REPORT OF AN AD-HOC *IARC MONOGRAPHS* ADVISORY GROUP ON PRIORITIES FOR FUTURE EVALUATIONS

Lyon, 16-18 September 1998

Contents

1. List of participants

(N.B. - Unable to attend : Dr W.T. Allaben, Food and Drug Administration, National Center for Toxicological Research 3900 NCTR Road (HFT-30), Jefferson AR 72079-9502, USA)

Dr V.N. Anisimov, N.N. Petrov Research Institute of Oncology, 68 Leningradskaya Street, Pesochny-2, 189646 Saint-Petersburg, Russian Federation

Dr H.B.S. Conacher, Bureau of Chemical Safety, Food Directorate, Health Protection Branch, Sir Frederick Banting Research Centre, Postal Locator: 2203G2, Tunney's Pasture, Ottawa, Ontario K1A 0L2, Canada

Dr E. Dybing, National Institute of Public Health, Department of Environmental Medicine, Postboks 4404 Torshov, N-0403 Oslo, Norway

Dr V.J. Feron, Toxicology Division, TNO Nutrition and Food Research Institute, Utrechtseweg 48, PO Box 360, 3700 AJ Zeist, The Netherlands

Dr J.M. Harrington, Institute of Occupational Health, University of Birmingham, PO Box 363, Birmingham B15 2TT, United Kingdom

Dr T. Kauppinen, Institute of Occupational Health, Topeliuksenkatu 41 a A, FIN-00250 Helsinki, Finland

Dr D. Longfellow, Chemical and Physical Carcinogenesis Branch, Division of Cancer Biology, National Cancer Institute, 6006 Executive Blvd, Suite 220, MSC 7055, Rockville MD 20892-7055, USA

(N.B. - Unable to attend: Dr P. Schmezer, Division of Toxicology and Cancer Risk Factors, German Cancer Research Center, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany)

Dr B.W. Stewart, Children's Leukaemia & Cancer Research Centre, The Prince of Wales Children's Hospital, High Street, Randwick, Sydney NSW 2031, Australia

Dr B. Terracini, Unit of Tumour Epidemiology, Department of Biological Science and Human Oncology, University of Torino, via Santena, 10126 Torino, Italy

Dr H. Tsuda, National Cancer Center Research Institute, Experimental Pathology and Chemotherapy Division, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104 , Japan

Dr S. Venitt, Institute of Cancer Research, Cotswold Road, Belmont, Sutton, Surrey SM2 5NG, United Kingdom

Dr E. Zeiger, Environmental Toxicology Program, National Institute of Environmental Health Sciences, PO Box 12233, Research Triangle Park NC 27709, USA

Representative of the National Institute of Environmental Health Sciences

Dr Ch. Schonwalder, Director of International Programs, National Institute of Environmental Health Sciences, PO Box 12233, Research Triangle Park NC 27709, USA

IARC Secretariat

Dr R.A. Baan
Dr M. Bleiter
Dr P. Boffetta
Dr D. McGregor
Mrs D. Mietton
Dr A.B. Miller
Mrs C. Partensky
Dr J.M. Rice
Dr E. Ward
Mr J.D. Wilbourn

Secretarial Assistance

Mrs E. Perez

Ms S. Reynaud

2. Introduction

The purpose of the *IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans* is to identify individual agents or environmental exposures that may be causes of human cancer, in order to provide a scientific basis for cancer prevention. That is to be accomplished by evaluating the strength of the published scientific evidence for carcinogenicity in humans and environmental factors or circumstances to which humans are exposed. The proliferation of scientific data on putative environmental carcinogens requires the setting of priorities for agents to be selected as topics for evaluation or re-evaluation in future monographs.

This report represents the deliberations and conclusions of the fifth Advisory Group convened by the *IARC Monographs Programme* to advise on priorities for future evaluations. Previous meetings were held in 1979, 1984, 1989 and 1993 and the results published as IARC Internal Reports. The agents and exposures listed will be considered during the period 2000-2005.

In making its recommendations the Advisory Group affirmed the need regularly to assess the scientific evidence on chemical, biological and physical agents relevant to the causation of human cancer. Such evaluations are considered complementary to the rapid developments in research on the molecular genetics of human cancers thereby strengthening the basis for cancer control.

3. Scientific data used in the assessment of carcinogenicity to humans

Since their inception, the IARC Monographs have based evaluations only on primary information published in the open scientific literature as the primary information that is in the public domain, such as national governments' reports, which are freely available for consultation. This is in contrast to many evaluations carried out both by national regulatory agencies and by various other programmes of the World Health Organization and other international organizations, which have access in confidence to proprietary information. This policy of not evaluating proprietary data has, in some cases, precluded the consideration by the Monographs Programme of some pharmaceutical drugs and agricultural chemicals.

The Advisory Group discussed this policy and concluded that it should remain unchanged. However, it was proposed that, in view of the rapid changes in mechanisms for publication of data and expansion in the use of the Internet for the exchange of scientific information, an *ad hoc* Working Group be convened to review the current criteria which govern the inclusion of data in the *IARC Monographs* and to propose such changes as may be warranted.

4. Principles for re-evaluation of agents or exposures considered in the *IARC Monographs*

The Advisory Group was asked to consider principles relevant to the re-evaluation of agents and exposures previously evaluated in the *IARC Monographs Programme*. The Advisory Group determined that the highest priority should be accorded to agents other than those already categorized as Group 1 (carcinogenic to humans). Highest priority should be accorded to agents and exposures currently classified as Group 2A (probably carcinogenic to humans) or Group 2B (possibly carcinogenic to humans) and, to a lesser extent, agents and exposures categorized as Group 3 (i.e. their carcinogenicity to humans cannot be classified). For all such agents, it was recommended that relevant data concerning current Group 2A and 2B agents be subject to regular review. When new relevant data are published that are thought likely to change an existing classification a strong case for re-evaluation can be made.

In comparison with the urgency accorded to the re-evaluation of Group 2A, 2B or Group 3 agents and exposures, the Advisory Group considered that low priority should be given to the re-evaluation of Group 1 agents (carcinogenic to humans). Nonetheless, a case for re-evaluation of Group 1 agents was recognized, specifically in response to new findings. These might include identification of human sites not recognized in existing evaluations. Examples include breast cancer and alcohol drinking, or leukaemia, stomach and colon cancer and tobacco smoke. Likewise, the availability of information concerning new mode(s) of exposure to a Group 1 agent could justify re-evaluation. Information concerning mechanism of action of agents and exposures already established as causing cancer in humans (i.e., Group 1 agents) are more appropriately addressed in the context of an IARC Scientific Publication rather than further Monograph evaluations.

The Advisory Group considered that when re-evaluating current *IARC Monographs* on industrial exposure circumstances, future working groups should address specific processes or specific chemicals rather than broad categories, in contrast to evaluating whole industries in which processes may have changed over time and place.

5. Preparations for the advisory group meeting

Nine months before the meeting, a questionnaire was sent to some 250 scientists at major national cancer research centres and at other national and international organizations, who were requested to nominate topics for evaluation or re-evaluation in the *IARC Monographs* series. The scientists were primarily identified as Group 2A (probably carcinogenic to humans) or exposure, giving reasons for the suggestion. Data sheets were also prepared by the Secretariat on agents or exposures that had been given high priority at previous meetings but had not yet been considered or already planned for consideration (see Table 1). The completed data sheets were used by the Advisory Group as a basis for its decisions regarding priorities.

The nomination process is thus limited to those agents of specific concern to individuals and does not reflect a systematic or comprehensive review of the toxicological literature. Accordingly, additional priorities may be identified that are not considered in this report, and these may be added to the list prepared by the Advisory Group.

6. Assignment of priorities

The Advisory Group discussed each agent or exposure and assigned either high or low priority or recommended deletion from the list. The assignment of high or low priority does not necessarily indicate the extent of exposure or the degree of concern about possible carcinogenicity, but primarily the availability of information for evaluation. Criteria for deletion included: inadequate data on carcinogenicity; insufficient new data to warrant a re-evaluation within the period 2000-2005; the availability only of unpublished information; and/or the possibility of considering the agent within a grouping of similar compounds or mechanisms of action. A list of agents or exposures discussed is given in Table 2. Agents were grouped as follows: industrial chemicals; complex mixtures; occupational exposures; lifestyle factors; pharmaceutical drugs; food additives, contaminants or components; naturally occurring substances; environmental contaminants; drinking water disinfectants and contaminants; and pesticides. "Reasons/comments" are necessarily brief, in view of the tabular format, but reflect the main reasons for the Advisory Group's decision; some are based on knowledge available to Group members that was not indicated on the data sheets.

Biological agents were not discussed in detail by the present Advisory Group since a future Advisory Group will be convened to advise on the evaluation or re-evaluation of these agents. Physical agents also were not discussed in detail as these were already advised upon by a special Advisory Group that met during 27-29 April 1998 (IARC, 1998).

7. Future direction of the programme

Electronic publications

The *IARC Monographs Programme* has traditionally published its evaluations as a series of monographs volumes including a cumulative index of agents considered. Each volume of monographs is printed in 3500 copies.

Recently the Preamble, the lists of evaluations and the summary and evaluations sections from all monographs have been made available in searchable electronic form on the Internet (http://www.iarc.fr). Genetic activity profiles prepared by the United States Environmental Protection Agency (EPA) on the basis of literature presented in the monographs on individual chemicals are also available on the Internet (http://www.epa.gov/gap-db).

The Advisory Group encouraged the further development of electronic presentation of the Monographs on Internet and CD-Rom.

Monographs organized by organ site

Suggestions have been made on several occasions that IARC address the issue of what agents have sufficient evidence to be cited as causes of specific cancers, possibly as a new approach in a separate monographs series.

The Advisory Group noted that for Group 1 compounds, it was usually implicit in the summaries which were the target organs in humans, and that increasingly working groups were making these assessments specific to organ sites. It was agreed that in the future, working groups should be urged to specify the target organs for Group 1, and wherever possible, Group 2A substances.

For agents previously categorised Group 1, and wherever possible, Group 2A, the Secretariat were invited to identify the relevant target sites. The Secretariat should also evaluate the possibility that a Working Group be convened to assess the data assembled by the Secretariat (in consultation with other relevant units in IARC), and, that the results of these deliberations be published as a volume in the IARC Scientific Publications series.

Meetings on mechanisms of carcinogenesis

Since 1992 a series of scientific Working Groups have been convened by the *IARC Monographs Programme* to publish proceedings within the IARC Scientific Publications series on topics related to Mechanisms of Carcinogenesis. Such publications have included a Consensus Report adopted by the Working Group presenting conclusions on the use of mechanistic data within the Monographs programme. After the first of such meetings (Vainio *et al.*, 1992), the Preamble to the Monographs was extended to include the use of mechanistic data in making overall evaluations of carcinogenicity to humans. Subsequently a series of meetings has been held on specialized topics relating to consideration of mechanisms of carcinogenesis in hazard identification. The proceedings of these meetings are published by IARC Press as IARC Scientific Publications (Vainio *et al.*, 1992; Kane *et al.*, 1996; Capen *et al.*; McGregor *et al.*, 1999) or as IARC Internal Technical Reports (IARC, 1995).

The Advisory Group noted with approval plans for a future meeting on mechanisms which may pertain to the production of forestomach and neuroendocrine tumours of the gastric fundus in rodents.

8. References

Capen, C.C., Dybing, E., Rice, J.M. & Wilbourn, J.D., eds (1999) *Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis* (IARC Scientific Publications No. 147), Lyon, IARC (in press)

IARC (1995) *Haloxidome Fluoridation and its role in Carcinogenesis* (IARC Technical Report No. 24), Lyon, IARC.

IARC (1998) *Report of an ad-hoc* IARC Monographs *Advisory Group on Physical Agents* (IARC Internal Report 98/002), Lyon, IARC.

Kane, A.B., Saracci, R., Boffetta, P. & Wilbourn, J.D., eds (1996) *Mechanisms of Fibre Carcinogenesis* (IARC Scientific Publications No. 140), Lyon, IARC.

McGregor, D.B., Rice, J.M. & Venitt, S., eds (1999) *The Use of Short- and Medium-term Tests for Carcinogens and Data on Genetic Effects in Carcinogenic Hazard Evaluation* (IARC Scientific Publications No. 146), Lyon, IARC (in press).

Vainio, H., Magee, P., McGregor, D.B. & McMichael, A.J., eds (1992) *Mechanisms of Carcinogenesis in Risk Identification* (IARC Scientific Publications No. 116), Lyon, IARC.

Table 1. Agents or exposures scheduled for evaluation or re-evaluation		
Year	**Time**	**Meeting topic**
1999	February	Some metallic and non-metallic surgical implants, prosthetic devices and foreign bodies
1999	June	Ionizing radiation, Part I: X-rays, γ-rays and neutrons
1999	October	Some antiviral agents (nucleoside analogues: AZT, DDI, etc.), anticancer drugs (etoposide, etc.), and other drugs
2000	February	Some industrial chemicals
2000	June	Ionizing radiation, Part II: α- and β-particle-emitting radionuclides
2000	October	Man-made mineral fibres
2001	February	Thyrotropic agents
2001	June	Non-ionizing radiation, Part I: Static and extremely low frequency electric and magnetic fields
2003	June	Non-ionizing radiation, Part II: Radiofrequency electromagnetic fields and radar

Table 2. Agents or Exposures Proposed for Evaluation or Re-evaluation* in future *IARC Monographs*

Industrial chemicals		
Agent and present evaluation	*Priority*	*Comments*
1-Amino-2,4-dibromoanthraquinone	Low	US National Toxicology Program bioassay: positive findings in mice and rats. Representative of a class of dyes; awaiting data on other anthraquinones; evaluate as a group
1,2,3-Benzotriazole	Delete	Inadequate animal data
2,2-Bis(bromomethyl)-1,3-propanediol	High	US National Toxicology Program bioassay: positive findings in mice and rats; genotoxic
1,3-Butadiene* (2A)	Delete	See text on re-evaluation of Group 2A, 2B and 3 agents
tert-Butyl alcohol	High	Metabolite of methyl-*t*-butyl ether (additive to gasoline),which will be evaluated in October 1998; some positive carcinogenic data
Chlorine		See drinking-water disinfectants and contaminants
Chlorine dioxide		See drinking-water disinfectants and contaminants
4-Chloro-*ortho*-toluidine* (2A)	High	Two new epidemiological studies
5-Chloro-*ortho*-toluidine	High	US National Cancer Institute bioassay: positive findings in mice
Coconut oil acid, diethanolamine condensate	Low	US National Toxicology Program bioassay: positive findings in mice; equivocal findings in rats. Consider with diethanolamine
Cyanacure (1,2-bis(2-aminophenylthio)ethane)	Delete	Inadequate data
2,3-Dibromo-1-propanol	High	US National Toxicology Program bioassay: positive findings in mice and rats
Diethanolamine	Low	US National Toxicology Program bioassay: positive findings in mice, negative findings in rats. Consider with triethanolamine and *N*-nitrosodiethanolamine
1,2-Diphenylhydrazine (hydrazobenzene)	High	US National Cancer Institute bioassay: positive findings in rats and female mice. Consider with hydrazines
Ethylbenzene	High	Widespread human exposure. US National Toxicology Program bioassay: some positive findings in mice and rats
Furfuryl alcohol	Delete	Inadequate data
Glycidol (2,3-Epoxy-1-propanol)	High	US National Toxicology Program bioassay: positive findings in mice and rats; positive in all genotoxicity tests
Some glycol ethers	Low	Testing under way at US National Toxicology Program; await findings
Isobutyl nitrite	Low	Limited human exposure. US National Toxicology Program bioassay: positive findings in mice and rats
Lead and lead compounds* (2B inorganic; 3 organic)	High	New epidemiological studies on occupationally exposed workers; separate inorganic from organic lead compounds
4-Methoxyphenol	Delete	Antioxidant; induces forestomach tumours in rats. Await mechanisms meeting
Methyl ethyl ketone	Low	Widespread exposure from use as solvent. Inadequate epidemiological studies on leukaemia
N-Methylhydrazine	Low	Metabolite of gyromycin (Group 3); possible genotoxic carcinogen to be considered with other hydrazines
Monochlorobenzene	Low	High production . US National Toxicology Program bioassay: equivocal findings in rats
Naphthalene	High	Widespread human exposure; component in bitumen fumes. US National Toxicology Program bioassay in progress Limited epidemiological studies
6-Nitrobenzimidazole	Delete	US National Toxicology Program bioassay: positive findings in mice. Probably no human exposure
Nitromethane	High	Widespread human exposure. US National Toxicology Program bioassay: positive findings in mice and female rats. Not mutagenic
N-Nitrosodiethanolamine* (2B)	High	High exposure; carcinogenic in animals
PBBs* (2B)	High	New epidemiological studies
PCBs* (2A)	High	New animal and epidemiological studies; possible confounding by EMF in electrical workers. Also present in foods.
Pyridine	High	High production. US National Toxicology Program bioassay: positive findings in mice and equivocal findings in rats. Not mutagenic
Rhodium and salts	Delete	Low exposure. Inadequate animal data
Sodium hypochlorite		See drinking-water disinfectants and contaminants
Talc(not containing asbestos) * (3)	Low	Widely used; several case-control studies investigating ovarian cancer. Uncertainties in exposure data
1,1,2,2-Tetrabromoethane	Delete	Inadequate animal data
Tetrahydrofuran	Low	Wide human exposure from use as solvent. US National Toxicology Program bioassay: positive findings in female mice and male rats
ortho-Toluidine* (2B)	High	New epidemiological data
Trichloroethylene (2A)	Delete	See text on re-evaluation of Group 2A, 2B and 3 agents
Complex Mixtures		
Agent and present evaluation	*Priority*	*Comments*
Bitumens* (3)	High	New epidemiological data
Diesel engine exhausts* (2A) and diesel fuels	High	Widespread human exposure; new epidemiological data.
Gasoline engine exhausts (2B) and leaded and unleaded gasoline* (2B)	High	Widespread human exposure. New epidemiological and mechanistic data
Welding fumes* (2B)	Low	Different types of welding; only a few epidemiological studies separating stainless steel from mild steel
Occupational exposures		
Agent and present evaluation	*Priority*	*Comments*
Aluminium production* (1)	Delete	See text on re-evaluation of occupational exposures/industries
Cooks	Delete	See text on re-evaluation of occupational exposures/industries. See also air pollutants
Leather goods manufacture* (3) Leather tanning & processing (3)	Delete	See text on re-evaluation of occupational exposures/industries
Pulp and paper manufacture* (3)	Delete	See text on re-evaluation of occupational exposures/industries
Rubber industry* (1)	Low	See text on re-evaluation of occupational exposures/industries. Some data on specific processes may become available
Lifestyle factors		
Agent and present evaluation	*Priority*	*Comments*
Alcohol drinking* (alcoholic beverages 1)	High	See text on re-evaluation of Group 1 agents
Betel quid without tobacco* (3)	Delete	Inadequate data
Moist oral snuff and associated nitrosamines* (Tobacco products smokeless 1)	High	Widespread use in US and Sweden. Epidemiological data available
Pharmaceutical drugs		
Agent and present evaluation	*Priority*	*Comments*
β -Carotene (± retinol) supplements	Low	Increased risk of lung cancer in current smokers and asbestos exposed workers. Poor animal carcinogenicity studies; more research needed
Chloral hydrate* (3)	Low	Used as sedative in children; drinking-water contaminant. Animal carcinogenicity studies in progress
Dehydroepiandrosterone (DHEA)	Delete	Inadequate animal data
Melatonin (5-methoxy-*N*-acetyltryptamine)	Delete	Inadequate animal data
Phenolphthalein	High	Widespread human exposure. US National Toxicology Program bioassay: positive findings in mice and rats
Primidone	High	Long-term use as antiepileptic. US National Toxicology Program bioassay: positive findings in mice
Salicylazosulfapyridine	High	Widespread human exposure. US National Toxicology Program bioassay: positive findings in mice and rats
Somatotropin	Delete	Inadequate animal data
Triamterene	Low	US National Toxicology Program bioassay: some positive findings in mice and rats
Vitamin K	High	Widespread use in newborn children. Several epidemiological studies
Food additives, contaminants or components		
Agent and present evaluation	*Priority*	*Comments*
Aspartame	Delete	No adequate data
BHT* (3)	Delete	Mechanistic studies
tert-Butylhydroquinone	Delete	US National Toxicology Program bioassay: negative findings
Caffeine* (3)	Delete	Discuss under chemoprevention programme
3-Chloropropanediol (3-CPD)	Delete	Inadequate animal data
Crotonaldehyde	Delete	Await results of an inhalation carcinogenicity study in progress in Japan
1,3-Dichloro-2-propanol (DCP)	Delete	Inadequate animal data
Fumonisin B1* (2B)	High	Widespread presence in maize/ corn. US National Toxicology Program bioassay in progress
5-Hydroxymethylfurfural (HMF)	Delete	Limited animal data
Lactose and lactitol	Delete	Leydig cell tumours in rats; doubtful relevance to humans.
Ochratoxin A* (2B)	Delete	Epidemiological data sparse; await new data
Pristane	Delete	Inadequate animal data
Sesamol	Delete	Low human exposure. Forestomach tumours in rats and mice. Await mechanisms meeting
Sodium nitrite		See nitates/nitrites
Naturally occurring substances		
Agent and present evaluation	*Priority*	*Comments*
Cylindrospermopsin	Delete	Inadequate animal data
Microcystin-LR	Delete	Inadequate animal data
Nitrates/ Nitrites and endogenous nitrosamines formation	High	Complex issue – planning meeting needed. Many studies
3-(Nitrosomethylamino)-propionaldehyde* (3)		See betel quid without tobacco
3-(Nitrosomethylamine)propionitrile* (2B)		See betel quid without tobacco
4-(*N*-Nitrosomethylamino)-4-(3-pyridyl)-1-butanal (NNA)* (3)		Consider with moist oral snuff
4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK)* (2B)		Consider with moist oral snuff
N′ -Nitrosonornicotine* (2B)		Consider with moist oral snuff
Nodularin	Delete	Inadequate animal data
Ozone		Consider with some air pollutants and drinking-water disinfectants and contaminants
Phomopsin A	Low	Limited animal data
Protein thermolysis products	Low	Heterocyclic amines considered in 1993. New epidemiological data may become available
Environmental contaminants		
Agent and present evaluation	*Priority*	*Comments*
Air pollution (some air pollutants)	High	Many epidemiological studies show a contribution to lung cancer in humans. Convene advisory meeting. Identify specific compounds (SO_2, , NO_2, ozone, dusts) in both indoor and outdoor air
Environmental oestrogenic compounds (endocrine disruptors)	Delete	Consider specific compounds
Fluoranthene* (3)		See air pollution
3-Nitrobenzanthrone		See diesel engine exhausts
Drinking water disinfectants and contaminants		
Chloral hydrate		See pharmaceutical drugs
Chlorine	High	Widespread human exposure. Animal carcinogenicity studies from US National Toxicology Program
Chlorine dioxide	High	See above
2-Chloroacetaldehyde	High	Limited animal data
3-Chloro-4(dichloromethyl)-5-hydroxy-2(5*H*)-furanone (MX)	High	Carcinogenicity study in rats; study in mice in progress
Ozone	High	Animal carcinogenicity study from US National Toxicology Program
Sodium hypochlorite	High	See above
Pesticides		
Agent and present evaluation	*Priority*	*Comments*
Alachlor	Delete	Widespread human exposure. No published carcinogenicity data
Benomyl	Low	Widespread use. Inadequate animal data
DDT* (2B)	High	New epidemiology data
2,4-D* (chlorophenoxy herbicides, 2B)	Low	Distinguish from 2,4,5-T and other chlorophenoxy herbicides
Folpet	Low	Widespread use. Limited animal data