2B
Pyrimethamine	13	1977	ND	L	3
Trichlorfon (Metrifonate)	30	1983	ND	I	3
Antiseptic agents					
Acridine orange	16	1978	ND	I	3
Acriflavinium chloride	13	1977	ND	I	3
Benzoyl peroxide (*see* Dermatological agents)					
Chrysoidine	Suppl. 7	1987	I	L	3
Eugenol (*used in dentistry*)	36	1985	ND	L	3
Hexachlorophene	20	1979	ND	I	3
Hydrogen peroxide	36	1985	ND	L	3
Phenol	47	1989	I	I	3
Proflavine salts	24	1980	ND	I	3
β-Propiolactone	4	1974	ND	S	2B
Scarlet Red	8	1975	ND	I	3
Tannic acid and tannins	10	1976	ND	L	3
Dermatological agents					
para-Aminobenzoic acid	16	1978	ND	I	3
Arsenic salts (Fowler's solution) (*also antineoplastic*)	Suppl. 7	1987	S	L	1[c]
Benzoyl peroxide (*also antiseptic*)	36	1985	I	I	3
Cantharidin	10	1976	ND	L	3
Coal-tars	Suppl. 7	1987	S	S	1

Table 1 (contd)

Agent	Vol. no.	Year	Evaluation[a]		
			Human	Animal	Overall
Dermatological agents (contd)					
Diacetylaminoazotoluene	8	1975	ND	I	3
Dithranol (Anthralin)	13	1977	ND	I	3
Hydroquinone	15	1977	ND	I	3
8-Hydroxyquinoline (*also antiseptic*)	13	1977	ND	I	3
5-Methoxypsoralen	Suppl. 7	1987	I	S	2A
8-Methoxypsoralen (Methoxsalen) + UV	Suppl. 7	1987	S	S	1
Resorcinol	15	1977	ND	I	3
Safrole (Oil of Sassafras)	10	1976	ND	S	2B
Selenium and selenium compounds	9	1975	I	I	3
Tannic acid and tannins (*see* Antiseptic agents)					
4,5′,8-Trimethylpsoralen	Suppl. 7	1987	I	I	3
Drugs for treating anaemia					
Iron-dextran complex	Suppl. 7	1987	I	S	2B
Iron-dextrin complex	2	1973	ND	L	3
Iron-sorbitol-citric acid complex	2	1973	ND	I	3
Saccharated iron oxide	2	1973	ND	L	3
Drugs for treating cardiovascular disorders					
Clofibrate (hypercholesterolaemia)	Suppl. 7	1987	I	L	3
Furosemide (Frusemide) (hypertension)	50	1990	I	I	3
Hydralazine (hypertension)	Suppl. 7	1987	I	L	3
Hydrochlorothiazide (hypertension)	50	1990	I	I	3
Phenoxybenzamine hydrochloride (hypertension)	24	1980	ND	S	2B
Reserpine (hypertension)	Suppl. 7	1987	I	L	3
Spironolactone (hypertension)	Suppl. 7	1987	I	L	3
Drugs for treating central nervous disorders					
Diazepam (anxiety)	Suppl. 7	1987	I	I	3
Oxazepam (anxiety)	13	1977	ND	L	3
Phenelzine sulphate (depression)	Suppl. 7	1987	I	L	3
Phenobarbital (epilepsy)	Suppl. 7	1987	I	S	2B
Phenytoin (epilepsy)	Suppl. 7	1987	L	L	2B
Drugs for treating thyroid disorders					
Methylthiouracil	7	1974	ND	S	2B
Propylthiouracil	Suppl. 7	1987	I	S	2B
Thiouracil	7	1974	ND	L	3
Thiourea	7	1974	ND	S	2B

Table 1 (contd)

Agent	Vol. no.	Year	Evaluation[a]		
			Human	Animal	Overall
Hormones					
Androgenic (anabolic) steroids					
Oxymetholone	Suppl. 7	1987	L	ND	2A
Testosterone	Suppl. 7	1987	L	S	2A
Oestrogens, progestins and combinations	Suppl. 7	1987			
Oestrogens					
Nonsteroidal oestrogens			S		1[c]
Diethylstilboestrol			S	S	1
Dienoestrol				L	
Hexoestrol				S	
Chlorotrianisene				I	
Steroidal oestrogens			S		1[c]
Oestrogen replacement therapy			S		1[c]
Conjugated oestrogens				L	
Oestradiol-17β and esters				S	
Oestriol				L	
Oestrone				S	
Ethinyloestradiol				S	
Mestranol				S	
Progestins			I		2B[c]
Medroxyprogesterone acetate			I	S	2B
Chlormadinone acetate				L	
Dimethisterone				I	
Ethynodiol diacetate				L	
17α-Hydroxyprogesterone caproate				I	
Lynoestrenol				I	
Megestrol acetate				L	
Norethisterone				S	
Norethynodrel				L	
Norgestrel				I	
Progesterone				S	
Oestrogen-progestin combinations					
Sequential oral contraceptives			S		1[c]
Dimethisterone and oestrogens				I	
Combined oral contraceptives			S		1[d]
Chlormadinone acetate and oestrogens				L	
Ethynodiol diacetate and oestrogens				L	
Lynoestrenol and oestrogens				I	

Table 1 (contd)

Agent	Vol. no.	Year	Evaluation[a]		
			Human	Animal	Overall
Hormones (contd)					
Megestrol acetate and oestrogens				L	
Norethisterone and oestrogens				L	
Norethynodrel and oestrogens				S	
Norgestrel and oestrogens				I	
Progesterone and oestrogens				L	
Oestrogen-progestin replacement therapy			I		3
Anti-oestrogens					
Clomiphene citrate	Suppl. 7	1987	I	I	3
Other hormones					
Prednisone	Suppl. 7	1987	I	I	3
Immunosuppressants					
Azathioprine	Suppl. 7	1987	S	L	1
Ciclosporin (Cyclosporin A)	50	1990	S	L	1
Traditional remedies of herbal origin					
Dantron (Chrysazin, 1,8-Dihydroxyanthraquinone) (*Aloe* sp., *Cassia senna*, *Rhamnus purshianus* or *Cascara sagrada*, and *Rheum officinale*)	50	1990	ND	S	2B
Hydroxysenkirkine (*Crotalaria* sp.)	10	1976	ND	I	3
Isatidine (*Senecio* sp.)	10	1976	ND	L	3
Jacobine (*Senecio* sp.)	10	1976	ND	I	3
Monocrotoline (*Crotalaria* sp.)	10	1976	ND	S	2B
Petasitenine (*Petasites japonicus*)	31	1983	ND	L	3
Retrorsine (*Senecio* sp.)	10	1976	ND	L	3
Riddelliine (*Crotalaria* sp.)	10	1976	ND	I	3
Seneciphylline (*Senecio* sp. and *Crotalaria* sp.)	10	1976	ND	ND	3
Senkirkine (*Senecio kirkii*)	31	1983	ND	L	3
Symphytine (*Symphytum officinale*)	31	1983	ND	I	3
Miscellaneous drugs and experimental agents					
2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole (gastritis)	7	1974	ND	S	2B
Angelicin + UVA (skin disorders)	40	1986	ND	L	3
Cimetidine (peptic ulcer)	50	1990	I	I	3
4,4′-Dimethylangelicin + UVA (skin disorders)	40	1986	ND	ND	3
4,5′-Dimethylangelicin + UVA (skin disorders)	40	1986	ND	L	3

Table 1 (contd)

Agent	Vol. no.	Year	Evaluation[a]		
			Human	Animal	Overall
Miscellaneous drugs and experimental agents (contd)					
Disulfiram (alcoholism)	12	1976	ND	I	3
Investigational oral contraceptives	Suppl. 7	1987	S	L	1[d]
Lasiocarpine (emetic)	10	1976	ND	S	2B
5-Methylangelicin + UVA (skin disorders)	40	1986	ND	L	3
N-Methyl-*N*-nitrosourea (antineoplastic)	17	1978	ND	S	2A
7-Methylpyrido[3,4-*c*]psoralen (skin disorders)	40	1986	ND	I	3
Nafenopin (hypercholesterolaemia)	24	1980	ND	S	2B
Pyrido[3,4-*c*]psoralen (skin disorders)	40	1986	ND	I	3
Sodium diethyldithiocarbamate (nickel poisoning)	12	1976	ND	I	3
4,4',6-Trimethylangelicin + UVA (skin disorders)	40	1986	ND	ND	3
Veterinary drugs					
Acriflavinium chloride (*see* Antiseptic agents)					
para-Aminobenzoic acid (*see* Dermatological agents)					
5-Amino-2-nitrothiazole	31	1983	ND	L	3
Arsanilic acid	Suppl. 7	1987	S	L	1[c]
Diacetylaminoazotoluene (*see* Dermatological agents)					
Furazolidone (*see* Antifungal, antiprotozoan and antiparasitic agents)					
Hexachloroethane	20	1979	ND	L	3
Hexachlorophene (*see* Antiseptic agents)					
Iron–dextran complex (*see* Drugs for treating anaemia)					
Lead arsenate	Suppl. 7	1987	S	L	1[e]
5-(Morpholinomethyl)-3-[(5-nitrofurfuryl-idene)amino]-2-oxazolidinone (Furaltadone)	7	1974	ND	S	2B
Nithiazide	31	1983	ND	L	3
5-Nitro-2-furaldehyde semicarbazone	7	1974	ND	I	3
N-[4-(5-Nitro-2-furyl)-2-thiazolyl] acetamide (*see* Antibacterial drugs)					

Table 1 (contd)

Agent	Vol. no.	Year	Evaluation[a]		
			Human	Animal	Overall
Veterinary drugs (contd)					
Nitrovin	31	1983	ND	I	3
Selenium (*see* Dermatological agents)					
Urethane	7	1974	ND	S	2B

[a]I, inadequate; S, sufficient; L, limited. For definitions of the symbols used, see Preamble, pp. 26–29.
[b]Combined therapy with nitrogen mustard, vincristine, procarbazine and prednisone
[c]This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group.
[d]There is also conclusive evidence that these agents have a protective effect against cancers of the ovary and endometrium.
[e]According to the overall evaluation of arsenic compounds

Derivatives of chloramphenicol without the NO_2 moiety have been developed; of these, thiamphenicol has been used extensively, but florfenicol is not used in man. Thiamphenicol and florfenicol were not considered in this volume, however, because there appear to be no published data with regard to their carcinogenicity. Similarly, ranitidine and famotidine are used therapeutically like cimetidine; but monographs on ranitidine and famotidine and their nitrosated derivatives were also not prepared due to a lack of relevant published studies.

In clinical use and in formulations, salts, esters and complexes of drugs are often designated by the name of the parent compound; this is the case with ampicillin and chloramphenicol. In the case of nitrofurantoin, products of different crystal size have been synthesized. While the Working Group attempted to distinguish these alternative forms, in some instances insufficient information was available to do so.

The primary source of human exposure to drugs is from their use in therapy. Other types of exposure may also occur, however: persons employed in the manufacture of drugs may be exposed, as well as nursing and other staff responsible for the preparation and administration of compounds and staff responsible for the care of treated patients. Veterinary use of drugs may result in their entry into the human food chain.

For the drugs considered here, as for many others, studies of human carcinogenicity present difficult problems. The symptoms of an undiagnosed cancer may prompt the use of drug, which is subsequently suspected as its cause. Alternatively, the condition for which the drug therapy is prescribed may itself be a risk factor for cancer. An additional problem is that patients commonly receive

more than one drug, and determination of the carcinogenicity of any single drug may not be feasible. Repeated reference is made in this volume to hypothesis-generating studies. These refer to sets of data containing information on many drugs and many outcomes, in which multiple comparisons are made. Statistically significant associations ($p < 0.05$) are noted, but in terms of probability theory many such associations may be due to chance. For this reason, the p values given in the text must be interpreted with caution, and independent examination of associations identified in hypothesis-generating studies is particularly desirable. This situation is substantially different from that in which a prior hypothesis exists before the data are analysed.

An increasing number of agents, including pharmaceutical drugs, have been shown to inhibit cancer development in animal models. Such properties may lead to new possibilities for cancer treatment and prevention. The Working Group noted that in long-term experiments with paracetamol, nitrofurantoin and nitrofural, reductions in tumour incidence were seen at some sites in some animal species, although such reductions may have other interpretations than an inhibition of tumour induction.

Exposure can generally be much more accurately measured for drugs than for other agents suspected or identified as human carcinogens, and therapeutic doses used in humans are often close to those tested in experimental animals. However, as is the policy in the *IARC Monographs*, no attempt was made to quantify cancer risk at specific dose levels. As stated in the Preamble, the *Monographs* represent the first stage in carcinogenic risk assessment. Subsequent stages, not attempted in the *Monographs*, may involve quantitative determinations. By extrapolation of available epidemiological data, and possibly experimental data, estimations of risk may be attempted for specific populations in respect of particular carcinogens. Such information may be a factor in regulatory or legislative processes, but no recommendation concerning these processes is given in the *Monographs*. However, the Working Group responsible for the present monographs observed that inference of carcinogenic hazard was likely to be a major factor in decision-making regarding the usage of many of the drugs considered.

Many (if not most) regulatory decisions concerning putative carcinogens necessitate consideration not only of perceived hazard but also of the benefit derived from particular chemicals. It is crucial, therefore, that decisions on the availability of drugs include assessment not only of potential carcinogenicity but also the health benefit derived from their usage.