********** NOTICE OF GRANT AWARD **********
RESEARCH PROJECT COOPERATIVE AGREEMENT Issue Date: 09/29/2000

Department of Health and Human Services
National Institutes Of Health
NATIONAL CANCER INSTITUTE
****

Grant Number: 2 U01 CA33193-19
Principal Investigator: RICE, JERRY M PHD
Project Title: EVALUATION OF CARCINOGENIC RISKS TO HUMANS

DIRECTOR, ADMIN & FINANCE
INTER AGENCY FOR RES ON CANCER
150 COURS ALBERT THOMAS
69372 LYON CEDEX 08
FRANCE

Budget Period: 09/30/2000 - 08/31/2001
Project Period: 09/01/1985 - 08/31/2005

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $636,331(see ''Award Calculation'' in Section I) to WORLD HLTH ORG INTL AGCY RES ON CANCER in support of the above referenced project. This award is pursuant to the authority of 42 USC 241 31 USC 6305 & 6306 and is subject to terms and conditions referenced below.

Acceptance of this award including the Terms and Conditions is acknowledged by the grantee when funds are drawn down or otherwise obtained from the grant payment system.

Award recipients are responsible for reporting inventions derived or reduced to practice in the performance of work under this grant. Rights to inventions vest with the grantee organization provided certain requirements are met and there is acknowledgement of NIH support. In addition, recipients must ensure that patent and license activities are consistent with their responsibility to make unique research resources developed under this award available to the scientific community, in accordance with NIH policy. For additional information, please visit http://www.iedison.gov.

I ou have any questions about this award, please contact the individual(s) referenced in t.. information below.

Sincerely yours,

Crystal Wolfrey
Grants Management Officer
NATIONAL CANCER INSTITUTE

See additional information below

SECTION I - AWARD DATA - 2 U01 CA33193-19

AWARD CALCULATION (U.S. Dollars):

Salaries and Wages	$283,815
Fringe Benefits	$108,545
Personnel Costs	$392,360
Consultant Services	$42,500
Travel Costs	$3,315
Other Costs	$124,950
Direct Costs	$563,125
F&A Costs	$73,206
APPROVED BUDGET	$636,331
TOTAL	$636,331

Recommended future year total cost support, subject to the availability of funds and satisfactory progress of the project, is as follows.

20
2
22
23 (b)(5) [redacted]

FISCAL INFORMATION:
CFDA Number: 93.393
EIN: 1900210016A1
Document Number: U1CA33193E

IC /	CAN	/	FY2000	/	FY2001	/	FY2002	/	FY2003	/	FY2004
CA /	8423133	/	636,331	/	(b)(5) [redacted]						

NIH ADMINISTRATIVE DATA:
PCC: 38AI3133 / OC: 41.4M /Processed: WOLFREYC 000927 1104

SECTION II - PAYMENT/HOTLINE INFORMATION - 2 U01 CA33193-19
RMS
For Payment and HHS Office of Inspector General Hotline Information, see the NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm

SECTION III - TERMS AND CONDITIONS - 2 U01 CA33193-19

This award is based on the application submitted to, and as approved by, the NIH on the above-titled project and is subject to the terms and conditions incorporated either directly or by reference in the following:

a. The grant program legislation and program regulation cited in this Notice of Grant Award.
b. The restrictions on the expenditure of federal funds in appropriations acts, to the extent those restrictions are pertinent to the award.
c. 45 CFR Part 74 or 45 CFR Part 92 as applicable.
d. The NIH Grants Policy Statement, including addenda in effect as of the beginning date of the budget period.
e. This award notice, INCLUDING THE TERMS AND CONDITIONS CITED BELOW.

(see NIH Home Page at http://grants.nih.gov/grants/policy/awardconditions.htm for certain references cited above.)

This grant is excluded from Expanded Authorities.

Treatment of Program Income:
Other Research (Add/Deduct Option)

2 U01 CA 33193-19

TERMS OF AWARD

INFORMATION This award is issued as a Cooperative Agreement, a financial assistance mechanism which requires cooperation between the awardee and the National Cancer Institute (NCI). The following Terms of Cooperation include (1) the Programmatic Responsibilities of the Awardees, the Nature of Assistance by NCI Staff, Collaborative Responsibilities, and Arbitration Procedures (Attachment 1); and (2) the following administrative terms.

These special Terms and Conditions of Award are in addition to and not in lieu of otherwise applicable OMB administrative guidelines, Federal Regulations, including HHS Grant Administration Regulations at 42 CFR Part 52, 45 CFR Parts 74 and 92, and other HHS, PHS, and NIH Grant Administration policy statements.

INFORMATION In accordance with the National Cancer Institute's (NCI's) implementation of the National Institutes of Health core principles for FY 2000 funding decisions, NCI staff have determined that critical program objectives can be met with the funding of this grant at 85% of the corrected recommended level*. Future year committed levels** have been adjusted accordingly.

* corrected recommended level: Summary Statement recommended level of support with arithmetic errors corrected, with adjustments made in accordance with applicable grant policies as appropriate, direct salaries and associated fringe benefits adjusted to comply with the $141,300 salary cap, and no more than a 3% cost of living factor used to calculate the level of support recommended for each future budget period.

** committed level: The level of support calculated by applying the NCI funding plan to the corrected recommended level for each budget category for all years of the project period.

INFORMATION Future year total cost commitments appearing on the award notice under "Recommended Future Year Total Cost Support" have been calculated by applying the negotiated facilities and administrative cost rate(s) in effect at the time of this FY 2000 award to the committed total direct cost level for each future year.

INFORMATION Although the budget period start date for this award is September 30, 2000, this award includes funds for 12 months of support. Future year budget periods will cycle on September 1. Allowable preaward costs may be charged to this award, in accordance with the conditions outlined in the NIH Grants Policy Statement, (October 1998), and with institutional requirements for prior approval.

INFORMATION Included in the Notice of Grant Award is a spreadsheet showing the committed level of funding for each year of this competitive segment. Spreadsheets showing the "Corrected Recommended levels" of funding and spreadsheets for individual projects and/or consortia (if applicable) are available upon request from the Grants Management Specialist referenced in the terms of award.

INFORMATION For administrative and management concerns, contact the Grants Management Specialist, Crystal Wolfrey, at (301) 496-8634, or via e-mail at crystal.wolfrey@nih.gov For programmatic and scientific concerns, contact the Program Director, Dr. David Longfellow, at (301) 496-5471.

INFORMATION In a continuing effort to provide exceptional customer service, the NCI Grants Administration Branch has set up a Feedback address on its web site (http://www.nci.nih.gov/admin/gab/index.htm). General concerns and issues related to NCI grants policies, procedures, and practices can be sent to the Customer Liaison using this feature. Specific questions or concerns related to this grant should be addressed to the

Grants Management Specialist listed in the Terms of Award.

DAVID G. LONGFELLOW, Program Official 301-496-5471 dl58s@nih.gov
Crystal Wolfrey, Grants Specialist (301) 496-8634 cw104j@nih.gov

SPREADSHEET
GRANT NUMBER: 2 U01 CA33193-19
P.I.: RICE, JERRY M
INSTITUTION: WORLD HLTH ORG INTL AGCY RES ON CANCER

	YEAR 19	YEAR 20	YEAR 21	YEAR 22	YEAR 23
Salaries and Wages	283,815	(b)(5)			
Fringe Benefits	108,545				
Personnel Costs	392,360				
Consultant Services	42,500				
Travel Costs	3,315				
Other Costs	124,950				
TOTAL DC	563,125				
TOTAL F&A	73,206				
TOTAL COST	636,331				

	YEAR 19	YEAR 20	YEAR 21	YEAR 22	YEAR 23
F&A Cost Rate 1	13.00%	(b)(5)			
F&A Cost Base 1	563,125				
F&A Costs 1	73,206				

AA

Department of Health and Human Services
Public Health Service

6 5 5 8 9 6 **nt Applic[illegible]n 1**

low instructions carefully.
cter length restrictions indicated on s.

NAME: RICE, JERRY M
APPL NO:2 U01 CA33193-19 **COUNCIL: 01/00**
DUAL: **RCVD:07-01-99**
IRG: ZCA1-SRC(99)

1. TITLE OF PROJECT
Evaluation of Carcinogenic Risks to Humans

2. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT [X] NO [ ] YES *(If "Yes," state number and title)*
Number: Title:

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR New Investigator [ ] YES

3a. NAME *(Last, first, middle)*
Rice, Jerry Mercer

3b. DEGREE(S)
Ph.D.

3c. SOCIAL SECURITY NO. *Provide on Form Page KK.*

3d. POSITION TITLE
Chief of Unit

3e. MAILING ADDRESS *(Street, city, state, zip code)*
International Agency for
Research on Cancer
150 cours Albert Thomas
69372 Lyon (Cédex 08)
France

3f. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Carcinogen Ident. & Evaluation

3g. MAJOR SUBDIVISION

3h. TELEPHONE AND FAX *(Area code, number and extension)*
TEL: (+33) 472 73 84 76
FAX: (+33) 472 73 83 19

E-MAIL ADDRESS: rice@iarc.fr

4. HUMAN SUBJECTS [X] No [ ] Yes
4a. If "Yes," Exemption no. or IRB approval date { Full IRB or Expedited Review
4b. Assurance of compliance no.

5. VERTEBRATE ANIMALS [X] No [ ] Yes
5a. If "Yes," IACUC approval date
5b. Animal welfare assurance no.

6. DATES OF PROPOSED PERIOD OF SUPPORT *(month, day, year—MM/DD/YY)*		7. COSTS REQUESTED FOR INITIAL BUDGET PERIOD		8. COSTS REQUESTED FOR PROPOSED PERIOD OF SUPPORT	
From	Through	7a. Direct Costs ($)	7b. Total Costs ($)	8a. Direct Costs ($)	8b. Total Costs ($)
03/01/00	02/28/05	711 500	803 995	3 676 435	4 154 372

9. APPLICANT ORGANIZATION
Name International Agency
Address for Research on Cancer
150 cours Albert Thomas
69372 Lyon (Cédex 08)
France

10. TYPE OF ORGANIZATION International
Public: → [ ] Federal [ ] State [ ] Local
Private: → [ ] Private Nonprofit
Forprofit: → [ ] General [ ] Small Business

11. ORGANIZATIONAL COMPONENT CODE 60

12. ENTITY IDENTIFICATION NUMBER
1900210016A1
DUNS NO. *(if available)*

Congressional District

13. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name M.P. Johnson
Title Director, Admin. & Finance
Address International Agency for
Research on Cancer
150 cours Albert Thomas
69372 Lyon (Cédex 08), France
Telephone (+33) 472 73 84 67
Fax (+33) 472.73 85 75
E-mail daf@iarc.fr

14. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name P. Kleihues
Title Director
Address International Agency for
Research on Cancer
150 cours Albert Thomas
69372 Lyon (Cédex 08), France
Telephone (+33) 472 73 84 85
Fax (+33) 472 73 85 75
E-mail kleihues@iarc.fr

15. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.

SIGNATURE OF PI / PD NAMED IN 3a. *(In ink. "Per" signature not acceptable.)*
Jerry M. Rice

DATE
28 June 1999

16. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with Public Health Service terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

SIGNATURE OF OFFICIAL NAMED IN 14. *(In ink. "Per" signature not acceptable.)*
Paul Kleihues

DATE
June 24 1999

DESCRIPTION. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

The objectives of the IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans are to critically review and evaluate the strength of the total published scientific evidence for carcinogenic risk from biological, physical, and chemical agents, complex mixtures, and exposure circumstances to which humans are exposed, and to publish these reviews and evaluations in book form as IARC Monographs. The long-term goal is to provide evaluations of all significant environmental contributing causes of human cancer, and to re-evaluate those for which evidence is incomplete at the time of initial evaluation whenever new findings provide additional evidence which may change a previous evaluation. A further goal for the immediate future is to supplement the existing hard-copy publications by complete, searchable electronic versions that will be available both on-line by internet and as CD-ROM.

The Preamble to the IARC Monographs defines the guiding principles for making evaluations of carcinogenicity on the basis of epidemiologic studies, bioassays for carcinogenicity in experimental animals, and other relevant data (e.g., toxicity, metabolism, genetic toxicology, and mechanisms of carcinogenic action). Nominations for evaluations are solicited worldwide and prioritized by ad-hoc international advisory groups of scientific and public health experts at intervals of approximately five years. The Programme sponsors scientific meetings on carcinogenic mechanisms and other subjects relevant to evaluations of carcinogenicity, and publishes (in electronic form on the Internet) a Directory of Agents being Tested for Carcinogenicity worldwide, to facilitate communication among scientists and to reduce unnecessary duplication of effort.

Each volume of the IARC Monographs results from the deliberations of an international working group of 20-25 experts in cancer epidemiology, experimental carcinogenesis and related disciplines from 8-12 countries which meets in Lyon for one week; three meetings are held each year. The Monographs are of value to scientists and public health officials as authoritative summaries of the published literature; to regulatory authorities as one source of information on which to base risk assessments and risk management initiatives; and to private individuals as a reliable reference text.

PERFORMANCE SITE(S) *(organization, city, state)*

International Agency for Research on Cancer
Lyon, France

KEY PERSONNEL. See instructions on Page 11. *Use continuation pages as needed* to provide the required information in the format shown below.

Name	Organization *	Role on Project
J. M. Rice, Ph.D.	CIE	Principal investigator. Overall planning and supervision of the Monographs programme; selection of priorities for future consideration and selection of experts.
R. A. Baan, Ph.D.	CIE	Assistance in organization of meetings and in planning, preparation and checking of sections on genetic effects. Responsible officer for one Monographs meeting each year.

* Organizational Unit within the International Agency for Research on Cancer:
CIE, Unit of Carcinogen Identification and Evaluation

CONTINUE ON PAGE: STAY WITHIN MARGINS INDICATED

D. McGregor, Ph.D.	CIE	Assistance in organization of meetings and in the planning, preparation and checking of sections on biochemical toxicology. Responsible officer for one Monographs meeting each year.
J. D. Wilbourn, B.Sc.	CIE	Assistance in selection of Monographs topics and in the planning, preparation and checking of sections on animal carcinogenicity. Responsible officer for one Monographs meeting each year.
C. Partensky, M.Sc.	CIE	Coordination of data on chemical properties of agents and on human exposures; technical editing and checking of documents for accuracy.

Type the name of the principal investigator/program director at the top of each printed page and each continuation page. (For type specifications, see instructions on page 6.)

RESEARCH GRANT

TABLE OF CONTENTS

*Type density and type size of the entire application must conform to limits provided in instructions on page 6.

Appendix *(Five collated sets. No page numbering necessary for Appendix.)*
Number of publications and manuscripts accepted or submitted for publication *(not to exceed 10)* 3
Other items *(list):*

[x] Check if Appendix is included

Internet posting: Overall Evaluations of Carcinogenicity to Humans
Internet posting: IARC Monographs Volume 71 (announcement)

DD

Principal Investigator/Program Director *(Last, first, middle)*: Rice, Jerry Mercer

DETAILED BUDGET FOR INITIAL BUDGET PERIOD
DIRECT COSTS ONLY

FROM: 01/03/00 THROUGH: 28/02/01

PERSONNEL *(Applicant organization only)*

NAME	ROLE ON PROJECT	TYPE APPT. *(months)*	% EFFORT ON PROJ.	INST. BASE SALARY	DOLLAR AMOUNT REQUESTED *(omit cents)* SALARY REQUESTED	FRINGE BENEFITS	TOTALS
J. Rice	Principal Investigator	(b)(4), (b)(6)	(b)(4), (b)(6)	(b)(4), (b)(6)	-	-	-
(vacant; vice M. Blettner)	Scientist				70 000	44 400	114 400
D. McGregor	Scientist				82 400	26 000	108 400
R. Baan	Scientist				63 300	20 000	83 300
Y. Grosse	Scientist				45 600	14 400	60 000
M. Lézère	Secretary				44 700	14 100	58 800
S. Ruiz	Clerk				27 900	8 800	36 700
SUBTOTALS →					333 900	127 700	461 600

CONSULTANT COSTS
Preparation of draft monographs 20 000
Editing of monographs 30 000 — 50 000

EQUIPMENT *(Itemize)* — 0

SUPPLIES *(Itemize by category)* — 0

TRAVEL One trip by principal investigator to USA for a scientific meeting and to consult with NCI program officials — 3 900

PATIENT CARE COSTS — INPATIENT
OUTPATIENT

ALTERATIONS AND RENOVATIONS *(Itemize by category)*

OTHER EXPENSES *(Itemize by category)*

See justifications pages 6, 7 and 8. — 147 000 ~~196 000~~

SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD — $ ~~711 500~~

CONSORTIUM/CONTRACTUAL COSTS — DIRECT COSTS — 0
FACILITIES AND ADMINISTRATION COSTS — 0

TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD *(Item 7a, Face Page)* → $ ~~711 500~~ 661 500

DD

BUDGET FOR ENTIRE PROPOSED PERIOD OF SUPPORT
DIRECT COSTS ONLY

BUDGET CATEGORY TOTALS		INITIAL BUDGET PERIOD *(from Form Page 4)*	ADDITIONAL YEARS OF SUPPORT REQUESTED 2nd	3rd	4th	5th
PERSONNEL: *Salary and fringe benefits Applicant organization only*		461 600	456 872	475 147	494 153	513 919
CONSULTANT COSTS		50 000	50 500	51 005	51 515	52 030
EQUIPMENT		0	0	0	0	0
SUPPLIES		0	0	0	0	0
TRAVEL		3 900	3 939	3 978	4 018	4 058
PATIENT CARE COSTS	INPATIENT	0	0	0	0	0
	OUTPATIENT	0	0	0	0	0
ALTERATIONS AND RENOVATIONS		0	0	0	0	0
OTHER EXPENSES		196 000	197 960	199 941	201 940	203 960
SUBTOTAL DIRECT COSTS		711 500	709 271	730 071	751 626	773 967
CONSORTIUM/ CONTRACTUAL COSTS	DIRECT					
	F&A					
TOTAL DIRECT COSTS		711 500	709 271	730 071	751 626	773 967

TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PERIOD OF SUPPORT *(Item 8a, Face Page)* → $ 3 676 435

JUSTIFICATION. Follow the budget justification instructions exactly. Use continuation pages as needed.

Foreign Justification: All programs of the International Agency for Research on Cancer are located in Lyon, France. The IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans is unique as a multidisciplinary, international consensus approach to carcinogenic hazard evaluation. The Monographs are considered authoritative world-wide and are of use in many countries including the USA, both as a basis for undertaking carcinogenic risk analysis and as a reference data base for scientists engaged in research on environmental carcinogens of all kinds.

Budget Justification (initial budget period, 1 March 2000 – 28 February 2001; total period of support requested, 5 years): By agreement with the NCI, the Cooperative Agreement provides salaries for specified members of the Monographs Programme staff, and support for the conduct of 2 of the 3 Monographs meetings held each year. Support for the third Monographs meeting and for scientific and programme advisory meetings is obtained from other sources. The budget requested essentially represents the cost of maintaining the ongoing programme.

Costs for years 2-5 are calculating assuming an annual increase of 4 per cent in personnel costs and of 1 per cent for other costs (see details p. 7).

ANNUAL DETAILS OF BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD, 1 MARCH 2000 TO 28 FEBRUARY 2005

	1 March 2000 28 February 2001	1 March 2001 28 February 2002	1 March 2002 28 February 2003	1 March 2003 29 February 2004	1 March 2004 28 February 2005	TOTAL PERIOD
PERSONNEL						
. 4 scientists	366,100	357,552	371,854	386,728	402,197	**1,884,431**
. 2 secretarial support	95,500	99,320	103,293	107,425	111,722	**517,260**
	461,600	**456,872**	**475,147**	**494,153**	**513,919**	**2,401,691**
CONSULTANT						
. Preparation of draft monographs	20,000	20,200	20,402	20,606	20,812	**102,020**
. Editing of monographs	30,000	30,300	30,603	30,909	31,218	**153,030**
	50,000	**50,500**	**51,005**	**51,515**	**52,030**	**255,050**
TRAVEL	**3,900**	**3,939**	**3,978**	**4,018**	**4,058**	**19,893**
OTHER DIRECT COSTS						
. Working groups	108,000	109,080	110,171	111,273	112,386	**550,910**
. Printing of monographs	30,000	30,300	30,603	30,909	31,218	**153,030**
. Distribution costs of free monographs	20,000	20,200	20,402	20,606	20,812	**102,020**
. Reprint requests	16,000	16,160	16,322	16,485	16,650	**81,617**
. Books, journals and reproduction costs	16,000	16,160	16,322	16,485	16,650	**81,617**
. Information databases on CD-ROM (Toxline & Medline)	6,000	6,060	6,121	6,182	6,244	**30,607**
	196,000	**197,960**	**199,941**	**201,940**	**203,960**	**999,801**
TOTAL DIRECT COSTS IN US$	**711,500**	**709,271**	**730,071**	**751,626**	**773,967**	**3,676,435**

Consultant expenses (per year):
Preparation of draft monographs: $400/expert x 25 experts x 2 working groups = $ 20,000
Editing of monographs: $15,000/monograph x 2 monographs = $ 30,000
Total $50,000

Travel: one trip per year by the principal investigator to the USA to visit the program official in the NCI and to attend an international meeting in the field of cancer research (economy air fare plus 7 days per diem @ $255/day): $3900

Other expenses:

Working groups (travel + per diem for non-U.S. govt participants)	$108,000
Printing and free-list distribution costs, 2 monographs per year	$ 50,000
Literature sources: books & journals, Medline/Toxline on CD-ROM, reproduction costs	$ 38,000

Personnel: Only the Principal Investigator and staff for whom salary is requested are listed above. All staff involved in the project, together with their roles and time devoted to the project, are listed at the end of the justification section.The vacant position for a senior scientist is to replace Dr Maria Blettner, an epidemiologist and biostatistician who left the Programme in February 1999 to accept a professorship in Germany.

The increase in staff for whom salary is being sought, from 2 scientists and 2 clerical support staff to 4 scientists and 2 clerical support staff, is needed to keep pace with the exponential growth in scientific literature that must be reviewed (and then checked for accuracy) in each Monograph volume. Monographs are now progressively much larger volumes than before. For example, in 1995, the first year of the current cooperative agreement, three volumes were produced totalling 1,365 pages. In 1996, three volumes comprised 1,516 pages and in 1997, three volumes comprised 1,696 pages. In 1998, volume 71 alone (a special effort involving the updating and re-evaluation of 111 organic compounds) consisted of 1,586 pages, and two other volumes resulting from meetings conducted during that year will each have approximately 600 pages.

Staff are paid either by this cooperative agreement, or by the regular IARC budget; there are no multiple-source positions. In addition to the staff paid by the Cooperative Agreement, 3 scientists and 3 support staff are paid by the regular budget.

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

Applicant Organization Employees involved in this Project

Name	Role on project	Appointment: Months	Per cent Effort
J. M. Rice, Ph.D. Scientist; Chief, CIE [a]	Principal investigator. Overall planning and supervision of the Monographs programme; selection of priorities for future consideration and selection of experts.	(b)(4), (b)(6)	(b)(4), (b)(6)
R. A. Baan, Ph.D. Scientist, CIE	Assistance in organization of meetings and in planning, preparation and checking of sections on genetic effects. Responsible officer for one Monographs meeting each year.		
D. McGregor, Ph.D. Scientist, CIE	Assistance in organization of meetings and in the planning, preparation and checking of sections on biochemical toxicology. Responsible officer for one Monographs meeting each year.		

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

J. D. Wilbourn, B.Sc. Scientist, CIE	Assistance in selection of Monographs topics and in the planning, preparation and checking of sections on animal carcinogenicity. Responsible officer for one Monographs meeting each year.
C. Partensky, M.Sc. CIE	Coordination of data on chemical properties of agents and on human exposures; technical editing and checking of documents for accuracy.
Y. Grosse, Ph.D. Scientist, CIE	Assistance in conduct of meetings and in checking of data prior to publication.
M. Lezere Clerk, CIE	Maintenance of website, typing of documents during meetings, preparing final documents for the printer.
J. Mitchell Secretary, CIE	Principal typist. Coordinates document production before and after meetings.
S. Reynaud Secretary, CIE	Unit secretary (CIE). General secretarial support.
S. Ruiz Clerk, CIE	Literature retrieval for document preparation. Assists in maintaining website.
D. Mietton Technical Assistant, CIE	Principal archivist. Supervises literature searches and computerized archiving of documents used in preparing Monographs.
P. Boffetta, M.D. Chief, ECE	To advise and assist in the preparation and checking of sections on epidemiology.
E. Cardis, Ph.D. Chief, RCA	To advise on biostatistics, cancer epidemiology and on organization of Monographs on physical agents.
M. Friesen, Ph.D. Scientist, GEI	To advise on chemistry and chemical analysis.
J. Hall-Posner, Ph.D. Scientist, MCA	To advise on molecular biology and biochemistry.
V. Krutovskikh, M.D. Scientist, MSC	To advise on histopathology and on bioassays for carcinogenicity.
C. Malaveille, Ph.D. Scientist, ECR	To advise on genetic and related effects and to assist in meetings.

(b)(4), (b)(6)

[a] Organizational Units within the International Agency for Research on Cancer:

CIE, Unit of Carcinogen Identification and Evaluation
ECE, Unit of Environmental Cancer Epidemiology

ECE, Unit of Environmental Cancer Epidemiology
RCA, Unit of Radiation and Cancer
GEI, Unit of Gene-Environment Interactions
MCA, Unit of Mechanisms of Carcinogenesis
ECR, Unit of Endogenous Cancer Risk Factors

[b] Temporary appointment; may not exceed 11 months at a time.

CONTINUA)N PAGE: STAY WITHIN MAF NS INDICATED

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2
Photocopy this page or follow this format for each person

NAME	POSITION TITLE
Rice, Jerry, Mercer	Unit Chief

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Wesleyan University, Middletown, CT, USA	BA	1962	Chemistry
Harvard University, Cambridge, MA, USA	PhD	1966	Biochemistry

RESEARCH AND PROFESSIONAL EXPERIENCE. Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

1966-1996	US Public Health Service Commissioned Corps (Reserve Corps, 1966-1971, Regular Corps, 1971-1996), Serial number 26440. Research Officer Group, 1991-1996, Highest grade Scientist Director (Captain; 0-6)
1966-1968	Investigator, Cytogenetics and Cytology Section, Biology Branch, Division of Cancer Cause and Prevention (DCCP), National Cancer Institute (NCI)
1968-1973	Senior Investigator, Bioassay Section, Experimental Pathology Branch, DCCP, NCI
Sept. 73-Sept 74	Acting Chief, Experimental Pathology Branch, DCCP, NCI
Oct 74-April 81	Head, Perinatal Carcinogenesis Section, Laboratory of Experimental Pathology, DCCP
May 81-March 94	Chief, Laboratory of Comparative Carcinogenesis, Division of Cancer Etiology, NCI
April 94-Sept. 95	Associate Director, NCI (Frederick Cancer Research and Development Center) and Acting Director, Division of Cancer Etiology, NCI
Oct. 95-May 96	Chief, Laboratory of Comparative Carcinogenesis, Division of Basic Sciences, NCI
June 1996-Present	Chief, Unit of Carcinogen Identification and Evaluation, International Agency for Research on Cancer, Lyon, France

List of publications

Diwan, B. A., Henneman, J. R., Rice, J M , & Nims, R W Enhancement of thyroid and hepatocarcinogenesis by 1,4-bis[2-(3,5-dichloropyridyloxy)]-benzene in rats at doses that cause maximal induction of CYP2B *Carcinogenesis* **17** 37-43, 1996

Muñoz, E.F., Diwan, B.A , Calvert, R.J , Weghorst, C.M., Anderson, J , Rice, J.M., & Buzard, G.S , Transplacental mutagenicity of cisplatin: H-*ras* codon 12 and 13 mutations in skin tumors of SENCAR mice *Carcinogenesis* **17**. 2741-2745, 1996

Giurgiovich, A.J., Diwan, B A , Oliverio, O A , Anderson, L.M , Rice, J M., & Poirier, M C.. Elevated mitochondrial cisplatin-DNA adduct levels in rat tissues after transplacental cisplatin exposure. *Carcinogenesis* **18**· 93-96, 1997

Sipowicz, M.A., Weghorst, C M , Shiao, Y -H , Buzard, G S , Calvert, R J , Anver, M.R , Anderson, L.M., & Rice, J M.. Lack of *p53* and *ras* mutations in *Helicobacter hepaticus*-induced liver tumours in A/JCr mice *Carcinogenesis* **18**, 233-236, 1997

Giurgiovich, A J , Anderson, L M , Jones, A B , Dove, L F , Moskal, T J , Rice, J M , Olivero, O A & Poirier, M C Transplacental cisplatin exposure induces persistent fetal mitochondrial and genomic DNA damage in patas monkeys *Reprod Toxicol* **11** 95-100, 1997

Kaufmann, W K , Byrd, L L , Palmieri, D , Nims, R W & Rice, J M TGF-alpha sustains clonal expansion by promoter-dependent, chemically initiated rat hepatocytes *Carcinogenesis* **18**, 1381-1387, 1997

Shiao, Y -H , Diwan, B A , Perantoni, A O , Calvert, R J , Zbar, B , Lerman, M I , & Rice, J M Polymerase chain reaction-single strand conformation polymorphism analysis for the *VHL* gene in chemically induced kidney tumors of rats using intron-derived primers *Mol Carcinog* **19** 230-235, 1997

Sipowicz, M A , Chomarat, P , Diwan, B A , Anver, M A , Awasthi, Y C , Ward, J M , Rice, J M , Kasprzak, K S , Wild, C P & Anderson, L M Increased oxidative DNA damage and hepatocyte overexpression of specific cytochrome P450 isoforms in hepatitis of mice infected with *Helicobacter hepaticus Am J Pathol* **151** 933-941, 1997

Olivero, O A , Anderson, L M , Diwan, B A , Haines, D C , Harbaugh, S W , Moskal, T J , Jones, A B , Rice, J M , Riggs, C W , Logsdon, D , Yuspa, S H & Poirier, M C Transplacental effects of 3'-azido-2',3'-dideoxythymidine (AZT) Tumorigenicity in mice and genotoxicity in mice and monkeys *J Natl Cancer Inst* **89** 2179-2190, 1997

Palli, D , Caporaso, N E , Shiao, Y -H , Saieva, C , Amorosi, A , Masala, G , Rice, J M , & Fraumeni, J F Jr Diet, *Helicobacter pylori* and *p53* mutations in gastric cancer A molecular epidemiology study in Italy *Cancer Epidemiol Biomarkers Prev* **6** 1065-1069, 1997

Zhang, Z , Diwan, B A , Anderson, L M , Logsdon, D , Olivero, O A Haines, D C , Rice, J M , Yuspa, S H & Poirier, M C Skin tumorigenesis and Ki-*ras* and Ha-*ras* mutations in tumors from adult mice exposed in utero to 3'-azido-2',3'-dideoxythymidine *Mol Carcinog* **23** 45-51, 1998

Shiao, Y -H , Rice, J M , Anderson, L M , Diwan, B A , & Hard, G C von Hippel-Lindau gene mutations in *N*-nitrosodimethylamine-induced rat renal epithelial tumours *J Natl Cancer Inst* **90** 1720-1723, 1998

Review papers and book chapters

Vainio, H & Rice, J M Editorial Beryllium revised *J Occup Environ Med* **39** 203-204, 1997

Cardis, E & Rice, J M Criteria for health risk assessment within the international EMF project *In* Bernhardt, J H , Matthes, R , & Repacholi, M H (Eds), *Non-Thermal Effects of RF Electromagnetic Fields* Munich, International Commission on Non-Ionizing Radiation Protection, 1997, pp 35-44

Wilbourn, J D , McGregor, D B , Partensky, C , & Rice, J M Meeting Report IARC evaluates silica and related substances *Environ Health Perspect* **105** 756-759, 1997

Cardis, E & Rice, J M Criteria for health risk assessment within the international EMF project *In* Matthes, R , Bernhardt, J H , & Repacholi, M H (Eds), *Biological Effects of Static and ELF Electric and Magnetic Fields* Munich, International Commission on Non-Ionizing Radiation Protection, 1997, pp 31-40

McGregor, D B , Partensky, C , Wilbourn, J , & Rice, J M An IARC evaluation of polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans as risk factors in human carcinogenesis *Environ Health Perspect* **106** (Suppl 2) 755-760, 1998

Sasco, A J & Rice, J M Editorial IARC evaluation of the carcinogenicity of antioestrogens Basic facts and rationale for appropriate use in medicine *Presentations in Focus* Medical Education Network (Europe) Ltd, 1998, Issue 2, pp 3-6

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2
Photocopy this page or follow this format for each person

NAME: Baan, Robert A

POSITION TITLE: Scientist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Faculty of Sciences, University of Leiden, The Netherlands	MSc	1967-72	Chemistry/ Biochemistry
Laboratory of Biochemistry, University of Leiden	Ph.D.	1973-77	Biochemistry
Division of Biology and Medicine, Brown University Providence RI USA	Post-doctoral training	1977-79	Biochemistry

RESEARCH AND PROFESSIONAL EXPERIENCE Concluding with present position, list, in chronological order, previous employment, experience, and honors Include present membership on any Federal Government public advisory committee List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application If the list of publications in the last three years exceeds two pages, select the most pertinent publications **DO NOT EXCEED TWO PAGES.**

Sept. 1979-Dec. 1986	Research scientist, Department of Genetic Toxicology, TNO Medical Biological Laboratory, Rijswijk, The Netherlands
Jan. 1987-May 1995	Head, Department of Genetic Toxicology, TNO Medical Biological Laboratory, Rijswijk, The Netherlands
June 1995-Sept. 1998	Senior scientist Genetic Toxicology, TNO Nutrition and Food Research Institute, Zeist, The Netherlands
Oct 1998- present	Scientist, Unit of Carcinogen Identification and Evaluation, International Agency for Research on Cancer, Lyon, France

List of publications

Fichtinger-Schepman AMJ, Welters MJP, Van Dijk-Knijnenburg HCM, Van der Sterre MLT, Tilby MJ, Berends F, (1996) Detection of adducts formed upon treatment of DNA with cisplatin and carboplatin. In: Platinum and other metal coordination compounds in cancer chemotherapy 2, Pinedo HM, Schornagel JH, Eds, Plenum Press, New York and London, pp 107-119

Van Delft JHM, Luiten-Schuite A, Souliotis V, Kyrtopoulos SA, Keizer HJ, Ouwerkerk J, Baan RA (1996) N7-methyl-guanine and O^6-methylguanine levels in DNA of white blood cells from cancer patients treated with dacarbazine Biomarkers 1, 94-98

Farmer PB, Sepai O, Lawrence R, Autrup H, Sabro Nielsen P, Vestergård AB, Waters R, Leuratti C, Jones NJ, Stone J, Baan RA, Van Delft JHM, Kyrtopoulos SA, Souliotis VL, Theodorakopoulos N, Bacalis NC, Natarajan AT, Tates AD, Haugen A, Andreassen Å, Øvrebø S, Shuker DEG, Amaning KS, Schouft A, Ellul A, Garner RC, Dingley KH, Abbondandolo A, Merlo F, Cole J, Aldrich K, Beare D, Capulas E, Rowley G, Waugh APW, Povey AC, Kirsch-Volders M, Van Hummelen P, Castelain Ph (1996) Biomonitoring human exposure to enviromental carcinogenic chemicals (Final Report of STEP-Biomonitoring Project EV5V-CT91-0013) Mutagenesis 11, 363-381

Wolterbeek APM, Ciotti MALT, Schoevers EJ, Roggeband R, Baan RA, Feron VJ, Rutten AAJJL (1996) Effect of Vitamin A on benzo(a)pyrene-induced cell proliferation in hamster tracheal epithelium cultured in different media. Toxicology in vitro 10, 359-369

Roggeband R, Wolterbeek APM, Van den Berg PTM, Rutten AAJJL, Feron VJ, Baan RA (1996) Cell proliferation and DNA adducts in hamster tracheal epithelium exposed to benzo(a)pyrene in organ culture. Toxicology in vitro 10, 371-375

Mientjes EJ, Steenwinkel M-JST, Van Delft JHM, Lohman PHM, Baan RA (1996) Comparison of the X-gal- and P-gal-based systems for screening of mutant λlacZ phages originating from the transgenic mouse strain 40.6. Mutation Res 360, 101-106

Mientjes EJ, Hochleitner K, Luiten-Schuite A, Van Delft JHM, Thomale J, Berends F, Rajewsky MF, Lohman PHM, Baan RA (1996) Formation and persistence of O^6-ethylguanine in genomic and transgene DNA of liver and brain of λlacZ transgenic mice treated with N-ethyl-N-nitrosourea Carcinogenesis 17, 2449-2454

Frijhoff AFW, Bol SA, Groot PC, Van Zeeland AA, Demant P, Baan RA (1996) Production of a congenic mouse train carrying the hairless mutation in a 129/Ola genetic background a suitable strain to generate transgenic and knockout mice for studies on toxicity and carcinogenesis of skin Mouse Genome 4, 866-867

Van Delft JHM, Steenwinkel M-JST, De Groot AJL, Van Zeeland AA, Eberle-Adamkiewicz G, Rajewsky MF, Thomale J, Baan RA (1997) Determination of N7- and O^6-methylguanine in rat liver DNA after oral exposure to hydrazine by use of immunochemical and electrochemical detection methods Fundam Appl Toxicol 35, 131-137

Van Delft JHM, Bergmans A, Baan RA (1997) Germ cell mutagenesis in λlacZ transgenic mice treated with ethylating and methylating agents, comparison with specific-locus test Mutation Res 388, 165-173

Frijhoff AFW, Rebel H, Mientjes EJ, Kelders MCJM, Steenwinkel M-JST, Baan RA, Van Zeeland AA, Roza L (1997) UVB-induced mutagenesis in hairless λlacZ-transgenic mice Environm and Molecular Mutagenesis 29, 136-142

Welters MJP, Fichtinger-Schepman AMJ, Baan RA, Hermsen MAJA, Van der Vijgh WJF, Cloos J, Braakhuis BJM (1997) Relationship between the parameters cellular differentiation, doubling time and platinum accumulation and cisplatin sensitivity in a panel of head and neck cancer cell lines Int J Cancer 71, 410-415

Baan RA, Steenwinkel M-JST, Van Asten JG, Roggeband R, Van Delft JHM (1997) The use of benzo(a)pyrene diolepoxide-modified DNA standards for adduct quantification in ^{32}P-postlabelling to assess exposure to polycyclic aromatic hydrocarbons application in a biomonitoring study Mutation Res 378 (Special Issue ^{32}P-postlabeling, DH Phillips, Ed), 41-50

Welters MJP, Maliepaard M, Jacobs-Bergmans AJ, Baan RA, Schellens JHM, Ma J, Van der Vijgh WJF, Braakhuis BJM, Fichtinger-Schepman AMJ (1997) Improved ^{32}P-postlabelling assay for the quantification of the major platinum-DNA adducts Carcinogenesis 18, 1767-1774

Mientjes EJ, Luiten-Schuite A, Van der Wolf E, Borsboom Y, Bergmans A, Berends F, Lohman PHM, Baan RA, Van Delft JHM (1998) DNA adducts, mutant frequencies and mutation spectra in various organs of λlacZ mice exposed to ethylating agents Environm and Molecular Mutagenesis 31, 18-31

Frijhoff AFW, Krul CAM, Kelders MCJM, De Vries A, Weeda G, Van Steeg H, Baan RA (1998) Influence of nucleotide excision repair on N-hydroxy-2-acetylaminofluorene-induced mutagenesis studied in λlacZ-transgenic mice Environm and Molecular Mutagenesis 31, 41-47

Welters MJP, Fichtinger-Schepman AMJ, Baan RA, Flens MJ, Scheper RJ, Braakhuis BJM (1998) Role of glutathione, glutathione-S-transferases and multidrug resistance-related proteins in cisplatin sensitivity of head and neck cancer cell lines Brit J Cancer 77, 556-561

Van Delft JHM, Steenwinkel M-JST, Van Asten JG, Van Es J, Kraak A, Baan RA (1998) Monitoring of occupational exposure to polycyclic aromatic hydrocarbons in a carbon-electrode manufacturing plant Ann occup Hyg 42, 105-114

Randerath K, Sriram P, Moorthy B, Aston JP, Baan RA, Van den Berg PTM, Booth ED, Watson WP (1998) Comparison of immunoaffinity chromatography enrichment and nuclease P1 procedures for ^{32}P-postlabelling analysis of PAH-DNA adducts Chem-Biol Interactions 110, 85-102

Souliotis V, Van Delft JHM, Steenwinkel M-JST, Baan RA, Kyrtopoulos SA (1998) DNA adducts, mutant frequencies and mutation spectra in λlacZ-transgenic mice treated with N-nitrosodimethylamine Carcinogenesis 19, 731-739

Van Delft JHM, Bergmans A, Van Dam FJ, Tates AD, Howard L, Winton DJ, Baan RA (1998) Gene-mutation assays in λlacZ transgenic mice comparison of lacZ with endogenous genes in splenocytes and small intestinal epithelium Mutation Res 415, 85-96

Van Delft JHM, Baan RA, Roza L (1998) Biological effect markers for exposure to carcinogenic compounds and their relevance for risk assessment Crit Rev Toxicol, 28, 477-510

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2
Photocopy this page or follow this format for each person

NAME	POSITION TITLE
McGregor, Douglas	Scientist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education such as nursing, and include postdoctoral training)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
King's College, University of London, UK	Bsc	1963	Zoology
King's College, University of London, UK	Ph D	1966	Zoology
Royal College of Pathologists, London, UK	FRC Path	1989	Toxicology

RESEARCH AND PROFESSIONAL EXPERIENCE Concluding with present position, list, in chronological order, previous employment, experience, and honors Include present membership on any Federal Government public advisory committee List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application If the list of publications in the last three years exceeds two pages, select the most pertinent publications **DO NOT EXCEED TWO PAGES.**

1966-1968	Scientific Officer, Department of Nutrition, Flour-Milling and Baking Research Association Association St Albans, Hertfordshire, England
1968-1973	Research Fellow, Nuffield Unit for Laboratory Animal Pathology, Royal (Dick) School of Veterinary Medicine, Edinburgh, Scotland
1973-1987	Head of Department, Mutagenesis & Cellular Toxicology, Inveresk Research International Ltd, Musselburgh, EH21 70B, Scotland
1987-1989	Section Leader, Safety Assessment Program, Department of Toxicology and Safety Assessment Boheringer Ingelheim Pharmaceuticals, Inc , 90, East Ridge, Ridgefield CT 06877, USA
1989-present	Scientist, Unit of Carcinogen Identification and Evaluation, International Agency for Research on Cancer

Recent relevant professional activities

1 Participated in the IARC Monographs meetings on the *Evaluation of Carcinogenic Risks to Humans* leading to the publication of Volumes 50-74 Worked mainly in the sub-group dealing with metabolism, general toxicology, genetic toxicology, reproductive toxicology and mechanisms of carcinogenic action in these meetings Responsible for the organisation of the meetings for Volumes 52, 57, 60, 63, 66, 69, 71 and 74

2 Participated in the IARC Monographs Programme supplementary meetings and another IARC scientific meeting leading to IARC Scientific Publications Nos 116 (*Mechanisms of Carcinogenesis*), 139 (*Principles of Chemoprevention*), 146 (*The Use of Short- and Medium-term Tests for Carcinogens and Data on Genetic Effects in Carcinogenic Hazard Evaluation*) and 147 (*Species differences in Chemical Carcinogenesis of the Thyroid Gland, Kidney and Urinary Bladder*)

3 Participated in expert committees of the World Health Organisation for (1) the Evaluation of Residues of Veterinary Drugs in Food, (2) the Evaluation of Pesticide Residues in Food, (3) the IPCS Environmental Health Criteria Monographs, and (4) the IPCS International Chemical Safety Cards programme Also participated in expert committees evaluating carcinogenic substances for the European Commission (Directorate Generale XI)

List of publications since the last grant application

McGregor, D (1996) Tumour incidence reductions in carcinogenicity bioassays In Stewart, B W , McGregor, D & Kleihues, P (Eds) *Principles of Chemoprevention*, IARC Scientific Publications No 139 pp 277-290

McGregor, D B , Riach, C , Cattenach, P , Edwards, I, Sheperd, W and Caspary, W J (1996) Mutagenic responses of L5178Y mouse cells at the *tk* and *hprt* loci *Toxicology In Vitro*, **10**, 643-647

Camus-Randon, A-M , Raffalli, F , Bérézıat, J-C , McGregor, D , Konstandi, M and Lang, M A (1996) Liver injury and expression of cytochromes P450 Evidence that regulation of CYP2A5 is different from other major xenobiotic metabolizing CYP enzymes *Toxicol Appl Pharmacol* , **138**, 40-148

McGregor, D B (1996) A review of some properties of ethylene glycol ethers relevant to their carcinogenic evaluation Occup Hyg , , **2,** 213-235

McGregor, D (1996) Mutagenicity In, Duffus, J H & Worth, H G J (Eds) *Fundamental Toxicology for Chemists* Royal Society of Chemistry, London, pp 79-89

McGregor, D (1996) Carcinogenicity In, Duffus, J H & Worth, H G J (Eds) *Fundamental Toxicology for Chemists* Royal Society of Chemistry, London, pp 90-100

McGregor, D & Partnesky, C (1997) Carcinogens and mutagens In, J Rose (Ed) *Environmental Toxicology* Gordon & Breach, Cambridge, pp 49-79

McGregor, D (1997) Toxicology relevant to the carcinogenic evaluation of polyethylene terephthalate refillable plastic containers *Eur J Onc* , **2**, 521-529

Wilbourn, J D , McGregor, D B , Partensky C and Rice, J M (1997) IARC Reevaluates silica and related substances *Environ Hlth Persp* , **105**, 756-759

McGregor, D B and Lang, M (1997) Carbon tetrachloride Genetic effects and other modes of action *Mutation Res* , **366,** 181-195

McGregor, D B , Partensky, C Wilbourn, J & Rice J M (1998) An IARC evaluation of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans as risk factors in human carcinogenesis *Env Hlth Persp* , **106** (Suppl 2) 755-760

McGregor, D (1998) Diets, food components and human cancer *Biotherapy,* **11**,189-200

McGregor, D (1998) Industrial chemicals and human cancer *Biotherapy,* **11**,181-188

McGregor, D (1998) Mutagenic chemicals their significance *Biotherapy*, **11** 69-180

Castegnaro, M & McGregor, D (1998) Carcinogenic risk assessment of mycotoxins *Rev Méd Vétérinaire,* **149**, 671-678

Anderson, D , Yu, Tian-Wei & McGregor, D B (1998) Comet assay responses as indicators of carcinogen exposure *Mutagenesis*, **13,** 539-555

McGregor, D & Anderson, D (1999) DNA damage and repair in mammalian cells *in vitro* and *in vivo* as indicators of exposure to carcinogens In McGregor, D B , Rice, J M & Venitt, S (Eds) *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, pp 309-354

Quillardet, P & McGregor, D (1999) Identification of carcinogenic substances by means of short-term tests in bacteria In McGregor, D B , Rice, J M & Venitt, S (Eds) *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, pp 487-498

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person

NAME	POSITION TITLE
Grosse, Yann, Jacques	Scientist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Faculty of Sciences, University of Metz, France	BSc	1990	Chemistry & Biochemistry
Faculty of Sciences, University of Strasbourg, France	MSc	1992	Environ Toxicology
INPT, University of Toulouse, France	Ph D	1996	Genetic Toxicology

RESEARCH AND PROFESSIONAL EXPERIENCE. Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

1996-1997 Postdoc , Unit of Gene & Environmental Interactions, IARC
1997-present Scientist, Unit of Carcinogen Identification & Evaluation, International Agency for Research on Cancer

Recent relevant professional activity

Participated in the IARC Monograph meetings on the Evaluation of Carcinogenic Risks to Humans leading to the publication of Volumes 69-74 Worked mainly in the sub-group dealing with metabolism, general and genetic toxicology, and the sub-group dealing with use and production data, environmental occurrence, occupational and accidental exposure

List of publications

Grosse, Y., Baudrimont, I Castegnaro, M Betbeder A -M , Creppy, E E , Dirheimer, G , & Pfohl-Leszkowicz, A (1995) Formation of ochratoxin A metabolites and DNA-adducts in monkey kidney cells *Chem Biol Interact* , **95**, 175-187

Pfohl-Leszkowicz, A , **Grosse, Y.**, Carriere, V , Cugnenc, P H , Berger, A , Carnot, F , de Waziers, I (1995) High levels of DNA adducts in human colon are associated with colorectal cancer *Cancer Res* , **55**, 5611-5616

Grosse, Y., Castegnaro, M , Mace, K , Mohr, U , Bartsch, H , Dirheimer, G Pinelli, E , Pfeifer, A & Pfohl-Leszkowicz, A (1995) Cytochrome P-450 isoforms implicated in ochratoxin A genotoxicity determined by DNA adduct formation *Clin Chem* , **41**, 1927-1929

Dubois, M , Pfohl-Leszkowicz, A , **Grosse, Y.** & Kremers, P (1995) DNA adducts and P450 induction in human, rat and avian liver cells after exposure to polychlorobiphenyls *Mutat Res* , **345**, 181-190

Obrecht-Pflumio, S , **Grosse, Y.**, Pfohl-Leszkowicz, A & Dirheimer, G (1996) Protection by indomethacin and aspirin against genotoxicity of ochratoxin A, particularly in the urinary bladder and kidney *Arch Toxicol* , **70**, 244-248

Fessard, V , **Grosse, Y.**, Pfohl-Leszkowicz, A , Puiseux-Dao, S (1996) Okadaic acid treatment induces DNA adduct formation in BHK21 C13 fibroblasts and HESV keratinocytes *Mutat Res* , **361**, 133-141

Dubois, M., **Grosse, Y.**, Thome, J.-P., Kremers, P. & Pfohl-Leszkowicz, A. (1997) Metabolic activation and DNA-adducts detection as biomarkers of chlorinated pesticide exposures. *Biomarkers*, **2**, 17-24

Grosse, Y., Chekir-Ghedira, L., Huc, A., Obrecht-Pflumio, S., Dirheimer, G., Bacha, H. & Pfohl-Leszkowicz, A. (1997) Retinol, ascorbic acid and alpha-tocopherol prevent DNA adduct formation in mice treated with the mycotoxins ochratoxin A and zearalenone. *Cancer Lett.*, **114**, 225-229

CONTINU/ ON PAGE: STAY WITHIN MA. .INS INDICATED

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2
Photocopy this page or follow this format for each person

NAME	POSITION TITLE
Partensky, Christiane	Technical Officer

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Lyon, France	BSc	1965	Chemistry, Physics

RESEARCH AND PROFESSIONAL EXPERIENCE Concluding with present position, list, in chronological order, previous employment, experience, and honors Include present membership on any Federal Government public advisory committee List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application If the list of publications in the last three years exceeds two pages, select the most pertinent publications **DO NOT EXCEED TWO PAGES.**

1966-68 Centre National de la Recherche Scientifique, Paris
Extractor for the "Bulletin Signaletique"

1969-70 Centre Régional de Documentation Pedagogique, Lyon
Adviser for teachers in biology

1970-71 IARC, Lyon Bibliographical research in pesticides

1971-93 IARC, Lyon Technical editor for the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Responsible for checking the content of the Monographs against the original cited papers

1994-present IARC, Lyon Technical editor for the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Responsible for coordinating the checking of the content of the Monographs against the original cited papers

1988-95 Member of the *ad hoc* Working Groups of the European Commission in Luxembourg for the publication of Monographs on the carcinogenicity of chemicals

Publications

Vainio, H , Heseltine, E , Shuker, L , McGregor, D & Partensky, C (1991) Meeting report occupational exposures in insecticide application and some pesticides *Eur J Cancer,* **27**, 284-289

Boffetta, P , Cardis, E , Vainio, H , Coleman, M P , Kogevinas, M , Nordberg, G , Parkin, D M , Partensky, C , Shuker, D & Tomatis, L (1991) Cancer risks related to eletricity production *Eur J Cancer*, **27**, 1504-1519

Vainio, H , Heseltine, E , Partensky, C & Wilbourn, J (1993) Meeting of the IARC working group on beryllium, cadmium, mercury and exposures in the glass manufacturing industry *Scand J Work Environ Health*, **19**, 360-363

Vainio, H , Wilbourn, J & Partensky, C (1994) Carcinogenicity of cadmium *Regul Toxicol Pharmacol* ,**19**, 342-343

Matos, E & Partensky, C (1994) National control measures *In* Pearce, N , Matos, E , Vainio, H , Boffetta, P & Kogevinas, M , eds, *Occupational Cancer in Developing Countries* (IARC Scientific Publications No 129), Lyon, IARC, pp 157-171

Vainio, H , Wilbourn, J D , Sasco, A J , Partensky, C , Gaudin, N , Heseltine, E , & Eragne, I (1995) Identification of human carcinogenic risk in IARC Monographs *Bull Cancer*, **82**, 339-348 (in French)

Wilbourn, J , Partensky, C & Morgan, W G (1996) IARC evaluates printing processes and printing inks, carbon black and some nitro compounds *Scand J Work Environ Health*, **22**, 154-156

Wilbourn, J D , McGregor, D B , Partensky & Rice, J M (1997) IARC reevaluates silica and related substances *Environ Health Perspect* , **105**, 756-759

McGregor, D B , Partensky, C , Wilbourn, J & Rice, J M (1998) An IARC evaluation of polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans as risk factors in human carcinogenesis *Environ Health Perspect* , **106**, 755-760

McGregor, D & Partensky, C (1998) Carcinogens and mutagens *In* Rose, J , ed , *Environmental Toxicology Current Developments*, Langhorne, P A , Gordon & Breach Science Publishers, pp 49-79

CONTINUA[illegible] ON PAGE: STAY WITHIN MA[illegible]INS INDICATED

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2
Photocopy this page or follow this format for each person

NAME	POSITION TITLE
Wilbourn, Julian	Scientist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of St Andrews, Scotland, UK	BSc	1967	Biological Sciences

RESEARCH AND PROFESSIONAL EXPERIENCE Concluding with present position, list, in chronological order, previous employment, experience, and honors Include present membership on any Federal Government public advisory committee List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application If the list of publications in the last three years exceeds two pages, select the most pertinent publications **DO NOT EXCEED TWO PAGES**

Professional experience

1968–70 Huntington Research Centre, United Kingdom
Long-term carcinogenicity testing in rodents — Study supervisor

1970–73 British Industrial Biological Research Association, United Kingdom
Information and Consultancy Department — Scientist

1973–to date International Agency for Research on Cancer France
IARC Monographs Programme — Scientist

***Publications relevant to the* IARC Monographs**

Tomatis, L , Agthe, C , Bartsch, H , Huff, J , Montesano, R , Saracci, R , Walker, E & **Wilbourn**, J (1978) Evaluation of the carcinogenicity of chemicals a review of the Monograph Program of the International Agency for Research on Cancer (1971 to 1977), *Cancer Res* , **38**, 877–885

Merletti, F , Heseltine, E , Saracci, R , Simonato, L , Vainio, H & **Wilbourn**, J (1984) Target organs for carcinogenicity of chemicals and industrial exposures in humans a review of results in the *IARC Monographs* on the evaluation of the carcinogenic risk of chemicals to humans *Cancer Res* , **44**, 2244–2250

Vainio, H , Hemminki, K & **Wilbourn**, J (1985) Data on the carcinogenicity of chemicals in the *IARC Monographs* programme *Carcinogenesis*, **6**, 1653–1665

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

Tomatis, L , Aitio, A , **Wilbourn**, J & Shuker, L (1989) Human carcinogens so far identified *Jpn J Cancer Res* , **80**, 795–807

Vainio, H , Coleman, M & **Wilbourn**, J (1991) Carcinogenicity evaluations and ongoing studies the IARC databases *Environ Health Perspect* , **96**, 5–9

Vainio, H & **Wilbourn**, J (1992) Identification of carcinogens within the *IARC Monograph* program *Scand J Work Environ Health*, **18** (Suppl 1), 64–73

Vainio, H , Heseltine, E , McGregor, D , Tomatis, L & **Wilbourn** J (1992) Working group on mechanism of carcinogenesis and evaluation of carcinogenic risks *Cancer Res* , **52**, 2357–2361

Vainio, H , **Wilbourn**, J & Heseltine, E (1992) Meeting of the IARC working group on the evaluation of carcinogenic risks to humans from occupational exposures to mists and vapours from strong inorganic acids, and other industrial chemicals (meeting report) *Scand J Work Environ Health*, **18**, 329–332

Vainio, H & **Wilbourn**, J (1993) Agents causally associated with human cancer *Pharmacol Toxicol* , **72**, 4–11

Vainio, H & **Wilbourn**, J (1993) Cancer etiology agents causally associated with human cancer *Pharmacol Toxicol* , **72**, 4–11

Vainio, H , Heseltine, E & **Wilbourn**, J (1993) Report on an IARC working group meeting on some naturally occurring substances *Int J Cancer*, **53**, 535–537

Vainio, H , Heseltine, E , Partensky, C & **Wilbourn**, J (1993) Meeting of the IARC working group on beryllium, cadmium, mercury and exposures in the glass manufacturing industry *Scand J Work Environ Health*, **19**, 360–363

Vainio, H , Heseltine, E & **Wilbourn**, J (1994) Priorities for future IARC Monographs on the Evaluation of Carcinogenic Risks to Humans *Environ Health Perspect* , **102**, 589–591

Vainio, H , **Wilbourn** J & Tomatis, L (1994) Identification of environmental carcinogens the first steps in risk assessment In Mehlman, M A & Upton, A , eds *The Identification and Control of Environmental and Occupational Diseases*, Princeton Scientific Publishers, Princeton, NJ pp 1–19

Vainio, H , **Wilbourn**, J & Partensky (1994) Carcinogenicity of cadmium *Regul Toxicol Pharmacol* , **19**, 342–343

Wilbourn, J & Vainio, H (1994) Identification of carcinogenic risks — Qualitative aspects In Richardson, M , ed , *Chemical Safety*, VCH Verlagsgesellsch mbH, Weinheim, pp 241–258

Boffetta, P , Kogevinas, M , Simonato, L , **Wilbourn**, J & Saracci, R (1995) Current perspectives on occupational cancer risks *Int J Occup Environ Health*, **1**, 315–325

Vainio, H , **Wilbourn**, J D , Sasco, A J , Partensky, C Gaudin, N Heseltine, E & Eragne, I (1995) Identification des facteurs cancerogenes pour l'homme dans les Monographies du CIRC [Identification of human carcinogenic risks in IARC Monographs] *Bull Cancer* (Paris), **82**, 339–348

Wilbourn, J , Heseltine, E & Møller, H (1995) IARC evaluates wood dust and formaldehyde *Scand J Work Environ Health*, **21**, 229–232

Boffetta, P , Saracci, R , Kogevinas, M , **Wilbourn**, J & Vainio, H (1996) Occupational carcinogens In Stellman, ed , *ILO Encyclopedia of Occupational Health and Safety*, 4th ed , vol 1, 2 4-2 8 ILO, Geneva

Wilbourn, J , Heseltine, E & Moller, H (1995) IARC evaluates wood dust and formaldehyde International Agency for Research on Cancer *Scand J Work Environ Health*, **21**, 229-232

Wilbourn, J , Partensky, C & Morgan, W G (1996) IARC evaluates printing processes and printing inks, carbon black and some nitro compounds *Scand J Work Environ Health*, **22**, 154-156

Wilbourn, J D , McGregor, D B , Partensky, C & Rice, J M (1997) IARC reevaluates silica and related substances *Environ Health Perspect* , **105**, 756-759

McGregor, D B , Partensky, C , **Wilbourn**, J & Rice, J M (1998) An IARC evaluation of polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans as risk factors in human carcinogenesis *Environ Health Perspect* , **106 Suppl 2**, 755-760

CONTINUA ON PAGE: STAY WITHIN MAI INS INDICATED

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2
Photocopy this page or follow this format for each person

NAME	POSITION TITLE
BOFFETTA, Paolo	Medical Officer (Unit Chief)

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
Faculty of Medicine and Surgery, Univ. of Turin	MD	1985	Medicine
School of Public Health, Columbia Univ., New York	Master	1988	Public Health
School of Specialization in Hygiene, Univ. of Turin	Diploma	1988	Hygiene and Prev. Med.

RESEARCH AND PROFESSIONAL EXPERIENCE Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application If the list of publications in the last three years exceeds two pages, select the most pertinent publications **DO NOT EXCEED TWO PAGES.**

Research and Professional Experience

Research Fellow at the Unit of Cancer Epidemiology of the University of Torino (1985-86)
Research Assistant at the Department of Statistics and Epidemiology of the American Cancer Society (1986-88)
Research Assistant at the Division of Epidemiology of the American Health Foundation (1988)
Research Assistant at the Unit of Cancer Epidemiology of the University of Torino (1989-1990)
Post-doctoral Associate at the Divison of Health Policy and Management of Columbia University School of Public Health (1989)
Medical officer (epidemiologist) at the Unit of Analytical Epidemiology of the International Agency for Research on Cancer, Lyon (1990-1994)
Medical officer (unit chief) at the Unit of Environmental Cancer Epidemiology of the International Agency for Research on Cancer, Lyon (1995-present)

Professional and Scientific Memberships

American Association for Cancer Research
International Commission of Occupational Health
International Epidemiological Association
Italian Epidemiological Association

Selected Publications

Boffetta P. Health effects of asbestos exposure in humans: a quantitative assessment. Med Lav (in press).

Boffetta P, Garcia-Gómez M, Pompe-Kirn V, Zaridze D, Bellander T, Bulbulyan M, Caballero JD, Ceccarelli F, Colin D, Dizdarevic T, Español S, Kobal A, Petrova N, Sällsten G, Merler E. Cancer occurrence among European mercury miners. Cancer Causes Control (in press)

(b)(4), (b)(6) [redacted]

Bulbulyan MA, Margaryan AG, Ilychova SA, Astashevsky SV, Uloyan SM, Cogan VY, Colin D, Boffetta P, Zaridze DG. Cancer incidence and mortality in a cohort of chloroprene workers from Armenia. Int J Cancer (in press)

.../...

Harrington JM, Boffetta P, Saracci R. Clinical and epidemiological aspects. In: Baxter P, Adams PH, Aw T-C, Cockcroft A, Harrington JM, eds. Hunter's Diseases of Occupations, 9th Edition. Arnold, London (in press)

Vineis P, Malats N, Lang M, d'Errico A, Caporaso, Cuzick, Boffetta P, eds. Metabolic Polymorphisms and Susceptibility to Cancer (IARC Scientific Publications No. 148). IARC, Lyon (in press)

Fortuny J, Kogevinas M, Chang-Claude J, González C-A, Hours M, Jöckel K-H, Bolm-Audorff U, Lynge E, 'T Mannetje A, Porru S, Ranft U, Serra C, Tzonou A, Wahrendorf J, Boffetta P. Tobacco, occupation and non-transitional-cell carcinoma of the bladder: an international case-control study. Int J Cancer 80: 44-46; 1999.

Boffetta P, ed. Cancer chapter. In: Stellman JM, ed. Encyclopaedia of Occupational Health and Safety, Vol I, 4th Edition. International Labour Office, Geneva, 1998, pp. 2.1-2.18.

Boffetta P. Exposure to man-made vitreous fibres and cancer risk: a review of epidemiological studies. In: Peters GA, Peters BJ, eds, Current Asbestos Issues (Sourcebook on Asbestos Diseases, Vol. 18). Lexis Publishing, Charlottesville, VA, 1998, pp. 191-218.

Boffetta P, Agudo A, Ahrens W, Benhamou E, Benhamou S, Darby SC, Ferro G, Fortes C, Gonzalez CA, Jöckel KH, Krauss M, Kreienbrock L, Kreuzer M, Mendes A, Merletti F, Nyberg F, Pershagen G, Pohlabeln H, Riboli E, Schmid G, Simonato L, Trédaniel J, Whitley E, Wichmann H-E, Winck C, Zambon P, Saracci R. Multicenter case-control study of exposure to environmental tobacco smoke and lung cancer in Europe. J Natl Cancer Inst 90: 1440-1450; 1998.

Boffetta P, Burdorf A, Goldberg M, Merler E, Siemiatycki J. Towards the coordination of European research on the carcinogenic effects of asbestos (Workshop report). Scand J Work Environ Hlth 24: 312-317; 1998.

Boffetta P, Sali D, Kolstad H, Coggon D, Olsen J, Andersen A, Spence A, Pesatori AC, Lynge E, Frentzel-Beyme R, Chang-Claude J, Lundberg I, Biocca M, Gennaro V, Teppo L, Partanen T, Welp E, Saracci R, Kogevinas M. Mortality of short-term workers in two international cohorts. J Occup Environ Med 40: 1120-1126; 1998.

Bulbulyan MA, Changuina OV, Zaridze DG, Astashevsky SV, Colin D, Boffetta P. Cancer mortality among Moscow shoe workers exposed to chloroprene (Russia). Cancer Causes Control 9: 381-387; 1998.

Consonni D, Boffetta P, Andersen A, Chang-Claude J, Cherrie JW, Ferro G, Frentzel-Beyme R, Hansen J, Olsen J, Plato N, Westerholm P, Saracci R. Lung cancer mortality among European rock/slag wool workers: exposure-response analysis. Cancer Causes Control 9: 411-416; 1998.

Demers PA, Stellman SD, Colin C, Boffetta P. Nonmalignant respiratory disease mortality among woodworkers participating in the American Cancer Society Cancer Prevention Study-II (CPS-II). Am J Ind Med 34: 238-243; 1998.

Gordon I, Boffetta P, Demers PA. A case study comparing a meta-analysis and a pooled analysis of studies of sinonasal cancer among wood workers. Epidemiology 9: 518-524; 1998.

Kogevinas M, Sala M, Boffetta P, Kazerouni N, Kromhout H, Hoar-Zahm S. Cancer risk in the rubber industry: a review of the recent epidemiological evidence. Occup Environ Med 55: 1-12; 1998.

Siemiatycki J, Boffetta P. Invited Commentary: Is it possible to investigate the quantitative relation between asbestos and mesothelioma in a community-based study? Am J Epidemiol 148: 143-147; 1998.

Vena J, Boffetta P, Becher H, Benn T, Bueno-de-Mesquita HB, Coggon D, Colin D, Flesch-Janys D, Green L, Kauppinen T, Littorin M, Lynge E, Mathews JD, Neuberger M, Pearce N, Pesatori AC, Saracci R, Steenland K, Kogevinas M. Exposure to dioxin and nonneoplastic mortality in the expanded IARC international cohort study of phenoxy herbicide and chlorophenol production workers and sprayers. Environ Hlth Persp 106 (suppl 2): 645-653; 1998.

Weiderpass E, Partanen T, Kaaks R, Vainio H, Porta M, Kauppinen T, Ojajärvi A, Boffetta P, Malats N. Occurrence, trends and environmental etiology of pancreatic cancer. Scand J Work Environ Hlth 24: 165-174; 1998.

Welp EA, Weiderpass E, Boffetta P, Vainio H, Vasama-Neuvonen K, Petralia S, Partanen TJ. Environmental risk factors of breast cancer. Scand J Work Environ Hlth 24: 3-7; 1998.

Wünsch-Filho V, Moncau JE, Mirabelli D, Boffetta P. Occupational risk factors of lung cancer in São Paulo, Brazil. Scand J Work Environ Health 24: 118-124; 1998.

Zaridze D, Maximovitch D, Zemlyanaya G, Aktakov ZN, Boffetta P. Exposure to environmental tobacco smoke and risk of lung cancer in non-smoking women from Moscow, Russia. Int J Cancer 75: 335-338; 1998.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2
Photocopy this page or follow this format for each person

NAME: CARDIS, Elisabeth

POSITION TITLE: SCIENTIST

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Ottawa, Canada	B.Sc.Honours	1979	Mathematics
University of Washington, Seattle, Wa.	M.S.	1983	Biomathematics
University of Washington, Seattle, Wa.	Ph.D.	1985	Biomathematics/ Epidemiology

RESEARCH AND PROFESSIONAL EXPERIENCE Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

October 1981 to December 1982	Visiting Research Fellow, Radiation Effects Research Foundation, Hiroshima, Japan
May 1985 to November 1986	Assistant Professor - Institut Armand Frappier, Epidemiology and Preventive Medicine Research Centre, Laval, Québec and IARC Cancer Research Training Fellow (IARC, Lyon)
November 1986 to June 1988	Consultant - International Agency for Research on Cancer, Lyon, France
July 1988 to December 1994	Scientist - International Agency for Research on Cancer, Lyon, France
January 1995 to present	Chief of Unit of Radiation and Cancer, IARC Lyon, France

Last three years' publications:

Moolgavkar S., Krewski D., Zeise L., Cardis E. Quantitative Estimation and Prediction of Risk. IARC Scientific Publication No.131 (in press)

(b)(4), (b)(6) [redacted]

Ivanov V.K., Gorski A.I., Pitkevitch V.A., Tsyb A.F., Cardis E., Storm H. Risk of Radiogenic Thyroid Cancer in Russia following the Chernobyl Accident. In: Karaoglou A., Williams E.D. eds. First International Seminar on Radiation and Thyroid Cancer, Cambridge 1998. World Scientific Publishing (in press)

Cardis E. and Martuzzi, M. (1998) Improving the estimates of radiation induced cancer risk. Seguridad Nuclear, No 6, 31-37

Fix J.J., Salmon L., Cowper G, Cardis E. (1997) A Retrospective Evaluation of the Dosimetry employed in an International Combined Epidemiological Study. Rad. Prot. Dos., Vol. 74, Nos. 1/2, 39-53.

Cardis E. (1997) Effects of low dose protracted exposures to ionizing radiation: nuclear worker studies. Physics and Society, Vol. 26, No.1

Cardis E (1997) Trop de Leucémies autour de La Hague? Peu vraisemblable La Recherche, No 301, 28-30

Boyle P Krewski D , Ashmore J P , Cardis E and Zielinski J M (1997) Radiation Epidemiology and National Dose Registers Eur J Cancer, Vol 3, Suppl 3, S1-S2

Zielinski J M , Krewski D , Ashmore J P and Cardis E (1997) The Use of National Registers of Radiation Exposure in Occupational Radiation Risk Assessment Eur J Cancer, Vol 3, Suppl 3, S3-S6

Cardis E , Martuzzi M and Amoros E (1997) International Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry II - Procedures Document - 1997 Revision, IARC Internal Report 97/002

Mylvaganam A , Cardis E , Black R (1997) Cancer and leukaemia clusters Radiation and Society Comprehending Radiation Risk (Proc Conf Paris, 1994), Vol 3, 119-137, International Atomic Energy Agency (IAEA), Vienna

Repacholi M H , Cardis E (1997) Criteria for EMF Health Risk Assessment, Radiation Protection Dosimetry, Vol 72, No 3-4, pp 305-312, Nuclear Technology Publishing

Cardis, E , Rice J M (1997) Criteria for Health Risk Assessment within the International EMF Project Proceedings of the International Seminar on Biological Effects of Static and ELF Electric and Magnetic Fields and Related Health Risks, Bologna, Italy, June 4 and 5, 1997, 31-40

Cardis E , Rice J M (1997) Criteria for Health Risk Assessment within the International EMF Project In Non-Thermal Effects of RF Electromagnetic Fields, ICNIRP 3/97, 35-44

Cardis, E (1997) Epidemiological studies of the Chernobyl accident - Present and future Proceedings of the WHO/HICARE Symposium on Radiological Accidents and Environmental Epidemiology, Hiroshima, 24-25 August 1996

Martuzzi M Cardis E (1996) Etude epidémiologique sur les travailleurs du nucléaire, Revue Génerale Nucleaire No 6, 42-45

Cardis E , Anspaugh L , Ivanov V K , Liktharev I , Mabuchi K , Okeanov A E , Prisyazhniuk A (1996) Estimated Long Term Health Effects of the Chernobyl Accident Proceedings of the EC/WHO/IAEA International Conference One decade after Chernobyl, 8-12 April 1996, 241-279

Sali D , Cardis E , Sztanyik L , Auvinen A , Bairakova A , Dontas N , Grosche B , Kerekes A , Kusic Z Kusoglu C , Lechpammer S , Lyra M , Michaelis J , Petridou E , Szybinski Z , Tominaga S , Tulbure R , Turnbull A , Valerianova Z (1996) Cancer Consequences of the Chernobyl Accident in Europe Outside the former USSR A Review Int J Cancer, 67, 343-352

Cardis E and Okeanov A E (1996) What's Feasible and Desirable in the Epidemiologic Follow-up of Chernobyl? In The radiological consequences of the Chernobyl accident A Karaoglou, G Desmet, G N Kelly and H G Menzel Eds ECSC-EC-EAEC, Brussels, Luxembourg, pp 835-850

Baverstock K and Cardis E (1996) The WHO Activities on Thyroid Cancer Proceedings of the First International Conference of the European Commission, Belarus, the Russian Federation and Ukraine on the consequences of the Chernobyl accident, Minsk, Belarus, 18-22 March 1996 IOS Press, Amsterdam, 715-726

Okeanov, A E , Cardis E , Antipova S I , Polyakov S M , Sobolev A V , Bazulko N V (1996) Health Status and follow-up of the liquidators in Belarus In The radiological consequences of the Chernobyl accident A Karaoglou, G Desmet, G N Kelly and H G Menzel Eds ECSC-EC-EAEC, Brussels, Luxembourg, pp 851-859

Cardis E , Gilbert E S , Carpenter L , Howe G (1996) Response to the Letters of Drs Schillaci and Uma Devi Rad Res 145, 648-649

Cardis E (1996) Epidemiology of accidental radiation exposures Environmental Health Perspectives, Vol 104, Supplement 3, 643-649

Cardis E , Jones S , Kleihues P (1996) The future of population monitoring in cancer research Environmental Health Perspectives, Vol 104, Supplement 3, 527-528

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person

NAME	POSITION TITLE
FRIESEN, Marlin	Scientist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Bethel College, N Newton Kansas	B A	1968	Chemistry
Kansas University, Manhattan, Kansas	M S	1974	Analytical Chemistry
Kansas University, Manhattan Kansas	Ph D	1977	Analytical Chemistry

RESEARCH AND PROFESSIONAL EXPERIENCE Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Employment

1975-1977 National Institute of Environmental Health Sciences Research Triangle Park, North Carolina USA (research served for Ph D Thesis) Application of negative ion chemical ionization mass spectrometry to the analysis of dibenzo dioxins in environmental samples

1977-1978 Post Doctoral Fellow in the Dept of Molecular Sciences Univ of Warwick, Coventry, UK with Prof K R Jennings Mechanisms of ion-molecule reactions by mass spectrometry

1978-1997 Mass Spectrometrist/Analytical Chemist, International Agency for Research on Cancer Identification and quantification of carcinogens, carcinogen metabolites and carcinogen-DNA adducts by mass spectrometry, oxidative damage to DNA, continuing participant in IARC monograph programme

1997-1998 Visiting Scientist in the Dept of Environmental Health Sciences of the Johns Hopkins School of Hygiene and Public Health in Baltimore MD, USA

1998-present Scientist, Unit of Unit of Gene-Environment Interactions IARC, Lyon, France Analysis of mutations in DNA by LC/MS

Publications

Kadlubar,F F , Kaderlik,R K , Mulder,G J , Lin,D , Butler,M A ,Teitel,C H , Minchin,R F , Ilett,K F , Friesen,M D , Bartsch,H , Nagao,M , Esumi,H ,Sugimura,T and Lang,N P (1995) Metabolic activation and DNA adduct detection of PhIP in dogs, rats, and humans in relation to urinary bladder and colon carcinogenesis In Adamson,R H , Gustafsson,J A , Ito,N , Nagao,M , Sugimura,T , Wakabayashi,K and Yamazoe,Y (eds) *Heterocyclic amines in cooked foods possible human carcinogens*, Princeton Scientific Publishing Co Princeton, pp 207-213

Nair,U J , Nair,J , Friesen,M D , Bartsch,H and Ohshima,H (1995) Ortho- and meta-tyrosine formation from phenylalanine in human saliva as a marker of hydroxyl radical generation during betel quid chewing *Carcinogenesis*, **16**, 1195-1198

Yermilov,V , Rubio,J , Becchi,M , Friesen,M D , Pignatelli,B and Ohshima,H (1995) Formation of 8-nitroguanine by the reaction of guanine with peroxynitrite *in vitro* *Carcinogenesis*, **16**, 2045-2050

Friesen,M D , Cummings,D A , Garren,L , Butler,R , Bartsch,H and Schut,H A J (1996) Validation in rats of two biomarkers of exposure to the food-borne carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) PhIP-DNA adducts and urinary PhIP *Carcinogenesis*, **17**, 67-72

Knassmuller,S , Friesen,M D , Holme,J A , Alexander,J , Sanyal,R , Kassie,F and Bartsch,H (1996) Effects of phenethyl isothiocyanate on metabolism and on genotoxicity of dimethylnitrosamine and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) *Mutat Res* **350**, 93-102

CONTINU, ON PAGE: STAY WITHIN MA. INS INDICATED

Friesen,M D , Cummings,D A , Garren,L , Butler,R , Bartsch,H and Schut,H A J (1996) Validation in rats of two biomarkers of exposure to the food-borne carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) PhIP-DNA adducts and urinary PhIP *Carcinogenesis*, **17** 67-72

Knassmuller,S , Friesen,M D , Holme,J A , Alexander,J , Sanyal,R , Kassie,F and Bartsch,H (1996) Effects of phenethyl isothiocyanate on metabolism and on genotoxicity of dimethylnitrosamine and 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) *Mutat Res* **350**, 93-102

Coggon,D and Friesen,M D (1997) Markers of internal dose chemical agents In Toniolo,P , Boffetta P , Shuker,D E G , Rothman,N ,Hulka,B and Pearce,N (eds) *Application of biomarkers to cancer epidemiology*, (IARC Scientific Publications, No 142) Lyon, IARC

Schut,H A J , Cummings,D A , Smale,M H E , Josyula,S and Friesen,M D (1997) DNA adducts of heterocyclic amines formation, removal and inhibition by dietary components *Mutat Res* **376**, 185-194

Atawodi,S E , Lea,S , Nyberg,F , Mukeria,A , Contantinescu,V ,Ahrens,W , Brueske-Hohlfeld,I , Fortes,C , Boffetta,P and Friesen,M D (1998) 4-Hydroxy-1-(3-pyridyl)-1-butanone-Hemoglobin adducts as biomarkers of exposure to tobacco smoke Validation of a method to be used in multicenter studies *Cancer Epidemiol , Biomarkers & Prev* **7**, 817-821

Laken, S J , Jackson, P E , Kinzler, K W , Vogelstein, B , Strickland, P T , Groopman, J D and Friesen, M D (1998) Genotyping by mass spectrometric analysis of short DNA fragments *Nature Biotech ,* **16,** 1352-1356

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2
Photocopy this page or follow this format for each person

NAME Janet HALL

POSITION TITLE Scientist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Dept of Biochemistry, Manchester Uni.	B.Sc.	1975-1978	Biochemistry
Dept of Medical Oncology Manchester University	Ph.D.	1978-1981	Med. Oncology

RESEARCH AND PROFESSIONAL EXPERIENCE Concluding with present position, list, in chronological order, previous employment, experience, and honors Include present membership on any Federal Government public advisory committee List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application If the list of publications in the last three years exceeds two pages, select the most pertinent publications **DO NOT EXCEED TWO PAGES.**

January 1988 - present

Staff scientist within the Unit of Mechanisms of Carcinogenesis, International Agency for Research on Cancer, Lyon, France.

January 1984 - December 1987

Scientific Non-Clinical Research Fellow within the Mammalian Cell DNA Repair Laboratory, Imperial Cancer Research Fund, Clare Hall Laboratories, South Mimms, Herts, in the laboratories of Dr T. Lindahl and Dr P. Karran. Research supported by European Science Foundation Research Fellowship in Toxicology from January 1984 to December 1984, and subsequently by an Imperial Cancer Research Fund Research Fellowship.

October 1981 - December 1983

Unit of Mechanisms of Carcinogenesis, International Agency for Research on Cancer, Lyon, France, in the laboratory of Dr R. Montesano, Chief, of the Unit. Recipient of a Research Training Fellowship of the International Agency for Research on Cancer/World Health Organization.

October 1978 - October 1981

Department of Medical Oncology, Manchester University. Based in Department of Chemical Carcinogenesis, Paterson Laboratories, Christie Hospital and Holt Radium Institute, Withington, Manchester, under the supervision of Dr R. Saffhill.

October 1975 - July 1978

Department of Biochemistry, Manchester University. Field of study: Biochemistry.

Publications

G. Hu, C. Han, C.P. Wild, J. Hall, and J.Chen (1992) Lack of effects of selenium on *N*-nitrosomethylbenzylamine-induced tumorigenesis, DNA methylation, and oncogene expression in rats and mice. Nutr. Cancer, 18, 287-295.

J. Hall, H. Brésil, F. Donato, C.P. Wild, N.A. Loktionova, O.I Kazanova, I.P. Komyakov, V.G. Lemekhov, A.J. Likhachev and R. Montesano (1993) Alkylation and oxidation-DNA damage repair activity in blood leucocytes of smokers and non-smokers. Int. J. Cancer, 54, 728-733.

J. Hall, D.R. English, M. Artuso, B.K. Armstrong and M. Winter (1994) DNA repair capacity as a risk factor for non-melanocytic skin cancer - a molecular epidemiological study. Int. J. Cancer, 58, 179-184.

M. Artuso, A. Esteve,H. Brésil, M. Vuillaume and J. Hall (1995) The role of the Ataxia telangiectasia gene in the p53, WAF1/CIP1(p21) and GADD45- mediated response to DNA damage by ionising radiation. Oncogene, 11, 1427-1435.

S.Takahashi, J. Hall and R. Montesano (1995) Temporal cell type specific mRNA expression of O^6-methylguanine-DNA-methyltransferases in liver of rats treated with dimethylnitrosamine. American J. Pathology, 148, 497-507.

J. Hall, M. Artuso and D. English (1995) Molecular Epidemiology of skin cancers : DNA repair and non-melanocytic skin cancer. New Trends in Molecular Epidemiology, Ann. Ist. Super. Sanità. 32, 43-51.

F. Bianchini, J. Hall, F. Donato and J. Cadet (1996) Monitoring urinary excretion of 5-hydroxymethyluracil for assessment of oxidative DNA damage and repair. Biomarkers, 1, 178-184.

W. Jongmans, M. Artuso, M. Vuillaume, H. Brésil, S.P. Jackson and J.Hall (1996) The role of Ataxia telangiectasia and the DNA-dependent protein kinase in the p53-mediated cellular response to ionising radiation. Oncogene, 13, 1133-1138.

R. Montesano, P. Hainaut and J. Hall (1996) Chemical-induced genetic alterations in human cancers : relevance to aetiology and pathogenesis. European Journal of Cancer Prevention, 5, 392-393.

R. Montesano, P. Hainaut and J. Hall (1997) The use of biomarkers to study the pathogenesis and mechanisms of cancer : oesophagus and skin cancer as models. In Toniolo, P, and Boffetta, P. (eds) Methodological Issues in the Uses of Biomarkers in Cancer Epidemiology, IARC Scientific Press, 142, 291-301.

W. Jongmans, M. Vuillaume, K. Chrzanowska, D. Smeets, K. Sperling and J. Hall (1997) Nijmegen Breakage Syndrome cells fail to induce the p53-mediated DNA damage response following exposure to ionising radiation. Molecular and Cellular Biology, 17, 5016-5022.

F Bianchini, F. Donato, H. Faure. J-L. Ravanat, J. Hall and J. Cadet (1998) Urinary excretion of 5-(hydroxylmethyl)uracil in healthy volunteers: effect of active and passive tobacco smoke. Int. J. Cancer, 77, 40-46.

W. Jongmans, M. Vuillaume, W.J. Kleijer, N.D Lakin and J. Hall (1998) The p53-mediated DNA damage response to ionising radiation in fibroblasts from ataxia-without-telangiectasia patients. Int. J. Radiat. Biol., 74, 287-295.

J. Hall and S. Angèle (1999) Radiation, DNA damage and cancer. Radiation, DNA damage and cancer. Molecular Medecine Today (in press).

A.A. van Zeeland, A.J.L. de Grott, J. Hall and F. Donato. 8-Hydroxydeoxyguanosine in DNA from leukocytes of healthy adults: relationship with cigarette smoking, environmental tobacco smoke, alcohol and coffee consumption. Mutat. Res. (in press).

W. Jongmans and J. Hall. (1999) Cellular responses to radiation and risk of breast cancer. European J. Cancer (in press).

J-O. Bay, N. Uhrhammer, J. Hall , D. Stoppa-Lyonnet , Y-J Bignon, Fonctions du gène *ATM* et aspects phenotypiques de l'Ataxie telangiectasie. Médecine & Sciences (in press).

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2
Photocopy this page or follow this format for each person

NAME	POSITION TITLE
KRUTOVSKIKH, Vladimir	Staff scientist

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education such as nursing and include postdoctoral training*)

INSTITUTION AND LOCATION	DEGREE (*if applicable*)	YEAR(s)	FIELD OF STUDY
I P Pavlov First Medical Institute, Leningrad, Russia	M D	1976-81	Medicine
Cancer Research Centre, Moscow, Russia	Ph D	1976-80	Medical Sciences

RESEARCH AND PROFESSIONAL EXPERIENCE Concluding with present position list in chronological order previous employment experience and honors Include present membership on any Federal Government public advisory committee List in chronological order the titles all authors and complete references to all publications during the past three years and to representative earlier publications pertinent to this application If the list of publications in the last three years exceeds two pages select the most pertinent publications **DO NOT EXCEED TWO PAGES.**

Research and professional experience

- 1976-1981 Post-graduate student, Department of Chemical Carcinogenesis, All-Union Cancer Research Center, Moscow, USSR (supervisor Dr V S Turusov)
  1981-1987 Scientist, Department of Chemical Carcinogenesis, All-Union Cancer Research Center, Moscow, USSR (supervisor Dr V S Turusov)
- 1987-1988 Senior Scientist, Department of Chemical Carcinogenesis, All-Union Cancer Research Center, Moscow, USSR (supervisor Dr V S Turusov)
- 1988-present Scientist, Unit of Multistage Carcinogenesis, International Agency for Research on Cancer, WHO, Lyon, France

Fellowships

- 1993 - Fellowship from Wannergren Foundation, Karolinska Institute, Stockholm, Sweden
- 1995-1996 Fellowship from Foundation for Promotion of Cancer Research, National Cancer Center Research Institute, Tokyo, Japan

Memberships

- Corresponding member of American Association for Cancer Research
- A member of Japanese Cancer Association

ist of recent publications

1 Bager Y , Kenne K , **Krutovskikh V** , Mesnil M , Traub O , Yamasaki H , & Warngard L (1994) - Alteration in expression of gap junction proteins in rat liver after treatment with 3,4,5,3',4'- Pentachlorobiphenyl *Carcinogenesis, v 15, 2439-2443*

2 Yamasaki H , Mesnil M , and **Krutovskikh V** (1994) Aberrant control of gap junctional intercellular communication during multistage carcinogenesis *Proceedings of the Conference Cancerogenesi ed Anticancerogenesi, Bologna, pp 53-67*

3 Troyanovsky S M , Troyanovsky R B , Eshkind L G , **Krutovskikh V.A.,** Leube R E & Franke W W (1994) Identification of the plakoglobin-binding domain in desmoglein and its role in plaque assambly and intermediate filament anchorage *The Journal of Cell Biology, 127 151-160*

4 Mesnil M , **Krutovskikh V.A.,** Piccoli C , Elfgang C , Traub O , Willecke K , and Yamasaki H (1995) Negative growth control of HeLa cells by connexin genes connexin-species specificity *Cancer Research, 55 629-639*

5 Mesnil M , **Krutovskikh V** , Piccoli C , Elfgand C , Traub O , Willecke K , and Yamasaki H (1995) Growth inhibition of connexin 26 in HeLa cells *Progress in Cell Res vol 4, Editors Y Kanno, K Kataoka, Y Shiba, Y Shibata and T Shimazu Elsevier Science B V (Amsterdam),pp 141-144*

6 **Krutovskikh V.,** and Yamasaki H (1995) *Ex vivo* dye transfer assay as an approach to study gap junctional intercellular communication *Progress in Cell Res vol 4, Editors Y Kanno, K Kataoka, Y Shiba, Y Shibata and T Shimazu Elsevier Science B V (Amsterdam) Pp 93-97*

7 Yamasaki H , Mesnil M , Omori Y , Mironov N and **Krutovskikh V.** (1995) Aberrant control cf connexin expression and functions in multistage rat and human hepatocarcinogenesis *Progress in Cell Res vol 4, Editors Y Kanno, K Kataoka, Y Shiba, Y Shibata and T Shimazu Elsevier Science B V (Amsterdam) pp 79-82*

8 **Krutovskikh V.,** Mesnil M , Mazzoleni G & Yamasaki H (1995) Inhibition of rat gap junction intercellular communication by tumor promoting agents *in vivo*, association with aberrant localization of connexin proteins *Lab Investigation, v 72, No 5, pp 571-577*

9 Guerrier A , Fonlupt P , Morand I , Rabilloud R , Audebet C , **Krutovskikh V** , Gros D , Rousset B & Munari-Silem Y (1995) Connexin 32 and connexin 43 expressed in thyroid epithelial cells assemble into separate gap junctions which are located in distinct regions of the lateral plasma membrane *J Cell Science, vol 108, part 7,pp 2609-2614*

10 Chaumontet C , Suschetet M , Honicman-Leban E , **Krutovskikh V.A** , Le Bon A -M , Berges R , Heberden C , Shahin M M , Yamasaki H & Martel P (1996) Lack of liver tumor promoting effects of flavonoids In vivo and in vitro studies on gap junctional intercellular communication *Nutrition and Cancer,vol 26, pp 251-263*

11 **Krutovskikh V.A** , Mironov N M and Yamasaki H (1996) Human connexin37 is polymorphic but not mutated in tumors *Carcinogenesis, vol 17, no 8 pp1761-1763*

12 Omori Y , **Krutovskikh V.A.,** Tsuda H , and Yamasaki H (1996) Connexin32 gene mutation in a chemically induced rat liver tumor *Carcinogenesis, vol 17 no 9, pp 2077-2080*

13 Tsuda H , Asamoto M , Iwahori Y , Hori T , Ota T , Baba-Toriyama H , Uehara N , Kim D J , **Krutovskikh V.A** , Takasuka N , Tsuchiya T , Mutai M , Tatematsu M and Yamasaki H (1996) Decreased connexin32 and a characteristic enzyme phenotype in clofibrate-induced preneoplastic lesions not shared with spontaneously occurring lesions in the rat liver *Carcinogenesis, vol 17, no 11, pp2441-2448*

14 Hori T , Asamoto , **Krutovskikh V** , Iwahori Y , Maeda M , Toriyama-Baba H , Takasuka N And Tsuda H (1997) Triazine derivatives inhibit rat hepatocarcinogenesis but do not enhance gap junctional intercellular communication *Jpn J Cancer Res , 88,12-17*

15 Sekine K , Watanabe E , Nakamura J , Takasuka N , Kim Dae Joong, Asamoto M , **Krutovskikh V.**, Baba-Toriyama H , Ota T , Moore M A , Masuda M Sugimoto H , Nishino H Kakizoe T and Tsuda H (1997) Inhibition of Azoxymethane-initiated colon tumor by bovine Lactoferrin administration in F344 rats *Jpn J Cancer Res* 88, 523-526

16 **Krutovskikh V.,** Asamoto M , and Tsuda H (1997) Differential dose-dependent effect of α–, β–carotenes and lycopene on gap junction intercellular communication in rat liver *in vivo Jpn J Cancer Research, 88 1121-1124*

17 Asamoto M , Toriyama-Baba H **, Krutovskikh V. A,** Cohen S M and Tsuda H (1998) Enhanced tumorigenicity of rat bladder carcinomas by abrogation of gap junctional intercellular communication *Jpn J Cancer Research, 89 481-486*

18 **Krutovskikh V. A**, Yamasaki Hiroshi, Tsuda Hiroyuki, and Asamoto Makoto (1998) Inhibition of intrinsic gap junction intercellular communication and enhancement of tumorigenicity of rat bladder carcinoma BC31 cell line by dominant-negative Cx43 mutant *Mol Carcinogenesis, 23 254-261*

19 Saito T , **Krutovskikh V.,** Bennett W P , Ishak K , Marion M -J and Yamasaki H (1999) Cx37 gene polymorphisms and mutations in human hemangiosarcomas associated with various exposures to vinyl chloride and thorotrast *Carcinogenesis* (Submitted)

20 Yamasaki H , **Krutovskikh V** , Mesnil M Tanaka T , Zaidan-Dagli M -L and Omori Y (1999) Role of connexin (gap junction) genes in cell growth control and carcinogenesis *Comptes-Rendus de l'Academie des Sciences* (Submitted)

`eviews

1 Yamasaki H , Mesnil M , Omori Y , Mironov N , **Krutovskikh V.** (1995) Intercellular communication and carcinogenesis *Mutation Research*, 333, 181-188

2 Mesnil M , **Krutovskikh V** , Omori Y and Yamasaki H (1996) Role of blocked gap junctional intercellular communication in non-genotoxic carcinogenesis *Toxicol Lett* 82/83,701-706

3 **Krutovskikh V.A.*** and Yamasaki H (1997) The role of gap junctional intercellular communication disorders in experimental and human carcinogenesis *Histology and Histopathology Journal*, 12 761-768 (*Invited reviewer)

4 (b)(4), (b)(6) [redacted]

Chapters in Monographs

- Zackheim H S , Zurcher C , **Krutovskikh V.A** & Troyanovsky S M (1990) Tumors of the skin In *Pathology of tumors in laboratory animals Tumors of the rat Eds Turusov V S & Mohr U IARC Scientific Publications No 99, Lyon, pp 1-35*
- **Krutovskikh V.A.** and Turusov V S (1994) Tumors of the intestines In *Pathology of tumors in laboratory animals Vol 2 - Tumors of the mouse Second edition Eds Turusov V S & Mohr U IARC Scientific Publications No 111, Lyon, pp 195-222*
- **Krutovskikh V.A**, and Yamasaki H (1998) Gap junction intercellular communication as a method to test, predict and interpret carcinogenicity *(Chapter for "CARCINOGENICITY Testing, predicting and interpreting carcinogenicity", by Marcel Dekker Inc , Edited by Kitchin K T pp 267-289)*

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME
MALAVEILLE, Christian

POSITION TITLE
Scientist

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
National Institute of Applied Sciences, Lyon, France	Engineer	1969	Biochemistry
University of Lyon, France	Dr. -Engineer	1973	Biochemistry

RESEARCH AND PROFESSIONAL EXPERIENCE. Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. **DO NOT EXCEED TWO PAGES.**

Employment

1969 - 1972 — Research Associate at the National Institute of Applied Sciences, Lyon, France. Laboratory of Biochemistry (Director: H. Pacheco). Transplacental chemical carcinogenesis: metabolism, DNA and protein binding of 3-methylcholanthrene in mouse tissues (mothers, foetuses and new-born).

1973-1993 — Scientist, Unit of Environmental Carcinogens and Host Factors, International Agency for Research on Cancer, Lyon, France. Bacterial short-term mutagenicity assays: development and validation studies. Characterization and identification of mutagens in complex mixtures. *In vivo* metabolic activation of environmental carcinogens. Drug and carcinogen comparative metabolism. Monoclonal antibody directed analysis of cytochrome P-450 dependent reactions. Development of non-invasive methods to assay carcinogen metabolism in man. Study on metabolic phenotypes as possible markers of susceptibility to chemical-induced cancer.

1994-to-date — Scientist, Unit of Endogenous Cancer Risk Factors, International Agency for Research on Cancer, Lyon, France. Role of *Helicobacter pylori* infection in stomach carcino-genesis. Role of genetic polymorphisms in detoxification/ antioxidant enzymes in cancer of the bladder, pancreas, stomach and lung. Dietary phenolics as anti-genotoxin/carcinogens in bladder of smokers.

Selected publications

Lin, D.X., Malaveille, C., Park, S.S., Gelboin, H.V. & Bartsch, H. (1990) Contribution of DNA methylation and benzylation to *N*-nitroso-*N*-benzyl-methylamine induced mutagenesis in bacteria: effects of rat liver cytochrome P450 isozymes and glutathione transferases. *Carcinogenesis*, **11**, 1653-1658

Peluso, M., Castegnaro, M., Malaveille, C., Friesen, M., Garren, L., Hautefeuille, A., Vineis, P., Kadlubar, F. & Bartsch, H. (1991) 32P-Postlabelling analysis of urinary mutagens from smokers of black tobacco implicate 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhiP) as a major DNA-damaging agent. *Carcinogenesis*, **12**, 713-717

Antilla, S., Vainio, H., Hietanen, E., Camus, A.-M., Malaveille, C., Brun, G., Husgafvel-Pursiainen, K., Heikkilä, L., Karjalainen, A. & Bartsch, H. (1992) Immunohistochemical detection of pulmonary cytochrome P450IA and metabolic activities associated with P450IA1 and P450IA2 isozymes in lung cancer patients. *Environ. Health Persp.*, **98**, 179-182

Malaveille, C., Hautefeuille, A., Brun, G., Vineis, P. & Bartsch, H. (1992) Substances in human urine strongly inhibit bacterial mutagenicity of 2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP) and related heterocyclic amines. *Carcinogenesis*, **13** (12) 2317-2320

Pignatelli, B., Malaveille, C. & Bartsch, H. (1993) Intragastric mutagens and altered anti-oxidant defence as risk factors for gastric cancer. *Eur J. Cancer Prev.*, **2** (Supplement 2), 9-11

Bartsch, H., Malaveille, C., Friesen, M., Kadlubar, F.F & Vineis, P. (1993) Black (air-cured) and blond (flue-cured) tobacco cancer risk. IV: Molecular dosimetry studies implicate aromatic amines as bladder carcinogens. *Eur. J. Cancer*, **29A** (8), 1199-1207

Pignatelli, B , Malaveille, C., Rogatko, A., Hautefeuille, A., Thuillier, P., Muñoz, N , Moulinier, B., Berger, F., De Montclos, H , Lambert, R., Correa, P , Ruiz, B., Sobala, G M , Schorah, C J , Axon, A.T R. & Bartsch, H (1993) Mutagens, *N*-nitroso compounds and their precursors in gastric juice from patients with and without precancerous lesions of the stomach. *Eur. J Cancer*, **29A** (14), 2031-2039

Vineis, P., Bartsch, H., Caporaso, N , Harrington, A.M., Kadlubar, F.F , Landi, M.T., Malaveille, C , Shields, P.G., Skipper, P., Talaska, G & Tannenbaum, S.R. (1994) Genetically based *N*-acetyltransferase metabolic polymorphism and low-level environmental exposure to carcinogens. *Nature*, **369**, 154-156

Malaveille, C., Brun, G. & Bartsch, H. (1994) Structure-activity studies in *E coli* strains on ochratoxin A (OTA) and its analogues implicate a genotoxic free radical and a cytotoxic thiol derivative as reactive metabolites. *Mutat. Res.* **307**, 141-147

Pignatelli, B., Bancel, B., Malaveille, C., Calmels, S., Correa, P., Patricot, L.M. & Ohshima, H. (1994) Defence against oxidative stress in relation to *Helicobacter pylori* infection and precancerous conditions of the stomach. *Eur. J Cancer Prev.*, **3**, 108-109

Bartsch, H., Rojas, M , Alexandrov, K., Camus, A -M , Castegnaro, M , Malaveille, C., Antilla, S , Hirvonen, K., Husgafvel-Pursiainen, K., Hietanen, E. & Vainio, H (1995) Metabolic polymorphism affecting DNA binding and excretion of carcinogens in humans *Pharmacogenetics*, **5**, 584-590

Vineis, P., Talaska, G., Malaveille, C., Bartsch, H., Martone, T , Sithisarankul, P. & Strickland, P. (1996) DNA adducts in urothelial cells: relationship with biomarkers of exposure to arylamines and aromatic hydrocarbons from tobacco smoke. *Int J. Cancer*, **65**, 314-316

Landi, M T , Zocchetti, C., Bernucci, I., Kadlubar, F.F., Tannenbaum, S., Skipper, P., Bartsch, H., Malaveille, C., Shields, P., Caporaso, N.E. & Vineis, P. (1996) Cytochrome P4501A2: enzyme induction and genetic control in determining 4-aminobiphenyl-hemoglobin adduct levels *Cancer Epidemiol. Biomarkers Prev* , **5**, 693-698

Malaveille, C., Hautefeuille, A., Pignatelli, B , Talaska, G., Vineis, P. & Bartsch, H (1996) Dietary phenolics as anti-mutagens and inhibitors of tobacco-related DNA adduction in the urothelium of smokers. *Carcinogenesis*, **17**, 2193-2200

Bartsch, H., Malaveille, C., Lowenfels, A., Maisonneuve, P., Hautefeuille, A , & Boyle, P. (1998) Genetic polymorphism of *N*-acetyltransferases, glutathion-S-transferase M1 and NAD(P)H: quinone oxidoreductase in relation to risk of pancreatic disease. *Eur. J. Cancer Prev.*, **7**, 215-223

Malaveille, C., Hautefeuille, A., Pignatelli, B., Talasaka, G., Vineis, P. & Bartsch, H. (1998) Antimutagenic dietary phenolics as antigenotoxic substances in urothelium of smokers. *Mutat. Res.*, **402**, 219-224

Peluso, M , Airoldi, L., Munnia, A., Martone, T., Coda, R., Malaveille, C., Giacomelli, G , Terrone, C., Casetta, G. & Vineis, P (1998) White blood cells DNA adducts, smoking, and NAT2 and GSTM1 genotypes in bladder cancer: a case-control study. *Cancer Epidemiol. Biomarkers Prev.*, **7**, 341-346

Martone, T., Airoldi, L., Magagnotti, C., Coda, R., Randone, D., Malaveille, C., Avanzi, G., Merletti, F., Hautefeuille, A. & Vineis, P. (1998) 4-Aminobiphenyl-DNA adducts and p53 mutations in bladder cancer. *Int. J Cancer*, **75**, 512-526

Saarikoski, S.T., Voho, A , Reinikainen, M. , Anttila, S , Karjalainen, A., Malaveille, C , Vainio, H., Husgafvel-Pursiainen, K. & Hirvonen, A. (1998) Combined effect of polymorphic *GST* genes on individual susceptibility to lung cancer. *Int. J. Cancer*, **77**, 516-521

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

Other Support—Dr. J. M. Rice, Principal Investigator
(Note: no other key personnel have "other support" available)

I. Active support

(b) (4) 01/01/99—12/31/99 (b) (4) %
$ 91 200

"IARC Monographs on Evaluation of Carcinogenic Risks to Humans"

Overlap: No overlap with NCI cooperative agreement. These funds represent institutional support of the Monographs Programme, other than salaries, and are for all costs incurred by IARC staff including supplies, computer equipment and software, duty travel, copier equipment, etc.

(b) (4) 01/09/98—31/08/99 (b) (4) %)
$27 800

"Cooperation between the European Union and the International Agency for Research on Cancer in relation to the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans."

Overlap: No overlap with NCI cooperative agreement. Funds used to support 3rd Monographs meeting each year and scientific or advisory meetings relevant to the Monographs Programme. No salaries included.

CR 824264-01 01/12/98—30/11/99 (b) (4) %)
U.S. Environmental Protection Agency $22 100

"International Research, Evaluation and Education in Environmental Carcinogenesis"

Overlap: No overlap with NCI cooperative agreement. Funds used to support 3rd Monographs meeting each year and scientific and advisory meetings relevant to the Monographs programme. No salaries included.

U.S. National Institute of Environmental Health Sciences **(no time limit)** (b) (4) %)
$79 600 in 1998

Donation in support of the Monographs Programme, used to support 3rd Monographs meeting each year and scientific and advisory meetings relevant to the Monographs. No salaries included.

II. Pending support

None

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

dk

Other Support—Dr. J. M. Rice, Principal Investigator
(Note: no other key personnel have "other support" available)

I. Active support

Regular Budget, International Agency for Research 01/01/99—12/31/99 20%
on Cancer (budgetary level subject to change from year to year) $ 91 200

"IARC Monographs on Evaluation of Carcinogenic Risks to Humans"

Overlap: No overlap with NCI cooperative agreement. These funds represent institutional support of the Monographs Programme, other than salaries, and are for all costs incurred by IARC staff including supplies, computer equipment and software, duty travel, copier equipment, etc.

SOC 98 201160 05F05
European Commission, Directorate General V 01/09/98—31/08/99 (0%)
$27 800

"Cooperation between the European Union and the International Agency for Research on Cancer in relation to the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans."

Overlap: No overlap with NCI cooperative agreement. Funds used to support 3rd Monographs meeting each year and scientific or advisory meetings relevant to the Monographs Programme. No salaries included.

CR 824264-01 01/12/98—30/11/99 (5%)
U.S. Environmental Protection Agency $22 100

"International Research, Evaluation and Education in Environmental Carcinogenesis"

Overlap: No overlap with NCI cooperative agreement. Funds used to support 3rd Monographs meeting each year and scientific and advisory meetings relevant to the Monographs programme. No salaries included.

U.S. National Institute of Environmental Health Sciences **(no time limit)** (5%)
$79 600 in 1998

Donation in support of the Monographs Programme, used to support 3rd Monographs meeting each year and scientific and advisory meetings relevant to the Monographs. No salaries included.

II. Pending support

None

CONTINUATION SHEET: STAY WITHIN MARGINS. INDICATED

RESOURCES

FACILITIES: Specify the facilities to be used for the conduct of the proposed research. Indicate the performance sites and describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary.

Laboratory:

Clinical:

Animal:

Computer: A network of PCS (Windows NT platforms) with Microsoft Word 97 word processing software and Quark desk-top publishing software are available for document preparation and for indexing, retrieval, and processing of scientific literature. A dedicated MacIntosh webserver is available.

Office: Excellent conference facilities, with multiple adjoining meeting rooms to accommodate both plenary and subgroup sessions and with modern audiovisual equipment.

Other: Multilingual staff members participating in the Monographs Secretariat can assist working groups of experts in on-the-spot translation and interpretation of articles published in virtually all modern scientific languages.

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

The IARC Library has subscribed to major scientific journals related to cancer research since its inception in 1967.

The Library, meeting rooms, and staff offices are all located on several floors of the main IARC building. All necessary computer equipment to support the programme is available.

RESEARCH PLAN

A. Specific aims

1. *Directory of Agents being Tested for Carcinogenicity*

The aims of this project are to survey which chemicals and other agents are being tested for carcinogenicity in experimental animals worldwide under circumstances in which publication of the results can reasonably be anticipated, and to make this information freely and publicly available. For each chemical or agent under test, the laboratory, principal investigator, species, strain, route of administration, dosage levels and the stage of the bioassay are recorded; references are provided to published results of bioassays previously documented. The expected availability of new bioassay information is used in the long-term planning of Monographs evaluations. Other significant aims are to increase communication among scientists, and to avoid unnecessary expense and duplication of effort. Extensive bioassays of novel pharmaceutical and agricultural agents that are proprietary to commercial firms and intended to support registration of these agents for sale are often not published and therefore will not be accessible to the Monographs Programme; the *Directory* does not include such bioassays.

2. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*

The basic aim of the IARC Monographs Programme is to publish timely, critical reviews of the published scientific literature on the possible carcinogenicity to humans of environmental agents (chemicals, groups of chemicals, complex mixtures, physical or biological agents) or exposure circumstances (occupational exposures, lifestyle and cultural habits). The reviews include evaluations of the strength of the total published scientific evidence that a carcinogenic hazard to humans exists. These are agreed upon through international co-operation in working groups of scientific experts. Working groups prepare monographs on a series of individual agents or exposures, which are published and widely distributed. Summaries of evaluations are also posted on the IARC internet website at http://www.iarc.fr. Selected agents are re-reviewed when an evaluation may change as a result of additional published data, or in light of advances in understanding of mechanisms of carcinogenic action in humans and in animals.

Wide dissemination of the information contained in the Monographs is an important goal. Each volume is printed in 3500 copies, many of which are distributed free of charge to libraries, governmental organizations, and interested scientists. This distribution is carried out by the U.S. National Cancer Institute for the USA and Canada, and by IARC for other regions. Monographs may also be purchased from IARC Press (Lyon) or from the World Health Organization, Distribution and Sales Service (Geneva).

To make the Monographs even more accessible, complete and searchable electronic versions of the complete set of Monographs published to date is planned for the next five-year period. These will include both CD-ROM and on-line internet versions that will be regularly updated and made available by subscription in parallel with the standard printed versions.

B. Background and significance

Shortly after the organization of IARC, requests were received from many sources for lists of proven and possible human carcinogens. It rapidly became clear that it would not be possible to summarize, in the form of simple lists, the extensive quantitative and qualitative data on individual agents. A tentative list of carcinogens could be compiled only after painstaking collection and critical analysis of the available data for each agent. It was decided that such analyses should be carried out by independent external scientific experts who had direct experience relevant to evaluation of a given agent, and that these experts would work in close collaboration with Agency staff in the preparation of these reviews.

This decision gave birth in 1969 to the IARC Monographs Programme, in which critical and comprehensive reviews were prepared of published scientific data on experimental carcinogenicity and on human cancer associated with exposure to chemicals or groups of chemicals. Priority for inclusion in the Monographs was initially given to specific chemicals for which carcinogenicity to humans was most strongly suspected, usually from occupational exposures. Subsequently, the scope of the Monographs was expanded to include exposures to complex mixtures of chemicals, such as those that occur in some occupations or as a result of personal habits such as use of tobacco [1,2] or alcoholic beverages [3], and later to physical and biological agents, including various forms of radiation [4,5] and infection with certain parasites [6], bacteria [6], and viruses [7-10]. Expansion of the programme was greatly assisted by the initiation in 1973 of financial support from the U.S. National Cancer Institute.

Each monograph begins with a brief description of the properties of the agent; methods for its detection and analysis; a description of methods and quantities of production and use (where appropriate); and data on occurrence and human exposures. All Monographs contain comprehensive summaries of case reports and epidemiological studies of cancer in humans associated with exposure to the agent, and comprehensive summaries of bioassays for carcinogenicity in experimental animals. Other relevant biological data, including metabolic pathways, other toxic effects, genetic toxicology, and data concerning mechanisms of carcinogenic action, that are relevant to an evaluation of carcinogenicity to humans, conclude each volume. The first part of this general scheme is modified appropriately when dealing with agents other than chemicals or chemical mixtures.

In 1987, in Supplement 7 to the Monographs [11], a system for formal classification of the strength of the total evidence for carcinogenic hazard to humans was introduced. Since that time, each Monographs review has concluded with a formal evaluation that places the agent or exposure that has been reviewed into one of five groups. These are:

Group 1—carcinogenic to humans;
Group 2A—probably carcinogenic to humans;
Group 2B—possibly carcinogenic to humans;
Group 3—cannot be classified as to carcinogenicity to humans; and
Group 4—probably not carcinogenic to humans.

Criteria for inclusion in each group are described in detail in the Preamble to the Monographs (Appendix: Attachment 1), together with the procedures followed by working groups in preparing the documents and arriving at their evaluations. The degrees of evidence for cancer in humans as a result of exposure to an agent, and for carcinogenicity to experimental animals in bioassays, are separately evaluated first, using predefined criteria. An overall evaluation is then made taking into consideration the human and the animal data, and also other relevant data, which vary according to the nature of the exposure under evaluation. For chemicals, they may include pathways of biotransformation in experimental animals and in humans; biomarkers of exposure and of tissue injury; genetic toxicology including patterns of mutation; and other evidence that may contribute to a judgement regarding the carcinogenic hazard posed to human beings by exposure to the agent.

These independent, scientific evaluations of carcinogenicity are useful to scientific investigators as authoritative reviews of the subject matter, and have proved valuable to national public health and regulatory authorities and to other international organizations as a basis for risk management initiatives. Information contained in the Monographs is restricted to the publicly available published literature, and is only one of many elements considered by decision makers in formulating risk management policies for exposures to carcinogens. The Monographs do not include quantitative estimations of cancer risk and do not extrapolate risk analyses beyond the levels of exposure reported in published studies.

New research findings relevant to an evaluation of carcinogenicity which are published in the scientific literature after an evaluation has taken place may modify the total evidence for carcinogenicity to such an extent that a new review and evaluation is required. Some especially well-studied agents have therefore been evaluated

as many as three or four times in the light of new research findings (e.g., polychlorinated dibenzodioxins in 1977, 1987, and 1997 [12-14]).

In 1992, the Preamble to the Monographs was revised, in the light of scientific advances in understanding the modes of action of various categories of carcinogenic agents, to allow inclusion of information on mechanisms of carcinogenic action in overall evaluations and classifications of carcinogenic agents [15]. As a result, certain agents (for example, chemically reactive alkylating agents such as diethyl sulfate [16]) for which there were no data for cancer in humans, but overwhelmingly positive data for carcinogenicity to animals were classified upward, from Group 2B to Group 2A, when the mechanism of carcinogenic action was well understood and there was clear evidence that the mechanism operated in humans as well as in animals. More recently, as evidence has accumulated that in some cases agents may induce neoplasms in experimental animals by mechanisms that do not predict carcinogenicity to humans, a few agents that do cause tumors in experimental animals (e.g., *d*-limonene and saccharin) have been classified or reclassified downward, from Group 2B to Group 3 [17]. The classification process is thus a dynamic one that takes into account both the publication of new data and advances in scientific understanding of carcinogenic processes.

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

Causative factors for many common human cancers have still not been identified or are poorly understood, and thus epidemiological and experimental research on cancer causation continues to be needed. Moreover, the data generated by such research must be compiled and critically reviewed to be useful for primary prevention of cancer. The comprehensive, critical reviews and independent evaluations by international working groups of experts in epidemiology, experimental carcinogenesis, and related scientific disciplines produced by the IARC Monographs have proved useful worldwide to national and international agencies involved in cancer risk assessment and management. During the period 1995—1999, 12 additional agents were added to Group 1,*carcinogenic to humans* (Table 1), clearly indicating that the list of environmental causes of human cancer is not yet complete.

Table 1. Agents evaluated as *carcinogenic to humans* (Group 1) during 1995-1999.

Volume	Year	Agent
62	1995	Wood dust
64	1995	Human Papillomavirus types 16 and 18
66	1996	Tamoxifen
67	1996	Human Immunodeficiency Virus 1; Human T-cell Lymphotropic Virus I
68	1997	Crystalline silica [a]
69	1997	2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (TCDD)
70	1997	Epstein-Barr Virus (Human herpesvirus 4)
72	1998	Combined oral contraceptives; postmenopausal oestrogen therapy
75	1999	X-rays and gamma-rays; neutrons

[a] Inhaled in the form of quartz or cristobalite from occupational sources

C. Progress report (6 May 1995—29 February 2000)

The cooperative agreement through which the U.S. National Cancer Institute contributes funding and expertise to the IARC Monographs Programme was last reviewed in 1995. Since the previous review, the *Directory of Agents being Tested for Carcinogenicity* has been converted from a hard-copy document published biannually, to an electronic publication available freely on the IARC website and updated several times each year. The final hard copy version of that series, Number 17, was published in May 1996. Monographs and related documents have been published at the rate of (usually) three volumes of Monographs and one or two additional documents annually. Reports related to Monographs evaluations have also been published in the scientific literature (see list of publications at the end of this application for titles).

Three scientific meetings have been convened to discuss special topics relevant to evaluations of carcinogenic risk. These dealt with mechanisms of carcinogenesis by inhalation of fibres (1996); the use of novel short- and medium-term tests for carcinogens and newer methods in genetic toxicology, including the use of genetically engineered animals as test subjects (1997); and interspecies differences in mechanisms of carcinogenesis in urinary bladder, renal cortex, and thyroid follicular epithelium (1997). Individually authored papers and a consensus report were published in book form in the IARC Scientific Publications series, and the conclusions of the meetings—summarized in the consensus report—were subsequently used to guide consideration of these topics in IARC Monographs working group meetings. In addition, the proceedings of an earlier similar meeting on peroxisome proliferation and its role in carcinogenesis was published as an IARC Technical Report.

Two international ad-hoc advisory groups were convened to consider how the Monographs Programme should address physical carcinogenic agents including non-ionizing radiation (April 1998), and to discuss priorities for evaluations (other than physical and biological agents) during the period 2000-2005 (September 1998). The conclusions and recommendations of these advisory groups were published as IARC Internal Reports No. 98/002 (Appendix: Attachment 2) and 98/004 (Appendix: Attachment 3), respectively.

Key personnel involved in the Programme have changed significantly during this period. The previous principal investigator, Dr. H. Vainio, left the Programme in June 1994 and Dr. H. Mpller, an epidemiolgist and toxicologist who had joined the Programme in 1992, served as its acting director until his departure in August 1995. Mr. J. D. Wilbourn then served as acting director of the Programme until Dr. J. M. Rice was recruited in June 1996 to direct the Programme and to serve as principal investigator. Dr. M. Blettner, an epidemiologist and biostatistician, was recruited to the Programme during September 1997—February 1999 and Dr. R. Baan, a genetic toxicologist, joined the Programme in October 1998.

1. *Directory of Agents being Tested for Carcinogenicity*

The *Directory* was originally compiled biannually and made available in hard copy as a published document. Because the information on bioassays is constantly changing, however, the books rapidly became outdated. Publication of the *Directory* in hard copy ceased with Number 17 (May 1996); since then, it has been maintained as an electronic publication freely available on the IARC internet website at http://www.iarc.fr. In this form it is updated several times each year as new information is provided by contributing laboratories, and thus is more up-to-date.

2. *Scientific advisory group meetings on special topics relevant to carcinogenic hazard identification*

Four scientific symposia have been convened in Lyon to address specific issues in carcinogenic hazard identification. The proceedings of each symposium have been published as IARC Technical Reports or Scientific Publications, and consist of invited papers authored by each participant, a scientific expert on the subject under discussion, together with a consensus report that is developed during the symposium. The consensus report gives guidance on the use of certain data on carcinogenic mechanisms, and these concepts are followed during

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

subsequent Monographs meetings. The Consensus Statements are also published electronically on the IARC website.

Peroxisome Proliferation and its Role in Carcinogenesis (IARC Technical Report No. 24, 1995) reviewed peroxisome proliferation as a mechanism for hepatocarcino-genesis in rodents by various classes of compounds, and developed criteria for identifying substances and circumstances in which this mechanism could be operative in rodents but not in humans.

Mechanisms of Fibre Carcinogenesis (IARC Scientific Publication No. 140, 1996) addressed the overall subject of carcinogenesis by inhaled particles, including particle size and dimensions and tissue reactions to fibres and to non-fibrous particles. The concepts developed in this meeting were subsequently applied to the evaluation of silica and other inhaled particles in IARC Monograph Volume 68, prepared in October 1996 and published in 1997.

The Use of Short- and Medium-term Tests for Carcinogens and Data on Genetic Effects in Carcinogenic Hazard Evaluation (IARC Scientific Publication No. 146, 1999) addressed the methodology of genetic toxicology, including novel assays for DNA damage (e.g, Comet); the use of genetically engineered rodents and of non-mammalian species for carcinogenicity and mutagenicity testing; the patterns of genetic alterations in cancer-related genes in tumors in humans and experimental animals; and the use of preneoplastic lesions and two-stage tumor induction protocols for the identification of chemical carcinogens.

Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis (IARC Scientific Publication No. 147, 1999) critically compared the pathogenesis of neoplasia in the thyroid follicular epithelium, renal cortex and urinary bladder urothelium in humans and in experimental animals. Causative agents known to target these tissues in animals and in humans were compared, and mechanisms of carcinogenesis that operate in rodents but that may not operate in humans under realistic conditions of human exposure were critically reviewed. Criteria were developed for applying mechanistic evidence to the overall evaluation of agents for which there is sufficient evidence for carcinogenicity in rodents at these organ sites, with or without neoplasms at additional sites, but for which there is inadequate evidence (or no data) for cancer in exposed humans. These criteria were first applied (for rodent tumors of kidney and urinary bladder) in Monographs Volume 73 (October, 1998), and will be applied to the re-evaluation of thyrotropic carcinogens in a future Monograph (tentatively planned for February 2001).

3. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*

To date, 71 volumes of IARC Monographs have appeared in print. Another four volumes are in preparation, representing the results and conclusions of four working groups convened in June and October of 1998 and in February and May of 1999. In the first 71 volumes, evaluations have been made for 834 agents, mixtures and exposures. Some of these have been evaluated more than once as additional data have been published. In Volumes 1-71, a total of 75 agents have been evaluated as carcinogenic to humans (Group 1); 59 as probably carcinogenic to humans (Group 2A); 225 as possibly carcinogenic to humans (Group 2B); 474 as unclassifiable as to carcinogenicity to humans on the basis of data currently available (Group 3), and one as probably not carcinogenic to humans (Group 4). The list of evaluations is appended (Attachment 4).

During the current period of the Cooperative Agreement, ten volumes of Monographs have been published (Volumes 62-71). An additional four working groups have met and prepared Volumes 72-75, which are currently in press or in preparation. A further two meetings are planned for October 1999 and February 2000. In IARC Monographs Volumes 1-73 and Supplements 1, 4, 6, and 7 a total of 805 scientific experts from 43 countries participated (Table 2).

Volume 62: Wood Dust and Formaldehyde (1995) reviewed the evidence for excess risk of cancer, particularly adenocarcinoma of the nasal cavities and paranasal sinuses, in woodworkers and concluded that there was sufficient evidence in humans for cancer hazard associated with exposure to wood dust, especially hardwood dust. There was inadequate evidence for cancer in experimental animals. Wood dust was classified as

CONTINUE ON PAGE: STAY WITHIN MARGINS INDICATED

carcinogenic to humans (Group 1). This was the first evaluation of wood dust *per se* by the IARC Monographs, although industries and occupations in which exposure to wood dust can occur had previously been reviewed in Volume 25 (1981). These data were subsequently updated in Supplement 7 (1987), when it was concluded on the basis of epidemiological studies of workers that furniture and cabinet-making entail exposures that are carcinogenic to humans (Group 1), and carpentry and joinery entail exposures that are possibly carcinogenic to humans (Group 2B). Exposures in the lumber and sawmill industries and the pulp and paper industries could not be classified as to their carcinogenicity to humans (Group 3) when evaluated in 1987.

Formaldehyde, which occurs as a natural product in most living systems as well as in the environment, was previously considered in Volume 29 (1982) and was first classified as probably carcinogenic to humans (Group 2A) in Supplement 7 (1987). There is sufficient evidence in animals for the carcinogenicity of formaldehyde, based principally on the induction of squamous-cell carcinomas of the nasal cavities in rats when given by inhalation at high concentrations. Excess risk of nasopharyngeal cancers including squamous-cell carcinoma was observed in some but not all epidemiological studies of industrial or professional groups exposed to formaldehyde, and suggest but do not conclusively establish a causal relationship. Evidence for cancer in humans remained limited and the overall evaluation of formaldehyde remained probably carcinogenic to humans (Group 2A).

Volume 63, Dry Cleaning, Some Chlorinated Solvents and other Industrial Chemicals (1995) included evaluation of employment in the dry cleaning industry, and of eight chlorinated solvents and related chemicals including some that are widely used in dry cleaning. Seven other industrial chemicals, including several with structural similarity to vinyl chloride, were also evaluated. Employment in the dry cleaning industry was classified as possibly carcinogenic to humans (Group 2B), solely on the basis of limited epidemiological data for cancer in humans. Many solvents used in dry cleaning are structurally similar to vinyl chloride which is a potent human carcinogen [18], and bioassay data were available for many of the eight chlorinated organic compounds evaluated. Trichloroethylene, tetrachloroethylene and 1,2,3-trichloropropane were classified in Group 2A; 1-chloro-2-methylpropene in Group 2B; and the other chlorinated compounds including chloral, chloral hydrate, dichloroacetic acid and trichloroacetic acid in Group 3. Of the other industrial chemicals, vinyl fluoride was classified in Group 2A; vinyl acetate, furan and benzofuran in Group 2B; and furfural, crotonaldehyde, and acrolein in Group 3. Other relevant data contributed to raising the final classifications of 1,2,3-trichloropropane, vinyl acetate, and vinyl fluoride.

CONTINUA ON PAGE: STAY WITHIN MA INS INDICATED

Table 2. Working Group participants, Volumes 1-73 and Supplements 1, 4, 6, and 7

COUNTRIES	NUMBERS OF PARTICIPANTS	COUNTRIES	NUMBERS OF PARTICIPANTS
ARGENTINA	2	KOREA	1
AUSTRALIA	18	LITHUANIA	1
AUSTRIA	2	LUXEMBOURG	1
BELGIUM	5	NETHERLANDS	25
BRAZIL	2	NEW ZEALAND	3
BULGARIA	2	NIGERIA	1
CANADA	25	NORWAY	8
CHINA	2	PAKISTAN	1
DENMARK	11	RUSSIAN FEDERATION	13
EGYPT	1	SERBIA	2
ESTONIA	1	SINGAPORE	1
FINLAND	22	SLOVAKIA	1
FRANCE	27	SOUTH AFRICA	13
GERMANY	57	SPAIN	3
GHANA	1	SWEDEN	30
GREECE	2	SWITZERLAND	17
HUNGARY	2	THAILAND	4
INDIA	3	TURKEY	1
IRELAND	1	UNITED KINGDOM	106
ISRAEL	1	UKRAINE	1
ITALY	40	USA	314
JAPAN	31		

TOTAL : 43 COUNTRIES and 805 PARTICIPANTS

CONTINU..ION PAGE: STAY WITHIN MA..3INS INDICATED

CONTINUA ON PAGE: STAY WITHIN MA. .INS INDICATED

Volume 64: Human Papillomaviruses (1995) was the third volume in the series on biological carcinogenic agents that began with *Volume 59: Hepatitis viruses* in 1994. Human papilloma virus (HPV) types 16 and 18 were classified as *carcinogenic to humans* (Group 1). HPV-16 causes invasive cervical carcinoma and probably carcinoma of the vulva, anus and penis, and HPV-18 is strongly linked to many squamous cancers and approximately half of the adenocarcinomas of the cervix. HPV types 31 and 33 were placed in Group 2A, and in recognition that this list of the carcinogenic HPVs is incomplete, a final evaluation was included that "some HPV types other than 16, 18, 31 and 33 are *possibly carcinogenic to humans* (Group 2B)."

Volume 65: Printing Processes and Printing Inks, Carbon Black and Some Nitro Compounds (1996) was the last volume in which an evaluation was made of a group of related industrial processes. Occupational exposures in printing processes were classified as *possibly carcinogenic to humans* (Group 2B) on the basis of limited evidence in humans, as was carbon black. Printing inks, however, could not be classified as to carcinogenicity to humans (Group 3). Of 13 aromatic nitro compounds or groups of compounds that were also classified in this volume, 7 were placed in Group 2B on the basis of sufficient evidence of carcinogenicity to animals in bioassays (tetranitromethane; nitrobenzene; 2-nitroanisole; 2,4-dinitrotoluene; 2,6-dinitrotoluene; 3,7-dinitrofluoranthene; and 3,9-dinitrofluoranthene). Six were not classifiable as to carcinogenicity to humans: nitrotoluenes (evaluated as a group); chloronitrobenzenes; 3,5-dinitrotoluene; 2,4,6-trinitrotoluene; musk ambrette; and musk xylene). The last two are di- and trinitrobenzene derivatives used in fragrances.

Volume 66: Some Pharmaceutical Drugs (1996) addressed members of three groups of prescription drugs: hypolipidemics, tissue-specific anti-oestrogens, and benzodiazepines and other tranquilizing or anti-convulsant drugs. Among the hypolipidemics, all of which cause peroxisome proliferation in rodent liver, clofibrate and gemfibrozil were both classified in Group 3 on the basis of less than sufficient evidence for carcinogenicity in experimental animals, and therefore consideration of the relevance to humans of peroxisome proliferation as a mechanism of carcinogenesis did not arise. Tamoxifen was classified as *carcinogenic to humans* (Group 1) on the basis of elevated risk for endometrial cancer in women given this drug; exceptionally, a note was added to the evaluation that "there is clear evidence that tamoxifen reduces the risk of contralateral breast cancer." Two other anti-oestrogens, toremifene and droloxifene, could not be classified as to carcinogenicity to humans (Group 3). Phenytoin (diphenylhydantoin) and oxazepam, a benzodiazepine tranquilizer, were both classified in Group 2B on the basis of sufficient evidence of carcinogenicity to experimental animals but inadequate evidence in humans. Another six benzodiazepines were classified in Group 3: diazepam, doxefazepam, estazolam, prozepam, ripazepam, and temazepam.

Volume 67: Human Immunodeficiency Viruses and Human T-cell Lymphotropic Viruses (1996) was the first Monograph on human retroviruses. The working group concluded that Human Immunodeficiency Virus-1 (HIV-1) is *carcinogenic to humans* (Group 1) on the basis of sufficient evidence in humans for increased risk of non-Hodgkins lymphoma mediated by HIV-1 related immune dysregulation and for increased risk of Kaposi's sarcoma, most likely in association with another infectious agent, possibly human herpesvirus-8. HIV-2 was evaluated as *possibly carcinogenic to humans* (Group 2B). Also, Human T-cell Lymphotropic Virus-I (HTLV-I) was evaluated as *carcinogenic to humans* (Group 1) based on sufficient evidence in humans for causation of adult T-cell leukemia/lymphoma. In contrast, there was inadequate evidence in humans for carcinogenicity of HTLV-II, which was evaluated as *not classifiable as to carcinogenicity to humans* (Group 3).

Volume 68: Silica, Some Silicates, Coal Dust and para-*aramid fibrils (1997)* re-evaluated a number of dusts and fibres to which humans are exposed by inhalation, applying principles articulated in the proceedings of the scientific advisory group previously convened to review the subject of inhalation carcinogenesis in depth (IARC, 1996). Special care was taken to define the subjects evaluated with great precision, to avoid possible over-interpretation of the findings by users of the resulting Monograph.

Crystalline silica, inhaled in the form of quartz or cristobalite from occupational sources, was evaluated as *carcinogenic to humans* (Group 1) based on sufficient evidence of increased lung cancer in workers employed in

certain industries where exposure to silica-containing mineral dusts was intensive, including granite quarrying and pottery manufacture, and in silicotics. Among other mineral dusts and fibres and related exposure, long palygorskite (attapulgite) fibres (>5 µm) were classified as *possibly carcinogenic to humans* (Group 2B) based on sufficient evidence for carcinogenicity to experimental animals. All other materials evaluated in this Monograph proved *not classifiable as to carcinogenicity to humans* (Group 3) as data were less than sufficient in both humans and animals. These materials included amorphous silica; *para*-aramid fibrils; coal dust; short palygorskite fibres (<5 µm); sepiolite; wollastonite; synthetic zeolites; and a number of natural zeolites including clinoptilolite, phillipsite, mordenite, and non-fibrous Japanese zeolite. An extensive explanatory chapter of General Remarks on the Substances Considered accompanied the Monographs.

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

Volume 69: Polychlorinated Dibenzo-para-*dioxins* [PCDDs] *and Polychlorinated Dibenzofurans (1997)* was the third review of PCDDs by the IARC Monographs, previous evaluations having taken place in 1977 and in 1987. The results reflect steadily increasing epidemiologic and experimental evidence for the carcinogenicity of the most toxic member of the PCDD series, 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD), that have accumulated during that twenty-year period. TCDD was classified as *carcinogenic to humans* (Group 1) on the basis of sufficient evidence of carcinogenicity to experimental animals, limited evidence of increased risk for all cancers combined in the most highly exposed industrial worker populations, and other relevant data including the following: (i) TCDD is a multi-site carcinogen in experimental animals that has been shown by several lines of evidence to act through a mechanism involving the Ah receptor; (ii) this receptor is highly conserved in an evolutionary sense and functions the same way in humans as in experimental animals; (iii) tissue concentrations are similar both in heavily exposed human populations in which an increased overall cancer risk was observed and in rats exposed to carcinogenic dosage regimens in bioassays. All other PCDDs, and the non-chlorinated parent compound, dibenzo-*para*-dioxin, were placed in Group 3, *not classifiable as to carcinogenicity to humans*. The lack of adequate bioassay data on all PCDDs other than TCDD precluded an evaluation based on carcinogenicity to animals, and there were no adequate epidemiological studies of cancer in humans for PCDDs other than TCDD. For similar reasons, all polychlorinated dibenzofurans were also placed in Group 3.

TCDD was only the second agent ever classified in Group 1 on the basis of sufficient evidence for carcinogenicity in animals but less than sufficient evidence for cancer in humans, buttressed by arguments based on mechanisms of carcinogenic action, and was the first non-genotoxic agent to be so classified.

Volume 70: Epstein-Barr Virus and Kaposi's Sarcoma Herpesvirus/Human Herpesvirus 8 (1997) was the final volume in the planned series of five Monographs on infectious agents as causes of human cancer. Epstein-Barr virus (EBV), the causative agent of infectious mononucleosis that is nearly ubiquitous in most human populations, was classified as *carcinogenic to humans* (Group 1) on the basis of epidemiologic data linking EBV infection with Burkitt's lymphoma, Hodgkin's disease, immunosuppression-related non-Hodgkin lymphoma, sinonasal angiocentric T-cell lymphoma, and nasopharyngeal carcinoma. Human herpesvirus 8, strongly implicated as the principle causative agent of Kaposi's sarcoma and primary effusion lymphoma on the basis of limited epidemiologic studies, was classified as *probably carcinogenic to humans* (Group 2A).

Volume 71: Some Organic Compounds, Hydrazine and Hydrogen Peroxide (1999) was undertaken to update the Monographs treatment of a large number of industrial chemicals and groups of chemicals (121 in all) that had previously been evaluated and classified in Groups 3, 2B, or 2A more than five years previously. Full monographs were prepared on four chemicals on which extensive new epidemiological and/or bioassay data had been published since the previous Monographs review: 1,3-butadiene, acrylonitrile, dichloromethane, and chloroprene. A summary of the conclusions of the meeting, the complete list of chemicals evaluated, and lists of chemicals for which any change in evaluation occurred, are given in the Appendix as Attachment 5, downloaded from the Monographs website (this also serves as an example of information on recent evaluations that is now openly available by internet).

Volume 72: Hormonal Contraception and Postmenopausal Hormone Therapy (in press) was convened in June 1998, and was scheduled at this time because of the very large number of women worldwide who take these substances, and the enormous literature that has accumulated since the most recent previous Monographs review

of these subjects (Supplement 7, 1987). Also, in a few years women who first took hormonal preparations for birth control in the late 1960s will pass the menopause and begin to receive postmenopausal hormone therapy, and thus there will be increasing difficulty in separating the two exposures in the future. Postmenopausal estrogen therapy was evaluated as *carcinogenic to humans* (Group 1) because of increased risk of endometrial carcinoma. For postmenopausal estrogen-progestogen therapy, in which a progestogen is included in the regimen to reduce the risk of endometrial carcinoma, there was nonetheless limited evidence for increased risk of endometrial carcinoma, and these regimens were classified as *possibly carcinogenic to humans* (Group 2B). Oral contraceptives combined (containing both estrogenic and progestogenic substances) were classified in Group 1 because of increased risk of liver cancer, but it was specifically noted that these regimens confer a significant protective effect for cancer of the ovary and uterine endometrium. Oral contraceptives containing progestogens only were classified as *possibly carcinogenic to humans* (Group 2B) solely on the basis of sufficient evidence for carcinogenicity to experimental animals in bioassays of a principal ingredient, medroxyprogesterone acetate; no epidemiological evidence suggested an increased risk of cancer at any site in users of these preparations.

Volume 73: Some Chemicals that Cause Kidney or Urinary Bladder Tumours in Rodents, and Some Other Substances (in preparation) was prepared in October 1998 and included evaluations or re-evaluations of 23 substances, some of which cause tumors of the urinary bladder in rats under conditions in which urinary calculi or phosphate-containing urinary precipitates are formed, which raised the issue of the predictive value of these assays for cancer hazard to humans. Also evaluated were some substances that induce epithelial tumors of the renal cortex in male rats, under conditions in which alpha-2-urinary globulin nephropathy occurs, also raising the issue of prediction of a human cancer hazard. This working group specifically sought to apply the principles for such evaluations developed at the scientific advisory group meeting that critically reviewed these issues in November 1998, and whose findings were published in IARC Scientific Publications No. 147 (1999). Substances re-evaluated with some change in the previous evaluations included atrazine, butyl benzyl phthalate, chlorothalonil, cyclamates, *ortho-* and *para*-dichlorobenzenes, hexachloroethane, *d*-limonene, melamine, paracetamol (acetaminophen), *ortho*-phenylphenol and its sodium salt, saccharin and its salts, and simazine.

Major mechanism-based evaluations resulted from this meeting. Saccharin and its salts were classified in Group 3, although the salts (but not the conjugate acid) are carcinogenic to the rat urinary bladder (but to no other organ site), because the irritant phosphate-containing urinary precipitate that mediates carcinogenesis in rats cannot form in human urine and thus the rat tumors do not predict human carcinogenic hazard [19, 20]. Melamine causes bladder tumors under conditions where urolithiasis occurs. Urinary tract calculi are a cancer hazard to humans, regardless of composition, [19, 21] and melamine was classified in Group 3 with the condition that this evaluation applied only to circumstances in which no bladder stones develop. *d*-Limonene was classified in Group 3, although it causes renal cortical tumors in male rats (and at no other site), because the alpha-2-urinary globulin nephropathy that leads to renal tumors in male rats does not occur in humans [19, 22]. However *para*-dichlorobenzene, which also causes renal tumors in male rats by the alpha-2-urinary globulin nephropathy mechanism, remained classified in Group 2B because it also causes liver tumors in mice, and the available data were inadequate to convince the working group that the liver tumors occurred by a mechanism that could with confidence be considered irrelevant to humans.

Other substances that were re-evaluated and for which no change was made in any element of the previous evaluation included allyl isothiocyanate, *ortho*-anisidine, chloroform, hexachlorobutadiene, nitrilotriacetic acid and its salts, potassium bromate, and quercetin. Methyl *tert*-butyl ether and *meta*-dichlorobenzene were evaluated for the first time and considered unclassifiable as to carcinogenicity to humans (Group 3).

Volume 74: Surgical Implants, Prosthetic Devices and Foreign Bodies (in preparation) was prepared in February 1999 and addressed the issue of foreign-body (solid state) carcinogenesis in humans by both metallic and non-metallic implants and foreign bodies. The most difficult issues were the complexity of composition of the devices actually used in humans, and the fact that most animal carcinogenicity data derived from studies of materials other than those used surgically in humans. A second difficult issue was that although there are many intriguing case reports of development of a cancer, usually a sarcoma, at the site of a pre-existing foreign body, in companion animals as well as in humans, there are few or no data that allow a computation of the expected

frequency of such co-occurrences and therefore an estimate of whether these cases result from chance alone. On the basis of bioassays in experimental animals, three categories of foreign bodies were evaluated as possibly carcinogenic to humans (Group 2B): polymeric implants prepared as thin, smooth films (with the exception of polyglycolic acid); metallic implants prepared as thin smooth films; and implanted foreign bodies of metallic cobalt, metallic nickel, and certain alloys of nickel, chromium and iron. All other implants and foreign bodies, including silicone breast implants, orthopedic implants, cardiac pacemakers, and dental materials were considered *not classifiable as to carcinogenicity to humans* (Group 3). The evidence for causation of breast cancer in women with silicone breast implants was consistently negative, meriting the evaluation of "evidence suggesting lack of carcinogenicity in humans," but it was considered too soon to make a similar evaluation for sarcomas of the breast because of the longer latency period for the latter neoplasms.

Volume 75: Ionizing Radiation, Part I: X-Rays, γ-Rays and Neutrons (in preparation) was prepared in June 1999. This was the first in a series of four planned meetings on physical carcinogenic agents that were recommended by an ad-hoc international advisory committee on priorities for evaluation of ionizing and non-ionizing radiation (Appendix: Attachment 2; see following section D on Research Design and Methods). The greatest importance of including these data in the Monographs is to complete the inventory of unequivocal human carcinogens that are physical agents and to provide context in which future evaluations of non-ionizing radiation can be made. X-rays, and more recently gamma rays, have been well documented as carcinogenic to exposed humans and were readily classified in Group 1. Neutrons, however, presented inadequate evidence for cancer in exposed humans but sufficient evidence for carcinogenicity to experimental animals. Strong supporting evidence for carcinogenesis-related chromosomal damage in exposed humans, together with other relevant data on mechanisms of carcinogenic action, were cited by the working group in elevating neutrons to Group 1 also, from what by default would have been Group 2B if only empirical carcinogenicity data had been considered in the evaluation. This is the first time that such a two-level escalation in the overall evaluation has occurred within the Monographs Programme on the basis of relevant data other than cancer endpoints.

In October 1999 a working group will convene to prepare *Volume 76: Some Antiviral and Antineoplastic Agents and Some Other Pharmaceutical Drugs.* This will be the first evaluation of nucleoside analogs that act as antiviral agents, especially antiretroviral agents, and was stimulated in part by the recent publication of findings that zidovudine (AZT), an effective antiretroviral agent now being given to pregnant HIV-infected women to prevent maternal-to-fetal HIV transmission, is an effective transplacental carcinogen in mice. [23] It will also be the first Monograph to consider carcinogenicity bioassays performed in genetically engineered mice, procedures for which were developed by the scientific advisory group that met in October 1997. [24] Drugs to be evaluated include the antiretroviral drugs zidovudine (AZT), zalcitabine (DDC), didanosine (DDI), and acyclovir; the topoisomerase inhibitors/antitumor drugs etoposide, mitoxantrone, and teniposide; the radiosensitizers bromo- and iododeoxyuridine; and various other pharmaceutical drugs including several vitamin K substances (acetomenaphthone, menadione, menadiol sodium phosphate, and phytomenadione), hydroxyurea and phenolphthalein. This listing has been posted on the IARC website.

In February 2000 a working group will convene to prepare *Volume 77: Some Industrial Chemicals,* including those compounds recommended most urgently by the September 1998 Advisory Committee on priorities for future evaluations (Appendix: Attachment 3). The issue of peroxisome proliferation as a mechanism of carcinogenesis in rodents and its predictive value for carcinogenic hazard to humans will arise in the course of this meeting. Specific compounds to be evaluated include: 2,2-bis(bromoethyl)-1,3-propanediol, 4- and 5-chloro-*ortho*-toluidine,cinnamyl anthranilate, coumarin, 2,3-dibromopropanol, diethanolamine, diethylhexyl phthalate, ethylbenzene, glycidol, naphthalene, nitromethane, N-nitrosodiethanolamine, pyridine, *ortho*-toluidine, and triethanolamine. This listing has been posted on the IARC website.

4. Ad-hoc Advisory Groups

During the last 5 years the Monographs Programme has been petitioned numerous times to evaluate various subjects of current popular concern, including various forms of non-ionizing radiation. This has focussed IARC's attention on the fact that physical carcinogenic agents—basically, various forms of radiation—have not yet

been systematically dealt with by the Monographs, despite the clear evidence of carcinogenicity of *ionizing* radiation to human beings, with the exceptions of ultraviolet and solar radiation [4,5] and radon. [25] An Ad-hoc Advisory Group on Physical Agents was convened in Lyon during 27-29 April 1998 to consider whether, and if so, in what manner, physical carcinogenic agents should be addressed within the Monographs. The Advisory Group recommended that forms of radiation that have not been previously reviewed should be systematically reviewed and evaluated in a series of four Monographs at yearly intervals, beginning in June 1999. The series should begin with ionizing radiation and progress to static and extremely low frequency electromagnatic fields (ELF) and finally to radiofrequency fields, including radar. The report of the Advisory Group has been published (Appendix: Attachment 2, IARC Internal Report No. 98/002). The first of these working groups has now met (June 1999) to prepare *IARC Monograph Volume 75: Ionizing Radiation, Part I: X-Rays, Gamma Rays and Neutrons*. It was further recommended that the future Monographs evaluation of carcinogenic hazards of non-ionizing radiation should be integrated with the international review of all environmental and health effects now being undertaken by the World Health Organization, and that the IARC evaluations should precede those of WHO. The IARC documents will be referenced in the WHO Environmental Health Criteria document, and the IARC effort will not be duplicated by WHO.

An Ad-hoc Advisory Group on Priorities was convened in Lyon during 16-18 September 1998 to review nominations for future evaluations that IARC solicited worldwide during the preceding year. The Advisory Group considered only chemicals and related exposures; physical agents were reviewed by the April 1998 Advisory Group and a second specialized Ad-hoc Advisory Group on Biological Agents will be convened to address this subject. The report of the Advisory Group was published (Appendix: Attachment 3, IARC Internal Report No. 98/004) and forms a principal basis for future Monographs evaluations (see Section D, Research Design and Methods).

5. Electronic publications and Internet website

A major accomplishment has been the establishment of the IARC Monographs Database within the IARC internet website at http://www.iarc.fr. This database, maintained on a dedicated server by staff of the Monographs Programme, became operational in December 1997 and allows searchable access to the complete listing of Monographs evaluations in English and French and to narrative summaries of Monographs evaluations in English, and to other information including the *Directory of Agents being Tested for Carcinogenicity*. The website is also used to announce selections of future subjects for evaluation and to report results of recent working group deliberations. Examples of files available from this website are appended as Attachment 4 (List of Overall Evaluations of Carcinogenicity to Humans) and Attachment 5 (Summary of Results from Monographs Working Group Meeting to prepare Volume 71, February 1998).

D. Research Design and Methods

The IARC Monographs programme is an integrated effort that combines: (1) maintenance of the *Directory of Agents being Tested for Carcinogenicity*; (2) occasional organization of ad-hoc scientific advisory groups to review various topics relevant to carcinogenic hazard identification, with published proceedings that include a consensus report; (3) periodic (approximately annual) convening of international ad-hoc advisory groups to advise on priorities and directions for the programme; and (4) the Monographs themselves, which are organized in accordance to input received from each of the preceding elements of the Programme. Finally (5), preparation of the Monographs Volumes and scientific documents for printing and for electronic publication is carried out by Programme staff. Research Design and Methods is organized into these five areas.

NCI support for this Programme is in the form of a cooperative agreement, to which NCI staff have historically contributed in several ways. IARC requests that the NCI continue to participate actively in this programme in the following ways, as it has in the past: (i) NCI program staff attendance at, and participation in, as many Monograph meetings, ad-hoc advisory group meetings, and scientific meetings as possible, to each of which IARC will send formal invitations to the Program Official; (ii) continuation of the separate NCI contract with TRI, Inc., to prepare use and exposure sections for monographs on chemicals; (iii) accepting approximately 350 copies

of each Monograph (whether the specific meeting was funded by the cooperative agreement or not) and distributing these throughout the USA and Canada, to addressees mutually agreed upon by NCI and IARC; and (iv) to advise informally on priorities, candidates for participation in various meetings and working groups, and other general aspects of the Programme and to share appropriate databases and other relevant resources as needed for specific activities, by mutual agreement of the NCI Program Official and the IARC Principal Investigator.

1.Directory of Agents being Tested for Carcinogenicity

The *Directory* will continue to be an electronic publication, available by internet on the dedicated server maintained by the Monographs Programme staff. This server is reachable either by way of the IARC home page, as specified above, or directly at http://193.51.164.11. Communication with contributors is facilitated by direct e-mail linkage to the server. Updating to reflect the progress of ongoing studies, publication of completed studies and initiation of new bioassays will occur several times yearly as new information is received.

2.Scientific Meetings on Topics Relevant to Evaluation of Carcinogenicity

A scientific advisory group modeled after the group that prepared Scientific Publication No. 147, *Species Differences in Thyroid, Kidney, and Urinary Bladder Carcinogenesis,* will meet in Lyon during 29 November – 1 December 1999 to critically assess the predictive value of rodent tumours of forestomach and of gastric neuroendocrine cell origin for evaluating carcinogenic risks to humans, and to develop criteria for the use of bioassay data that include these neoplasms as endpoints in future Monographs evaluations. The proceedings of this meeting will include individually authored papers and a consensus report, and will be published by IARC in one of its scientific publication series. The criteria developed by this advisory group will be applied to the re-evaluation of certain chemicals whose current evaluations are derived from these tumours as bioassay endpoints, currently scheduled for October 2001 (see section D.4).

3.International ad-hoc Advisory Groups

In addition to the three Monographs meetings held annually, an average of one additional advisory meeting, on a scientific or policy-related subject, is convened each year. During the period 1999 – 2003 the ad-hoc advisory groups envisaged are listed in Table 3. Meetings to be conducted during 2002 – 2003 reflect the complexity of some of the topics recommended for Monographs evaluation or re-evaluation by the September 1998 ad-hoc advisory group on priorities, and are intended as planning meetings for subsequent Monographs.

CONTINU, ION PAGE: STAY WITHIN MA..GINS INDICATED

Table 3. *IARC Monographs* Advisory Meetings, 1999–2003

Year	Subject
1999	Scientific Advisory Meeting: Tumours of rodent forestomach and gastric neuroendocrine origin in carcinogenic hazard evaluation (IARC Scientific Publication)
2000	Ad-hoc Advisory Meeting: Revision and update of Preamble
2001	Ad-hoc Advisory Meeting on Biological Agents to be Evaluated or Re-evaluated in Future IARC Monographs
2002	Ad-hoc Advisory Meeting on Approaches to the Evaluation of Nitrates and Nitrites in Food and Drinking Water, and Endogenous Nitrosamine Formation as possible Carcinogenic Hazards
2003	Ad-hoc Advisory Meeting on Approaches to the Evaluation of Carcinogenic Hazard to Humans of Air Pollutants (other than gasoline, diesel fuels, and gasoline and diesel engine exhausts)

CONTINU, ION PAGE: STAY WITHIN MA..3INS INDICATED

4. IARC Monographs

Topics for evaluation are identified by continuing surveys of the scientific literature, and are selected by the Director of the Monographs Programme one year in advance of the proposed meeting date. This effort is assisted by suggestions and advice from the IARC Director and the IARC Scientific Council, and from representatives of IARC member states through their scientific and public health organizations. In the United States of America, these include the National Cancer Institute, the National Institute for Environmental Health Sciences, and the Environmental Protection Agency. To involve the scientific and public health community worldwide in this process, nominations for future evaluations are solicited by direct mailing and by open advertisement on the IARC website at intervals of approximately five years, requesting both specific nominations and references to the scientific literature on which the nomination is based. An ad-hoc working group of public health and scientific experts is then convened to review the nominations, and to advise IARC: (a) to accept or decline each nomination; and (b) to assign high or lower priority for review to those nominations that are accepted. The most recent such working group met in Lyon during 16-18 September 1998. Their report, published as IARC Internal Report No. 98/004 (Appendix: Attachment 3), will guide selection of topics for review during the period for which financial support is requested in this application. Based to a major extent on that report, a tentative list of topics to be evaluated or re-evaluated during 1999-2003 is attached as Table 4.

As nominations received in reply to the IARC request is necessarily limited to those agents of specific concern to individuals and does not reflect a systematic or comprehensive review of the toxicological or epidemiological literature, additional priorities may be identified that are not addressed in the report of the ad-hoc working group, and these may be added from time to time to the list suggested by the advisory group.

Participants are (with rare exceptions) scientists who are actively engaged in research on some aspect of the subject to be reviewed, and are invited to join each working group primarily on the basis of their personal contributions to the primary scientific literature. Secondarily, after a preliminary list of potential participants is compiled through electronic literature searches by subject (Medline, Toxline) a second criterion of appropriate geographic distribution of participants is applied in making the final selection of invitees. An average working group consists of 20-25 participants from 8-12 countries, and the "ideal" working group includes approximately 5

individuals who have had previous experience in the Monographs Programme who are invited to chair the overall meeting and the specialty subgroups.

In the interests of transparency and to avoid real or apparent conflicts of interest, candidates for Monographs working groups are now requested in their preliminary letter of invitation to declare to the Responsible Officer and the Programme Director, in confidence and before agreeing to join a working group, any aspect of his/her personal and professional relationship to the subject to be evaluated that might appear to a reasonable person to constitute a possible conflict of interest. Individuals who declare a clear financial conflict of interest are released from consideration for that particular working group. Other declarations are evaluated on an individual basis.

5. Electronic publications and internet website

The preparation of electronic versions of the entire IARC Monographs, in a uniform and searchable format that will be available both on-line by internet and by CD-ROM, is underway in cooperation with a commercial enterprise in the United States. It is anticipated that the CD-ROM will be updated annually, and the on-line version several times annually as new volumes of the Monographs are prepared. The electronic versions will not replace the printed versions; both will be available during and after 2000. The existing Monographs website will continue to be maintained and will be an up-to-date source for Monographs evaluations and summaries, the *Directory*, and information about the Monographs Programme, and will be continue to be freely accessible.

Table 4. *IARC Monographs* Meetings, 1999-2003

Volume	Month/year	Title
74	Feb 1999	Surgical implants, prosthetic devices, and foreign bodies
75	Jun 1999	Ionizing Radiation I: X-rays, γ rays and neutrons
76	Oct 1999	Antiviral and some antitumor drugs
77	Feb 2000	Industrial chemicals (recommended by Advisory Group)
		Current NCI Cooperative Agreement expires, 29 Feb 2000
78	Jun 2000	Ionizing Radiation II: α- and β-emitting radionuclides
79	Oct 2000	Man-made mineral fibres
80	Feb 2001	Thyrotropic agents
81	Jun 2001	Non-ionizing radiation I: Static and ELF fields
82	Oct 2001	Agents that target forestomach and gastric neuroepithelium in rodent bioassays
83	Feb 2002	Fumonisin B1 and related mycotoxins
84	Jun 2002	Drinking water disinfectants and contaminants
85	Oct 2002	Nitrites, nitrates, and endogenous nitrosamines; and moist oral snuff and associated nitrosamines
86	Feb 2003	Bitumens and component compounds
87	Jun 2003	Non-ionizing radiation II: Radiofrequency fields and radar
88	Oct 2003	Multidrug antitumor regimens

Other topics that have high priority for evaluation include:

- Lead and inorganic lead compounds
- Leaded and unleaded gasoline, diesel fuels, and gasoline and diesel exhausts
- Air pollutants (other than the above)

CONTINU, ION PAGE: STAY WITHIN MA..GINS INDICATED

List of Selected Publications, 1995-1999

IARC Monographs Volumes

Volume 62: Wood Dust and Formaldehyde, IARC, Lyon (1995), 405 pp.

Volume 63: Dry Cleaning, Some Chlorinated Solvents and other Industrial Chemicals IARC, Lyon (1995), 551 pp.

Volume 64: Human Papillomaviruses, IARC, Lyon (1995), 409 pp.

Volume 65: Printing Processes and Printing Inks, Carbon Black and Some Nitro Compounds, IARC, Lyon (1996), 578 pp.

Volume 66: Some Pharmaceutical Drugs, IARC, Lyon (1996), 514 pp.

Volume 67: Human Immunodeficiency Viruses and Human T-Cell Lymphotropic Viruses, IARC, Lyon (1996), 424 pp.

Volume 68: Silica, Some Silicates, Coal Dust and *para*-Aramid Fibrils, IARC, Lyon (1997), 506 pp.

Volume 69: Polychlorinated Dibenzo-*para*-dioxins and Polychlorinated Dibenzofurans, IARC, Lyon (1997), 666 pp.

Volume 70: Epstein-Barr Virus and Kaposi's Sarcoma Herpesvirus/Human Herpesvirus 8, IARC, Lyon (1997), 524 pp.

Volume 71: Some Organic Compounds, Hydrazine, and Hydrogen Peroxide, IARC, Lyon (1999), 1589 pp. (set of 3 volumes)

Volume 72: Hormonal Contraception and Postmenopausal Hormone Therapy, IARC, Lyon, June 1998 (in press, 1999)

Volume 73: Some Chemicals that Cause Kidney or Urinary Bladder Tumours in Rodents, and Some Other Substances, IARC, Lyon, October 1998 (in preparation)

Volume 74: Surgical Implants, Prosthetic Devices and Foreign Bodies, IARC, Lyon, February 1999 (in preparation)

Volume 75: Ionizing Radiation, Part I: X-rays, γ Rays and neutrons, IARC, Lyon, June 1999 (in preparation)

Meneghel, A. & Wilbourn, J.D. (1996) *Directory of Agents being tested for Carcinogenicity, No. 17,* IARC, Lyon [final printed volume in the series, which is now an electronic publication available on the IARC website at http://www.iarc.fr].

IARC Scientific Publications

Kane, A.B., Boffetta, P., Saracci, R. & Wilbourn, J.D., eds (1996) *Mechanisms of Fibre Carcinogenesis* (IARC Scientific Publications No. 140), IARC, Lyon, 135 pp.

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), IARC, Lyon, 536 pp.

CONTINU, ION PAGE: STAY WITHIN MA..GINS INDICATED

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), IARC, Lyon, 225 pp.

IARC Technical Reports

Peroxisome Proliferation and its Role in Carcinogenesis (1995) (IARC Technical Report No. 24), IARC, Lyon, 85 pp.

CONTINUE ON PAGE: STAY WITHIN MARGINS INDICATED

IARC Internal Reports

Report of an ad-hoc IARC Monographs *Advisory Group on Physical Agents* (1998) (IARC Internal Report No. 98/002), IARC, Lyon

Report of an ad-hoc IARC Monographs *Advisory Group on Priorities for Future Evaluations* (1998) (IARC Internal Report No. 98/004), IARC, Lyon

Meeting Reports

McGregor, D.B., Heseltine, E. & Mpller, H. (1995) Dry cleaning, some solvents used in dry cleaning and other industrial chemicals. *Scand. J. Work Environ. Health*, **21**, 310-312

Möller, H., Heseltine, E. & Vainio, H. (1995) Working Group Report on schistosomes, liver flukes and *Helicobacter pylori*. *Int. J. Cancer*, **60**, 587-589

Wilbourn, J., Heseltine, E. & Mpller, H. (1995) IARC evaluates wood dust and formaldehyde. *Scand. J. Work Environ. Health,* **21**, 229-232

Wilbourn, J., Partensky, C., & Morgan, G. (1996) Meeting report: IARC evaluates printing processes and printing inks, carbon black and some nitro compounds. *Scand. J. Work Environ. Health*, **22**, 154-156

Wilbourn, J.D., McGregor, D.B., Partensky, C. & Rice, J.M. (1997) Meeting report: IARC evaluates silica and related substances. *Environ. Health Persp.*, **105**, 756-759

McGregor, D.B., Partensky, C., Wilbourn, J. & Rice, J.M. (1998) An IARC evaluation of polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans as risk factors in human carcinogenesis. *Environ. Health Persp.*, **106**, (Suppl. 2) 755-760

Papers on the Monographs Programme

Vainio, H., Wilbourn, J.D., Sasco, A.J., Partensky, C., Gaudin, N., Heseltine, E. & Eragne, I. (1995) Identification des facteurs cancérogènes pour l'homme dans les Monographies du CIRC. *Bull. Cancer (Paris)*, **82**, 339-348

Vainio, H. & Rice, J.M. (1997) Editorial: Beryllium revisited. *J. Occup. Environ. Med.*, **39**, 203-204

Cardis, E. & Rice, J.M. (1997) Criteria for health risk assessment within the international EMF project. In Bernhardt, J.H., Matthes, R. & Repacholi, M.H., eds, *Non-thermal Effects of RF Electromagnetic Fields*. International Commission on Non-Ionizing Radiation Protection, Munich, pp. 35-44

Sasco, A. & Rice, J.M. (1998) Editorial: IARC evaluation of the carcinogenicity of antioestrogens. Basic facts and rationale for appropriate use in medicine. *Presentations in Focus.* Medical Education Network (Europe), Ltd., Issue 2, pp. 3-6

Rice, J.M., Baan, R.A., Blettner, M., Genevois-Charmeau, C., Grosse, Y., McGregor, D.B., Partensky, C. & Wilbourn, J.D. (1999) Rodent tumours of urinary bladder, renal cortex and thyroid gland in *IARC Monographs* evaluations of carcinogenic risk to humans. *Toxicol. Sci.* (in press)

Rice, J.M. (1999) Carcinogenicity of dioxins in experimental animals and humans: evaluations by the *IARC Monographs. Environ. Mutagen Res.* (in press)

CONTINUE ON PAGE: STAY WITHIN MARGINS INDICATED

Literature cited

[1] IARC (1985) Tobacco habits other than smoking; betel-quid and areca-nut chewing; and some related nitrosamines. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Volume 37. International Agency for Research on Cancer, Lyon, 291 pp.

[2] IARC (1986) Tobacco Smoking. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Volume 38. International Agency for Research on Cancer, Lyon, 394 pp.

[3] IARC (1988) Alcohol Drinking. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 44. International Agency for Research on Cancer, Lyon, 378 pp.

[4] IARC (1986) Appendix: Ultraviolet radiation. IARC Monographs on the Evaluation of Carcinogenic Risks of Chemicals to Humans, Volume 40. International Agency for Research on Cancer, Lyon, pp. 379-415.

[5] IARC (1992) Solar and ultraviolet radiation. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 55. International Agency for Research on Cancer, Lyon, 290 pp.

[6] IARC (1994) Schistosomes, liver flukes, and *Helicobacter pylori*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 61. International Agency for Research on Cancer, Lyon, 241 pp.

[7] IARC (1994) Hepatitis viruses. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 59. International Agency for Research on Cancer, Lyon, 255 pp.

[8] IARC (1995) Human papillomaviruses. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 64. International Agency for Research on Cancer, Lyon, 378 pp.

[9] IARC (1996) Human immunodeficiency viruses and human T-cell lymphotropic viruses. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 67. International Agency for Research on Cancer, Lyon, 395 pp.

[10] IARC (1997) Epstein-Barr virus and Kaposi's sarcoma herpesvirus/human herpesvirus 8. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 70. International Agency for Research on Cancer, Lyon, 494 pp.

[11] IARC (1987) Preamble. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 7: Overall evaluations of carcinogenicity – an updating of IARC Monographs Volumes 1 to 42. International Agency for Research on Cancer, Lyon, pp.17-32.

[12] IARC (1977) Some fumigants, the herbicides 2,4-D and 2,4,5-T, chlorinated dibenzodioxins and miscellaneous industrial chemicals. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Volume 15. International Agency for Research on Cancer, Lyon, 340 pp.

[13] IARC (1987) 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin (TCDD). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 7: Overall evaluations of carcinogenicity – an updating of IARC Monographs Volumes 1 to 42. International Agency for Research on Cancer, Lyon, pp. 350-354.

[14] IARC (1997) Polychlorinated dibenzo-*para*-dioxins and polychlorinated dibenzofurans. International Agency for Research on Cancer, Lyon, 636 pp.

[15] IARC (1992) Preamble. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 54. International Agency for Research on Cancer, Lyon, pp. 13-32.

[16] IARC (1992) Diethyl sulfate. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 54. International Agency for Research on Cancer, Lyon, pp. 213-228.

[17] IARC (1999, in preparation) Some chemicals that cause kidney or urinary bladder tumours in rodents, and some other chemicals. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 73. International Agency for Research on Cancer, Lyon.

[18] IARC (1987) Vinyl chloride. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Supplement 7: Overall evaluations of carcinogenicity – an updating of IARC Monographs Volumes 1-42. International Agency for Research on Cancer, Lyon, pp. 373-376.

[19] Capen CC, Dybing E, Rice JM and Wilbourn JD (eds.) (1999) Consensus report. *Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis*, IARC Scientific Publication No. 147. International Agency for Research on Cancer, Lyon, pp. 1-14.

[20] Cohen SM (1999) Calcium phosphate-containing urinary precipitate in rat urinary bladder carcinogenesis. In: CC Capen, E Dybing, JM Rice and JD Wilbourn (eds.), *Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis,* IARC Scientific Publication No. 147. International Agency for Research on Cancer, Lyon, pp. 175-189.

[21] La Vecchia C and Airoldi L (1999) Human bladder cancer: epidemiological, pathological and mechanistic aspects. In: CC Capen, E Dybing, JM Rice and JD Wilbourn (eds.), *Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis,* IARC Scientific Publication No. 147. International Agency for Research on Cancer, Lyon, pp. 139-157.

[22] Swenberg JA and Lehman-McKeeman LD (1999) alpha$_2$-Urinary globulin associated nephropathy as a mechanism of renal tubule cell carcinogenesis in male rats. In: CC Capen, E Dybing, JM Rice and JD Wilbourn (eds.), *Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis,* IARC Scientific Publication No. 147, Lyon, pp. 95-118.

[23] Olivero OA, Anderson LM, Diwan BA, Fornwald LW, Aswathi YC, Anver MR, Rice JM, Anderson LM and Wild CP (1997) Transplacental effects of 3'-azido-2',3'-dideoxythymidine (AZT): Tumorigenicity in mice and genotoxicity in mice and monkeys. *J. Natl. Cancer Inst.* 89: 1602-1608.

[24] McGregor DB, Rice JM and Venitt S (eds.) (1997) Consensus Report. *The Use of Short- and Medium-term Tests for Carcinogens and Data on Genetic Effects in Carcinogenic Hazard Evaluation,* IARC Scientific Publication No. 146. International Agency for Research on Cancer, Lyon, pp. 1-18.

[25] IARC (1988) Radon. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 43. International Agency for Research on Cancer, Lyon, pp. 173-259.

CONTINUE ON PAGE: STAY WITHIN MARGINS INDICATED

CHECKLIST

TYPE OF APPLICATION *(Check all that apply.)*

[ ] NEW application. *(This application is being submitted to the PHS for the first time.)*

[ ] REVISION of application number: _____
(This application replaces a prior unfunded version of a new, competing continuation, or supplemental application.)

[X] COMPETING CONTINUATION of grant number: 5U01 CA33193-18
(This application is to extend a funded grant beyond its current project period.)

INVENTIONS AND PATENTS *(Competing continuation appl.only)*
[X] No
[ ] Yes. If "Yes," [ ] Previously reported [ ] Not previously reported

[ ] SUPPLEMENT to grant number: _____
(This application is for additional funds to supplement a currently funded grant.)

[ ] CHANGE of principal investigator/program director.
Name of former principal investigator/program director: _____

[X] FOREIGN application or significant foreign component.

1. ASSURANCES/CERTIFICATIONS

The following assurances/certifications are made and verified by the signature of the Official Signing for Applicant Organization on the Face Page of the application. Descriptions of individual assurances/certifications begin on page 27 of Section III. If unable to certify compliance where applicable, provide an explanation and place it after this page.

•Human Subjects; •Vertebrate Animals; •Debarment and Suspension; •Drug-Free Workplace *(applicable to new [Type 1] or revised [Type 1] applications only);* •Lobbying; •Delinquent Federal Debt; •Research Misconduct; •Civil Rights (Form HHS 441 or HHS 690); •Handicapped Individuals (Form HHS 641 or HHS 690); •Sex Discrimination (Form HHS 639-A or HHS 690); •Age Discrimination (Form HHS 680 or HHS 690); •Financial Conflict of Interest.

2. PROGRAM INCOME *(See instructions, page 19.)*

All applications must indicate whether program income is anticipated during the period(s) for which grant support is requested. If program income is anticipated, use the format below to reflect the amount and source(s).

Budget Period	Anticipated Amount	Source(s)

3. FACILITIES AND ADMINISTRATION COSTS (F & A)

Indicate the applicant organization's most recent F & A cost rate established with the appropriate DHHS Regional Office, or, in the case of forprofit organizations, the rate established with the appropriate PHS Agency Cost Advisory Office. If the applicant organization is in the process of initially developing or renegotiating a rate, or has established a rate with another Federal agency, it should, immediately upon notification that an award will be made, develop a tentative F & A cost rate proposal. This is to be based on its most recently completed fiscal year in accordance with the principles set forth in the pertinent *DHHS Guide for Establishing Indirect Cost Rates,* and submitted to the appropriate DHHS Regional Office or PHS Agency Cost Advisory Office. F & A costs will ***not*** be paid on foreign grants, construction grants, grants to Federal organizations, grants to individuals, and conference grants. Follow any additional instructions provided for Research Career Awards, Institutional National Research Service Awards, and specialized grant applications.

[ ] DHHS Agreement dated: _____ No Facilities and Administration Costs Requested.

[ ] DHHS Agreement being negotiated with _____ Regional Office.

[X] No DHHS Agreement, but rate established with J. Wayne Berry, Accountant Date 18 October 1983

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information. Supplying the following information on F & A costs is optional for forprofit organizations.)*

a. Initial budget period: Amount of base $ 711 500 x Rate applied 13 % = F & A costs (1) $ 92 495

b. Entire proposed project period: Amount of base $ 3 676 435 x Rate applied 13 % = F & A costs (2) $ 477 937

(1) Add to total direct costs from form page 4 and enter new total on Face Page, Item 7b.
(2) Add to total direct costs from form page 5 and enter new total on Face Page, Item 8b.

*Check appropriate box(es):

[ ] Salary and wages base [ ] Modified total direct cost base [X] Other base *(Explain)*
[ ] Off-site, other special rate, or more than one rate involved *(Explain)*

on total direct costs

Explanation *(Attach separate sheet, if necessary.):*

4. SMOKE-FREE WORKPLACE

Does your organization currently provide a smoke-free workplace and/or promote the nonuse of tobacco products or have plans to do so?

[X] Yes [ ] No *(The response to this question has no impact on the review or funding of this application.)*