********** NOTICE OF GRANT AWARD **********

RESEARCH PROJECT COOPERATIVE AGREEMENT

Issue Date: 07/15/2005

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

**********

Grant Number: 2 U01 CA033193-24
Principal Investigator: Cogliano, Vincent J PHD
Project Title: Evaluation of Carcinogenic Risks to Humans


DIRECTOR, ADMIN & FINANCE
INTERNATIONAL AGENCY FOR CAN RES
150 COURS ALBERT THOMAS
69372 LYON CEDEX 08, FRANCE

FRANCE

Budget Period: 09/01/2005 - 08/31/2006
Project Period: 09/01/1985 - 08/31/2010

Dear Business Official:

The National Institutes of Health hereby awards a grant in the amount of $730,522(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.

If you have any questions about this award, please contact the individual(s) referenced in the information below.

Sincerely yours,

Barbara Liesenfeld
Grants Management Officer
NATIONAL CANCER INSTITUTE

See additional information below

SECTION I - AWARD DATA - 2 U01 CA033193-24

AWARD CALCULATION (U.S. Dollars):

| | |
|---|---|
| Salaries and Wages | $365,771 |
| Fringe Benefits | $124,738 |
| Personnel Costs | $490,509 |
| Consultant Services | $44,200 |
| Travel Costs | $2,125 |
| Other Costs | $109,646 |
| Federal Direct Costs | $646,480 |
| Federal F&A Costs | $84,042 |
| APPROVED BUDGET | $730,522 |
| TOTAL FEDERAL AWARD AMOUNT | $730,522 |

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

25 (b)(5) [redacted]
26
27
28

FISCAL INFORMATION:
CFDA Number: 93.393
EIN: 1900210016A1
Document Number: UCA033193F

| IC / | CAN | / FY2005 | / FY2006 | / FY2007 | / FY2008 | / FY2009 |
|---|---|---|---|---|---|---|
| CA / | 8423126 | / 730,522 | / (b)(5) [redacted] | | | |

NIH ADMINISTRATIVE DATA:
PCC: M5CG3126 / OC: 41.4M /Processed: LIESENFELB 050712 0409

SECTION II - PAYMENT/HOTLINE INFORMATION - 2 U01 CA033193-24

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 CA033193-24

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.)

Carry over of an unobligated balance into the next budget period requires Grants Management Officer prior approval.

Treatment of Program Income:
Additional Costs

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 the Programmatic Responsibilities of the Grantees, the Nature of Assistance by NCI Staff, Collaborative Responsibilities, and Arbitration Procedures (Attachment 1).

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.

The following administrative terms also apply:

INFORMATION This award has been issued in accordance with the National Cancer Institute's (NCI's) Fiscal Year (FY) 2005 funding policies. Future year committed levels* have been adjusted accordingly.

* 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 2005 award to the committed total direct cost level for each future year.

INFORMATION For administrative and management concerns, contact the Grants Management Specialist, Barbara J. Liesenfeld, at (301) 496-3265. For programmatic and scientific concerns, contact the Program Director, Dr. Shen K. Yang, at (301) 435-4473.

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.

Shen K Yang, Program Official
Phone: (301) 435-4473 Email: yangsh@mail.nih.gov Fax: (301) 496-2025

Barbara Liesenfeld, Grants Specialist
Phone: 301-496-3265 Email: liesenfb@mail.nih.gov

SPREADSHEET

GRANT NUMBER: 2 U01 CA033193-24

P.I.: Cogliano, Vincent J

INSTITUTION: WORLD HLTH ORG INTL AGCY RES ON CANCER

| | YEAR 24 | YEAR 25 | YEAR 26 | YEAR 27 | YEAR 28 |
|---|---|---|---|---|---|
| Salaries and Wages | 365,771 | (b)(5) | | | |
| Fringe Benefits | 124,738 | | | | |
| Personnel Costs | 490,509 | | | | |
| Consultant Services | 44,200 | | | | |
| Travel Costs | 2,125 | | | | |

| | YEAR 24 | YEAR 25 | YEAR 26 | YEAR 27 | YEAR 28 |
|---|---|---|---|---|---|
| Other Costs | 109,646 | (b)(5) | | | |
| TOTAL FEDERAL DC | 646,480 | | | | |
| TOTAL FEDERAL F&A | 84,042 | | | | |
| TOTAL COST | 730,522 | | | | |

| | YEAR 24 | YEAR 25 | YEAR 26 | YEAR 27 | YEAR 28 |
|---|---|---|---|---|---|
| F&A Cost Rate 1 | 13.00% | (b)(5) | | | |
| F&A Cost Base 1 | 646,480 | | | | |
| F&A Costs 1 | 84,042 | | | | |

5 U01 CA33193-

Collaborative Terms of Award

Nature of Collaboration with NCI Staff

NCI has certain responsibilities in terms of this cooperative agreement which involve assistance, information support, and scientific collaboration.

1. Scientific Resource

Since the monographs on each chemical which appear in the volumes published by IARC are fundamentally an international information resource and data bank on carcinogenesis and evaluation of qualitative risk of chemicals to humans, NCI, in an assistance and cooperative role, provides information and data which assist IARC staff in the preparation of certain sections of the final monograph (Sections 1.1 to 2.3). Sections 3.1 to 4.3 are developed by the Working Groups which consist of international scientists who review all these documents at the time of the meetings (3 per year) in Lyon, France. The National Cancer Institute, through arrangements with a contractor will provide such assistance.

2. Planning for Meetings of the Working Group

The IARC project is one of international support with NCI being the USA supporter for the monograph and the Information Bulletins on the Survey of Chemicals Being Tested for Carcinogenicity. This bulletin is a listing of chemicals being tested in laboratories throughout the world. Under the Cooperative Agreement, NCI:

a. Makes suggestions to IARC on types of chemicals that should be evaluated at the three planned working group meetings per year held in Lyon, France.

b Makes suggestions and gives assistance to IARC as to USA resource people who should attend and participate in Working Group meetings. Personnel from regulatory agencies and trade associations should attend as observers.

3. Program Involvement in Relation to Input from NCI

Under the section on scientific resources, reference was made to NCI input as to data on production, occurrence, analysis, and use of chemicals. NCI, also provides information relevant to carcinogenicity on chemicals tested in U.S. laboratories. These data are then incorporated in the Information Bulletin on the Survey of Chemicals Being Tested for Carcinogenicity.

Collaborative Terms of Award

In discussing certain phases of work that involve assistance and collaboration on the part of the NCI with IARC, reference was made to the essentiality of effective liaison and support. Participation by the NCI Program Director in the working group meetings in Lyon, France could be either as an observer or as a representative of NCI or as a full member of the working group in his personal capacity as a scientist

4. Reporting Requirements

NCI wishes to continue a semi-annual reporting requirement with scheduling or due dates for reports worked out by mutual arrangement between NCI staff and the IARC principal investigator. The volumes of monographs, supplements and survey bulletins are actually exhibits of achievements and accomplishments Consequently, the semi-annual reports should dwell on planning, participation, selection of chemicals, problems of interfacing and cooperation and logistical matters. In addition, an annual report to be included in the required continuation applications should reflect that the project continues to conform to the purposes, objectives, and conditions of the award and has substantial programmatic involvement by NCI with the performer of the project.

5. Publication and Distribution

One of the significant features of the IARC project in development of this international, authoritative reference source is the publication and distribution, on a world-wide basis, of these volumes, including the supplements to the volumes listing Chemicals and Industrial Processes Associated with Cancer in Humans, as well as the Survey Bulletins.

The National Cancer Institute will receive approximately 400 copies of each volume published. The NCI distributes these copies to NCI staff, representatives of other agencies interested in environmental and occupational carcinogenesis, selected university scientists engaged in carcinogenesis research, public health organizations and medical libraries. Therefore, many organizations and scientists in the USA and abroad benefit from this program, which is partially supported by the National Cancer Institute.

Form Approved Through 05/2004

Department of Health and Human Services
Public Health Services

9 5 7 1 5 3

ation JUN 28 2004

*PI: COGLIANO, VINCENT J  Council: 01/2005
2 U01 CA033193-24  IPF:337706
Dual:
IRG: ZCA1 SRC(99)  Received: 06/28/2004

...strictions indicated.

1. TITLE OF PROJECT *(Do not exceed 56 characters, including spaces and punctuation.)*
Evaluation of Carcinogenic Risks to Humans

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

**3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR** | **New Investigator** ☐ No ☒ Yes

3a. NAME *(Last, first, middle)*
COGLIANO, Vincent James

3b. DEGREE(S)
Ph.D

3c. POSITION TITLE
Chief of Unit

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

3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT
Carcinogen Identification and Evaluation

3f. MAJOR SUBDIVISION

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

E-MAIL ADDRESS:
cogliano@iarc.fr

4. HUMAN SUBJECTS RESEARCH
☒ No
☐ Yes

4a. Research Exempt ☐ No ☐ Yes
If "Yes," Exemption No.

4b. Human Subjects Assurance No.

4c. NIH-defined Phase III Clinical Trial ☐ No ☐ Yes

5. VERTEBRATE ANIMALS ☒ 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 ($) | 8b. Total Costs ($) |
| 09/01/05 | 08/31/10 | $760,564 | $859,437 | $4,037,936 | $4,562,868 |

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

Institutional Profile File Number (if known)

10. TYPE OF ORGANIZATION
Public: → ☐ Federal ☐ State ☐ Local
Private: → ☐ Private Nonprofit
For-profit: → ☐ General ☐ Small Business
☐ Woman-owned ☐ Socially and Economically Disadvantaged

11. ENTITY IDENTIFICATION NUMBER
1900210016A1
DUNS NO.
Congressional District

12. ADMINISTRATIVE OFFICIAL TO BE NOTIFIED IF AWARD IS MADE
Name: M. Johnson
Title: Director, Administration and Finance
Address: International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon cedex 08, France
Tel: (+33) 472 73 84 67  FAX: (+33) 472 73 85 75
E-Mail: daf@iarc.fr

13. OFFICIAL SIGNING FOR APPLICANT ORGANIZATION
Name: P. Boyle
Title: Director
Address: International Agency for Research on Cancer
150 cours Albert Thomas
69372 Lyon cedex 08, France
Tel: (+33) 472 73 85 77  FAX: (+33) 472738564
E-Mail: director@iarc.fr

14. 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.)*
Vincent James Cogliano

DATE
11 june 2004

15. 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 Services 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 13. *(In ink. "Per" signature not acceptable.)*
Peter Boyle

DATE
22 June 2004

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 abstract 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 IARC Monographs on the Evaluation of Carcinogenic Risks to Humans represent an international expert-consensus approach to carcinogen hazard identification. The long-term objective is to critically review and evaluate the published scientific evidence for all carcinogenic hazards to which humans are exposed. These include chemicals, complex mixtures, occupational exposures, lifestyle factors, and physical and biological agents. National and international health agencies use the IARC Monographs as an authoritative source of scientific information and as the scientific basis for their efforts to control cancer.

Each IARC Monograph includes a critical review of the pertinent scientific literature and an evaluation of the weight of the evidence that an agent or exposure may be carcinogenic to humans. Agents are selected for evaluation based on evidence of human exposure and some evidence of carcinogenicity. Agents can be re-evaluated if significant new data become available. The programme also collaborates on scientific meetings on mechanisms of carcinogenesis and other topics pertinent to evaluations of carcinogenicity.

A written Preamble to each volume of IARC Monographs describes the principles and procedures that are followed, including the scientific criteria that guide the evaluations. Each IARC Monograph is developed by a working group selected on two principles: to invite the best-qualified experts and to avoid real or apparent conflicts of interests. Working groups typically consist of 20-25 scientists from 10-12 countries, with expertise in cancer epidemiology, experimental carcinogenesis, and related disciplines. The working group meets to review and reach consensus on drafts prepared by the experts before the meeting, and to develop and reach consensus on the evaluation. Later, IARC scientists review the text and tables to ensure their scientific accuracy and clarity, and the volume is edited and published.

Funds are requested to support two of the three volumes produced each year.

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

International Agency for Research on Cancer
Lyon, France

KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Principal Investigator. List all other key personnel in alphabetical order, last name first.

| Name | Organization | Role on Project |
|---|---|---|
| Cogliano, Vincent James, PhD | IARC/CIE | Principal investigator |
| Baan, Robert A, PhD | IARC/CIE | Scientist; responsible officer |
| El Ghissassi, Fatiha, PhD | IARC/CIE | Scientist |
| Grosse, Yann, PhD | IARC/CIE | Scientist; responsible officer |
| Secretan, Béatrice, PhD | IARC/CIE | Scientist |
| Straif, Kurt, MD, PhD | IARC/CIE | Scientist; responsible officer |

| | | |
|---|---|---|
| IARC/CIE | International Agency for Research on Unit of Carcinogen Identification and | Cancer Identification |

***Disclosure Permission Statement.*** Applicable to SBIR/STTR Only. See instructions. ☐ Yes ☐ No

Principal Investigator/Program Director (Last, First, Middle): COGLIANO, Vincent James

The name of the principal investigator/program director must be provided at the top of each printed page and each continuation page.

## RESEARCH GRANT
## TABLE OF CONTENTS



(Items A-D: not to exceed 25 pages*)

* *SBIR/STTR Phase I: Items A-D limited to 15 pages.*

**Appendix** *(Five collated sets. No page numbering necessary for Appendix.)*

Check if Appendix is Included

Appendices NOT PERMITTED for Phase I SBIR/STTR unless specifically solicited. ☒

Number of publications and manuscripts accepted for publication *(not to exceed 10)* 1

Other items (list):

Preamble to the IARC Monographs
List of IARC Monographs Volumes and Supplements
List of IARC Monograph Evaluations
Volume 83

Principal Investigator/Program Director (Last, First, Middle): COGLIANO, Vincent James

## DETAILED BUDGET FOR INITIAL BUDGET PERIOD
## DIRECT COSTS ONLY

FROM 09/01/05 THROUGH 08/31/06

| PERSONNEL (Applicant organization only) | | | | | DOLLAR AMOUNT REQUESTED (omit cents) | | |
|---|---|---|---|---|---|---|---|
| NAME | ROLE ON PROJECT | TYPE APPT. (months) | % EFFORT ON PROJ. | INST. BASE SALARY | SALARY REQUESTED | FRINGE BENEFITS | TOTAL |
| COGLIANO, V.J. | Principal Investigator | (b)(4), (b)(6) | | | -0 | -0 | -0 |
| BAAN, R | Scientist | | | | 104,287 | 38,572 | 142,859 |
| EL-GHISSASSI, F. | Scientist | | | | 63,055 | 17,117 | 80,172 |
| GROSSE, Y. | Scientist | | | | -0 | -0 | -0 |
| SECRETAN, B. | Scientist | | | | 63,055 | 17,117 | 80,172 |
| STRAIF, K. | Scientist | | | | 101,080 | 37,386 | 138,466 |
| EGRAZ, S. | Archivist | | | | 41,722 | 15,432 | 57,154 |
| LEZERE, M. | Publ. support | | | | 57,120 | 21,126 | 78,246 |
| MITCHELL, J. | Publ. support | | | | -0 | -0 | -0 |
| PEREZ, E. | Secretary | | | | -0 | -0 | -0 |
| | **SUBTOTALS** → | | | | 430,319 | 146,750 | 577,069 |

| | | |
|---|---|---|
| CONSULTANT COSTS<br>See justification page 11 | | 52,000 |
| EQUIPMENT *(Itemize)* | | 0 |
| SUPPLIES *(Itemize by category)* | | 0 |
| TRAVEL One trip by principal investigator to USA to visit NCI program officials | | 2,500 |
| PATIENT CARE COSTS | INPATIENT | 0 |
| | OUTPATIENT | 0 |
| ALTERATIONS AND RENOVATIONS *(Itemize by category)* | | 0 |
| OTHER EXPENSES *(Itemize by category)*<br>See Justification page 11 | | 128,995 |
| **SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD** | | $ 760,564 |
| CONSORTIUM/CONTRACTUAL COSTS | DIRECT COSTS | 0 |
| | FACILITIES AND ADMINISTRATIVE COSTS | 0 |
| **TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD** *(Item 7a, Face Page)* → | | $ 760,564 |

**SBIR/STTR Only: FEE REQUESTED**

## BUDGET FOR ENTIRE PROPOSED PROJECT PERIOD
## 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.* | | 577,069 | 598,298 | 620,382 | 643,354 | 667,253 |
| CONSULTANT COSTS | | 52,000 | 52,000 | 52,000 | 52,000 | 52,000 |
| EQUIPMENT | | 0 | 0 | 0 | 0 | 0 |
| SUPPLIES | | 0 | 0 | 0 | 0 | 0 |
| TRAVEL | | 2,500 | 2,500 | 2,500 | 2,500 | 2,500 |
| 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 | | 128,995 | 130,583 | 132,000 | 133,234 | 134,268 |
| SUBTOTAL DIRECT COSTS | | 760,564 | 783,381 | 806,882 | 831,088 | 856,021 |
| CONSORTIUM/ CONTRACTUAL COSTS | DIRECT | 0 | 0 | 0 | 0 | 0 |
| | F&A | 0 | 0 | 0 | 0 | 0 |
| **TOTAL DIRECT COSTS** | | 760,564 | 783,381 | 806,882 | 831,088 | 856,021 |

**TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PROJECT PERIOD** *(Item 8a, Face Page)* —— **$** 4,037,936

| **SBIR/STTR Only Fee Requested** | 0 | 0 | 0 | 0 | 0 |
|---|---|---|---|---|---|

**SBIR/STTR Only: Total Fee Requested for Entire Proposed Project Period**
(Add Total Fee amount to "Total direct costs for entire proposed project period" above and Total F&A/indirect costs from Checklist Form Page, and enter these as "Costs Requested for Proposed Period of Support on Face Page, Item 8b.) **$** 0

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

See Continuation pages as follows:

page 6 for foreign justification,

page 7 for annual details of budget for entire proposed project period;

pages 8, 9 and 10 for applicant organization employees involved in project;

page 11 for justification for initial budget period; and

page 12 for budget calculation in accordance with the budget cap policy.

## Foreign justification

All programs of the International Agency for Research on Cancer (part of the World Health Organization) are located in Lyon, France. The *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* have become the world's encyclopedia of agents and exposures that contribute to the global burden of cancer. Many national health agencies, including those in the United States, use the *IARC Monographs* as a scientific basis for undertaking cancer risk analyses or as scientific support for public health programs and efforts to control cancer. In addition, scientists engaged in cancer research consult the *IARC Monographs* as an international resource of information on studies of cancer in humans and experimental animals, plus other data relevant to carcinogenicity and its mechanisms.

The authority and usefulness of the *IARC Monographs* follows from their unique status as an international, interdisciplinary, expert-consensus approach to carcinogen hazard identification. Each *IARC Monograph* is developed by an international working group of expert scientists, and IARC is unmatched in its ability to convene international working groups and to conduct evaluations in an atmosphere free from regulatory pressures, national interests, and commercial interests. It is unlikely that carcinogen evaluations carrying the same degree of authority and influence could be developed anyplace else.

**Annual details of budget for entire proposed project period, 1 September 2005 to 31 August 2010**

| | YEAR 24 | YEAR 25 | YEAR 26 | YEAR 27 | YEAR 28 | |
|---|---|---|---|---|---|---|
| | 1-Sept-05 to 31-Aug-06 | 1-Sept-06 to 31-Aug-07 | 1-Sept-07 to 31-Aug-08 | 1-Sept-08 to 31-Aug-09 | 1-Sept-09 to 31-Aug-10 | US $ TOTAL |
| PERSONNEL | | | | | | |
| 4 scientists | 441,669 | 456,128 | 471,103 | 486,611 | 502,673 | 2,358,184 |
| 2 technical and secretarial support | 135,400 | 142,170 | 149,279 | 156,743 | 164,580 | 748,172 |
| **Total** | **577,069** | **598,298** | **620,382** | **643,354** | **667,253** | **3,106,355** |
| CONSULTANT COSTS | | | | | | |
| Preparation of draft monographs | 16,000 | 16,000 | 16,000 | 16,000 | 16,000 | 80,000 |
| Editing of Monographs | 36,000 | 36,000 | 36,000 | 36,000 | 36,000 | 180,000 |
| **Total** | **52,000** | **52,000** | **52,000** | **52,000** | **52,000** | **260,000** |
| DUTY TRAVEL | | | | | | |
| 1 trip to USA | **2,500** | **2,500** | **2,500** | **2,500** | **2,500** | **12,500** |
| OTHER EXPENSES | | | | | | |
| Working groups | 70,000 | 71,500 | 72,900 | 72,900 | 73,800 | 361,100 |
| Printing of monographs | 50,000 | 50,000 | 50,000 | 51,200 | 51,200 | 252,400 |
| Distribution of free monographs | 5,000 | 5,000 | 5,000 | 5,000 | 5,000 | 25,000 |
| Books, journals, reproduction costs | 3,995 | 4,083 | 4,100 | 4,134 | 4,268 | 20,580 |
| **Total** | **128,995** | **130,583** | **132,000** | **133,234** | **134,268** | **659,080** |
| **TOTAL DIRECT COSTS** | **760,564** | **783,381** | **806,882** | **831,088** | **856,021** | **4,037,936** |
| INDIRECT COSTS (13%) | 98,873 | 101,840 | 104,895 | 108,041 | 111,283 | 524,932 |
| **TOTAL COST** | **859,437** | **885,221** | **911,777** | **939,129** | **967,304** | **4,562,868** |

## Applicant organization employees involved in this project

| Name | Role on project | Months per year | % effort | % effort charged to grant |
|---|---|---|---|---|
| **KEY PERSONNEL** | | | | |
| VJ Cogliano PhD<br>Scientist & Chief, CIE | Principal investigator and head of programme. Responsible for overall planning and supervision of the programme, selection of topics to be evaluated and selection of experts for the working groups. | | | |
| RA Baan PhD<br>Scientist, CIE | Responsible officer for one *IARC Monograph* volume each year. Plans the sections on *Other data relevant to an evaluation of carcinogenicity and its mechanisms* and serves as rapporteur for that section during each meeting. Reviews that section to ensure its scientific accuracy and clarity. | | | |
| F El Ghissassi PhD<br>Scientist, CIE | Serves as co-rapporteur for the section on *Other data relevant to an evaluation of carcinogenicity and its mechanisms* during each meeting. Reviews that and other sections to ensure their scientific accuracy and clarity. | | | |
| Y Grosse PhD<br>Scientist, CIE | Responsible officer for one *IARC Monograph* volume each year. Plans the sections on *Cancer in experimental animals* and serves as rapporteur for that section during each meeting. Reviews that section to ensure its scientific accuracy and clarity. | | | |
| B Secretan PhD<br>Scientist, CIE | Plans the sections on *Exposure data* and serves as rapporteur for that section during each meeting. Reviews that and other sections to ensure their scientific accuracy and clarity. | | | |
| K Straif MD<br>Scientist, CIE | Responsible officer for one *IARC Monograph* volume each year. Plans the sections on *Cancer in humans* and serves as rapporteur for that section during each meeting. Reviews that section to ensure its scientific accuracy and clarity. | | | |

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

| Name | Role on project | Months per year | % effort | % effort charged to grant |
|---|---|---|---|---|
| **TECHNICAL AND SECRETARIAL SUPPORT** | | | | |
| S Egraz<br>Literature specialist, CIE | Principal archivist. Supervises literature searches and computerised archival of documents cited by the *Monographs* | (b)(4), (b)(6) | | |
| M Lézère<br>Publication support, CIE | Typing of revised manuscripts during *Monograph* meetings. Preparation of final *Monographs* for printing. Maintenance of *Monograph* website. | | | |
| J Mitchell<br>Publication support, CIE | Principal typist. Coordinates manuscript preparation before, during, and after *Monograph* meetings. | | | |
| E Perez<br>Unit Secretary, CIE | Unit secretary. Responsible for all administrative matters, including correspondence and travel of meeting participants. | | | |
| **IARC SCIENTISTS WHO PARTICIPATE IN MEETINGS OR ADVISE ON SPECIFIC TOPICS** | | | | |
| P Boffetta MD<br>Scientist & Chief, ECE | Advises and assists on cancer epidemiology. | (b)(4), (b)(6) | | |
| P Brennan PhD<br>Scientist, ECE | Advises and assists on cancer epidemiology. | | | |
| E Cardis PhD<br>Scientist & Chief, RCA | Advises and assists on cancer epidemiology and biostatistics, serves as a specialist on radiation. | | | |
| S Franceschi MD<br>Scientist & Chief FIS | Advises and assists on cancer epidemiology. | | | |
| M Friesen PhD<br>Scientist, NTR | Advises and assists on chemistry and chemical analysis. | | | |
| J Hall PhD<br>Scientist & Chief, REP | Advises and assists on molecular biology and biochemistry. | | | |
| R Kaaks PhD<br>Scientist & Chief, HOC | Advises and assists on hormonally induced cancers. | | | |
| V Krutovskikh MD PhD<br>Scientist, GEI | Advises and assists on experimental carcinogenesis and mechanisms. | | | |
| H Ohgaki DVM PhD<br>Scientist & Chief, MPA | Advises and assists on molecular pathology. | | | |
| H Ohshima PhD<br>Scientist & Chief, ECR | Advises and assists on experimental carcinogenesis and mechanisms. | | | |
| A Sasco MD PhD<br>Scientist & Chief, ECP | Advises and assists on cancer epidemiology. | | | |
| W-M Tong MD DSc<br>Scientist, GEI | Advises and assists on experimental carcinogenesis and mechanisms. | | | |
| Z-Q Wang PhD<br>Scientist & Chief, GEI | Advises and assists on experimental carcinogenesis and mechanisms. | | | |

## Applicant organization employees involved in this project (cont'd)

Footnotes to preceding table and organization abbreviations

* 20% of time is allocated to general IARC management responsibilities
** Temporary appointment not to exceed 11 months per year
CIE Carcinogen Identification and Evaluation
ECE Environmental Cancer Epidemiology
ECP Epidemiology for Cancer Prevention
ECR Endogenous Cancer Risk Factors
GEI Gene Environment Interactions
FIS Field and Intervention Studies
HOC Hormones and Cancer
MPA Molecular Pathology
NTR Nutrition and Cancer
RCA Radiation and Cancer
REP DNA Repair

Justification for initial budget period

Consultant costs

| | | |
|---|---|---|
| -Preparation of draft monographs: | | |
| $400/expert x 20 experts x2 working groups = | | $ 16,000 |
| - Editing of monographs : $18,000 x 2 monographs = | | $ 36,000 |
| | Total | $ 52,000 |

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.

| | | |
|---|---|---|
| - Apex fare | | $ 1,100 |
| - Per diem: 6 days x $235/day = 1,410 i.e. | | $ 1,400 |
| | Total | $ 2,500 |

Other expenses

| | |
|---|---|
| - 2 Working groups (travel + per diem for non-US Govt participants) | $ 70,000 |
| - Printing cost of 2 monographs per year | $ 50,000 |
| - Distribution cost of free copies of 2 monographs per year | $ 5,000 |
| - Books, journals and reproduction costs* | $ 3,995 |
| Total | $128,995 |

*This amount represents only part of the total costs of scientific literature acquisition. In order to remain within the 20% cap increase imposed by Budget Cap Policy, some of the costs of literature acquisition will be charged to other sources of funding.

## Budget calculation in accordance with the Budget Cap Policy

### 1. Determination of budget level for Year 1 of competing continuation

| | Staff costs | Non-staff costs | Total direct costs | Increase / (decrease) percentage |
|---|---|---|---|---|
| **Last non-competing year budget** | **441,604** | **192,199** | **633,803** | |
| **PLUS:** | | | | |
| Increase due to currency exchange rates | 143,357 | 28,137 | 171,494 | **27.1%** |
| Increase due to inflationary adjustments | 8,832 | 3,846 | 12,678 | **2.0%** |
| **LESS:** | | | | |
| Cost reductions | -16,724 | -40,687 | -57,411 | **-9.1%** |
| **Year 1 budget of competing continuation (US $)** | **577,069** | **183,495** | **760,564** | **20%** |

The funds requested from the National Cancer Institute for the initial budget period amount to total direct costs of $760,564, compared with the recommended support of $633,803 for the last year of the current 5-year period. The budget essentially represents the cost of maintaining the ongoing programme, i.e. NCI funds will be used to support development of two of the three IARC Monograph volumes produced each year. The number of full-time equivalent positions included in the competing continuation budget is the same as in the current grant: 4 scientists and 2 technical staff.

The previous budget was developed in 1999 with an exchange rate of €1.065 to the US dollar, compared with the rate of €.804 used for the present application. This drop in the dollar value results in an increase of about 32% of the dollar equivalent of Euro expenditure.

In order to remain within the 20% cap increase imposed by the Budget Cap Policy, measures already taken to reduce costs will be reinforced. Part of the costs to be incurred for the production of two Monographs, such as meeting, distribution and literature acquisition, can be charged to other sources of funding.

### 2. Costs for total period of support

| | Competing continuation budget | | | | |
|---|---|---|---|---|---|
| | Year 24 | Year 25 | Year 26 | Year 27 | Year 28 |
| STAFF COSTS | 577,069 | 598,298 | 620,382 | 643,354 | 667,253 |
| *Year-over-year increase* | | *3.68%* | *3.69%* | *3.70%* | *3.71%* |
| NON-STAFF COSTS | 183,495 | 185,083 | 186,500 | 187,734 | 188,768 |
| *Year-over-year increase* | | *0.87%* | *0.77%* | *0.66%* | *0.55%* |
| TOTAL (US $) | 760,564 | 783,381 | 806,882 | 831,088 | 856,021 |
| *Year-over-year increase* | | *3.00%* | *3.00%* | *3.00%* | *3.00%* |

Costs for years 2 to 5 are calculated assuming an annual increase of 3.7% in staff costs for inflation and statutory increments, and less than 1% for other costs. This results in a 3% increase for each year, in accordance with the Budget Cap Policy.

| BIOGRAPHICAL SKETCH | |
|---|---|
| NAME<br>**COGLIANO, Vincent James** | POSITION TITLE<br>Chief, Carcinogen Identification and Evaluation |

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 |
|---|---|---|---|
| Catholic University, Washington DC, USA | BA | 1973 | Mathematics |
| University of Michigan, Ann Arbor MI, USA | MA | 1975 | Mathematics |
| Cornell University, Ithaca NY, USA | MS, PhD | 1981, 1982 | Operations Research |

**A. Positions and Honors.**

**Employment**

1975-1978 **Mathematician**, U.S. Defense Communications Agency, Washington DC.
1978,1979 **Regulatory Policy Analyst**, Office of Pesticide Programs, U.S. Environmental Protection Agency.
1981-1983 **Manufacturing Engineer**, IBM Corporation, Endicott NY.
1983-1985 **Statistician**, Office of Policy, Planning, and Evaluation, U.S. Environmental Protection Agency.
1985-1990 **Statistician (Biology), Carcinogen Assessment Group**, U.S. Environmental Protection Agency.

1990-1995 **Chief, Carcinogen Assessment Statistics and Epidemiology Branch**, U.S. Environmental Protection Agency, Washington DC.
1995-2001 **Chief, Quantitative Risk Methods Group**, U.S. Environmental Protection Agency, Washington DC. [Served as Acting Division Director during 2000-2001.]
2001-2003 **Chair, Cancer Guideline Writing Group** (special assignment), U.S. Environmental Protection Agency.

2003-present **Chief, Carcinogen Identification and Evaluation** (*IARC Monographs Programme*), International Agency for Research on Cancer, Lyon France.

**Fellowships**

1969-1973 **Merit Scholarship**, Catholic University, Washington DC.
1978-1981 **Research Assistantship**, School of Operations Research, Cornell University, Ithaca NY.
1973-1975 **Teaching Fellowship**, Department of Mathematics, University of Michigan, Ann Arbor MI.

**Selected honors**

1984 **EPA *Silver Medal*** for critical analyses supporting action on ethylene dibromide.
1996 **EPA *Bronze Medal*** for chairing workgroup that develops consensus on cancer assessments.
1998 **EPA *Gold Medal*** for developing innovative assessment of PCB health hazards.
1998 **EPA *Bronze Medal*** for managing the international training program on health risk assessment.
2002 **EPA *Silver Medal*** for developing guidance on assessing health risks of chemical mixtures.
*Also:* Four ***Scientific and Technological Achievement Awards*** for outstanding scientific publications (1993, 1998, 2001, 2001). [Manuscripts are reviewed and recommended for award by EPA's Science Advisory Board.]

**B. Selected peer-reviewed publications.**

Schruben L, Cogliano VJ (1987). An experimental procedure for simulation response surface model identification. Communications of the ACM 30(8): 716-730.

Preuss PW, Cogliano VJ, White PD (1989). The perils of prudence. In: Mohr U, Bates DV, Dungworth DL, Lee PN, McClellan RO, Roe FJC, eds, Assessment of Inhalation Hazards: Integration and Extrapolation Using Diverse Data. Berlin: Springer-Verlag, 337-347.

Cogliano VJ, Farland WH, Preuss PW, Wiltse JA, Rhomberg LR, Chen CW, Mass MJ, Nesnow S, White PD, Parker JC, Wuerthele SM (1991). Carcinogens and human health: part 3. Science 251(4994): 606-607 (letter)

Cogliano VJ, Parker JC (1992). Some implications of toxicology and pharmacokinetics for exposure assessment. Journal of Exposure Analysis and Environmental Epidemiology, Suppl 1: 189-207.

Hiatt GFS, Cogliano VJ, Becker RA, Siegel DM, Den AR (1993). Vinyl chloride action levels: indoor air exposures at a Superfund site. In: U.S. DHHS, ed, Hazardous Waste and Public Health: International Congress on the Health Effects of Hazardous Waste. Princeton: Princeton Scientific Publishing.

Vater ST, Velazquez SF, Cogliano VJ (1995). A case study of cancer data set combinations for PCBs. Regulatory Toxicology and Pharmacology 22: 2-10.

Velazquez SF, Schoeny R, Cogliano VJ, Rice GE (1996). Cancer risk assessment: historical perspectives, current issues, and future directions. In: Fan AM, Chang LW, eds, Toxicology and Risk Assessment: Principles, Methods, and Applications. New York: Marcel Dekker, 219-243.

Velazquez SF, Schoeny R, Rice GE, Cogliano VJ (1996). Cancer risk assessment: historical perspectives, current issues, and future directions. Drug and Chemical Toxicology 19(3): 161-185.

Cogliano VJ, Hiatt GFS, Den A (1996). Quantitative cancer risk assessment for vinyl chloride: indications of early-life sensitivity. Toxicology 111: 21-28.

Maull EA, Cogliano VJ, Siegel Scott C, Barton HA, Fisher JW, Greenberg M, Rhomberg L, Sorgen SP (1997). Trichloroethylene health risk assessment: a new and improved process. Drug and Chemical Toxicology 20(4): 427-442.

Cogliano VJ (1997). Plausible upper bounds: are their sums plausible? Risk Analysis 17(1): 77-84.

Cogliano VJ (1998). Assessing the cancer risk from environmental PCBs. Environmental Health Perspectives 106(6): 317–323.

Zapponi GA, Cogliano J (1998). Dose-response analysis and biologically-based risk assessment for initiator and promoter carcinogens. Summary report of NATO/CCMS Study. Cent Eur J Public Health 6(4): 317-320.

Cogliano VJ, Luebeck EG, Zapponi GA, eds (1999). *Perspectives on biologically based cancer risk assessment.* New York: Kluwer Academic/Plenum Publishers.

Brouwer A, Longnecker MP, Birnbaum LS, Cogliano J, Kostyniak P, Moore J, Schantz S, Winneke G (1999). Characterization of potential endocrine-related health effects at low-dose levels of exposure to PCBs. Environmental Health Perspectives 107(suppl 4): 639-650.

Woodruff TJ, Caldwell J, Cogliano VJ, Axelrad DA (2000). Estimating cancer risk from outdoor concentrations of hazardous air pollutants in 1990. Environmental Research Section A 82: 194-206.

Scott CS, Cogliano VJ, eds (2000). Trichloroethylene health risks—state of the science. Environmental Health Perspectives 108(suppl 2).

Cogliano VJ (2001). Considerations for setting reference values for environmental PCBs. In: Roberston LW, Hansen LG, eds, PCBs: Recent Advances in the Environmental Toxicology and Health Effects. Lexington: University of Kentucky Press.

Cogliano VJ, Caldwell JC, Scott CS (2001). Risk assessment and risk management in the European Community and in the United States. In: Chyczewski L, Niklinski J, Pluygers E, eds, Endocrine Disrupters and Carcinogenic Risk Assessment. Amsterdam: IOS Press.

Cogliano VJ, Caldwell JC, Scott CS (2001). The use of modeling in risk assessment. In: Chyczewski L, Niklinski J, Pluygers E, eds, Endocrine Disrupters and Carcinogenic Risk Assessment. Amsterdam: IOS Press.

Cogliano VJ, Scott CS, Caldwell JC, Farland WH (2001). Trichloroethylene: using new information to improve the cancer characterization. Human and Ecological Risk Assessment 7(4): 755-766.

Rice C, Birnbaum LS, Cogliano J, Mahaffey K, Needham L, Rogan WJ, vom Saal FS (2003). Exposure assessment for endocrine disruptors: some considerations in the design of studies. Environ Health Perspect 111(13): 1683-1690.

*Also:* Principal authorship or co-authorship of several major government publications that were peer-reviewed.

**C. Research support.**

**U.S. National Cancer Institute** (U01-CA033193) Evaluation of Carcinogenic Risks to Humans, 1982-2005.
Goal: To develop *IARC Monographs* on agents and exposures that contribute to human cancer.
Role: Principal investigator.

**European Commission** (VS/2003/0118) 1986-2003 (renewal pending).
Goal: To support, in part, a third *IARC Monograph* each year.
Role: Co-investigator.

**U.S. Environmental Protection Agency** (R-82938801) 2001-2004.
Goal: To support, in part, a third *IARC Monograph* each year.
Role: Principal investigator.

**U.S. National Institute of Environmental Health Sciences** (PR252717) 1992-present.
Goal: To support scientific workshops and advisory meetings related to the *IARC Monographs*.
Role: Co-investigator.

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| BAAN, Robert Alexander | Senior 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 |
|---|---|---|---|
| State University, Leiden, The Netherlands | MSc | 1972 | Chemistry/biochemistry |
| State University, Leiden, The Netherlands | PhD | 1977 | Biochemistry |
| Brown University, Providence, RI, USA | post-doc | 1977-1979 | Biochemistry |

## A. Positions and Honors

Positions and Employment

1973-1977 Postgraduate research, Department of Biochemistry, State University, Leiden
1977-1979 Postdoctoral research, Division of Biology and Medicine, Brown University, Providence, RI, USA
1979-1986 Research scientist position, Department of Genetic Toxicology, TNO Medical Biological Laboratory, Rijswijk, The Netherlands
1987-1995 Research management position as Head, Department of Genetic Toxicology, TNO Medical Biological Laboratory, Rijswijk, The Netherlands (since 1994: TNO Nutrition and Food Research Institute)
1995-1998 Senior staff position as Senior Scientist Genetic Toxicology, Toxicology Division, TNO Nutrition and Food Research Institute, Zeist, The Netherlands
1998- Senior Scientist, Unit of Carcinogen Identification and Evaluation, WHO – International Agency for Research on Cancer, Lyon, France

Other Experience and Professional Memberships

1992-1994 Member, Editorial Board, *Carcinogenesis*
1992-1997 Secretary (1992) and Chairman (1993-97), Section of Genetic Toxicology, Netherlands Society of Toxicology (i.e., the Dutch Section of the European Environmental Mutagen Society, EEMS)
1995-1998 Secretary, Working group Carcinogenesis and Mutagenesis, Netherlands Cancer Foundation
1995-1998 Member, Scientific Advisory Board, JA Cohen Institute for Radiopathology and Radiation Protection The Netherlands
1996- Treasurer, European Environmental Mutagen Society, EEMS
1997- Webmaster of the EEMS web site (http://193.51.164.11/eems/index.htm)
1997- Corresponding Member, American Association for Cancer Research
1997-2000 Member, Editorial Board, *The International Journal of Biochemistry and Cell Biology*
1997-2003 EEMS Councillor for The Netherlands (1997 - 2003)
1998-2001 Member, Editorial Board, *Mutation Research*, Genetic Toxicology and Environmental Mutagenesis
2001- Editor (Europe, Africa, Australasia), *Mutation Research*, Genetic Toxicology and Environmental Mutagenesis
2003- Member, Task Force on Carcinogenicity, European Centre for the Validation of Alternative Methods (ECVAM), European Commission, Joint Research Centre, Ispra (VA), Italy
2004- Member, Expert Committee on the evaluation of chemical risks, French Agency for environmental Health Safety (AFSSE)

**B. Selected peer-reviewed publications** (1993 - present; selected from 116 publications)


Steenwinkel M-JST, Roggeband R, Van Delft JHM, Baan RA (1993) Improvements in the $^{32}$P-postlabelling procedure to quantify bulky aromatic DNA adducts. In: Postlabelling Methods for Detection of DNA Adducts, Phillips DH, Castegnaro M, and Bartsch H, Eds, IARC Scientific Publications No 124, IARC, Lyon, France, pp 65-70

Van Delft JHM, Van Winden MJM, Van den Ende AMC, Baan RA (1993) Determination of N7-alkyl-guanine adducts by immunochemical methods and by HPLC with electrochemical detection; applications in animal studies, and in monitoring of human exposure to alkylating agents. Env Health Persp 99, 25-32

Vink AA, Berg RJW, De Gruijl FR, Lohman PHM, Roza L, Baan RA (1993) Detection of thymine dimers in suprabasal and basal cells of chronically UV-B exposed hairless mice. J Invest Dermatol 100, 795-799

Roggeband R, Wolterbeek APM, Rutten AAJJL, Baan RA (1993) Comparative $^{32}$P-postlabeling analysis of benzo(a)pyrene-DNA adducts formed *in vitro* upon activation of benzo(a)pyrene by human, rabbit and rodent liver microsomes. Carcinogenesis 14, 1945-1950

Mientjes EJ, Van Delft JHM, Op 't Hof BM, Gossen JA, Vijg J, Lohman PHM, Baan RA (1994) An improved selection method for *λlacZ*$^-$ phages based on galactose sensitivity. Transgenic Res 3, 67-69

Roggeband R, Van den Berg PTM, Van der Wulp CJM, Baan RA (1994) Detection of DNA adducts in basal and non-basal cells of the hamster trachea exposed to benzo(a)pyrene in organ culture. J Histochem Cytochem 42, 1427-1434

Baan RA, Steenwinkel M-JST, Van den Berg PTM, Roggeband R, Van Delft JHM (1994) Molecular dosimetry of DNA damage induced by polycyclic aromatic hydrocarbons; relevance for exposure monitoring and risk assessment. Hum & Exp Toxicol 13, 880-887

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, 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

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

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}$3 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 *λlac*Z-transgenic mice treated with N-nitrosodimethylamine. Carcinogenesis 19, 731-739

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

Rice JM, Baan RA, Blettner M, Genevois-Charmeau C, Grosse Y, McGregor DB, Partensky C, Wilbourn JD (1999) Rodent tumors of urinary bladder, renal cortex and thyroid gland in IARC Monographs Evalations of carcinogenic risk to humans. Toxicological Sciences, 49, 166-171

Baan RA, Szyfter K (1999) Editorial, Mutation Research Special Issue on 'Biomarkers in monitoring of occupational and environmental exposure to organic genotoxic substances', Mutation Res 445, 137

Hooser SB, Van Dijk-Knijnenburg WCM, Waalkens-Berendsen IDH, Smits-Van Prooije AE, Snoeij NJ, Baan RA, Fichtinger-Schepman AMJ (2000) Cisplatin-DNA adduct formation in rat spermatozoa and its effect on fetal development. Cancer Letters 151, 71-80

McGregor DB, Baan RA, Partensky C, Rice JM, Wilbourn JD (2000) Evaluation of the carcinogenic risks to humans associated with surgical implants and other foreign bodies - a report of an *IARC Monographs* Programme meeting. Eur J Cancer 36, 307-313

Krul CAM, Luiten-Schuite A, Baan RA, Verhagen H, Mohn GR, Feron VJ, Havenaar R (2000) Application of a dynamic *in vitro* gastrointestinal tract model to study the availability of food mutagens, using heterocyclic aromatic amines as model compounds. Food Chem Toxicol 38, 783-792

Pletsa V, Steenwinkel MJST, Soikidou M, Van Delft JHM, Baan RA, Katsouyanni K, Kyrtopoulos SA (2002) Monitoring for DNA damage of humans occupationally exposed to methyl bromide. Anticancer Research 22, 997-1000

Baan RA, Rice JM (2003) Correspondence: Carcinogenicity of EBDCs: Response. Environ Health Perspect. 111, A266-A267

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| EL GHISSASSI Fatiha | 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 |
|---|---|---|---|
| Scientific and Medical University of Grenoble, France | B Sc | 1980 | Degree in Structural and Metabolic Biochemistry and Degree in Organic Chemistry |
| University Claude Bernard, Lyon I | Master of Science | 1982 | Molecular Biology and Physicochemistry<br>Endocrine Biochemistry |
| University Claude Bernard, Lyon I | DEA | 1983 | Biochemistry Option Pharmacology |
| University Claude Bernard, Lyon I | Doctorate in Sciences | 1986 | Biochemistry |
| University Claude Bernard, Lyon I, France | PhD | 1995 | Biochemistry (Toxicology ) |

**Positions**

Aug 02 to present Scientist, Carcinogen Identification & Evaluation, IARC, Lyon (Supervisor Dr R. Baan). Reviewed and ensured the scientific accuracy of IARC monographs, summaries of studies on absorption, distribution, metabolism and excretion; toxic effects; reproductive and developmental effects; and genetic and related effects (section 4 of each monograph). This was done for the monographs on "Tobacco smoke"(vol 83), "Some drinking-water disinfectants and contaminants, including arsenic" (vol 84) and "Betel-quid and areca-nut chewing and some related nitrosamines " (vol 85)

Participated as co-rapporteur in the sub-group-section 4 in the IARC monograph meeting on "Betel Quid and areca-nut chewing and some related nitrosaminese (vol 85), on "some metals used in the hard metal and semiconductor industry " (vol 86) and "Inorganic and organic lead and lead compounds" (vol 87)

Feb 02-July 02 Visiting Scientist in Molecular Carcinogenesis Group (Chief: Dr P. Hainaut), IARC, Lyon "Induction of p53 protein activity by the aminothiol WR2721 (amifostine): a possible involvement of polyamine moiety in the mechanism of cytoprotection"

1997-2001 Post-doctoral fellowship in Léon Bérard Center, Fundamental and Applied Oncology Department, INSERM U453, Lyon "Study of biologic function of p53 target gene, BTG2 : effect of its expression on neuronal proliferation, differentiation and apoptosis of PC12 cells" Supervisor Pr A. Puisieux. Post-doctoral fellowship awarded by the Regional Center of Research on Cancer 'Léon Bérard'

1996-1997 Post-doctoral fellowship in Unit of Mechanisms of Carcinogenesis (MCA), IARC, Chief Dr R. Montesano "Modulation of DNA-Binding activity of the tumour supressor protein p53 by an antioxidant Amifostine: mechanism of cytoprotection" Supervisor Dr P. Hainaut
Post-doctoral fellowship awarded by IARC and USB Pharma

1991-1996 Ph.D Thesis in Unit of Environmental Carcinogens and Host Factors, (ECH), IARC, Chief Pr H. Bartsch "Study of metabolic factors which could modulate the formation of ethenoadducts, potential biomarkers of carcinogenesis by vinyl chloride and by lipid peroxidation " Supervisor Dr A. Barbin
Student fellowship awarded by IARC, INSERM and Elf-Atochem

1987–1991 Technician in Unit of Environmental Carcinogens and Host Factors, IARC "Comparison of effects of diet and gut bacteria on microcapsule trapping and benzo(a)pyrene metabolism" Supervisor Dr I. O'Neill. 057 "N-nitrosamine metabolites analysis by Gas Chromatography-Thermal-Energy-Analyser (GC-T.E.A)" Supervisor Dr H. Ohshima

1982-1987 Studentship in Doctoral Biochemistry third cycle. Laboratory of Endocrine Biochemistry, in Sainte-Eugénie Hospital, Lyon Sud. "Analysis of bile acids and cholesterol by gas chromatography in meconium of normal newborn and new-born affected by cystic fibrosis" Supervisor Pr A. Revol, Director Pr D. Gautheron

## PUBLICATIONS

**El Ghissassi F.**, Valsesia-Wittmann S., Falette N., Duriez C., Walden P.D. & Puisieux A. (2002) BTG2(TIS21/PC3) induces neuronal differentiation and prevents apoptosis of terminally differentiated PC12 cells. *Oncogene*, **21**, 6772-6778

North S., Pluquet O., Maurrici D., **El Ghissassi F.** & Hainaut P. (2002) Restoration of wild-type conformation and activity of a temperature-sensitive mutant of p53 ($p53^{v272M}$) by the cytoprotective aminothiol WR1065 in the esophageal cancer cell line TE-1. *Mol Carcinog*, **33**, 181-188

North S., **El Ghissassi F.**, Pluquet O., Verhaegh G. & Hainaut P. (2000) The cytoprotective aminothiol WR1065 activates p21waf-1 and down regulates cell cycle progression through a p53-dependent pathway. *Oncogene*, **19**, 1206-14
North S. and El Ghissassi F. contributed equally to this paper

Cortes U., Moyret-Lalle C., Falette N., Duriez C., **Ghissassi E.F.**, Barnas C., Morel AP., Hainaut P., Magaud J-P. & Puisieux A. (2000) BTG gene expression in the p53-dependent and independent cellular response to DNA damage. *Mol Carcinog*, **27**, 57-64

**El Ghissassi F.**, Barbin A. & Bartsch H. (1998) Metabolic activation of vinyl chloride by rat liver microsomes: low-dose kinetics and involvement of cytochrome P450 2E1. *Biochem Pharmacol*, **55**, 1445-1452

Guichard Y., **El Ghissassi F.**, Nair J., Bartsch H. & Barbin A. (1996) Formation and accumulation of DNA ethenobases in adult Sprague-Dawley rats exposed to vinyl chloride. *Carcinogenesis*, **17**, 1553-1559

**El Ghissassi F.**, Barbin A., Nair J. & Bartsch H. (1995) Formation of 1,$N^6$-ethenoadenine and 3,$N^4$-ethenocytosine by lipid peroxidation products and nucleic acids bases. *Chem. Res. Toxicol*, **8**, 278-283

**El Ghissassi F.**, Boivin S., LeFrançois L., Barbin A. & Marion M.J. (1995) Glutathione transferase Mu1-1 (*GSTM1*) genotype in individuals exposed to vinyl chloride in relation to "vinyl chloride disease" and liver angiosarcoma. *Clinical chemistry (Suppl)*, **41**, 1922-1924

Sierra R., Ohshima H., Munoz N., Teuchmann S., Pena A-S., Malaveille C., Pignatelli B., Chinnock A., **El Ghissassi F.** & Chen C. (1991) Exposure to N-nitrosamines and other risk factors for gastric cancer in Costa Rican children. IARC-Sci-Publ., **105**, 162-167

O'Neill I.K., Goldberg M., **El Ghissassi F.** & Rojas-Moreno M. (1991) Dietary fibre, fat and beef modulation of colonic nuclear aberrations and microcapsule trapped G.I metabolites of Benzo(a)pyrene treated C57~B6 mice consuming human diets. *Carcinogenesis*, **12**, 175-180

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

| 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, Univ. of Metz, France | BSc. | 1990 | Chem. & Biochem. |
| Faculty of Sciences, Univ. of Strasburg, France | MSc. | 1992 | Environm. toxicol. |
| INPT, University of Toulouse, France | Ph.D. | 1996 | Genetic toxicol. |
| International Agency for Research on Cancer | Postdoc. | 1997 | Genetic toxicol. |

**Position**

1997-present Scientist, Unit of Carcinogen Identification and Evaluation, International Agency for Research on Cancer

**Selected peer-reviewed publications**

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.**, 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

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

**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

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

Rice, J.M., Baan, R.A., Blettner, M., Genevois-Charmeau, C., **Grosse, Y.**, McGregor, D.B., Partensky, C. & Wilbourn, J.D. (1999) Rodent tumors of urinary bladder, renal cortex, and thyroid gland in IARC Monographs evaluations of carcinogenic risk to humans. *Toxicol. Sci.*, **49**, 166-171

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| Marie Béatrice Secretan | 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 Geneva, Switzerland | Licence (BSc) | 1985-1989 | Biochemistry |
| University of Geneva, Switzerland | Diplôme (MSc) | 1989-1991 | Biochemistry |
| St. Bartholomew and the Royal London School of Medicine and Dentistry, London, UK | PhD | 1992-1996 | Toxicology |
| Ibidem | Post-doc | 1996-1997 | Chemical carcinogenesis |
| Harvard School of Public Health, Boston, MA | Post-doc | 1998-2001 | Cancer cell biology |
| UCLA School of Public Health, Los Angeles, CA | Post-doc | 04-06 2001 | Cancer cell biology |
| IARC/WHO, Lyon, France | Post-doc | 2001-2002 | Gene-environment interactions |

**Work experience**

Sept. 2002 - present: Unit of Carcinogen Identification and Evaluation, IARC/WHO, Lyon, France
Reviewing and ensuring the scientific accuracy of the manuscripts for the publication of "IARC monographs on the evaluation of carcinogenic risks to humans", published by IARC. Monographs currently being reviewed are:

- Betel-quid and areca nut chewing
- Some metals used in industry
- Organic and inorganic lead compounds
- Formaldehyde and other aldehydes

Sept. 2001 - Aug. 2002: Unit of Gene-Environment Interactions, IARC/WHO, Lyon, France (laboratory of Dr E. van Dyck)

- Biological characterisation of RDM-1, a novel Rad52 homologue

Jan. 1998 - June 2001: Dept. of Cancer Cell Biology, Harvard School of Public Health, Boston, MA (Jan. 1998 – Feb. 2001) and Dept. of Environmental Health, UCLA School of Medicine and Public Health, Los Angeles, CA (March-June 2001): laboratory of Dr R.H. Schiestl

- Double strand break repair by recombination in DNA-repair deficient CHO cell lines
- P53 involvement in X-ray induced intrachromosomal recombination in mice
- Delayed re-induction of p53 and oxidative stress in irradiated human diploid fibroblasts

Oct. 1992 – Oct. 1997: Dept. of Toxicology, St. Bartholomew & the Royal London School of Medicine and Dentistry, London, UK, under the supervision of Dr C.J. Powell

- Relationship between toxicity, mitogenicity and carcinogenicity in the rat liver

Oct. 1991 – Sept. 1992: *GlaxoWellcome*, Biomedical Research Institute, Geneva, Switzerland, under the supervision of Dr J. Whelan

- Activation by NF*k*B of the ELAM-1 promoter sequence in *S.Pombe*

Oct. 1990 – July 1991: ISREC, Dept. of Chemical Carcinogenesis, Epalinges s/ Lausanne, Switzerland, under the supervision of Dr R.M. Tyrrell

- Determination of DNase I hypersensitive sites in the human heme oxygenase gene

### Work experience in scientific writing

Reports: compilation, summarisation and critical evaluation of toxicology reports for the European Union review on food contact chemicals (indirect food additives)

Translations: Biomedical translations of questionnaires used for surveys in hospitals and other medical institutions from French into English and vice-versa, and from German into English.

### Languages and computer literacy

Languages: French (mother tongue), English (excellent), German (excellent), Italian (good), Spanish (basic knowledge)
Computer literacy: Word, Excel, Power Point, Harvard Graphics, Harvard ChartXL, Cricket Graph, Gene Construction Kit, EndNote

### Fellowships and bursaries

Jan. 1999 – Dec. 1999: Post-doctoral fellowship awarded by the Swiss Cancer League

Jan. 1998 – Dec. 1998: Post-doctoral fellowship awarded by the Swiss National Fund

Oct. 1992 - April 1996: PhD studentship awarded by *GlaxoWellcome*, R & D, Ware, UK

March 1994 and 1996: Student bursary awarded by the British Toxicology Society for the participation at international scientific meetings

### Publications

**Secretan MB**, Scuric Z, Oshima J, Bishop AJR, Howlett NG, Yau D and Schiestl RH (2004) Effect of Ku86 and DNA-PKcs Deficiency on Non-homologous End-Joining and Homologous Recombination Using a Transient Transfection Assay. *Mutation Research* (accepted with revisions)

Rugo RE, **Secretan MB** and Schiestl RH (2002) X-radiation causes a persistent induction of reactive oxygen species and a delayed reinduction of TP53 in normal human diploid fibroblasts. *Radiation Resarch*, **158** (2), 210-9.

Aubrecht J, **Secretan MB**, Bishop AJR and Schiestl RH (1999) Involvement of p53 in X-ray induced intrachromosomal recombination in mice. *Carcinogenesis*, **20** (12), 2229-36.

**Secretan MB**, Cottrell S and Powell CJ (1997) Progression of precarcinogenic effects in methapyrilene-treated rats. *Human Exp. Toxicol.* **16 (1)**, 53.

Freathy C, Cottrell S, **Secretan MB** and Powell CJ (1997) Young rats are more susceptible than old rats to the relative induction of preneoplastic lesions after a 13 week exposure to a non-genotoxic carcinogenic drug. *Human Exp. Toxicol.* **16 (1)**, 46.

Powell CJ and **Secretan MB** (1995) Induction and reversibility of genotoxic and non-genotoxic carcinogen-induced altered hepatocyte foci in rats. *Toxicol. Pathol.* **23 (6)**, 757-758.

Cottrell S, **Secretan MB** and Powell CJ (1995) Chronic methapyrilene administration increases cell proliferation in diploid hepatocytes with a concomitant decrease in polyploidisation. *Human Exp. Toxicol.* **14**, 770.

**Secretan MB** and Powell CJ (1995) Reversibility of the toxic and precarcinogenic effects of methapyrilene in rats. *Human Exp. Toxicol.* **14**, 769.

**Secretan MB** and Powell CJ (1994) Early toxic and carcinogenic effects of methapyrilene in rat liver. *Toxicol. Lett.* **74 (suppl. 1)**, 77.

Powell CJ, **Secretan MB** and Cottrell S (1994) Preneoplastic changes during non-genotoxic hepatocarcinogenesis. In: Skouteris, G.G. (Ed.) *Liver carcinogenesis, NATO ASI Series, Vol. H88,* pp. 215-229. Berlin - Heidelberg: Springer-Verlag.

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| Straif, Kurt | 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 Bonn, Medical School | M.D. | 1984 | Medicine |
| UCLA, School of Public Health | M.P.H. | 1991 | Public Health |
| UCLA, School of Public Health | Ph.D. | 2001 | Epidemiology |

**NOTE: The Biographical Sketch may not exceed four pages. Items A and B (together) may not exceed two of the four-page limit. Follow the formats and instructions on the attached sample.**

**A. Positions and Honors.** List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

**1984-1990** Medical Residency, Instructor and Fellow in Internal Medicine, Oncology, University of Bonn, Medical School
**1991** Visiting Scientist, Dept. of Environmental Sciences, School of Public Health, Columbia University of New York
**1991-1995** Instructor, Fellow and Assistant Professor, Occupational and Social Medicine, University of Giessen, Medical School
**1995-2001** Assistant and Associate Professor, Head of Unit on Cancer and Occupational Epidemiology, Epidemiology and Social Medicine, University of Muenster, Medical School
**2001-** Scientist, International Agency for Research on Cancer

**Other Experience and Professional Memberships**
**1990** Board Certification in Internal Medicine
**1994** Board Certification in Occupational Medicine
**1990** German Cancer Society
**1990** German Epidemiological Association (dae)
**1990** German Society for Occupational and Environmental Medicine (dgaum)
**1991** German Industrial Berufsgenossenschaften Scientific Task Force "Wismut"
**1995** Scientific Committee Epidemiology in Occupational Health, ICOH
**1997** Initiator and Chair, Working Group Occupational Epidemiology (dae, dgaum)
**1997** Deutsche Forschungsgemeinschaft, Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area
**2001** Commission on Prevention, German Cancer Society
**2001-2002** German Industrial Berufsgenossenschaften Scientific Advisory Group for Studies on Secondary Prevention of Asbestos Related Cancers
**2002** National Agency for Radiation Safety, Scientific Advisory Committee: Epidemiologic Study of Childhood Leukemia in the Vicinity of Nuclear Power Plants

**Honors**
**1990-1991** Fellowship, German Academic Exchange Office
**1992** Fellowship, German Academic Exchange Office
**1994** Fellowship, German Academic Exchange Office
**1996** Fellowship, German Academic Exchange Office

B. **Selected peer-reviewed publications (in chronological order).**

Jacob BJ, Straif K, Thomas G, Ramadas K, Mathew B, Brennan P, Zhang ZF, Sankaranarayanan R, Hashibe M.Betel Quid Without Tobacco as a Risk Factor for Oral Precancers. Oral Oncology (accepted)

Brandt B, Hermann S, Straif K, Tidow N, Buerger H, Chang-Claude J. Modification of breast cancer risk in young women by a polymorphic sequence in the egfr gene. Cancer Research 2004; 64:7-12

Vineis P, Alavanja M, Buffler P, Fontham E, Franceschi S, Gao YT, Gupta PC, Hackshaw A, Matos E, Samet J, Sitas F, Smith J, Stayner L, Straif K, Thun MJ, Wichmann HE, Wu AH, Zaridze D, Peto R, Doll R. Tobacco and cancer: recent epidemiological evidence. JNCI 2004; 96:99-106

Sun Y, Taeger D, Weiland SK, Keil U, Straif K. Job titles and work areas as surrogate indicators of occupational exposure. Epidemiology 2003,14:361-367

Straif K. Re: Meta-analysis of risk estimates for prostate cancer among rubber workers J Occup Environ Med 2001; 43:593-595

Straif K, Keil U, Taeger D, Holthenrich D, Sun Y, Bungers M, Weiland SK. Exposure to nitrosamines, carbon black, asbestos, and talc and mortality from stomach, lung and laryngeal cancer among a cohort of rubber workers. Am J Epidemiol 2000;152:297-306

Taeger D, Sun Y, Keil U, Straif K. A standalone windows application for computing exact person-years, standardized mortality ratios and confidence intervals in epidemiologic studies. Epidemiology 2000; 11:607-608

Straif K, Weiland SK, Bungers M, Holthenrich D, Taeger D, Sun Y, Keil U. Exposure to high concentrations of nitrosamines and cancer mortality among a cohort of rubber workers. Occup Environ Med 2000; 57:180-187

Straif K, Chambless L, Weiland SK, Wienke A, Bungers M, Taeger D, Keil U. Occupational risk factors for mortality from stomach and lung cancer among rubber workers: an analysis using internal controls and refined exposure assessment. Int J Epidemiol 1999;28:1037-1043

Straif K, Weiland SK, Bungers M, Holthenrich D, Keil U. Exposure to nitrosamines and mortality from salivary gland cancer among rubber workers. Epidemiology 1999; 10: 786-787 (letter)

Mundt KA, Weiland SK, Bucher AM, Straif K, Werner B, Chambless L, Keil U. An occupational cohort mortality study of women in the German rubber industry: 1976 to 1991. J Occup Environ Med 1999; 41:807-812

Straif K, Weiland SK, Werner B, Wienke A, Keil U. Elevated mortality from nonalcohol-related chronic liver disease among female rubber workers: Is it associated with exposure to nitrosamines? Am J Ind Med 1999; 35:264-271

Weiland SK, Straif K, Chambless L, Werner B, Mundt KA, Bucher AM, Birk T, Keil U. Workplace risk factors for cancer in the German rubber industry: part 1. Mortality from respiratory cancers. Occup Environ Med 1998; 55:317-24

Straif K, Weiland SK, Werner B, Chambless L, Mundt KA, Keil U. Workplace risk factors for cancer in the German rubber industry: part 2. Mortality from non-respiratory cancers. Occup Environ Med 1998; 55:325-32

Straif K, Weiland SK, Keil U. Re: Occupational risk factors for gastric cancer: a review. Am J Epidemiol 1998; 147:608-9 (letter)

Schneider J, Straif K, Woitowitz H-J. Pleural Mesothelioma and Household Exposure to Asbestos. Reviews on Environmental Health 1996; 11:65-70

Braun A, Straif K, Konietzko N, Wiesner B, Loeffler S, Presek P, Woitowitz H-J. Detection of oncogene and tumor suppressor gene products in serum of former uranium miners for secondary prevention of radon-induced lung cancer. Clinical Chemistry 1995;41:1913-5

**BIOGRAPHICAL SKETCH**

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| NAME | POSITION TITLE |
|---|---|
| BOFFETTA, Paolo | Medical Officer (Unit Chief), International Agency for Research on Cancer (IARC/WHO), Lyon, France |

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 |
|---|---|---|---|
| Univ. of Turin Faculty of Medicine and Surgery | MD | 1985 | Medicine |
| Columbia Univ. School of Publ. Health, New York | Master | 1988 | Public Health |
| Univ. of Turin School of Specialization in Hygiene | Diploma | 1988 | Hygiene & Prev. Med. |

## A. Positions and Honors

Research Fellow and Research Assistant, Cancer Epidemiology Unit, University of Turin, Italy (1985-90).
Research Assistant at the Department of Statistics & Epidemiology of the American Cancer Society (1986-88) and at the Division of Epidemiology of the American Health Foundation (1988), New York.
Graduate Research Assistant at the Division of Environmental Sciences and Post-Doctoral Associate at the Division of Health Policy and Management, Columbia Univ. School of Public Health, New York (1988-89).
Medical Officer (Epidemiologist), Unit of Analytical Epidemiology, IARC/WHO, Lyon, France (1990-94).
Visiting Scientist, Division of Cancer Epidemiology and Genetics, NCI, Washington (1998-99).
Professor of Clinical Epidemiology and Division Chief, German Cancer Research Centre, Heidelberg, Germany (2003).
Foreign Adjunct Professor at the Department of Medical Epidemiology and at the Microbiology and Tumour Biology Centre, Karolinska Institute, Stockholm, Sweden (2000-).
Chief of the Unit of Environmental Cancer Epidemiology (1995-) and Head of the Courses Programme (2000-), International Agency for Research on Cancer (IARC)/ World Health Organization (WHO), Lyon, France.

## B. Selected Peer-Reviewed Publications (out of 245)

Boffetta P. Epidemiology of environmental and occupational cancer. Oncogene (in press).
Hung RJ, Boffetta P, Brennan P, Malaveille C, Gelatti U, Placidi D, Carta A, Hautefeuille A, Porru S. Genetic polymorphisms of MPO, COMT, MnSOD, NQO1, interactions with environmental exposures and bladder cancer risk. Carcinogenesis (in press).
Scelo G, Constantinescu V, Csiki I, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, Lissowska J, Fabianova E, Cassidy A, Slamova A, Foretova L, Janout V, Fevotte J, Fletcher T, Mannetje A 't, Brennan P, Boffetta P. Occupational exposure to vinyl chloride, acrylonitrile and styrene and lung cancer risk. Cancer Causes Control (in press).
Buffler P, Rice J, Baan R, Bird M, Boffetta P, eds, Mechanisms of Carcinogenesis: Considerations of Molecular Epidemiology (IARC Scientific Publication No 157). IARC, Lyon, 2004.
Boffetta P, Burstyn I, eds. Cancer Mortality among European Asphalt Workers: Selected Papers from a Study of Cancer Risk in the European Asphalt Industry Coordinated by the International Agency for Research on Cancer. Am J Ind Med 43: 1-108, 2003.
Boffetta P, Matisane L, Mundt KA, Dell LD. Meta-analysis of studies of occupational exposure to vinyl chloride in relation to cancer mortality. Scand J Work Environ Health 29: 220-229, 2003.
Boffetta P, Nyberg F. Contribution of environmental factors to cancer risk. Br Med Bull 68: 71-94, 2003.

Boffetta P, Richiardi, Berrino F, Estève J, Pisani P, Crosignani P, Raymond L, Zubiri L, Del Moral A, Lehmann W, Donato F, Terracini B, Tuyns A, Merletti F. Occupation and larynx and hypopharynx cancer: an international case-control study in France, Italy, Spain, and Switzerland. Cancer Causes Control 14: 203-212, 2003.

Gajalakshmi V, Hung RJ, Mathew A, Varghese C, Brennan P, Boffetta P. Tobacco smoking and chewing, alcohol drinking and lung cancer risk among men in southern India. Int J Cancer 107: 441-447, 2003.

Hung RJ, Boffetta P, Brockmöller J, Butkiewicz D, Cascorbi I, Clapper ML, Garte S, Haugen A, Hirvonen A, Anttila S, Kalina I, Le Marchand L, London SJ, Rannug A, Romkes M, Salagovic J, Schoket B, Gaspari L, Taioli E. CYP1A1 and GSTM1 genetic polymorphisms and lung cancer risk in Caucasian non-smokers: a pooled analysis. Carcinogenesis 24: 875-882, 2003.

Bhurgri Y, Decullier E, Bhurgri A, Nassar S, Usman A, Brennan P, Boffetta P. A case-control study of lung cancer in Karachi, Pakistan. Int J Cancer 98: 952-955, 2002.

Boffetta P, Nyberg F, Mukeria A, Benhamou S, Constantinescu V, Batura-Gabryel H, Brüske-Hohlfeld I, Schmid G, Simonato L, Pelkonen P, Hall J. O6-alkylguanine-DNA-alkyltransferase activity in peripheral leukocytes, smoking and risk of lung cancer. Cancer Lett 180; 33-39, 2002.

Kjaerheim K, Boffetta P, Hansen J, Cherrie J, Chang-Claude J, Eilber U, Ferro G, Guldner K, Olsen JH, Plato N, Proud L, Saracci R, Westerholm P, Andersen A. Lung cancer among rock and slag wool production workers. Epidemiology 13: 445-453, 2002.

Boffetta P, Kreuzer M, Benhamou S, Agudo A, Wichmann HE, Gaborieau V, Simonato L. Risk of lung cancer from tobacco smoking among young women from Europe. Int J Cancer 91: 745-746, 2001.

Boffetta P, Sällsten G, Garcia-Gómez M, Pompe-Kirn V, Zaridze D, Bulbulyan M, Caballero J-D, Ceccarelli F, Kobal AB, Merler E. Mortality from cardiovascular diseases and exposure to inorganic mercury. Occup Environ Med 58: 461-466, 2001.

Boffetta P, Silverman DT. A meta-analysis of bladder cancer and diesel exhaust exposure. Epidemiology 12: 125-130, 2001.

Ward E, Boffetta P, Andersen A, Colin D, Comba P, Deddens JA, De Santis M, Engholm G, Hagmar L, Langard S, Lundberg I, McElvenny D, Pirastu R, Sali D, Simonato L. Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry. Epidemiology 12: 710-718, 2001.

Boffetta P, Trédaniel J, Greco A. Risk of childhood cancer and adult lung cancer after childhood exposure to passive smoke: a meta-analysis. Environ Health Persp 108: 73-82, 2000.

Matos EL, Vilensky M, Mirabelli D, Boffetta P. Occupational exposures and lung cancer in Buenos Aires, Argentina. J Occup Environ Med 42: 653-659, 2000.

Boffetta P, Andersen A, Hansen J, Olsen JH, Plato N, Teppo L, Westerholm P, Saracci R. Cancer incidence among European man-made vitreous fiber production workers. Scand J Work Environ Hlth 25: 222-226, 1999.

Boffetta P, Butler J, Maynadié M, Brennan P. Lymphomas. In: Neugut AI, Meadows AT, Robinson E, eds, Multiple Primary Cancers. Lippincott Williams & Wilkins, Philadelphia, 1999, pp 277-301.

Boffetta P, Merler E, eds. Occupational Cancer in Europe. Environ Health Persp 107 (Suppl 2): 225-303, 1999.

Boffetta P, Pershagen G, Jöckel K-H, Forastiere F, Gaborieau V, Heinrich J, Jahn I, Kreuzer M, Merletti F, Nyberg F, Rösch F, Simonato L. Cigar and pipe smoking and lung cancer risk: a multicenter study from Europe. J Natl Cancer Inst 91: 697-701, 1999.

Boffetta P, ed. Cancer. 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, 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.

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 (SSuppl 2): 645-653, 1998.

## C. Research Support

Ongoing Research Support

(b)(4), (b)(6) Brennan (PI) 1 January 2001 - 30 June 2004
(b)(4), (b)(6)
Environmental exposures and lymphoid neoplasms
The major goal is to coordinate a multicentre case-control study of environmental exposures and lymphoid neoplasms.
Role: Co-Investigator

(b)(4), (b)(6) Norppa (PI) 1 January 2001 - 30 November 2004
(b)(4), (b)(6)
Cytogenetic biomarkers and human cancer risk
The major goals are to assess the risk of cancer following cytogenetic abnormalities and extend the project to countries from Central Europe.
Role: Co-Investigator

(b)(4), (b)(6) Brennan (PI) 1 August 2001 - 31 July 2004
(b)(4), (b)(6)
Epidemiological study of the dramatic fall in life expectancy in Russia in the 1990s
The major goal is to establish a large retrospective cohort of 100,000 Russian adults who died in the 1990s.
Role: Co-Investigator

(b)(4), (b)(6) Brennan (PI) 1 January 2002 - 30 June 2005
(b)(4), (b)(6)
Alcohol-related cancer and genetic susceptibility in Europe
The major goal is to coordinate a study of head and neck cancer in Western Europe.
Role: Co-Investigator

1R03-CA101442 Brennan (PI) 1 August 2003 - 31 July 2005
NIH National Cancer Institute (DDCCPS)
Multicentric pooled analysis of second primary cancer
The major goal is to conduct a systematic analysis of second cancers from cancer registry information.
Role: Co-Investigator

1R01-CA92039 Brennan (PI) 1 September 2003 - 31 August 2006
NIH National Cancer Institute
Genetics of tobacco and alcohol related cancers
The major goal is to identify genetic risk factors for lung and upper aero-digestive tract cancers in Central Europe and South America.
Role: Co-Investigator

(b)(4), Brennan (PI) 1 October 2003 - 30 September 2006
(b)(4), (b)(6)
The role of DNA repair and cell-cycle control gene polymorphisms in the development of lung cancer
The major goal is to identify a role for novel DNA repair genes in lung cancer development.
Role: Co-Investigator

Completed Research Support

(b)(4), (b) Brennan (PI) 20 February 2002 - 30 September 2003
(b)(4), (b)(6)
European kidney cancer study
The major goal is to coordinate a study of kidney cancer in Central and Eastern Europe.
Role: Co-Investigator

263-MQ-312730 Brennan (PI) 6 March 2003 - 9 September 2003
NIH National Cancer Institute
Oesophageal cancer in the South Asian Cancer Belt
The major goal is to provide questionnaire and biological sample material from 1000 individuals participating in a pilot study in Iran.
Role: Co-Investigator

(b)(4), (b)(6) Boffetta (PI) 1 November 2000 - 1 November 2002
(b)(4), (b)(6)
Serum cotinine, smoking status, passive smoking and lung cancer risk in the Janus cohort
The major goal was to investigate the risk of lung cancer in non-smokers according to serum cotinine level.
Role: PI

(b)(4), (b)(6) Boffetta (PI) 1 January 1998 - 31 December 2001
(b)(4), (b)(6)
Environmental and occupational cancer in Mercosul countries
The major goal was to coordinate a multicentric case-control study of laryngeal cancer in Brazil and Argentina.
Role: PI

(b)(4), (b)(6) Boffetta (PI) 1 January 1998 - 31 December 2001
(b)(4), (b)(6)
Occupation, environment and lung cancer in C/E Europe
The major goal was to coordinate a multicentric case-control study of lung cancer in Central and Eastern Europe.
Role: PI

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| BRENNAN, Paul | Scientist, International Agency for Research on Cancer (IARC/WHO), Lyon, France |

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 Leicester | BSc | 1988 | Mathematics (Hons) |
| University of Leicester | MSc | 1989 | Medical Statistics |
| Royal College of Physicians | Diploma | 1994 | Epidemiology |
| Faculty of Medicine, University of Manchester | PhD | 1995 | Genetic epidemiology |

### A. Positions and Honors

Lecturer in Epidemiology and Medical Statistics, ARC Epidemiology Research Unit, University of Manchester Medical School, UK (1989-1996)

Scientist, Unit of Environmental Cancer Epidemiology, International Agency for Cancer Research, Lyon, France (1997-)

### B. Peer-Reviewed Publications (2001-)


Balbi JC, Larrinaga MT, De Stefani E, Mendilaharsu M, Ronco AL, Boffetta P, Brennan P. Foods and risk of bladder cancer: a case-control study in Uruguay. *Eur J Cancer Prev* 10: 453-458, 2001.

Boffetta P, Järvholm B, Brennan P, Nyrén O. Incidence of lung cancer in a large cohort of non-smoking men from Sweden. *Int J Cancer* 94: 591-593, 2001.

Bray I, Brennan P, Boffetta P. Recent trends and future projections of lymphoid neoplasms - a Bayesian age-period-cohort analysis. *Cancer Causes Control* 12: 813-820, 2001.

Brennan P, Bogillot O, Greiser E, Chang-Claude J, Wahrendorf J, Cordier S, Jöckel K-H, Lopez-Abente G, Tzonou A, Vineis P, *et al.* The contribution of cigarette smoking to bladder cancer in women (pooled European data). *Cancer Causes Control* 12: 411-417, 2001.

De Stefani E, Correa P, Boffetta P, Ronco A, Brennan P, Deneo-Pellegrini H, Mendilaharsu M. Plant foods and risk of gastric cancer: a case-control study in Uruguay. *Eur J Cancer Prev* 10: 357-364, 2001.

De Stefani E, Ronco A, Brennan P, Boffetta P. Meat consumption and risk of stomach cancer in Uruguay: a case-control study. *Nutr Cancer* 40: 103-107, 2001.

Lewis S, Brennan P, Nyberg F, Ahrens W, Constantinescu V, Mukeria A, Benhamou S, Batura-Gabryel H, Brüske-Hohlfeld I, Simonato L, *et al.* Re: 'Dietary intake of isothiocyanates: evidence of a joint effect with Glutathione S-Transferase polymorphisms in lung cancer risk'. *Cancer Epidemiol Biomarkers Prev* 10: 1105-1106, 2001.

Oreggia F, De Stefani E, Boffetta P, Brennan P, Deneo-Pellegrini H, Ronco AL. Meat, fat and risk of laryngeal cancer: a case-control study in Uruguay. *Oral Oncol* 37: 141-145, 2001.

Pitard A, Brennan P, Clavel J, Greiser E, Lopez-Abente G, Chang-Claude J, Wahrendorf J, Serra C, Kogevinas M, Boffetta P. Cigar, pipe, and cigarette smoking and bladder cancer risk in European men. *Cancer Causes Control* 12: 551-556, 2001.

Simonato L, Agudo A, Ahrens W, Benhamou E, Benhamou S, Boffetta P, Brennan P, Darby SC, Forastiere F, Fortes C, *et al.* Lung cancer and cigarette smoking in Europe: an update of risk estimates and an assessment of inter-country heterogeneity. *Int J Cancer* 91: 876-887, 2001.

Benhamou S, Lee WJ, Alexandrie A-K, Boffetta P, Bouchardy C, Butkiewicz D, Brockmöller J, Clapper ML, Daly A, Dolzan V, *et al.* Meta- and pooled analyses of the effects of glutathione S-transferase M1 polymorphisms and smoking on lung cancer risk. *Carcinogenesis* 23: 1343-1350, 2002.

Bhurgri Y, Decullier E, Bhurgri A, Nassar S, Usman A, Brennan P, Boffetta P. A case-control study of lung cancer in Karachi, Pakistan. *Int J Cancer* 98: 952-955, 2002.

Brennan P. Gene-environment interaction and aetiology of cancer: what does it mean and how can we measure it? *Carcinogenesis* 23: 381-387, 2002.

Brennan P, Bray I. Recent trends and future directions for lung cancer mortality in Europe. *Br J Cancer* 87: 43-48, 2002.

De Stefani E, Brennan P, Boffetta P, Mendilaharsu M, Deneo-Pellegrini H, Ronco A, Olivera L, Kasdorf H. Diet and adenocarcinoma of the lung: a case-control study in Uruguay. *Lung Cancer* 35: 43-51, 2002.

De Stefani E, Brennan P, Ronco A, Fierro L, Correa P, Boffetta P, Deneo-Pellegrini H, Barrios E. Food groups and risk of lung cancer in Uruguay. *Lung Cancer* 38: 1-7, 2002.

De Stefani E, Correa P, Deneo-Pellegrini H, Boffetta P, Piñeyro Gutiérrez L, Ronco A, Brennan P, Mendilaharsu M. Alcohol intake and risk of adenocarcinoma of the lung: a case-control study in Uruguay. *Lung Cancer* 38: 9-14, 2002.

Deneo-Pellegrini H, Boffetta P, De Stefani E, Ronco A, Brennan P, Mendilaharsu M. Plant foods and differences between colon and rectal cancers. *Eur J Cancer Prev* 11: 369-375, 2002.

Gemignani F, Landi S, Vivant F, Zienolddiny S, Brennan P, Canzian F. A catalogue of polymorphisms related to xenobiotic metabolism and cancer susceptibility. *Pharmacogenetics* 12: 459-463, 2002.

Korte JE, Brennan P, Henley SJ, Boffetta P. Dose-specific meta-analysis and sensitivity analysis of the relation between alcohol consumption and lung cancer risk. *Am J Epidemiol* 155: 496-506, 2002.

Lee WJ, Brennan P, Boffetta P, London SJ, Benhamou S, Rannug A, To-Figueras J, Ingelman-Sundberg M, Shields P, Gaspari L, Taioli E. Microsomal epoxide hydrolase polymorphisms and lung cancer risk: a quantitative review. *Biomarkers* 7: 230-241, 2002.

De Stefani E, Deneo-Pellegrini H, Ronco AL, Boffetta P, Brennan P, Muñoz N, Castellsagué, Correa P, Mendilaharsu M. Food groups and risk of squamous cell carcinoma of the oesophagus: a case-control study in Uruguay. *Br J Cancer* 89: 1209-1214, 2003.

Gajalakshmi V, Hung RJ, Mathew A, Varghese C, Brennan P, Boffetta P. Tobacco smoking and chewing, alcohol drinking and lung cancer risk among men in southern India. *Int J Cancer* 107: 441-447, 2003.

Hashibe M, Brennan P, Strange RC, Bhisey R, Cascorbi I, Lazarus P, Oude Ophuis MB, Benhamou S, Foulkes WD, Katoh T, *et al.* Meta- and pooled analyses of GSTM1, GSTT1, GSTP1, and CYP1A1 genotypes and risk of head and neck cancer. *Cancer Epidemiol Biomarkers Prev* 12: 1509-1517, 2003.

Mannetje A 't, Fevotte J, Fletcher T, Brennan P, Legoza J, Szeremi M, Paldy A, Brzeznicki S, Gromiec J, Ruxanda-Artenie C, *et al.* Assessing exposure misclassification by expert assessment in multicenter occupational studies. *Epidemiology* 14: 585-592, 2003.

Men T, Brennan P, Boffetta P, Zaridze D. Russian mortality trends for 1991-2001: analysis by cause and region. *BMJ* 327: 964-966, 2003.

Parikh S, Brennan P, Boffetta P. Meta-analysis of social inequality and the risk of cervical cancer. *Int J Cancer* 105: 687-691, 2003.

Sewram V, De Stefani E, Brennan P, Boffetta P. Maté consumption and the risk of squamous cell esophageal cancer in Uruguay. *Cancer Epidemiol Biomarkers Prev* 12: 508-513, 2003.

Shen M, Hung RJ, Brennan P, Malaveille C, Donato F, Placidi D, Carta A, Hautefeuille A, Boffetta P, Porru S. Polymorphisms of the DNA repair genes XRCC1, XRCC3, XPD, interaction with environmental exposures, and bladder cancer risk in a case-control study in northern Italy. *Cancer Epidemiol Biomarkers Prev* 12: 1234-1240, 2003.

Znaor A, Brennan P, Gajalakshmi V, Mathew A, Shanta V, Varghese C, Boffetta P. Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. *Int J Cancer* 105: 681-686, 2003.

Brennan P, Buffler PA, Reynolds P, Wu AH, Wichmann HE, Agudo A, Pershagen G, Jöckel K-H, Benhamou S, Greenberg RS, *et al.* Secondhand smoke exposure in adulthood and risk of lung cancer among never-smokers: a pooled analysis of two large studies. *Int J Cancer* 109: 125-131, 2004.

Brennan P, Lewis S, Hashibe M, Bell DA, Boffetta P, Bouchardy C, Caporaso N, Chen C, Coutelle C, Diehl SR, *et al.* Pooled analysis of alcohol dehydrogenase genotypes and head and neck cancer: a HuGE review. *Am J Epidemiol* 159: 1-16, 2004.

Cohet C, Borel S, Nyberg F, Mukeria A, Brüske-Hohlfeld I, Constantinescu V, Benhamou S, Brennan P, Hall J, Boffetta P. Exon 5 polymorphisms in the O6-alkylguanine DNA alkyltransferase gene and lung cancer risk in non-smokers exposed to second-hand smoke. *Cancer Epidemiol Biomarkers Prev* 13: 320-323, 2004.

Abnet CC, Saadatian-Elahi M, Pourshams A, Boffetta P, Feizzadeh A, Brennan P, Taylor PR, Kamangar F, Dawsey SM, Malekzadeh R. Reliability and validity of opiate use self-report in a population at high risk for esophageal cancer in Golestan, Iran. *Cancer Epidemiol Biomarkers Prev* (in press).

Brennan P. Commentary: Mendelian randomization and gene-environment interaction. *Int J Epidemiol* (in press).

Hung RJ, Boffetta P, Brennan P, Malaveille C, Gelatti U, Placidi D, Carta A, Hautefeuille A, Porru S. Genetic polymorphisms of MPO, COMT, MnSOD, NQO1, interactions with environmental exposures and bladder cancer risk. *Carcinogenesis* (in press).

Hung RJ, Boffetta P, Brennan P, Malaveille C, Hautefeuille A, Donato F, Gelatti U, Spaliviero M, Placidi D, Carta A, *et al.* GSTs, NATs, SULT1A1, CYP1B1 genetic polymorphisms, interactions with environmental exposures and bladder cancer risk in a high-risk population. *Int J Cancer* (in press).

Scelo G, Constantinescu V, Csiki I, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, Lissowska J, Fabianova E, Cassidy A, Slamova A, *et al.* Occupational exposure to vinyl chloride, acrylonitrile and styrene and lung cancer risk. *Cancer Causes Control* (in press).

## C. Research Support

Ongoing Research Support

(b)(4), (b)(6) Brennan (PI) 1 January 2001 - 30 June 2004
(b)(4), (b)(6)
Environmental exposures and lymphoid neoplasms
The major goal is to coordinate a multicentre case-control study of environmental exposures and lymphoid neoplasms.
Role: PI

(b)(4), (b)(6) Brennan (PI) 1 August 2001 - 31 July 2004
(b)(4), (b)(6)
Epidemiological study of the dramatic fall in life expectancy in Russia in the 1990s
The major goal is to establish a large retrospective cohort of 100,000 Russian adults who died in the 1990s.
Role: PI

(b)(4), (b)(6) Brennan (PI) 1 January 2002 - 30 June 2005
(b)(4), (b)(6)
Alcohol-related cancer and genetic susceptibility in Europe
The major goal is to coordinate a new study of head and neck cancer in Western Europe.
Role: PI

1R03-CA101442 Brennan (PI) 1 August 2003 - 31 July 2005
NIH National Cancer Institute (DDCCPS)
Multicentric pooled analysis of second primary cancer
The major goal is to conduct a systematic analysis of second cancers from cancer registry information.
Role: PI

1R01-CA92039 Brennan (PI) 1 September 2003 - 31 August 2006
NIH National Cancer Institute
Genetics of tobacco and alcohol related cancers
The major goal is to identify genetic risk factors for lung and upper aero-digestive tract cancers in Central Europe and South America.
Role: PI

(b)(4), Brennan (PI) 1 October 2003 - 30 September 2006
(b)(4), (b)(6)
The role of DNA repair and cell-cycle control gene polymorphisms in the development of lung cancer
The major goal is to identify a role for novel DNA repair genes in lung cancer development.
Role: PI

Completed Research Support

(b) Brennan (PI) 1 November 1999 - 31 October 2003
(b)(4), (b)(6)
Examination of alcohol, alcohol metabolizing genes and oesophageal cancer in Central & Eastern Europe
The major goal is to examine the role of alcohol in oesophageal cancer in a high-risk area.
Role: PI

(b)(4), (b) Brennan (PI) 20 February 2002 - 30 September 2003
(b)(4), (b)(6)
European kidney cancer study
The major goal is to coordinate a study of kidney cancer in Central and Eastern Europe.
Role: PI

263-MQ-312730 Brennan (PI) 6 March 2003 - 9 September 2003
NIH National Cancer Institute
Oesophageal cancer in the South Asian Cancer Belt
The major goal is to provide questionnaire and biological sample material from 1000 individuals participating in a pilot study in Iran.
Role: PI

(b)(4), (b)(6) Brennan (PI) 1 December 1998 - 30 November 2002
(b)(4), (b)(6)
Genetic, infectious and lifestyle risk factors behind two increasing cancers in Central Europe
The major goal was to coordinate a multicentric case-control study of oral and larynx cancer in Central and Eastern Europe.
Role: PI

(b)(4), (b)(6) Brennan (PI) 1 October 1998 - 1 October 2002
(b)(4), (b)(6)
Multicentre case-control study of lymphomas
The major goal was to coordinate an assessment of occupational exposures in five ongoing case-control studies of lymphoma.
Role: PI

263-MQ-918202/006148/015834/104630/112373 Brennan(PI) 15 September 1999 - 26 September 2002
NIH National Cancer Institute
Case-control study of kidney cancer in C/E Europe
The major goal was to coordinate a study of kidney cancer in Central and Eastern Europe.
Role: PI

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| Dr Elisabeth CARDIS | Chief, Unit of Radiation and Cancer |

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 | B. Sc. Honours | 1979 | Mathematics, Sciences |
| University of Washington. | M.Sc | 1983 | Biostatistics |
| University of Washington | PhD | 1985 | Biostatistics |
| International Agency for Research on Cancer, Lyon | Post-doctoral fellowship | 1986 | Biostatistics and epidemiology |

**NOTE: The Biographical Sketch may not exceed four pages. Items A and B (together) may not exceed two of the four-page limit. Follow the formats and instructions on the attached sample.**

**A. Positions and Honors.** List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

### Positions and Employment

1975 – 1979: Teaching Assistant, Department of Mathematics, University of Ottawa, Ottawa, Canada
1979 – 1981: Graduate Student Research Assistant - Department of Biostatistics, University of Washington, Seattle, WA
1980 & 1983: Graduate Student Teaching Assistant - Department of Biostatistics, University of Washington, Seattle, WA
1981 – 1982: Visiting Research Fellow, Radiation Effects Research Foundation, Hiroshima, Japan
1983 – 1985: Graduate Student Research Assistant - Department of Biostatistics, University of Washington, Seattle, WA
1985: Assistant Professor - Institut Armand Frappier, Epidemiology and Preventive Medicine Research Centre, Laval, Québec
1985 – 1986: IARC Research Training Fellow - International Agency for Research on Cancer, Lyon, France
1986 – 1988: Consultant - International Agency for Research on Cancer, Lyon, France
1988 – 1994: Scientist - International Agency for Research on Cancer, Lyon, France
1995 – 1998: Head of Programme on Radiation and Cancer
1998 to present: Chief, Unit of Radiation and Cancer, International Agency for Research on Cancer, Lyon, France

### Other Experience and Professional Membership

1998-2002: International Commission for non-Ionising Radiation Protection (ICNIRP) - Member Standing Committee on Epidemiology
2002 - International Commission for non-Ionising Radiation Protection (ICNIRP) - Corresponding Member
2000: US National Academy of Sciences Committee on the Biological Effects of Ionising Radiation (BEIR) VII
2003: Scientific Council of the "Agence française de sécurité sanitaire environnementale"

### Honors

1985-1986: IARC Cancer Research Training Fellowship
1990: ASA Coolfont Radiation Fellowship

**B. Selected peer-reviewed publications (in chronological order).**
(Publications selected from 100 peer-reviewed publications)

Gilbert, E.S., Thierry-Chef, I., Cardis, E., Fix, J.J., Marshall, M. External Dose Estimation for Nuclear Worker Studies. Radiat. Res.(in press)

Kesminiene A, Cardis E, Tenet V, Ivanov VK, Kurtinaitis J, Malakhova I, Stengrevics A and Tekkel M (2002). Studies of cancer risk among Chernobyl liquidators: materials and methods. J of Radiol. Prot. 22: 137-141.

Cardis E, Ivanov VK, Kesminiene A, Malakhova IV, Shibata Y and Tenet T. (2002) Joint Belarus/Russia/EU/IARC/SMHF case-control studies of thyroid cancer in young people following the Chernobyl accident. In: Yamashita S, Shibata Y., Hoshi M and Fujimura K, eds. Chernobyl: Message for the 21st Century. Elsevier, Amsterdam. pp. 105-113

Thierry-Chef I., Pernicka F., Marshall M., Cardis E., and Andreo P. (2002) Study of a selection of 10 historical types of dosemeter: variation of the response to $H_p(10)$ with photon energy and geometry of exposure. Radiation Protection Dosimetry. 102(2): 101-113.

Pearce MS, Cardis E. Depleted Uranium - Cause for concern or just a good story? [Editorial] Pediatric Hematology and Oncology 2001; 18: 367-370.

Ahlbom A., Cardis E, Green A., Linet M., Savitz D., and Swerdlow A. (2001) Review of the epidemiological literature on EMF and health. ICNIRP proceedings, Environm. Health Perspectives. 109(6): 911- 934.

Thierry-Chef, I., Cardis, E., Ciampi, A., Delacroix, D., Marshall, M., Amoros, E., Bermann F. (2001) A Method to Assess Predominant Energies of Exposure in a Nuclear Research Centre - Saclay (France). Radiation Protection Dosimetry

Cardis, E. and Kilkenny, M. (2000) Epidemiologic studies of the health consequences of radiofrequency radiation - methodological limitation and difficulties of interpretation. Comptes-Rendus de l'Académie des Sciences (Nov. 2000)

Cardis, E., Richardson, D. (2000) Invited editorial: health effects of radiation exposure at uranium processing facilities. Journal of Radiation Protection, 2000 Jun; 20(2), 111-137

Cardis, E., Richardson, D., Kesminiene, A. (2000) Radiation Risk Estimates in the Beginning of the 21st Century. Health Physics. 80(4):349-361; 2001

Cardis E. and Kilkenny M. (1999) International Case-Control Study of Adult Brain, Head and Neck Tumours: Results of the Feasibility Study. Radiation Protection Dosimetry, Vol. 83, Nos 1-2, 179-183

Moolgavkar S., Krewski D., Zeise L., Cardis E. (1999) Quantitative Estimation and Prediction of Human Cancer Risks. IARC Scientific Publications No.131, IARC, Lyon

Cardis E., Amoros E., Kesminiene A, Malakhova I.V., Poliakov S.M., Piliptsevitch N.N., Demidchik E.P., Astakhova L.N., Ivanov V.K., Konogorov A.P., Parshkov E.P. and Tsyb A.F. (1999) Observed and Predicted Thyroid Cancer Incidence Following the Chernobyl Accident. Evidence for Factors Influencing Susceptibility to Radiation Induced Thyroid Cancer. In: G. Thomas, A. Karaoglou, E.D. Williams, eds. Radiation and Thyroid Cancer, World Scientific Publishing, pp.395-405

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

Cardis E., Anspaugh L., Ivanov V.K., Liktharlev 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

Cardis E., Gilbert E.S., Carpenter L., Howe G., Kato I., Armstrong B.K., Beral V., Cowper G., Douglas A., Fix J., Fry S.A., Kaldor J., Lavé C., Salmon L., Smith P.G., Voelz G.L., Wiggs L.D. Effects of low doses and low dose-rates of external ionizing radiation: Cancer mortality among nuclear industry workers in three countries (1995) Radiation Research, 142, 117-132

Hours M., Dananche B., Fevotte J., Bergeret A., Ayzac L., Cardis E., Etard, J.F., Pallen C. Roy P., Fabry J. Bladder cancer and occupational exposures. (1994) Scand. J. Work Environ. Health, 20, 322--330

IARC Study Group on cancer risk among nuclear industry workers. Direct estimates of cancer mortality due to low doses of ionising radiation: an international study (1994) The Lancet, Vol. 344, 1039-1043

**C. Research Support.** List selected ongoing or completed (during the last three years) research projects (federal and non-federal support). Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and your role (e.g. PI, Co-Investigator, Consultant) in the research project. Do not list award amounts or percent effort in projects.

## Ongoing Research Support

| Years | Source and title of support | Role |
|---|---|---|
| *2004-2008* | EC – Framework Programme 6 / "Quality of life and management of living resources"<br>Coordinated action<br>*EMF NET* | Partner, steering committee |
| 2003-2004 | EC – Framework Programme 5 – "Nuclear Energy – Nuclear Fission and Radiation Protection"<br>Shared cost RTD Project<br>*Gene-Radiation Interaction: their influence on pre-menopausal breast cancer risk after Chernobyl (GENE-RAD-INTERACT)* | Coordinator |
| 2002-2004 | EC – Framework Programme 5 – "Nuclear Energy – Nuclear Fission and Radiation Protection"<br>Concerted action<br>*Risk of thyroid cancer following exposure to I-131 early in life (CHILD-THYR)* | Coordinator |
| 2001-2005 | UICC (International Union against Cancer)<br>*INTERPHONE Study* | Coordinator |
| 2001-2003 | EC – Framework Programme 5 – "Quality of life and management of living resources"<br>Concerted action<br>*Environmental and host factors in the risk of thyroid cancer (THYR-RISK)* | Coordinator |
| 2000-2004 | EC – Framework Programme 5 – "Quality of life and management of living resources" –<br>Shared cost RTD Project<br>*International case-control studies of cancer in relation to mobile telephone use (INTERPHONE Study)* | Coordinator |
| 1993-2004 | Radiation Effects Association, Tokyo, Japan<br>*International Collaborative Study of Cancer Risk among Nuclear Industry Workers* | Coordinator |

## Completed Research Support (in the last 3 years)

| | | |
|---|---|---|
| 1996-2003 | Atomic Energy Board of Canada<br>*International Collaborative Study of Cancer Risk among Nuclear Industry Workers* | Coordinator |
| 1999-2002 | Sasakawa Memorial Health Foundation<br>*Agreement on the collaboration in the case-control studies of thyroid cancer in Belarus and Russia* | |

| | | |
|---|---|---|
| 2000-2002 | EC – Framework Programme 5 – "Nuclear Energy – Nuclear Fission and Radiation Protection" Concerted action<br>*International collaborative study of cancer risk among radiation workers in the nuclear industry (LOWDOSERISK).* | Coordinator |
| 1998-2002 | EC – Framework Programme 5 – "Nuclear Energy – Nuclear Fission and Radiation Protection"<br>Shared cost RTD Project<br>*Cancer risk following chronic radiation exposure in the nuclear industry in the Russian Federation, Hungary, the Slovak Republic and Lithuania (CANUC)* | Coordinator |

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| Franceschi, Silvia | 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 |
|---|---|---|---|
| Milan University, Italy | MD | 1979 | |
| Oxford University, United Kingdom | M.Sc. | 1981 | Epidemiology |
| Milan University, Italy | Post-grad. diploma | 1983 | Obstetrics and gynecology |
| Pavia University, Italy | Post-grad. diploma | 1987 | Medical statistics |

**A. Professional experience and academic appointments**

1979-1980, 1983-1984 Research Fellow at "Mario Negri" Institute for Pharmacological Research, Milan, Italy (for both periods)
1981-1983 Research Fellow at Division of Epidemiology, Imperial Cancer Research Fund, Oxford Univ., UK
1984-2000 Chief of Epidemiology Unit, Aviano Cancer Institute, Aviano, Italy
May 2000-present Chief of Field and Intervention Studies Unit, International Agency for Research on Cancer, Lyon, France
1993-2000 Professor, Epidemiology & Biostatistics, Post-graduate School of Oncology, Udine University, Italy
1996-pres. Professor, Master in Epidemiology, Italian Epidemiology Association

**B. Selected peer-reviewed publications (in chronological order 2002-2004)**

Castellsagué X, Bosch FX, Muñoz N, Meijer CJLM, Shah KV, de Sanjosé S, Eluf-Neto J, Ngelangel CA, Chichareon S, Smith JS, Herrero R, Moreno V, **Franceschi S.** for the IARC Multi-centric Cervical Cancer Study Group. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. *New Engl J. Med.* 346: 1105-1112 (2002)

**Franceschi S**, Castellsagué X, Dal Maso L, Smith JS, Plummer M, Ngelangel C, Chichareon S, Eluf-Neto J, Shah KV, Snijders PJF, Meijer CJLM, Bosch FX, Muñoz N. Prevalence and determinants of human papillomavirus genital infection in men. *Br. J. Cancer* 86: 705-711 (2002)

Moreno V, Bosch FX, Muñoz N, Meijer CJLM, Shah KV, Walboomers JMM, Herrero R, **Franceschi S** for the IARC Multicentric Cervical Cancer Study Group. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multi-centric case-control study. *Lancet* 359: 1085-1092 (2002)

Muñoz N, **Franceschi S**, Bosetti C, Moreno V, Herrero R, Smith J, Shah KV, Meijer CJLM, Bosch FX for the IARC Multicentric Cervical Cancer Study Group. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. *Lancet* 359: 1093-1101 (2002)

Smith JS, Muñoz N, Herrero R, Eluf-Neto J, Ngelangel C, **Franceschi S** et al Evidence for Chlamydia trachomatis as a human papillomavirus cofactor in the etiology of invasive cervical cancer in Brazil and the Philippines. *J. Infect. Dis.* 185: 324-331 (2002)

Smith J, Herrero R, Bosetti C, Muñoz N, Bosch FX, Eluf-Neto J, Castellsagué X, Meijer CJLM, van den Brule AJC, **Franceschi S**, Ashley R. Herpes simplex virus-2 as a human papillomavirus cofactor in the etiology of invasive cervical cancer. *J. Natl Cancer Inst.* 94: 1604-1613 (2002)

Terry PD, Rohan TE, **Franceschi S**, Weiderpass E. Cigarette smoking and endometrial cancer risk. *Lancet Oncol.* 3: 470-480 (2002)

Altieri A, **Franceschi S**, Ferley J, Smith J, La Vecchia C. Epidemiology and aetiology of gestational trophoblastic diseases. *Lancet Oncol.*, 4: 670-679 (2003)

Anh PTH, Hieu NT, Herrero R, Vaccarella S, Smith JS, Thuy NT, Nga NH, Duc NB, Ashley R, Snijders PJF, Meijer CJLM, Muñoz N, Parkin DM, **Franceschi S.** Human papillomavirus infection among women in South and North Vietnam. *Int. J. Cancer* 104: 213-220 (2003)

Clifford GM, Smith JS, Aguado T, **Franceschi S.** Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis. *Br. J. Cancer*, 89: 101-105 (2003)

Clifford GM, Smith JS, Plummer M, Muñoz N, **Franceschi S.** Human papillomavirus in invasive cervical cancer worldwide: a meta-analysis. *Br. J. Cancer* 88: 63-73 (2003)

Dal Maso L, **Franceschi S.** Epidemiology of non-Hodgkin lymphomas and other haemolymphopoietic neoplasms in people with AIDS. *Lancet Oncol.* 4: 110-119 (2003)

**Franceschi S**, Rajkumar T, Vaccarella S et al. Human papillomavirus and risk factors for cervical cancer in Chennai, India: a case-control study. *Int. J. Cancer* 107: 127-133 (2003)

**Franceschi S**, Dal Maso L, Pezzotti P et al. for the Cancer and AIDS Registry Linkage Study. Incidence of AIDS-defining cancers after AIDS diagnosis among people with AIDS in Italy, 1986-1998. *J. Acq. Immun. Def. Syndr.* 34: 84-90 (2003)

Green J, Berrington de Gonzalez A, Smith JS, **Franceschi S**, Appleby P, Plummer M, Beral V. Human papillomavirus infection and use of oral contraceptives. *Br. J. Cancer* 88: 1713-1720 (2003)

Herrero R, Castellsagué X, Pawlita M .... **Franceschi S** for the IARC Multi-centric Oral Cancer Study Group. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. *22 J. Natl Cancer Inst.* 95: 1772-1783 (2003)

Molano M, van den Brule A, Plummer M, Weiderpass E, Posso H, Arslan A, Meijer CJLM, Muñoz N, **Franceschi S** and the HPV Study Group. Determinants of clearance of HPV infections in women with normal cytology from Colombia. A population-based, five-year follow-up study. *Am. J. Epidemiol.* 158: 486-494 (2003)

Shin HR, Lee DH, Herrero R, Smith J, Vaccarella S, Hong SH, Jung KY, Kim HH, Park UD, Cha HS, Park S, Muñoz N, Snijers PJF, Meijer CJLM, Coursaget P, **Franceschi S.** Prevalence of human papillomavirus infection in women in Busan, South Korea. *Int. J. Cancer* 103: 413-421 (2003)

Smith JS, Green J, Berrington de Gonzalez A, Appleby P, Peto J, Plummer M, **Franceschi S**, Beral V. Cervical cancer and use of hormonal contraceptives: a systematic review. *Lancet* 361: 1159-1167 (2003)

Sukvirach S, Smith JS, Tunsakul S, Muñoz N, Kesararat W, Opasatian O, Chichareon S, Kaenploy V, Ashley R, Meijer CJLM, Snijders PJF, Coursaget P, **Franceschi S**, Herrero R. Population-based human papillomavirus prevalence in Lampang and Songkla, Thailand. *J. Infect. Dis.* 187: 1246-1256 (2003)

Dai M, Clifford GM, le Calvez F, Castellsagué X, Snijders P, Pawlita M, Herrero R, Hainaut P, **Franceschi S** for the IARC Multi-center Oral Cancer Study Group. Human papillomavirus type 16 and *TP53* mutation in oral cancer: matched analysis of the IARC multicenter study. *Cancer Res.* 64: 468-471 (2004)

Thomas JO, Herrero R, Omigbodun AA, Ojemakinde K, Ajayi IO, Fawole A, Oladepo O, Smith JS, Arslan A, Muñoz N, Snijders PJF, Meijer CJLM, **Franceschi S.** Prevalence of papillomavirus infection in women in Ibadan, Nigeria: a population-based study. *Br. J. Cancer* 90: 638-645 (2004)

Vineis P, Alavanja M, Buffler P, Fontham E, **Franceschi S** et al. Tobacco and cancer: recent epidemiological evidence. *J. Natl Cancer Inst.* 96: 99-106 (2004)

**C. Research Support.** List selected ongoing or completed (during the last three years) research projects

Oncosuisse: Risk of cancer in persons infected with HIV. Principal investigator.
Swissbridge Award 2001: Prevalence survey of human papillomavirus infection in Ambillikai, Southern India. Principal investigator.
WHO grant: A cohort study on the role of hormonal contraception in the natural history of HPV infection and CIN lesions. Principal investigator at IARC.
WHO grant: Collaborative International STD prevalence surveys of sexually transmitted infections. Principal investigator.
European Cervical Cancer Screening Network. Long-term monitory and epidemiological evaluation of the cervical screening in several European regions. French partner in network.

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| Friesen, Marlin D. | 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, KS | B.A. | 1968 | Chemistry |
| Kansas State University, Manhattan, KS | M.S. | 1974 | Analytical Chemistry |
| Kansas State University, Manhattan, KS | Ph.D. | 1977 | Analytical Chemistry |
| Univ. of Warwick, Coventry, U.K. | Post Doc. | 1977-1978 | Mass Spectrometry |

## A. Positions and Honors

**Positions and Employment**

1975-1977 Research Assistant, National Institute of Environmental Health Sciences, Research Triangle Park, NC
1978-1997 Analytical Chemist, International Agency for Research on Cancer, Lyon, France
1997-1998 Visiting Scientist, Johns Hopkins School of Hygiene and Public Health, Baltimore, MD
1998-present Scientist, Unit of Nutrition and Cancer, IARC, Lyon, France

**Other Experience and Professional Memberships**

1976-present Member, American Chemical Society
1978-present Member, American Association for Mass Spectrometry
1995-present Member, American Association for Cancer Research

## B. Selected peer-reviewed publications (in chronological order)

(publications selected from 95 peer-reviewed publications)

1. Hass, J.R., Friesen, M.D., Harvan, D.J., and Parker, C.E. (1978) Determination of polychlorinated dibenzo-p-dioxins in biological samples by negative chemical ionization mass spectrometry. *Anal.Chem.,* 50, 1474-1479.
2. Friesen, M., O'Neill, I.K., Malaveille, C., Garren, L., Hautefeuille, A., Cabral, J.R., Galendo, D., Lasne, C., Sala, M., Chouroulinkov, I., Mohr, U., Turusov, V., Day, N.E., and Bartsch, H. (1985) Characterization and identification of 6 mutagens in opium pyrolysates implicated in oesophageal cancer in Iran. *Mutat.Res.,* 150, 177-191.
3. Friesen, M., O'Neill, I.K., Malaveille, C., Garren, L., Hautefeuille, A., and Bartsch, H. (1987) Substituted hydroxyphenanthrenes in opium pyrolysates implicated in oesophageal cancer in Iran: structures and in vitro metabolic activation of a novel class of mutagens. *Carcinogenesis,* 8, 1423-1432.
4. Ohshima, H., Friesen, M., Brouet, I., and Bartsch, H. (1990) Nitrotyrosine as a new marker for endogenous nitrosation and nitration of proteins. *Food Chem.Toxicol.,* 28, 647-652.
5. Friesen, M.D., Garren, L., Prevost, V., and Shuker, D.E. (1991) Isolation of urinary 3-methyladenine using immunoaffinity columns prior to determination by low-resolution gas chromatography-mass spectrometry. *Chem.Res.Toxicol.,* 4, 102-106.
6. Friesen, M.D., Garren, L., Béréziat, J.C., Kadlubar, F., and Lin, D. (1993) Gas chromatography-mass spectrometry analysis of 2-amino-1- methyl-6-phenylimidazo[4,5-b]pyridine in urine and feces. *Environ.Health Perspect.,* 99, 179-181.

7. Friesen, M.D., Kaderlik, K., Lin, D., Garren, L., Bartsch, H., Lang, N.P., and Kadlubar, F.F. (1994) Analysis of DNA adducts of 2-amino-1-methyl-6-phenylimidazo[4,5- b]pyridine in rat and human tissues by alkaline hydrolysis and gas chromatography/electron capture mass spectrometry: validation by comparison with 32P-postlabeling. *Chem.Res.Toxicol.*, 7, 733-739.
8. Friesen, M.D., Cummings, D.A., Garren, L., Butler, R., Bartsch, H., and Schut, H.A. (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.
9. Atawodi, S.E., Lea, S., Nyberg, F., Mukeria, A., Constantinescu, 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.
10. 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. *Nat.Biotechnol.*, 16, 1352-1356.
11. He, Y.H., Friesen, M.D., Ruch, R.J., and Schut, H.A. (2000) Indole-3-carbinol as a chemopreventive agent in 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) carcinogenesis: inhibition of PhIP-DNA adduct formation, acceleration of PhIP metabolism, and induction of cytochrome P450 in female F344 rats. *Food Chem Toxicol,* 38, 15-23.
12. Jackson, P.E., Qian, G.S., Friesen, M.D., Zhu, Y.R., Lu, P., Wang, J.B., Wu, Y., Kensler, T.W., Vogelstein, B., and Groopman, J.D. (2001) Specific p53 mutations detected in plasma and tumors of hepatocellular carcinoma patients by electrospray ionization mass spectrometry. *Cancer Res,* 61, 33-35.
13. Friesen, M.D., Rothman, N., and Strickland, P.T. (2001) Concentration of 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine (PhIP) in urine and alkali-hydrolyzed urine after consumption of charbroiled beef. *Cancer Lett,* 173, 43-51
14. Suzuki, T., Masuda, M., Friesen, M.D., Fenet, B., and Ohshima, H. (2002) Novel products generated from 2'-deoxyguanosine by hypochlorous acid or a myeloperoxidase-H2O2-Cl- system: identification of diimino-imidazole and amino-imidazolone nucleosides. *Nucleic Acids Res,* 30, 2555-2564.
15. Mauget-Faysse, M., Vuillaume, M., Quaranta, M., Moullan, N., Angele, S., Friesen, M.D. and Hall, J. (2003) Idiopathic and radiation-induced ocular telangiectasia: the involvement of the ATM gene. *Invest Ophthalmol Vis Sci.* 44, 3257-3262.
16. Angele, S., Romestaing, P., Moullan, N., Vuillaume, M., Chapot, B., Friesen, M., Jongmans, W., Cox, D.G., Pisani, P., Gerard, J.P. and Hall, J. (2003) ATM haplotypes and cellular response to DNA damage: association with breast cancer risk and clinical radiosensitivity. *Cancer Res.* 63, 8717-25.
17. Lleonart, M.E., Ramon y Cajal, S., Groopman, J.D., Friesen, M.D. (2004) Sensitive and specific detection of K-ras mutations in colon tumors by short oligonucleotide mass analysis. *Nucleic Acids Res.* 32:e53.

## C. Research Support

**Ongoing Research Support**

R03 CA96398 Friesen (PI) 7/03/2002-6/30/2004
NIH/NCI
Estrogen metabolite analysis in blood
The goal of this grant is to develop a GC/MS method for 10 estrogens and estrogen metabolites is plasma.
Role: PI

**Completed Research Support**

PO1-ES06052 Groopman (PI) 6/01/1997-5/31/2002
NIEHS
Molecular biomarkers for environmental carcinogens
The objective of this research is to develop and validate biomarkers of exposure to heterocyclic amines.
Role : Subcontract

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| JANET HALL | Head, DNA Repair Group |

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 |
|---|---|---|---|
| Manchester University, UK | B.Sc (Hons)2.1 | 1978 | Biochemistry |
| Manchester University, UK | Ph.D | 1981 | Chemical carcinogenesis |

### A. Positions and Honours

***Positions and Employment***

*October 1981 - December 1983* - Unit of Mechanisms of Carcinogenesis, International Agency for Research on Cancer, Lyon, France. Recipient of a Research Training Fellowship of the International Agency for Research on Cancer/World Health Organization.

*January 1984 - December 1987* Scientific Non-clinical Research Fellow, Mammalian Cell DNA Repair Laboratory, Imperial Cancer Research Fund, Clare Hall Laboratories, South Mimms, Herts, EN6 3LD, UK. Research supported by European Science Foundation Research Fellowship in Toxicology (January 1984 to December 1984) and an Imperial Cancer Research Fund Research Fellowship (January 1985 to December 1987).

*January 1988 – November 1999* - Staff scientist, Unit of Mechanisms of Carcinogenesis, International Agency for Research on Cancer, Lyon, France.

*November 1999 to Present* – Group Leader, DNA Repair Group, International Agency for Research on Cancer, Lyon, France.

***Awards***

*July - August 1990*: ICRETT Fellowship, held at the Johns Hopkins University, Baltimore, USA, in the laboratory of Professor L. Grossman.

*August 1990*: British Association for Cancer Research Travel Fellowship, to visit research laboratories in The United States of America

***Membership of Professional Societies***

American Association for Cancer Research
Association pour la Recherche sur l'Ataxie Télangiectasie
Biochemical Society
British Association for Cancer Research
DNA Repair Network
European Association for Cancer Research
Société Française de Toxicologie Génétique

### B. Selected peer-reviewed publications

J.-O.Bay, N. Uhrhammer, D. Stoppa-Lyonnet and J. Hall (2000) Rôle du gène *ATM* dans la prédisposition génétique aux cancers. Bull. Cancer 87, 29-34.

S. Angèle and J. Hall (2000) The *ATM* 20 gene and breast cancer: is it really a risk factor? Mutation Research, 462 (2-3), 167-178.

S. Angèle, I. Treilleux, P. Tanière, G. Martel-Planche, M. Vuillaume, C. Bailly, Brémond, R. Montesano and J. Hall (2000) Abnormal expression of the *ATM* and TP53 genes in sporadic breast carcinomas. Clinical Cancer Research, 6, 3536-3544.

S. Angèle, P. Tanière and J. Hall (2001) Que savons-nous de l'expression de la protéine ATM dans le tissu mammaire? Bulletin du Cancer, 88, 671-675.

R. Montesano and J. Hall (2001) Environmental causes of human cancers. European J. Cancer, 37, S67-S87.

P. Boffetta, F. Nyberg, A. Mukeria, S. Benhamou, V. Constantinescu, H. Batura-Gabryel, I. Brüske-Hohlfield, G. Schmid, L. Simonato, P. Pelkonen and J. Hall (2002) $O^6$-alkylguanine-DNA-alkytransferase activity in peripheral leukocytes, smoking and risk of lung cancer. Cancer Letters, 180, 33-39.

S. Gutiérrez-Enríquez and J. Hall (2003) Use of the cytokinesis-block micronucleus assay to measure radiation-induced chromosome damage in lymphoblastoid cell lines. Mutation Research, 535, 1-13.

S. Angèle, A. Laugé, M. Fernet, N. Moullan, P. Beauvais, J. Couturier, D. Stoppa Lyonnet and J. Hall (2003) Phenotypic cellular characterization of an Ataxia telangiectasia patient carrying a causal homozygous missense mutation. Human Mutation, Mutation in Brief, 21, 169-170.

Fernet, S. Angèle, T. Dörk and J. Hall (2003) Variation in radiation-induced apoptosis in Ataxia telangiectasia lymphoblastoid cell lines. Int. J Radiat Biol, 79, 193-202.

Mauget-Faÿsse, M. Vuillaume, M. Quaranta, N. Moullan, S. Angèle, M.D. Friesen and J. Hall (2003) Idiopathic and radiation-induced ocular telangiectasias: the involvement of the *ATM* gene. Investigative Ophthalmology & Visual Science, 44, 3257-3262.

S. Angèle, I. Treilleux, A. Brémond, P. Tanière and J. Hall (2003) Altered expression of DNA double-strand break detection and repair proteins in breast carcinomas. Histopathology, 43, 347-53.

Moullan, D.G. Cox, S. Angèle, P. Romestaing, J.-P. G_e9rard and J. Hall (2003) Polymorphisms in the DNA repair gene XRCCI, breast cancer risk and response to radiotherapy. Cancer Epidemiology Biomarkers & Prevention, 12, 1168-1174.

S. Angèle, P. Romestaing, N. Moullan, M. Vuillaume, B. Chapot, M. Friesen, W. Jongmans, D.G. Cox, P. Pisani, J.-P. Gérard and J. Hall (2003) *ATM* haplotypes and cellular response to DNA damage: association with breast cancer risk and clinical radiosensitivity. Cancer Research, 63, 8717-8725.

S. Angèle, A. Falconer, C.S. Foster, P. Tanière, R.A. Eeles and J. Hall (2004) ATM protein over-expression in prostate tumors: possible role in telomere maintenance. American Journal of Clinical Pathology, 121, 231-236.

M. Fernet, N. Moullan, A. Lauge, D. Stoppa-Lyonnet and J. Hall (2004) Cellular responses to ionising radiation of *ATM* heterozygotes: differences between missense and truncating mutation carriers. British Journal of Cancer, 90, 866-873.

C. Cohet, S. Borel, F. Nyberg, A. Mukeria, I. Brüske-Hohlfeld, V. Constantinescu, S. Benhamou, P. Brennan, J. Hall and P. Boffetta (2004) Exon-5 polymorphisms in the $0^6$-alkyltransferase gene and lung cancer risk in non-smokers exposed to second-hand smoke. Cancer Epidemiology Biomarkers & Prevention, 13, 320-323.

F. Gemignani, V. Moreno, S. Landi, N. Moullan, A. Chabrier, S. Gutièrrez-Enriquez, J. Hall, E. Guino, M. Peinado, G. Capellà, F. Canzian. A TP53 polymorphism is associated with colorectal cancer risk and reduced levels of p53 mRNA. Oncogene 2004) in press

S. Gutiérrez-Enriquez, M. Fernet, T. Dörk, M. Bremer, A. Lauge, D. Stoppa-Lyonet, N. Moullan, S. Angèle and J. Hall. Functional consequences of *ATM* sequence variants on chromosomal radiosensitivity. Genes, Chromomes and Cancer. (2004 ) in press.

**C. Research Support**

**On-going Research Support**

«Role of *Ataxia telangiectasia* (*AT*) genes in cancer predisposition : establishment of cohort of female AT family members», (b)(4), (b)(6), December 2001 to December 2004

«Genetic determinants and molecular mechanisms of radiosensitivity», (b)(4), (b)(6), 2004

«Genetic determinants and molecular mechanisms of radiosensitivity», (b)(4), (b)(6), 2004

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| Kaaks, Rudolf | Epidemiologist, Head Hormones and Cancer Group |

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 Wageningen, Netherlands | MSc | 1987 | Human Nutrition |
| University of Wageningen, Netherlands | PhD | 1994 | Nutritional Epidemiology |

**NOTE: The Biographical Sketch may not exceed four pages. Items A and B (together) may not exceed two of the four-page limit. Follow the formats and instructions on the attached sample.**

## A. Positions and Honors

**Positions and Employment**

1986-1987 Research fellow, International Agency for Research on Cancer (IARC), Lyon, France.
1987-1988 Research assistant, Department of Epidemiology, Utrecht University, The Netherlands.
1988-2001 Epidemiologist, Unit of Nutrition and Cancer, International Agency for Research on Cancer (IARC), Lyon, France.
1997-now Adjunct position at the Dept. of Nutrition, University of Umea, Sweden
1997-now Adjunct position at the Dept. of Epidemiology, University of Utrecht, The Netherlands
Jan. 2002 Head of research group on Hormones & Cancer, International Agency for Research on Cancer, Lyon, France.

## B. Selected peer-reviewed publications (in chronological order)..


1. Kaaks R, Toniolo P, Akhmedkhanov A, Lukanova A, Biessy C, Déchaud H, Rinaldi S, Zeleniuch-Jacquotte A, Shore RE, Riboli E. Serum C-peptide, insulin-like growth factor (IGF)-I, IGF-binding proteins and colorectal cancer risk in women. *J Natl Cancer Inst,* 2000; 92: 1592-1600
2. Stattin P, Bylund A, Rinaldi S, Biessy C, Dechaud H, Stenman UH, Egevad L, Riboli E, Hallmans G, Kaaks R. Plasma insulin-like growth factor-I, insulin-like growth factor-binding proteins, and prostate cancer risk; a prospective study. *J Natl Cancer Inst,* 2000; 92: 1910-1917
3. Kaaks R, Lukanova A, Sommersberg B. Plasma androgens, IGF-I, body size, and prostate cancer risk: a synthetic review. *Prostate Cancer & Prostatic Diseases,* 2000; 3: 157-172
4. Riboli E, Kaaks R. Invited commentary: the challenge of multi-center cohort studies in the search for diet and cancer links. *Am J Epidemiol,* 2000; 151: 371-374
5. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and IGF-I. *Proc Nutr Soc,* 2001; 60: 91-106
6. Berrino F, Bellati C, Secreto G, Camerini E, Pala V, Panico S, Allegro G, Kaaks R. Reducing bioavailable sex hormones through a comprehensive change in diet: the diet and androgens (DIANA) randomized trial. *Cancer Epidem Biom Prev,* 2001; 10: 25-33
7. Rinaldi S, Dechaud H, Biessy C, Morin-Raverot V, Toniolo P, Jacquotte-Zeleniuch A, Akhmedkhanov A, Shore R, Secreto G, Ciampi A, Riboli E, Kaaks R. Reliability and validity of commercially available, direct immunoassays for measurement of blood androgens and estrogens in postmenopausal women. *Cancer Epidemol Biomarkers Prev,* 2001; 10: 757-765

8. Voskuil D, Bueno de Mesquita HB, Kaaks R, van Noord PAH, Rinaldi S, Riboli E, Grobbee DE, Peeters PHM. Determinants of circulating insulin-like growth factor (IGF)-I and IGF-binding proteins -1, -2 and -3 in premenopausal women: physical activity and anthropometry. *Cancer Causes Control, 2001;* 12: 951-958

9. Lukanova A, Toniolo P, Akhmedkhanov A, Shore R, Jacquotte A, Rinaldi S, Biessy C, Riboli E, Kaaks R. A prospective study of insulin-like growth factor-I, IGF-binding proteins -1, -2 and -3, and lung cancer risk in women. *Int J Cancer*, 2001; 92: 888-892

10. Stattin P, Rinaldi S, Bergh A, Riboli E, Hallmans G, Kaaks R. Plasma prolactin and prostate cancer risk: a prospective study. *Int J Cancer*, 2001; 92: 463-465

11. Palmqvist R, Hallmans G, Rinaldi S, Biessy C, Stenling R, Riboli E, Kaaks R. Plasma insulin-like growth factor-I, insulin-like growth factor binding protein-3, and risk of colorectal cancer: a prospective study in northern Sweden. *Gut* 2002; 50: 642-646

12. Kaaks R, Lundin E, Rinaldi S, Manjer J, Biessy C, Söderberg S, Lenner P, Janzon L, Riboli E, Berglund G, Hallmans G. Prospective study of IGF-I, IGF-binding proteins and breast cancer risk, in Northern and Southern Sweden. *Cancer Causes Control,* 2002;13: 307-316

13. Le Marchand L, Donlon T, Seifried A, Kaaks R, Rinaldi S, Wilkens LR. Association of a common polymorphism in the GH-1 gene with colorectal neoplasia. J Natl Cancer Inst 2002; 94:454-460

14. Lukanova A, Toniolo P, Lundin E, Micheli A, Akhmedkhanov A, Muti P, Zeleniuch-Jacquotte A, Biessy C, Lenner P, Krogh V, Berrino F, Hallmans G, Riboli E, Kaaks R. Body mass index in relation to ovarian cancer: a multi-centre nested case-control study. *Int J Cancer,* 2002; 99: 603-608

15. Kaaks R, Lukanova A. Body weight, physical activity and cancer risk: hormonal mechanisms. *Ann NY Acad Sci*, 2002; 963: 268-281

16. Lukanova A, Söderberg S, Stattin P, Palmqvist R, Lundin E, Biessy C, Rinaldi S, Riboli E, Hallmans G, Kaaks R. Non-linear relationship of insulin-like growth factor (IGF)-I and IGF-I/IGF-binding protein-3 ratio with indices of adiposity and plasma insulin concentrations. *Cancer Causes Control,* 2002; 13: 509-516

17. Bianchini F, Kaaks R, Vainio H. Overweight, obesity and cancer risk. *Lancet Oncology,* 2002; 3: 565-574

18. Hunt KJ, Toniolo P, Akhmedkhanov A, Lukanova A, Dechaud H, Rinaldi S, Zeleniuch-Jacquotte A, Shore RE, Riboli E, Kaaks R. Insulin-like growth factor-II and colorectal cancer risk. *Cancer Epidemiol Biom Prev,* 2002; 11: 901-905

19. Slimani N, Kaaks R, Ferrari P, Casagrande C, Clavel F, Lotze G, Kroke A, Trichopoulos D, Trichopolou A, Lauria C, Bellegotti M, Ocké MC, Peeters PHM, Engeset D, Lund E, Agudo A, Larranaga N, Mattison I, Andren C, Johansson I, Davey G, Welch A, Overvad K, Tjønneland A, van Staveren WA, Saracci R, Riboli E. EPIC calibration study: Rationale, design and population characteristics. *Public Health Nutr,* **5**,1125-1145

20. Rinaldi S, Geay A, Déchaud H, Biessy C, Zeleniuch-Jacquotte A, Akhmedkhanov A, Shore R, Riboli E, Toniolo P, Kaaks R. Validity of free testosterone and free estradiol determinations in serum samples from postmenopausal women by theorectical calculations. *Cancer Epidemiol Biom Prev*, 2002; 11: 1065-1071

21. Lukanova A, Lundin E, Toniolo P, Micheli A, Akhmedhanov A, Rinaldi S, Muti P, Lenner P, Biessy C, Krogh V, Zeleniuch-Jacquotte A, Berrino F, Hallmans G, Riboli E, Kaaks R. Circulating levels of insulin-like growth factor-I and risk of ovarian cancer. *Int J Cancer*, 2002; 101: 549-554

22. Kaaks R, Lukanova A, Kurzer M. Obesity, endogenous hormones and endometrial cancer: a synthetic review. *Cancer Epidemiol Biom Prev*, 2002; 11: 1531-1543

23. Kaaks R, Bellati C, Venturelli E, Rinaldi S, Secreto G, Biessy C, Pala V, Sieri S, Berrino F. Effects of dietary intervention on IGF-I and IGF-binding proteins, and related changes in sex steroid metabolism: the Diet and Androgens (DIANA) Randomized Trial. *Eur J Clin Nutr*, **57**, 1079-1088

**C. Research Support.** List selected ongoing or completed (during the last three years) research projects (federal and non-federal support). Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and your role (e.g. PI, Co-Investigator, Consultant) in the research project. Do not list award amounts or percent effort in projects.

**KAAKS, R.J.**

ACTIVE

DAMD 17-01-1-0275 (Kaaks) 09/01 – 09/04
US Army Department of Defense
"Breast cancer risk in relation to serum IGF-I, IGFBP-3 and their genetic determinants: A study within the European prospective into cancer (EPIC)".

The major goal of this project is to identify genetic polymorphisms (14 candidate genes) that predict variation in circulating IGF-I levels, and then to examine the relationships of those selected polymorphisms with risk of breast cancer.

DAMD 17-02-1-0422(Kaaks) 09/01/02-09/30/05
Department of Defense
"Breast cancer risk in relation to Urinary estrogen metabolites, and their genetic determinants: a study within the Dutch 'DOM' cohort."

The major goal of this project is to study the relationship between urinary sex-steroid hormones and genetic polymorphisms that predict variations in their levels with risk of breast cancer.

1RO3 CA96398-01 (Friesen) 07/03/02-06/30/04
NCI
"Estrogen metabolite analysis in blood."

A grant to develop a sensitive mass-spectrometric method for measurement of hydroxy and methoxy metabolites of estrogens, in blood.

(b)(4), (Stattin) 01/03-12/05
(b)(4), (b)(6)
"The metabolic syndrome and cancer risk; A longitudinal study in the Northern Sweden Health and Disease Cohort."

The major goal of this project is to relate risk of major cancers (breast, colorectum prostate, endometrium) and overall cancer incidence to levels of fasting and postload glucose, triglycerids, total cholesterol and plasma C-peptide in a Swedish prospective cohort (Northern Sweden Health and Disease Study).

PC 020606(Kaaks) 06/03-05/05
US Department of Defense
"Prostate cancer risk in relation to IGF-I and its genetic determinants: A case-control study within the Cancer Prostate Sweden (CAPS) project".

The major goal of this project is to relate prostate cancer risk to genetic determinants of circulating IGF-I levels in a large case-control study in Sweden

(b)(4), (b)(6) (Maskarinec) 08/02-07/04
"Soy intake, insulin-like growth factor I and breast cancer risk"

The major goal of this project is to examine the effect of two soy-based interventions on serum levels of IGF-I and IGFBP-3 and sex steroids, as well as on mammographic densities.

1 RO1 CA09821601 (Riboli; Kaaks) 07/03-05/07
NCI
"Breast & prostate cancer & hormone-related gene variants

This application is one of four submitted concurrently to allow large-scale analyses of breast and prostate cancer risk in relation to genetic polymorphisms and gene-environment interactions that affect hormone metabolism. These proposals combine the resources of six large prospective cohorts. The interaction of genetic variants with hormonal, lifestyle and anthropometric factors know to be associated with breast and prostate cancer will be examined. In a subset of studies, the association of these variants with markers of breast and prostate cancer risk (i.e. plasma steroid hormone levels and IGF-I levels will be investigated).

1RO1CA102460-01 (Kaaks) 10/03-09/06
NCI
"Lifestyle, insulin, IGF-I and colorectal cancer"

The major goal of this project is to relate cancer risk to blood levels of insulin, IGF-I, IGF-binding proteins and lifestyle determinants of these hormone levels to be conducted within the EPIC cohort.

(b)(4), (b)(6) (Kaaks) 12/03 - 12/04

"Excess weight, endogenous hormones and endometrial cancer risk: a prospective study"

The major goal of this project is to relate endometrial cancer risk to endogenous hormone levels (sex steroids, SHBG, C-Peptide) in pre- and postmenopausal women, conducted within the EPIC cohort.

BC030208 (Kaaks) 04/04-03/07
Department of Defense
"Fatty acid synthesis gene variants and breast cancer risk: a study with the European Prospective Investigation into Cancer and Nutrition (EPIC)"

The major goal of this project is to evaluate that genes involved in cellular fatty acid synthesis may be centrally implicated in mammary gland carcinogenesis and that certain polymorphic alleles that increase the expression or activity of these genes confer increased breast cancer susceptibility.

1 RO3 CA105948-01 (Maskarinec) 01/04 - 12/05
NCI
"Breast Density, IGF-I & Prolactin in Four Populations

The major goal of this project is to compare mammographic densities among four populations at different breast cancer risk , examine the relation of IGF-I, IGFBP-3 and prolactin with mammographic densities, and investigate the relation between these hormones and mammographic density separately by ethnicity and menopausal status.

1U54CA100971-01 (Hunter) 09//03-08/04
NCI
Folate, 1-Carbon Nutrients, Gene Variants & Colon Cancer

To combine data from three large of prospective cohort studies to address three principal hypotheses concerning the effects of homocysteine and colorectal cancer.

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| **KRUTOVSKIKH, Vladimir** | 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 |
|---|---|---|---|
| First Medical Institute Pavlov, Leningrad, Ex-USSR | M.D. | 1976 | Medicine |
| All-Union Cancer Research Center AMS USSR, Moscow, Ex-USSR | Ph.D | 1980 | Carcinogenesis |

**NOTE: The Biographical Sketch may not exceed four pages. Items A and B (together) may not exceed two of the four-page limit. Follow the formats and instructions on the attached sample.**

**A. Positions and Honors.** List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

**Positions and Employment**

| | |
|---|---|
| 1976-1981 | Post-graduate student, Department of Chemical Carcinogenesis, All-Union Cancer Research Center, Moscow, ex-USSR (supervisor: Dr VS Turusov) |
| 1981-1987 | Scientist, Department of Chemical Carcinogenesis, All-Union Cancer Research Center, Moscow, ex-USSR (supervisor: Dr VS Turusov) |
| 1987-1988 | Senior Scientist, Department of Chemical Carcinogenesis, All-Union Cancer Research Center, Moscow, ex-USSR (supervisor: Dr VS Turusov) |
| 1988-2000 | Scientist, Unit of Multistage Carcinogenesis, International Agency for Research on Cancer, WHO, Lyon, France |
| 2000-present | Scientist, Unit of Gene-Environment Interactions, International Agency for Research on Cancer, WHO, Lyon, France |

**Professional Memberships**

Active member of American Association for Cancer Research (#13618)
Member of the Japanese Cancer Association
Member of the American Society for Cell Biology (#31645)

**Honors**

| | |
|---|---|
| 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 |

**B. Selected peer-reviewed publications (in chronological order).**

**Krutovskikh VA**, Oyamada M, Yamasaki H. (1991) Sequential Changes of Gap Junctional Intercellular Communications During Multistage Rat Liver Carcinogenesis: Direct Measurement of Communication In Vivo. *Carcinogenesis,* **12**, 1701-1706

**Krutovskikh V**, Mazzoleni G, Mironov N, Omory Y, Aguelon AM, Mesnil M, Berger F, Partensky C, Yamasaki H. (1994) Altered Homologous and Heterologous Gap Junctional Intercellular Communication in Primary Human Liver Tumors Associated With Aberrant Protein Localization but Not Gene Mutation of Connexin 32. *International Journal of Cancer,* **56**, 87-94

Mesnil M, **Krutovskikh VA,** Piccoli C, Elfgang C, Traub O, Willecke K, Yamasaki H. (1995) Negative Growth Control of HeLa Cells by Connexin Genes: Connexin-Species Specificity. *Cancer Research,* **55**, 629-639

**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. *Laboratory Investigation*, **72**, 571-577

**Krutovskikh VA**, Mironov NM, Yamasaki H. (1996) Human Connexin37 is Polymorphic but Not Mutated in Tumors. *Carcinogenesis,* **17** , 1761-1763

Omori Y, **Krutovskikh VA,** Tsuda H, Yamasaki H. (1996) Connexin32 Gene Mutation in a Chemically Induced Rat Liver Tumor. *Carcinogenesis*, **17**, 2077-2080

Sekine K, Watanabe E, Nakamura J, Takasuka N, Kim Dae Joong, Asamoto M, **Krutovskikh V**, Baba-Toriyama H, Ota T, Moore MA, Masuda M, Sugimoto H, Nishino H, Kakizoe T, Tsuda H. (1997) Inhibition of Azoxymethane-Initiated Colon Tumor by Bovine Lactoferrin Administration in F344 rats. *Jpn. The Journal of Cancer Research*, **88**, 523-526

**Krutovskikh V,** Asamoto M, Tsuda H. (1997) Differential Dose-Dependent Effect of □□Carotenes and Lycopene on Gap Junction Iintercellular Communication in Rat Liver *In Vivo. Jpn. The Journal of Cancer Research,* **88**, 1121-1124

Asamoto M, Toriyama-Baba H, **Krutovskikh VA**, Cohen SM, Tsuda H. (1998) Enhanced Tumorigenicity of Rat Bladder Carcinomas by Abrogation of Gap Junctional Intercellular Communication. Jpn. *The Journal of Cancer Research*, **89**, 481-486

**Krutovskikh VA,** Yamasaki H, Tsuda H, Asamoto M. (1998) Inhibition of Intrinsic Gap-Junction Intercellular Communication and Enhancement of Tumorigenicity of the Rat Bladder Carcinoma Cell Line BC31 by a Dominant-Negative Connexin 43 Mutant. *Molecular Carcinogenesis*, **23**, 254-261

Saito T, **Krutovskikh V,** Marion M-J, Ishak K, Bennett WP, Yamasaki H. (2000) Human Hemangiosarcomas Have a Common Polymorphism but No Mutations in the Connexin 37 Gene. *International Journal of Cancer,* **86**, 67-70

**Krutovskikh V,** Troyanovsky SM, Piccoli C, Tsuda H, Asamoto M, Yamasaki H. (2000) Differential Effect of Subcellular Localization of Communication Impairing Gap Junction Protein Connexin43 on Tumor Cell Growth *In Vivo. Oncogen,e* **19**, 505-513

**Krutovskikh V,** Piccoli C, Yamasaki H. (2002) Gap Junction Intercellular Communication Propagates Cell Death in Cancerous Cells. *Oncogene,*

**fs22 21**, 1989-1999

Dubina MV, Iatckii NA, Popov DE, Vasil'ev SV, **Krutovskikh VA.** (2002) Connexin 43, but Not Connexin 32, is Mutated at Advanced Stages of Human Sporadic Colon Cancer. *Oncogene*, **21**(32), 4992-4996

Berke G, **Krutovskikh V,** Yamasaki H. (2003) Connexin 37 Gene is Not Mutated in Lung Carcinomas 3LL and CMT. *Cancer Letters*, **195**, 67-72

Upham BL, Suzuki J, Chen G, Wang Y, McCabe LR, Chang C-C, **Krutovskikh VA**, Yamasaki H, Trosko JE. (2003) Reduced Gap Junctional Intercellular Communication and Altered Biological Effects in Mouse Osteoblast and Rat Liver Oval Cell Lines Transfected With Dominant-Negative Connexin 43. *Molecular Carcinogenesis,* **37**, 192-201

Dagli M-L, Yamasaki H, **Krutovskikh V**, Omori Y. (2004) Delayed Liver Regeneration and Increased Susceptibility to Chemical Hepatocarcinogenesis in Transgenic Mice Expressing a Dominant-Negative Mutant of Connexin32 Only in Liver. *Carcinogenesis*, **25**, 483-492.

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| Hiroko Ohgaki | Chief, Unit of Molecular Pathology |

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 |
|---|---|---|---|
| Tokyo University of Agriculture and Technology | DVM | 1979 | Veterinary Medicine |
| National Cancer Center Research Institute, Tokyo | PhD | 1986 | Medical Science |

**NOTE: The Biographical Sketch may not exceed four pages. Items A and B (together) may not exceed two of the four-page limit. Follow the formats and instructions on the attached sample.**

**A. Positions and Honors.** List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

**Positions and employment**

1980-1989 Research Associate, Biochemistry Division, National Cancer Center Research Institute, Tokyo, Japan
1990-1992 Postdoctoral Fellow, University of Zurich, Switzerland
1992-1995 Special Expert of Pathology, National Cancer Institute, USA
1995- Chief, Unit of Molecular Pathology, International Agency for Research on Cancer

**Professional membership**

1980- Japanese Cancer Association
1995- American Association of Cancer Research
2003- American Association of Neuropathologists

**Editorial Board**

2000- Brain Pathology
2003- Journal of Neuropathology and Experimental Neurology

**Honors**

1985 Incitement Award of the Japanese Cancer Association
1996 Lucien J. Rubinstein Awards in the American Association of Neuropathologists
2001 Lucien J. Rubinstein Awards in the American Association of Neuropathologists

**B. Selected peer-reviewed publications (Publications selected from 121 peer-reviewed publications).**

Fujisawa H, Kurrer M, Reis R, Yonekawa Y, Kleihues P, Ohgaki H. Acquisition of the glioblastoma phenotype during astrocytoma progression is associated with LOH on chromosome 10q25-qter. *Am. J. Pathol.* 155: 387-394 (1999)

Huang H, Fujii H, Sankila A, Mahler-Araujo BM, Mastuda M, Cathomas G, Ohgaki H. β-catenin mutations are frequent in human hepatocellular carcinomas associated with hepatitis C virus infection. *Am. J. Pathol.* 155: 1795-1801 (1999)

Fujisawa H, Reis RM, Nakamura M, Colella S, Yonekawa Y, Kleihues P, Ohgaki H. Loss of heterozygosity on chromosome 10 is more extensive in primary *(de novo)* than in secondary glioblastomas. *Lab. Invest.* 80: 65-72 (2000)

Huang H, Mahler-Araujo BM, Sankila A, Chimelli L, Yonekawa Y, Kleihues P, Ohgaki H. APC mutations in sporadic medulloblastomas. *Am. J. Pathol.* 156: 433-437 (2000)

Reis RM, Konu-Leblebicioglu D, Lopes JM, Kleihues P, Ohgaki H. enetic profile of gliosarcomas. Am. *J. Pathol.* 156: 425-432 (2000)

Ohgaki H, Huang H, Haltia M, Vainio H, Kleihues P. More about: Cell and molecular biology of Simian Virus 40: Implications for human infections and disease. *J. Nat. Cancer Inst.* 92: 495-496 (2000)

Ohgaki H, Fukuda M, Tohma Y, Huang H, Stoica G, Tatematsu M, Donehower LA. Effect of intragastric application of *N*-methylnitrosourea (MNU) in *p53* knockout mice. *Mol. Carcinog.* 28: 97-101 (2000)

Huang H, Colella S, Kurrer M, Yonekawa Y, Kleihues P, Ohgaki H. Gene expression profiling of low-grade diffuse astrocytomas by cDNA arrays. *Cancer Res.* 60: 6868-6874 (2000)

Nakamura M, Yonekawa Y, Kleihues P, Ohgaki H. Promoter hypermethylation of the *RB1* gene in glioblastomas. *Lab. Invest.* 81: 77-82 (2001)

Roth W, Isenmann S, Nakamura M, Platten M, Wick W, Kleihues P, Bähr M, Ohgaki H, Ashkenazi A, Weller M. Soluble decoy receptor 3 is expressed by malignant gliomas and suppresses CD95 ligand-induced apoptosis and chemotaxis. *Cancer Res.* 61: 2759-2765 (2001)

Struss AK, Romeike BFM, Munnia A, Nastainczyk W, Steudel WI, König J, Ohgaki H, Feiden W, Fischer U, Meese E. PHF3-specific antibody responses in over 60% of patients with glioblastoma multiforme. *Oncogene* 20: 4107-4114 (2001)

Colella S, Ohgaki H, Ruediger R, Yang F, Nakamura M, Fujisawa H, Kleihues P, Walter G. Reduced expression of the Aα subui of PP2A in human gliomas in the absence of Mutations in The Aα and Aβ Subunit Genes. *Int. J. Cancer* 93: 798-804 (2001)

Masuoka J, Brandner S, Paulus W, Soffer D, Vital A, Chimelli L, Jouvet A, Yonekawa Y, Kleihues P, Ohgaki H. Germline *SDHD* mutation in paraganglioma of the spinal cord. *Oncogene* 20: 5084-5086 (2001)

Nakamura M, Watanabe T, Yonekawa Y, Kleihues P, Ohgaki H. Promoter Methylation of the DNA repair gene *MGMT* in astrocytomas is frequently associated with G:C → A:T mutations of the *TP53* tumor suppressor gene. *Carcinogenesis* 22: 1715-1719 (2001)

Wischhusen J, Jung G, Radovanovic I, Beier C, Steinbach J, Rimmer A, Huang H, Schulz JB, Ohgaki H, Aguzzi A, Rammensee HG, Weller M. Identification of CD70-mediated apoptosis of immune effector cells as a novel immune escape pathway of human glioblastoma. *Cancer Res.* 62: 2592-2599 (2002)

Tong WM, Cortes U, Hande MP, Ohgaki H, Cavalli LR, Lansdorp PM, Haddad BR, Wang ZQ. Synergistic role of Ku80 and poly (ADP-ribose) polymerase in suppressing chromosomal aberrations and liver cancer formation. *Cancer Res.* 62: 6990-6996 (2002)

Tong WM, Ohgaki H, Huang H, Granier C, Kleihues P, Wang ZQ. Null mutation of DNA strand break-binding molecule poly (ADP-ribose) polymerase causes medulloblastomas in $p53^{-/-}$ mice. *Am J. Pathology,* 162: 343-352 (2003)

Baeza N, Masuoka J, Kleihues P, Ohgaki H. *AXIN1* mutations but not deletions in medulloblastomas. *Oncogene* 22: 632-636 (2003)

Burkhard C, Di Patre PL, Schüler D, Schüler G, Ysargil MG, Yonekawa Y, Lütolf UM, Kleihues P, Ohgaki H. A population-based study on the incidence and survival rates of patients with pilocytic astrocytoma. *J Neurosurg.* 98: 1170-1174 (2003)

Biernat W, Huang H, Yokoo H, Kleihues P, Ohgaki H. Predominant expression of mutant *EGFR (EGFRvIII)* is rare in primary glioblastomas. *Brain Pathol.* in press (2004)

**C. Research Support.** List selected ongoing or completed (during the last three years) research projects (federal and non-federal support). Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and your role (e.g. PI, Co-Investigator, Consultant) in the research project. Do not list award amounts or percent effort in projects.

**Ongoing Research support**

1997-2004 Research grant from the Foundation for Promotion of Cancer Research, Japan

2001-2004 NIH (NINDS) Grant (R01 NS40958-01), USA

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| Ohshima, Hiroshi | 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 |
|---|---|---|---|
| Tokyo University of Ocean Science, Japan | B.Sc. | 1973 | Marine Biochemistry |
| Tokyo University of Ocean Science, Japan | M.Sc. | 1975 | Biochemistry |
| University of Tokyo, Japan | Ph.D. | 1987 | Biochemistry |

## A. Positions

| | |
|---|---|
| 1975 -1979 | Research associate, the National Institute of Health, Dept of Biomedical Research on Foods, Tokyo, Japan |
| Nov. 1988 | Visiting scientist at the Institute of Medical Science, Dept of Molecular Carcinogenesis, Tokyo, Japan (UICC, ICRETT fellowship award) |
| Sept 1989 - June 1991 | Visiting scientist at the National Cancer Center Research Institute Division of Biochemistry, Tokyo, Japan (Fellowship awarded by the Foundation for the Promotion of Cancer Research) |
| 1979 - Dec. 93 | Scientist, International Agency for Research on Cancer, Unit of Environmental Carcinogens & Host Factors, Lyon, France |
| Jan 94 - todate | Chief, Unit of Endogenous Cancer Risk Factors, International Agency for Research on Cancer, Lyon, France |

## B. Selected peer-reviewed publications (in chronological order)

(Publications selected from 210 peer-reviewed publications)

Tsuda, M., Kurashima, Y., Kosaka, H., Ohshima, H., Sugimura, T. & Esumi, H. (1995) Marked increase in urinary excretion of nitrate and N-nitrosothioproline in the osteogenic disordered syndrome rats, lacking ascorbic acid biosynthesis, by administration of lipopolysaccharide and thioproline. Carcinogenesis, **16**, 2653-2657.

Calmels, S., Hainaut, P. & Ohshima, H. (1997) Nitric oxide induces conformational and functional modifications of wild-type p53 tumor-suppressor protein. Cancer Res., **57**, 3365-3369.22

Szabo, C. & Ohshima, H. (1997) DNA damage induced by peroxynitrite: subsequent biological effects. (Review). Nitric Oxide: Biol. Chem., **1**, 373-385.

Ohshima, H., Yoshie, Y. & Auriol, S. & Gilibert, I. (1998) Antioxidant and pro-oxidant actions of flavonoids: effects on DNA damage induced by nitric oxide, peroxynitrite and nitroxyl anion. Free Radical Biol. Med., **25**, 1057-1065.

Ohshima, H., Gilibert, I. & Bianchini, F. (1999) Induction of DNA strand breakage and base oxidation by nitroxyl anion through hydroxyl radical production. Free Radical Biol. Med., **26,** 1305-1313.

Ahn, B., Han, B.S., Kim, D.J., Ohshima, H. (1999) Immunohistochemical localization of inducible nitric oxide synthase and 3-nitrotyrosine in rat liver tumors induced by *N*-nitrosodiethylamine. Carcinogenesis, **20**, 1337-1344

Chazotte-Aubert, L., Oikawa, S., Gilibert, I., Bianchini, F., Kawanishi, S. & Ohshima, H. (1999) Cytotoxicity and site-specific DNA damage induced by nitroxyl anion ($NO^-$) in the presence of hydrogen peroxide: implications for various pathophysiological conditions. J. Biol. Chem., **274**, 20909-20915

Masuda, M., Mower, H.F., Pignatelli, B., Celan, I., Friesen, M.D., Nishino, H. & Ohshima, H. (2000) Formation of *N*-nitrosamines and *N*-nitramines by the reaction of secondary amines with peroxynitrite and other reactive nitrogen species: comparison with nitrotyrosine formation. Chem. Res. Toxicol., **13**, 301-308

Pignatelli, B., Li, C.Q., Boffetta, P., Chen, Q., Ahrens, W., Nyberg, F., Mukeria, A., Bruske-Hohlfeld, I., Fortes, C., Constantinescu, V., Ischiropoulos, H. & Ohshima, H. (2001) Nitrated and oxidized plasma proteins in smokers and lung cancer patients. Cancer Res., 61, 778-784

Pignatelli, B., Bancel, B., Plummer, M., Toyokuni, S., Patricot, L.-M. & Ohshima, H. (2001) *H. pylori* eradication attenuates oxidative stress in human gastric mucosa. Am. J. Gastroenterol., 96, 1758-1766

Suzuki, T., Masuda, M., Friesen, M.D. & Ohshima, H. (2001) Formation of spiroimino-dihydantoin nucleoside by reaction of 8-oxo-7,8-dihydro-2'-deoxyguanosine with hypochlorous acid or a myeloperoxidase $-H_2O_2$-$Cl^-$ system. Chem. Res. Toxicol., **14**, 1163-1169 Suzuki, T., Masuda, M., Friesen, M.D. & Ohshima, H. (2001) Formation of spiroimino-dihydantoin nucleoside by reaction of 8-oxo-7,8-dihydro-2'-deoxyguanosine with hypochlorous acid or a myeloperoxidase $-H_2O_2$-$Cl^-$ system. Chem. Res. Toxicol., **14**, 1163-1169

Masuda, M., Suzuki, T., Friesen, M.D., Ravanat, J.-L., Cadet, J., Pignatelli, B., Nishino, H. & Ohshima, H. (2001) Chlorination of guanosine and other nucleosides by hypochlorous acid and myeloperoxidase of activated human neutrophils: catalysis by nicotine and trimethylamine. J. Biol. Chem., **276**, 40486-40496

Ahn, B. & Ohshima, H. (2001) Suppression of intestinal polyposis in $Apc^{Min}$/+ mice by inhibiting nitric oxide production. Cancer Res., **61**, 8357-8360

Masuda, M., Nishino, H. & Ohshima, H. (2002) Formation of 8-nitroguanosine in cellular RNA as a biomarker of exposure to reactive nitrogen species. Chem.-Biol. Interact., **139**, 187-197

Suzuki, T., Masuda, M., Friesen, M.D., Fenet, B. & Ohshima, H. (2002) Novel products generated from 2'-deoxyguanosine by hypochlorous acid or a myeloperoxidase-$H_2$fs22 $O_2$-$Cl^-$ system: identification of diimino-imidazole and amino-imidazolone nucleosides. Nucleic Acids Res., **30**, 2555-2564

Suzuki, T., Friesen, M.D. & Ohshima, H. (2003) Identification of products formed by reaction of 3',5'-di-O-acetyl-2'-deoxyguanosine with hypochlorous acid or a myeloperoxidase-$H_2O_2$-$Cl^-$ system. Chem. Res. Toxicol., **16**, 382-389

Ohshima, H., Tatemichi, M. & Sawa, T. (2003) Chemical basis of inflammation-induced carcinogenesis. Arch. Biochem. Biophys., **417**, 3-11

Suzuki, T., Nakano, T, Masuda, M. & Ohshima, H. (2004) Epigallocatechin gallate markedly enhances formation of 8-oxo-7,8-dihydro-2'-deoxyguanosine in reaction of 2'-deoxyguanosine with hypochlorous acid. Free Rad. Biol. Med., in press

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| Annie J. Sasco, MD, Dr PH | Chief, Unit of Epidemiology for Cancer Prevention,International Agency for Research on Cancer, Director of Research, Institut National de la Santé et de la Recherche Médicale, Lyon, France |

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 |
|---|---|---|---|
| Academy of Bordeaux, France | B.Sc | 1961-1969 | Mathematics/Natural Sciences |
| ECFMG, USA | Certificate ECFMG | 1977 | Medicine |
| University of Bordeaux II, France | CES (post doc) | 1976-1977 | Occupational Medicine |
| University Paul Sabatier, Toulouse, France | CES (post doc) | 1976-1977 | Preventive Medicine & Hygiene |
| University of Bordeaux II, France | AEA (post doc) | 1977 | Social Medicine |
| University of Bordeaux II, France | DU (post doc) | 1977 | Sociology and Social Sciences |
| University of Bordeaux II, France | DU (post doc) | 1977 | Ergonomy |
| **University of Bordeaux II, France** | **MD (honors)** | **1969-1978** | **Medicine** |
| University of Bordeaux II, France | CES (post doc) | 1977-1978 | Aeronautical & Spatial Medicine |
| **Harvard University, Boston, USA** | **MPH** | **1978-1979** | **Public Health** |
| **Harvard University, Boston, USA** | **MS** | **1979-1980** | **Biostatistics and Epidemiology** |
| **Harvard University, Boston, USA** | **Dr PH** | **1980-1986** | **Epidemiology, Biostatistics and Behavioural Sciences** |
| **University Claude Bernard, Lyon I, France** | **HDR** Highest French University Research degree | **1996** | **Epidemiology Prevention** |

## A. Positions and Honors

**Positions and Employment**

1979-83: Teaching Assistant, Departments of Biostatistics and Epidemiology, Harvard University School of Public Health
1980-99: Researcher, INSERM, France
1981-84: Teaching Fellow in Epidemiology, Harvard University
1983-86: Scientist, Unit of Biostatistics, IARC
From 1984: Chargée de cours, Université Claude Bernard, Lyon I
1986-94: Scientist, Unit of Analytical Epidemiology, IARC
1995-97: Head, Programme of Epidemiology for Cancer Prevention, IARC
1996-97: Acting Chief, Programme for Cancer Control, WHO
From 1996: Chargée de cours, Université de la Méditerranée, Marseille
From 1998: Chief, Unit of Epidemiology for Cancer Prevention, IARC
From 1999: Director of Research, INSERM, France
From 2001: Chargée de cours, Université Victor Ségalen, Bordeaux II, France

**Other professional activities**

**International level**

1993-1995 Member of the UICC group on collection of tobacco-related data in Africa.
From 1999 Member of the European group of experts on the assessment of potential risks to human health from hormone residues in bovine meat and meat products.
2000-2002 Member of the IARC ethical committee.
From 2003 Member of the IARC STA (Special Trainee Award) committee.

**National (France)/regional level**

1986-1994 Member of the expert committee on cancer risk in research laboratory workers of the Pasteur institute, Paris.
1987-1989 Member of the national commission on cancer risk linked to the manipulation of mutagens and carcinogens.
1990-2000 Member of the scientific and administrative committee of breast cancer screening in the Rhône.
1992-2000 Member of the administrative and scientific committee of the breast cancer registry in the Rhône (President 1991-1994).
1990-2000 Member of the scientific committee of a student association for the fight against cancer in France (ALEC).
From 1992 Member of the technical regional committee on cancerology (Rhône-Alpes).
1994-2000 Member of a national expert group on screening for colorectal cancer.
1996-1998 Member (as deputy of Prof. Kleihues) of the administrative committee of Claude Bernard Lyon I University.
1996 Expert for the general directorate of health on cancer registries.
From 1996 Member of the administrative committee of the National cancer league for the Rhône.
1996-2001 Member of the scientific council of the national committee on respiratory diseases and tuberculosis.
1996-2000 Member of the public health and cancer committee of the Fondation de France.
1996-2000 Member of the national group of experts for public health (RNSP).
1997-2000 Member of the national commission on diagnostic innovation, therapeutics and prevention research of the association for cancer research (ARC).
1998-1999 Member and chief of the cancer group of national experts on the assessment of potential risks to human health from hormone residues in bovine meat and meat products (France).
From 1999 Elected to the board of the association of French speaking epidemiologists (ADELF).
2000 Member of a national group of experts for risks linked to contaminated human growth hormone.
From 2000 Member of the administrative and scientific committee of Avenir Santé.
From 2000 Member of the scientific council of the French observatory on drugs and toxicomania.
2001-2002 Member for the general directorate of health of a national group of experts on passive smoking.
2001-2002 Member for the general directorate of health of a national group of experts on harm reduction in smoking.
From 2002 Member of a national group of experts on mammography screening (ANAES and InVS).
From 2003 Member of a national group of experts on smoking prevention (INPES).
From 2003 Elected member of the administrative committee of the National Committee against Tobacco (CNCT)

**Honors:**

1994: Prix de la Charente de la Ligue Nationale Contre le Cancer
1980-83: Victor Emmanuel Chapman Memorial Fellowship from Harvard University
1978-80: Boursière du Ministère des Affaires Etrangères, France

## B. Selected peer-reviewed publications (in chronological order)

Sasco AJ, Paffenbarger RS Jr. Measles infection and Parkinson's disease. *American Journal of Epidemiology*, 122(6):1017-1031, 1985.

Sasco AJ, Day NE, Walter SD. Case-control studies for the evaluation of screening. *Journal of Chronic Diseases*, 39(5):399-405, 1986.

Sasco AJ, Paffenbarger RS Jr. Smoking and Parkinson's disease. *Epidemiology*, 1(6):460-465, 1990.

Sasco AJ, Fontanière B, Charbaut-Lagarde MO, Kliebsch U, Hamandjian P, Cornu-Lugrin AE, Schnebelen JP, Sciortino V, Fabry J. A systematic survey of breast cancer incidence in the département of Rhône, France. *European Journal of Cancer*, 27(12):1696-1701, 1991.

Sasco AJ, Paffenbarger RS Jr, Gendre I, Wing AL. The role of physical exercise in the occurrence of Parkinson's disease. *Archives of Neurology*, 49(4):360-365, 1992.

Belli S, Comba P, De Santis M, Grignoli M, Sasco AJ. Mortality study of workers employed by the Italian National Institute of Health, 1960-1989. *Scandinavian Journal of Work and Environmental Health*, 18(1):64-67, 1992.

Sasco AJ, Lowenfels AB, Pasker-de Jong P. Epidemiology of male breast cancer. A meta-analysis of published case-control studies and discussion of selected aetiological factors. *International Journal of Cancer*, 53(4):538-549, 1993.

Sasco AJ, Pobel D, Benhaïm V, de Bruin K, Stiggelbout A, Tuyns A. Smoking habits in French adolescents. *Revue duote Epidémiologie et de Santé Publique*, 41(6):461-472, 1993.

Liu Q, Sasco AJ, Riboli E, Hu MX. Indoor air pollution and lung cancer in Guangzhou, People's Republic of China. *American Journal of Epidemiology*, 137(2):145-154, 1993.

Sasco AJ. Epidémiologie et prévention des cancers : quelques réflexions sur l'éthique des démarches de santé publique. [Epidemiology for cancer prevention: some considerations on the ethics of public health interventions]. *Bulletin de l'Académie Nationale de Médecine*, 179(5):987-1007, 1995.

Sasco AJ, Chaplain G, Amoros E, Saez S. Endometrial cancer following breast cancer: effect of tamoxifen and castration by radiotherapy. *Epidemiology*, 7(1):9-13, 1996.

Sasco AJ, Rey F, Reynaud C, Bobin JY, Clavel M, Niveleau A. Breast cancer prognostic significance of some modified urinary nucleosides.*Cancer Letters*, 108(2):157-162, 1996.

Hosek RS, Flanders WD, Sasco AJ. Bias in case-control studies of screening effectiveness. *American Journal of Epidemiology*, 143(2):193-201, 1996.

Brown TP, Paulson J, Pannett B, Coupland C, Coggon D, Chilvers CED, Sasco AJ: Mortality pattern among biological research laboratory workers. *British Journal of Cancer*, 73(9):1152-1155, 1996.

Satgé D, Sasco AJ, Carlsen NLT, Stiller CA, Rubie H, Hero B, de Bernardi B, de Kraker J, Coze C, Kogner P, Langmark F, Hakvoort-Cammel FGAJ, Beck D, von der Weid N, Parkes S, Hartmann O, Lippens RJJ, Kamps WA, Sommelet D. A lack of neuroblastoma in Down syndrome. A study from 11 European countries. *Cancer Research,* 58(3):448-452, 1998.

Davis DL, Axelrod D, Bailey L, Gaynor M, Sasco AJs20 . Rethinking breast cancer risks and the environment: the case for the precautionary principle. *Environmental Health Perspectives*, 106(9):523-529, 1998.

Sasco AJ, Vainio H. From in utero and childhood exposure to parental smoking to childhood cancer: a possible link and the need for action.*Human and Experimental Toxicology*, 18(4):192-201, 1999.

Sasco AJ, Kleihues P. Why can't we convince the young not to smoke? *European Journal of Cancer*, 35(14):1933-1940, 1999.

Wennborg H, Yuen J, Axelsson G, Ahlbom A, Gustavsson P, Sasco AJ. Mortality and cancer incidence in biomedical laboratory personnel in Sweden. *American Journal of Industrial Medicine*, 35(4):382-389, 1999.

Satgé D, Sasco AJ, Pujol H, Réthoré MO.Les cancers mammaires des femmes trisomiques 21. [Breast cancer in women with Down syndrome].*Bulletin de l'Académie Nationale de Médecine*, 185 (7): 1239-1254, 2001.

Chaplain G, Quantin C, Brunet-Lecomte P, Mottot C, Michiels-Marzais D, Sasco AJ. Quality assessment of cervical screening: a population-based case-control study in the "Côte-d'Or" region, France. *Cancer Detection and Prevention,* 25 (1): 40-47, 2001.

Sasco AJ, Laforest L, Benhaïm-Luzon V, Poncet M, Little RE. Smoking and its correlates among pre-adolescent children in France. *Preventive Medicine*, 34 (2): 226-334, 2002.

Sasco AJ, Merrill RM, Dari I, Benhaïm-Luzon V, Carriot F, Cann CI, Bartal M. A case-control study of lung cancer in Casablanca, Morocco. *Cancer Causes and Control*, 13 (7) : 609-616, 2002.

Schwartz L, Balasso J, Baillet F, Brun B, Amman JP, Sasco AJ. Cancer : the role of extra-cellular disease. *Medical Hypotheses,* 58(4) : 340-346, 2002.

Sasco AJ, Merrill RM, Benhaïm-Luzon V, Gérard JP, Freyer G. Trends in tobacco smoking among adolescents, in Lyon, France. *European Journal of Cancer*, 39 (4): 496-504, 2003.

Sasco AJ, Kaaks R, Little RE. Breast cancer : occurrence, risk factors and hormone metabolism. *Expert Review in Anticancer Therapy*, 3 (4): 546-562, 2003.

Satgé D, Sasco AJ, Chompret A, Orbach D, Méchinaud F, Lacour B, Roullet B, Martelli H, Bergeron C, Bertand Y, Lacombe D, Pérel Y, Monteil P, Nelken B, Bertozzi AI, Munzer M, Kanold J, Bernard F, Vekemans MJ, Sommelet D. A 22-year French experience on solid tumors in children with Down syndrome. *Pediatric Hematology and Oncology*, 20 (7): 517-529, 2003.

Vecchio D, Sasco AJ, Cann CI. Occupational risk in health care and research. *American Journal of Industrial Medicine*, 43 (4): 369-397, 2003.

Kauppinen T, Pukkala E, Saalo A, Sasco AJ. Exposure to chemical carcinogens and risk of cancer among Finnish laboratory workers. *American Journal of Industrial Medicine*, 44 (4): 343-350, 2003.

Besson H, Renaudier P, Merrill RM, Coiffier B, Sebban C, Fabry J, Trepo C, Sasco AJ. Smoking and non-Hodgkin's lymphoma: a case-control study in the Rhône-Alpes region of France. *Cancer Causes and Control*, 14 (4): 381-389, 2003.

van Barneveld TA, Sasco AJ, van Leeuwen FE. A cohort study of cancer mortality among biology reserch laboratory workers in the Netherlands. *Cancer Causes and Control*, 15 (1): 55-66, 2004.

## C. Research Support

Breast cancer:
- Breast cancer, oestrogen levels and pesticides: a collaborative approach Case-control study in Tunisia: (b)(4), Role: Principal Investigator
- Breast cancer survival and recurrence study: (b)(4), (b)(6) Role: Principal Investigator
- Study of second cancers and tamoxifen (EuroDeucaTam project): (b)(4), (b)(6) Principal Investigator

Tobacco:
- *Tobacco and pregnancy:* (b)(4), (b)(6) *Role: Principal Investigator*
- Tobacco and adolescents: (b)(4), (b)(6) Role: Principal Investigator
- Pregnant women and tobacco smoking: (b)(4), (b)(6) Role: Principal Investigator

*Cancer risk in biology research laboratory workers study:*
- (b)(4), (b)(6) Role: Principal Investigator
- (b)(4), (b)(6) Role : Principal Investigator
- Worksafe: European Digital Content Sharing Services for Health Protection of Workers and Workplace Safety. (b)(4), (b)(6) . Role Co-investigator

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| **TONG, Wei-Min** | 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 |
|---|---|---|---|
| China Medical University, Shenyang, P.R. China | M.D. | 1986 | Medicine |
| Norman Bethune University of Medical Sciences, Changchun, P.R. China | M.Sc. | 1991 | Pathology |
| University of Vienna, Austria | Dr. Sc. | 1996 | Biochemistry |

**NOTE: The Biographical Sketch may not exceed four pages. Items A and B (together) may not exceed two of the four-page limit. Follow the formats and instructions on the attached sample.**

**A. Positions and Honors.** List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

**Positions and Employment**

Jul. 1986-Sep. 1988 **Assistant Professor** in the Department of Forensic Medicine, Norman Bethune University of Medical Sciences, Changchun, P. R. China

Sep. 1988-Feb. 1994 **Residency** in the Department of Pathology, Norman Bethune University of Medical Sciences, Changchun, P. R. China

Feb. 1992-Sep. 1993 **Visiting Scientist,** Institute of General and Experimental Pathology, University of Vienna Medical School, Vienna, Austria

Feb. 1994-Sep. 1997 **Research Assistant,** Institute of General and Experimental Pathology, University of Vienna Medical School, Vienna, Austria

Sep. 1997-Aug. 2000 **Postdoctoral fellow,** International Agency for Research on Cancer (IARC), Lyon, France

Sep. 2000-present: **Staff Scientist,** International Agency for Research on Cancer (IARC), Lyon, France

**Honors**

Sep. 1997-Aug. 2000 Special Trainee Award, International Agency for Research on Cancer (IARC), Lyon, France

Jul. 1997-Sep. 1997 Postdoctoral fellowship from the Bender-Wien Corp, Austria

Jun. 1996-Jun. 1997 Fellowship from the Herzfelder Foundation, Austria

Mar. 1994-Mar. 1996 Fellowship from the Austrian Science Foundation (FWF), Austria

Feb. 1992-Sep. 1993 Fellowship from the Austrian Academic Exchange Service (OEAD), Austria

**B. Selected peer-reviewed publications (in chronological order).** s20 Do not include publications submitted or in preparation.


1. d'Adda di Fagagna F, Hande MP, **Tong WM**, Lansdorp PM, Wang ZQ, Jackson SP. (1999) Functions of PARP in controlling telomere length and chromosomal stability. *Nature Genetics,* **23**, 76-80
2. **Tong WM**, Galendo D, Wang ZQ. (2000) Role of DNA break-sensing molecule poly(ADP-ribose) polymerase (PARP) in cellular function and radiation toxicity. *Cold Spring Harbor Symposia on Quantative Biology,* **65**, 583-591
3. Luo JL, Yang Q, **Tong WM**, Hergenhahn M, Wang ZQ, Hollstein M. (2001) Knock-in mice with a chimeric human/murine p53 gene develop normally and show wild-type p53 responses to DNA damaging agents: a new biomedical research tool. *Oncogene*, **20**, 320-328
4. d'Adda di Fagagna F, Hande MP, **Tong WM**, Roth D, Lansdorp PM, Wang ZQ, Jackson SP. (2001) Effects of DNA nonhomologous end-joining factors on telomere length and chromosomal stability in mammalian cells. *Current Biology,* **11**, 1192-1196
5. **Tong WM**, Hande MP, Lansdorp PM, Wang ZQ. (2001 ) DNA-strand break-sensing molecule PARP cooperate with p53 in telomere function, chromosomal stability and tumor suppression. *Molecular and Cellular Biology,* **21**, 4046-4054
6. Luo JL, **Tong WM**, Yoon JH, Hergenhahn M, Koomagi R, Yang Q, Pfeifer GP, Wang ZQ, Hollstein M. (2001) UV-induced DNA damage and mutations in *Hupki* (human p53 knock-in) mice recapitulate p53 patterns in sun-exposed human skin. *Cancer Research,* **61**, 8158-8163
7. **Tong WM**, Cortes U, Wang ZQ. (2001) Poly(ADP-ribose) polymerase: a guardian angel protecting genome and suppressing tumorigenesis. *Biochimica and Biophysica Acta,* **1552**, 27-37
8. Lai JP, Tong CL, Hong C, Xiao JY, Tao ZD, Zhang Z, **Tong WM**, Betz CS. (2002) Association between high initial tissue levels of cyclin D1 and recurrence of nasopharyngeal carcinoma. *Laryngoscope,* **112**, 402-408
9. **Tong WM**, Cortes U, Hande MP, Ohgaki H, Cavalli LR, Lansdorp PM, Haddad BR, Wang ZQ. (2002) Haplo-insufficiency of Ku80 promotes hepatocellular carcinoma formation in mice mutant for poly(ADP-ribose) polymerase. *Cancer Research,* **62**, 6990-6996
10. **Tong WM**, Ohgaki H, Huang H, Granier, C, Kleihues P, Wang ZQ. (2003) Null mutation of DNA strand break-binding molecule poly(ADP-ribose) polymerase, causes medulloblastomas in $p53^{-/-}$ mice. *American Journal of Pathology,* **162**, 343-352
11. Kanai M, **Tong WM**, Sugihara E, Wang ZQ, Fukasawa K, Miwa M. (2003) Involvement of poly(ADP-ribose) polymerase-1 and poly(ADP-ribosyl)ation in regulation of centrosome function. *Molecular Cellular Biology,* **23**, 2451-2462
12. Bertolino P, **Tong WM**, Herrera PL, Huguette Casse H, Zhang CX, Wang ZQ. (2003) Pancreatic β-cell-specific ablation of the Multiple Endocrine Neoplasia type 1 (*MEN1*) gene causes full penetrance of insulinoma development in mice. *Cancer Research,* **63**, 4836-4841
13. Bertolino P, **Tong WM**, Galendo D, Wang ZQ, Zhang CX. (2003 ) Heterozygous Men1 Mutant Mice Develop a Range of Endocrine Tumors Mimicking Multiple Endocrine Neoplasia Type 1. *Molecular Endocrinology,* **17**, 1880-1892
14. **Tong WM**, Li C, Badiali M, Sumegi J, Latour S, Wang ZQ, Romeo R. (2003) Mice deficient in the X-linked lymphoproliferative gene *sap* exhibit dysgammaglobulinemia and a decreased B cell function. *Journal of Molecular Virology,* **71**, 446-455
15. Dumon-Jones V, Frappart PO, **Tong WM**, Sajithlal G, Hulla W, Schmid G, Herceg Z, Digweed M, Wang ZQ. (2003) Nbn heterozygosity renders mice susceptible to tumor formation and ionizing radiation-induced tumorigenesis. *Cancer Research,* **63**, 7263-7269
16. Ghabreau L, Roux JP, Frappart PO, Mathevet P, Patricot LM, Mokni M, Wang ZQ, **Tong WM**, Frappart L. (2004) Poly(ADP-ribose) polymerase-1, a novel partner of progesterone receptors in endometrial cancer and its precursors. *International Journal of Cancer,* **109**, 317-321.

## BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed for Form Page 2.
Follow the sample format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME | POSITION TITLE |
|---|---|
| **WANG, Zhao-Qi** | 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 |
|---|---|---|---|
| Shandong University, China | B.Sc. | 1982 | Biology |
| Peking Union Medical College (PUMC), China | M.Sc. | 1985 | Cell Biology |
| Innsbruck University, Austria | Ph.D... | 1993 | Biochemistry |

**NOTE: The Biographical Sketch may not exceed four pages. Items A and B (together) may not exceed two of the four-page limit. Follow the formats and instructions on the attached sample.**

**A. Positions and Honors.** List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

**Positions and Employment**

| | |
|---|---|
| 1985-1988 | Lecturer, Institute of Basic Medical Sciences, Peking Union Medical College (PUMC), China |
| 1988 (Jul.-Oct.) | Postdoc, European Molecular Biology Laboratory (EMBL), Heidelberg, Germany |
| 1988-1993 | Postdoc, Research Institute of Molecular Pathology (IMP), Vienna, Austria |
| 1993-1995 | Staff Scientist, Research Institute of Molecular Pathology (IMP), Vienna, Austria |
| 1995-1997 | Scientist, Research Institute of Molecular Pathology (IMP), Vienna, Austria |
| Feb. 1997-present | Unit Chief, Unit of Gene-Environment Interactions, International Agency for Research on Cancer (IARC), Lyon, France |

**B. Selected peer-reviewed publications (in chronological order).**

**Since 2001**


1. Luo JL, Yang Q, Tong WM, Hergenhahn M, **Wang ZQ** , Hollstein M. (2001) Knock-In Mice With a Chimeric Human/Murine p53 Gene Develop Normally and Show Wild-Type p53 Responses to DNA Damaging Agents: A New Biomedical Research Tool. *Oncogene,* **20,** 320-328
2. Tong WM, Hande MP, Lansdorp PM, **Wang ZQ.** (2001) DNA Strand Break-Sensing Molecule Poly(ADP-Ribose) Polymerase Cooperates with p53 in Telomere Function, Chromosome Stability, and Tumor Suppression. *Molecular and Cellular Biology,* **21**(12), 4046-4054
3. Herceg Z, **Wang ZQ.** (2001) Functions of Poly(ADP-ribose) Polymerase (PARP) in DNA Repair, Genomic Integrity and Cell Death. *Mutation Research,* **477,** 97-110
4. D'Adda di Fagagna F, Hande MP, Tong WM, Roth D, Lansdorp PM, **Wang ZQ,** Jackson SP. (2001) Effects of DNA Non-Homologous End-Joining Factors on Telomere Length and Chromosomal Stability in Mammalian Cells. *Current Biology,* **11,** 1192-1196
5. Herceg Z, Hulla W, Gell D, Cuenin C, Lleonart M, Jackson S, **Wang ZQ.** (2001) Disruption of *Trrap* Causes Early Embryonic Lethality and Defects in Cell Cycle Progression. *Nature Genetics,* **29,** 206-211

6. Luo JL, Tong WM, Yoon JH, Hergenhahn M, Koomagi R, Yang Q, Galendo D, Pfeifer GP, **Wang ZQ**, Hollstein M. (2001) UV-Induced DNA Damage and Mutations in Hupki (Human p53 Knock-In) Mice Recapitulate p53 Hotspot Alterations in Sun-Exposed Human Skin. *Cancer Research,* **61,** 8158-8163
7. Tong WM, Cortes U, **Wang ZQ.** (2001) Poly(ADP-Ribose) Polymerase: a Guardian Angel Protecting the Genome and Suppressing Tumorigenesis. *Bioch. Bioph. Acta (Review),* **1552,** 27-37
8. Rosenthal DS, Simbulan-Rosenthal CM, Liu WF, Velena A, Anderson D, Benton B, **Wang ZQ,** Smith W, Ray R, Smulson ME. (2001) PARP Determines the Mode of Cell Death in Skin Fibroblasts, but not Keratinocytes, Exposed to Sulfur Mustard. *The Journal of Investigative Dermatology,* **117**, 1566-1573
9. Los M, Mozoluk M, Ferrari D, Stepczynska A, Stroh C, Renz A, Herceg Z, **Wang ZQ,** Schulze-Osthoff, K. (2002) Activation and Caspase-Mediated Inhibition of PARP: A Molecular Switch Between Fibroblast Necrosis and Apoptosis in Death Receptor Signaling. *Molecular Biology of the Cell*, **13**, 978-988
10. Herceg Z, Pétrilli V, Wutz A, Auer B, Cros MP, **Wang ZQ.** (2002) Functional Testing of Human PARP in Proliferation, Endotoxic Shock and Radiosensitivity: A Genetic Rescue Study. In: "PARP as a Therapeutic Target", Zhang J. (ed.), CRC Press, Boca Raton, pp 67-81
11. Tong WM, Cortes U, Hande MP, Ohgaki H, Cavalli L, Lansdorp PM, Haddad B, **Wang ZQ.** (2002) Synergystic Role of Ku80 and Poly(ADP-Ribose) Polymerase in Suppressing Chromosomal Aberrations and Liver Cancer Formation. *Cancer Research,* **62,** 6990-6996
12. **Wang ZQ.** (2003) Animal Models for Mechanistic Cancer Research. In: *Mechanisms in Carcinogenesis and Cancer Prevention,* Vainio H, Hietanen E. (eds.), Handbook of Experimental Pharmacology (**Vol 156**), Springer-Verlag, Heidelberg, pp 271-288
13. Tong WM, Ohgaki H, Huang H, Granier C, Kleihues P, ...(2003) Null Mutation of DNA Strand Break-Binding Molecule Poly(ADP-ribose) Polymerase Causes Medulloblastomas in p53 $^{-/-}$ Mice. *American Journal of Pathology,* **162**(1) 343-352
14. Kanai M, Tong WM, Sugihara E, **Wang ZQ**, Fukasawa K, Miwa M. (2003) Involvement of Poly(ADP-Ribose) Polymerase 1 and Poly(ADP-Ribosyl)ation in Regulation of Centrosome Function. *Molecular and Cellular Biology,* **23**(7), 2451-2462
15. Bertolino P, Radovanovic I, Casse H, Aguzzi A, **Wang ZQ**, Zhang CX. (2003) Genetic Ablation of the Tumor Suppressor Menin Causes Lethality at Mid-Gestation with Defects in Multiple Organs. *Mechanisms of Development,* **120**, 549-560
16. Bertolino P, Tong WM, Herrera PL, Huguette Casse H, Zhang CX, **Wang ZQ.** (2003) Pancreatic (Beta Sign)-Cell-Specific Ablation of the Multiple Endocrine Neoplasia type 1 (MEN1) Gene Causes Full Penetrance of Insulinoma Development in Mice. *Cancer Research,* **63**, 4836-4841
17. Bertolino P, Tong WM, Galendo D, **Wang ZQ**, Zhang CX. (2003) Heterozygous Men1 Mutant Mice Develop a Range of Endocrine Tumors Mimicking Multiple Endocrine Neoplasia Type 1. *Molecular Endocrinology,* **17**, 1880-1892
18. Yin L, Al-Alem U, Liang J, Tong WM, Li C, Badiali M, Médard JJ, Sumegi J, **Wang ZQ**, Romeo G. (2003) Mice Deficient in the X-Linked Lymphoproliferative Disease Gene *sap* Exhibit Increased Susceptibility to Murine Gammaherpesvirus-68 and Hypo-Gammaglobulinemia. *Journal of Medical Virology,* **71**, 446-455
19. Dumon-Jones V, Frappart PO, Tong WM, Sajithal G, Hulla W, Schmid G, Herceg Z, Digweed M, **Wang ZQ.** (2003) *Nbn* Heterozygosity Renders Mice Susceptible to Tumor Formation and Ionizing Radiation-Induced Tumorigenesis. *Cancer Research,* **63**, 7263-7269
20. Herceg Z, Li H. Cuenin C, Shukla V, Radolf M, Steinlein P, **Wang ZQ.** (2003) Genome-Wide Analysis of Gene Expression Regulated by the HAT Cofactor Trrap in Conditional Knockout Cells. *Nucleic Acids Research,* **31**(23), 7011-7023
21. Ghabreau L, Roux JP, Frappart PO, Mathevet P, Patricot LM, Mokni M, **Wang ZQ,** Tong WM, Frappart L. (2004) Poly(ADP-Ribose) Polymerase-1, a Novel Partner of Progesterone Receptors in Endometric Cancer and its Precursors. *International Journal of Cancer,* **109**, 317-321
22. Yang YG, Cortes U, Patnaik S, Jasin M, **Wang ZQ.** (2004) Ablation of PARP-1 Does not Interfere with the Repair of DNA Double-Strand Breaks, but Compromises the Reactivation of Stalled Replication Forks. *Oncogene*, in Press.

## 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:
Not applicable

Clinical:
Not applicable

Animal:
Not applicable

Computer:
A network of personal computers with word-processing software and Quark desk-top publishing software are available for document preparation, PubMed and internet search engines are used for electronic retrieval, and Reference Manager for indexing and processing of scientific literature. A dedicated webserver is available.

Office:
Excellent conference facilities, with multiple adjoining meeting rooms to accommodate both plenary and subgroup sessions. Modern communications and audiovisual equipment, including microphones for all meeting participants.

Other:
The IARC Library subscribes to the major scientific journals related to cancer research. The use of on-line databases for rapid retrieval of scientific papers has been increasing. The IARC Library has agreements with other scientific libraries to facilitate timely retrieval of hard-to-obtain papers, often on an overnight basis.

IARC's multilingual scientific staff can assist with on-the-spot translation and interpretation of papers published in virtually any language used for modern scientific publications.

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

The meeting rooms, library, staff offices, and cafeteria are all located in the main IARC building. This facilitates efficient conduct of the meetings.

A computer services group is available in-house.

IARC's multilingual staff can assist international participants with any queries that may arise.

# RESEARCH PLAN

The global burden of cancer continues to increase. There were an estimated 10.1 million new cases, 6.2 million deaths, and 22.4 million persons living with cancer in the year 2000 (IARC, 2003). This represents an increase of 19% in incidence and 18% in mortality since 1990. Given current trends in smoking prevalence and other factors, the annual number of new cases is estimated to reach 15 million by 2020. It is possible to prevent at least one-third of these new cases through better use of existing knowledge. Understanding how cancer develops creates opportunities for cancer prevention or early detection. An important part of this effort is to identify the agents and exposures that cause cancer in humans.

## a. SPECIFIC AIMS

The aim of the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* is to critically review and evaluate the published scientific evidence for carcinogenic hazards to which humans are exposed. These include chemicals, complex mixtures, occupational exposures, lifestyle factors, and physical and biological agents. International, interdisciplinary working groups of expert scientists prepare the critical reviews and consensus evaluations, which are published in the *IARC Monographs* series.

Wide dissemination of the information developed in the *IARC Monographs* is an important objective. Each volume is printed in 2500 or more copies, many of which are distributed free of charge to libraries and government agencies. Lists of the evaluations developed to date, along with summaries of all *IARC Monographs*, are available through the Programme's website (http://monographs.iarc.fr). As new evaluations are developed, the summary is placed on the website within a few weeks. New evaluations of great importance or widespread interest are announced immediately through a press release or press conference. To make the *IARC Monographs* even more accessible, a complete and searchable electronic version of all volumes published to date is available, both in CD-ROM format and on-line through the Internet (http://monographs.iarc.fr).

During each year of the project period, IARC will convene three separate working groups on different agents or exposures suspected of causing cancer in humans. (The NCI funding being requested will support two of these working groups each year.) The topics will be selected from the list of high priorities for future evaluations recommended by an *IARC Monographs* Advisory Group in February 2003. These are listed in section c.5, and the most urgent are noted in section d.1. Additional topics will be scheduled as significant new scientific information becomes available or as national health agencies identify an urgent public health need related to human cancer.

## b. BACKGROUND AND SIGNIFICANCE

### Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of exposure to various chemicals, including requests for lists of known and

suspected human carcinogens. It was clear that it would not be a simple task to adequately summarize the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this subject. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended, " . . . that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented." The IARC Governing Council, too, considered a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation of carcinogenic risk of chemicals to man, which became the initial title of the Programme.

In 1971 the first *IARC Monograph* working group was convened. The objective of the Programme was "to achieve a balanced evaluation of data through the deliberations of an international group of experts in chemical carcinogenesis and to put into perspective the present state of knowledge with the final aim of evaluating the data in terms of possible human risk, as well as to indicate the need for research efforts" *(IARC 1972)*. With the first monographs, the basic elements of the overall approach began to take shape. Chemicals were selected for evaluation based on evidence of carcinogenicity and evidence of human exposure. The evaluation considered papers published or accepted for publication. Pertinent data were compiled, reviewed, and evaluated by international, interdisciplinary working groups of expert scientists. The resulting monographs summarized the evidence of carcinogenicity in a condensed, uniform manner.

Initially, no attempt was made to interpret the animal data in terms of possible human risk, in the absence of human data. Volume 1 promised to develop guidance, with the help of experts, after the *IARC Monographs* had provided some case studies as necessary background material *(IARC 1972)*. In Supplement 1 an overall evaluation of carcinogenicity to humans was first made, based on the combined evidence from studies of cancer in humans and cancer in experimental animals *(IARC 1979)*. In Supplement 7 this guidance was broadened to an overall evaluation based on a combined weight of the evidence that also included other relevant data, primarily the results of tests for genetic and related effects *(IARC 1987)*. Since that time, each *IARC Monograph* includes an evaluation that characterizes the agent or exposure as either:

*Carcinogenic to humans* (Group 1)
*Probably carcinogenic to humans* (Group 2A)
*Possibly carcinogenic to humans* (Group 2B)
*Not classifiable as to its carcinogenicity to humans* (Group 3)
*Probably not carcinogenic to humans* (Group 4)

Throughout this period and in the succeeding years, the scope of the *IARC Monographs* was expanded and different categories of carcinogenic agents were evaluated. Initially, *IARC Monographs* were developed for individual chemicals, groups of related chemicals, and complex mixtures of chemicals. Topics for evaluation now include occupational exposures, lifestyle factors (such as tobacco use), physical agents (including various forms of radiation), and biological agents (bacteria and viruses). In 1988 the phrase "of chemicals" was dropped from the title, which assumed its present form, the *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

With the increased understanding of mechanisms of carcinogenesis, a greater proportion of the pertinent scientific literature now comes from mechanistic studies. To provide more specific guidance on how mechanistic information can be used as part of the overall evaluation of the weight of the

evidence, the *Preamble* (which discusses the principles and procedures used in developing *IARC Monographs*, including guidance for developing the evaluations) was expanded in 1992. Mechanistic information now can play a determining role in classifying an agent into any Group. In particular, strong evidence in exposed humans that an agent acts through a relevant mechanism of carcinogenicity can be used to upgrade an agent when evidence in humans is less than sufficient. Conversely, strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans can be used to classify an agent with sufficient evidence in experimental animals in a category of lower concern *(IARC 2004)*.

As the importance of mechanistic understanding has continued to increase, the Programme has become an integrated and balanced activity that combines regular development of new *IARC Monographs* with special scientific workshops on pertinent issues involving mechanisms of carcinogenesis. Like the *IARC Monographs*, the workshops bring together international, interdisciplinary working groups of expert scientists. Each workshop seeks to determine whether scientific knowledge has accumulated to develop a consensus in a particular area. The results of these workshops generally are published as IARC Scientific Publications and distributed to the scientific research community. Publications related to the use of mechanistic information in *IARC Monograph* evaluations include:

— *Mechanisms of carcinogenesis in risk identification* (IARC Scientific Publication 116, 1992).

— *Peroxisome proliferation and its role in carcinogenesis* (IARC Technical Report 24, 1995).

— *Mechanisms of fibre carcinogenesis* (IARC Scientific Publication 140, 1996).

— *The use of short- and medium-term tests for carcinogens and data on genetic effects in carcinogenic hazard evaluation* (IARC Scientific Publication 146, 1999).

— *Species differences in thyroid, kidney and urinary bladder carcinogenesis* (IARC Scientific Publication 147, 1999).

— *Predictive value of rodent forestomach and gastric neuroendocrine tumours in evaluating carcinogenic risks to humans* (IARC Technical Report 39, 2003).

— *Mechanisms of carcinogenesis: Contributions of molecular epidemiology* (IARC Scientific Publication 157, 2004).

A new consensus on a mechanism of carcinogenesis may prompt a re-evaluation of agents that cause cancer through that mechanism. In addition, new epidemiological, experimental, and mechanistic data on a specific agent may prompt a re-evaluation of that agent. Thus the evaluation process is a dynamic one that reflects both new scientific results and emerging scientific understanding.

To ensure that the *IARC Monographs* remain relevant to the needs of government health agencies and the scientific research community, the Programme periodically seeks advice from scientists at national health agencies and leading research institutions. Advisory Groups have been convened approximately every 5 years (1979, 1984, 1989, 1993, 1998, 2003) to recommend chemical agents for evaluation or re-evaluation. In addition, Advisory Groups have been convened to recommend physical agents (1998) and biological agents (2001) for future evaluation. The Advisory

Groups also provide useful information about major studies in progress that, when published, will make a new evaluation timely. The Programme also reports progress and seeks advice at annual meetings of IARC's Scientific Council, consisting of senior scientists from leading institutions around the world, and IARC's Governing Council, consisting of the Director-General of the World Health Organization and Representatives from 16 countries.

NCI has supported the *IARC Monographs* through a cooperative agreement, under which NCI scientists participate through several forms of substantial involvement: (1) NCI scientists have a standing invitation to participate in *IARC Monograph* meetings, scientific workshops, and Advisory Group meetings, (2) NCI has awarded a separate contract to Technical Resources International, Inc, to contribute sections on exposure for chemical-related *IARC Monographs*, (3) NCI distributes copies of *IARC Monographs* throughout the United States and Canada, (4) the NCI Program Official may advise informally on priorities for evaluation, candidates for working groups, and other general aspects of the program, and (5) NCI and IARC share databases and other relevant resources, as appropriate, by mutual agreement between the NCI Program Official and the IARC Principal Investigator.

NCI funds are not used for the scientific workshops and Advisory Group meetings; these meetings are mentioned here for the sake of completeness in describing the overall Programme. NCI funds also are not used to pay expenses for working group participants employed by the U.S. government.

**Significance**

The *IARC Monographs* evaluate the carcinogenic potential of individual chemicals, groups of related chemicals, complex mixtures, occupational exposures, lifestyle factors, physical and biological agents, and any other kind of agent or exposure condition suspected of causing cancer in humans. In the 87 volumes developed to date, nearly 900 agents and exposures have been evaluated. Among these, nearly 400 potentially carcinogenic agents and exposures have been identified.

| | | |
|---|---|---|
| Group 1 | *Carcinogenic to humans* | 91 agents |
| Group 2A | *Probably carcinogenic to humans* | 67 agents |
| Group 2B | *Possibly carcinogenic to humans* | 240 agents |

National and international health agencies use the *IARC Monographs* as an authoritative source of scientific information and as the scientific basis for their efforts to control cancer. The evaluations indicate where exposure reductions may be useful in reducing the future incidence of cancer. This is true for both developed and developing countries. National health agencies in developed countries make frequent reference to the *IARC Monographs*. The *IARC Monographs* are an important reference in developing countries that do not have sufficient resources to devote to evaluating cancer and chronic health hazards. As these countries become more industrialized, exposures to carcinogens and other hazardous chemicals have increased, especially where environmental and workplace standards are not adequate or not enforced.

The *IARC Monographs* are also a resource to the scientific community for general information on agents suspected of causing cancer. Each begins with a section on exposure that discusses chemical and physical properties; analytical methods; production levels; uses; occurrence in the environment, workplace, and human tissues and body fluids; and regulations and guidelines. Then

follow detailed sections on cancer in humans and cancer in experimental animals, which include a factual synopsis of each study's design and results, plus the working group's assessment of the study's strengths and limitations. An expanded section on other relevant data includes detailed information on absorption, distribution, metabolism, and excretion; toxic effects; reproductive and developmental effects; genetic and related effects; and mechanistic considerations. Then follows a section containing concise summaries of the preceding sections, concluding with evaluations of the evidence of cancer in humans and in experimental animals, and the overall evaluation.

The principles used in *IARC Monograph* evaluations have influenced and continue to influence those of other carcinogen identification and evaluation programmes. For example, the U.S. Environmental Protection Agency's 1986 cancer guidelines reflected the definitions of *sufficient evidence*, *limited evidence*, and *inadequate evidence* found in IARC's *Preamble*, and its 2003 revision followed IARC's lead in allowing strong mechanistic evidence in exposed humans to contribute to the characterization of an agent as *carcinogenic to humans*. The *Report on Carcinogens* published by the U.S. National Toxicology Program makes similar use of strong mechanistic evidence in exposed humans. In addition, the Globally Harmonized System of Classification and Labelling of Chemicals, being developed through the United Nations and the Organization for Economic Cooperation and Development, has incorporated elements from IARC's classification process.

*IARC Monograph* evaluations have been confirmed by later evaluations of other authoritative agencies. For example, the most recent tenth edition of the *Report on Carcinogens* includes five new listings of agents "known to be human carcinogens" *(NTP 2002)*. All had been characterized earlier by IARC as *carcinogenic to humans* (Group 1): beryllium and beryllium compounds (IARC volume 58, 1993), steroidal estrogens (IARC supplement 7, 1987), nickel and nickel compounds (IARC volume 49, 1990), broad spectrum, solar ultraviolet radiation (IARC volume 55, 1992), and wood dust (IARC volume 62, 1995). In the same edition, there are ten new listings of agents "reasonably anticipated to be human carcinogens." Nine had been characterized earlier by IARC as *probably carcinogenic to humans* (Group 2A) or *possibly carcinogenic to humans* (Group 2B). The lone exception, methyleugenol, was discussed by an IARC Advisory Group and was recommended as a low priority for evaluation because of low human exposure.

The *IARC Monographs* provide a unique reference that is truly international in character. The first 87 volumes of *IARC Monographs* have drawn on the collective expertise of 962 expert scientists from 47 countries. Since the previous NCI application in 2000, scientists from Bangladesh, Chile, the Czech Republic, and Mexico have participated for the first time in *IARC Monograph* working groups, and a scientist from Saudi Arabia will participate as a working group member for *IARC Monograph* volume 89. The continuing addition of new countries to this list demonstrates the serious commitment to continue the *IARC Monographs* as a forum for international consensus.

**Origins of working group members for *IARC Monograph* volumes 1-87**

| | | | | | |
|---|---|---|---|---|---|
| Argentina | 3 | France | 39 | Norway | 10 |
| Australia | 23 | Germany | 75 | Pakistan | 1 |
| Austria | 3 | Ghana | 1 | Russian Federation | 18 |
| Bangladesh | 1 | Greece | 2 | Singapore | 3 |
| Belgium | 11 | Hungary | 2 | Slovakia | 1 |
| Brazil | 3 | India | 11 | South Africa | 5 |
| Bulgaria | 2 | Ireland | 1 | Spain | 3 |
| Canada | 28 | Israel | 1 | Sweden | 38 |
| Chile | 1 | Italy | 43 | Switzerland | 14 |

| | | | | | |
|---|---|---|---|---|---|
| China | 7 | Japan | 45 | Thailand | 4 |
| Cuba | 1 | Korea, Republic of | 1 | Turkey | 1 |
| Czech Republic | 1 | Lithuania | 1 | Ukraine | 1 |
| Denmark | 16 | Mexico | 1 | United Kingdom | 139 |
| Egypt | 1 | Netherlands | 29 | United States | 333 |
| Estonia | 1 | New Zealand | 4 | Yugoslavia | 1 |
| Finland | 31 | Nigeria | 1 | | |

# c. PROGRESS REPORT

## c.1. Progress during the current project period (Sept 2000 to present time)

The last competitive review of this project occurred in 2000, and the current cooperative agreement covers the period from September 2000 through August 2005. During the 3½ years of the 5-year period that have elapsed, *IARC Monographs* have continued to be developed at a rate of approximately three per year, plus one major scientific publication or report on a topic related to the *IARC Monographs*. The NCI cooperative agreement covers development and production costs of two of the three *IARC Monographs* each year.

Since September 2000, nine *IARC Monograph* meetings have been held (volumes 79-87), and plans are underway for the next four meetings (volumes 88-91). Seven *IARC Monograph* volumes have been printed, and the remaining recent volumes are being prepared for printing during 2004. In addition, two scientific workshops were held, resulting in IARC Scientific Publications 157 (printed in 2004) and 158 (in preparation). Later in this section appear brief summaries of each *IARC Monograph* volume (see sections c.2 and c.3), scientific publication (see section c.4), and Advisory Group report (see section c.5).

One particularly significant set of *IARC Monographs*, volume 83 on tobacco smoke and involuntary smoking, has taken longer than usual to prepare for printing. This is because of the unprecedented number of studies cited (more than 3500), the number of pages of text (more than 1400), and the number of tables that require detailed verification for accuracy (more than 700). To help with this task, Programme scientists have devoted extra time to verifying the accuracy of the text and tables, and IARC has hired some additional scientists on a temporary basis. This work has been completed, and volume 83 was distributed in May 2004. The focus on completing volume 83 has caused a backlog in the printing of the later volumes. Most of the work of preparing volumes 84-86 has been finished, and these volumes should be printed during 2004, eliminating the backlog and allowing a return to a normal production schedule.

Several agents were newly evaluated as *carcinogenic to humans* (Group 1) in evaluations conducted during the current project period. These include herbal remedies containing plant species of the genus *Aristolochia* (volume 82), involuntary smoking (volume 83), betel quid without tobacco (volume 85), and areca nut (volume 85). This shows that new human carcinogens are still being found. Some existing Group 1 agents were updated because new information had become available on additional human cancer sites or on mechanistic aspects. These agents, for which the Group 1 classification was reaffirmed, include naturally occurring mixtures of aflatoxins (volume 82), tobacco smoke (volume 83), arsenic in drinking-water (volume 84), betel quid with tobacco (volume 85), and gallium arsenide (volume 86). The fact that every Group 1 agent that undergoes re-evaluation

remains in Group 1 demonstrates the robust and definitive nature of the classification *carcinogenic to humans*.

Mechanistic data have played an increasingly important role in *IARC Monograph* evaluations. During the current project period, several agents were upgraded based on mechanistic data, including glycidol to group 2A (volume 77), MX to group 2B (volume 84), and areca nut to group 1 (volume 85). During the same period, some other agents with sufficient evidence in experimental animals were re-classified from *possibly carcinogenic to humans* (group 2B) to *not classifiable* (group 3) based on the working group's finding of strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans. These include di(2-ethylhexyl) phthalate (volume 77), amitrole (volume 79), ethylenethiourea (volume 79), and sulfamethazine (volume 79).

There have been several changes in key personnel since the last competitive review in 2000. These are summarized in the table below. The previous principal investigator, Dr Jerry Rice, retired in October 2002 (at IARC, retirement is mandatory at a certain age), then Dr Robert Baan served as acting chief until March 2003, when Dr Vincent Cogliano was recruited to direct the Programme and serve as principal investigator. Two of the three senior scientists who previously served as responsible officers for one *IARC Monograph* volume each year, Dr Douglas McGregor and Mr Julian Wilbourn, retired in 2000. They have been succeeded by Dr Kurt Straif, who was recruited in 2001, and Dr Yann Grosse, who was listed as a scientist in 2000 and has shown the ability to assume the duties of responsible officer. The scientist responsible for covering exposure data, Ms Christiane Partensky, retired in 2003. Two new scientists, Dr Béatrice Secretan and Dr Fatiha El Ghissassi, were recruited in 2002 to cover the responsibilities for exposure data and for verifying the scientific accuracy of *IARC Monograph* text and tables previously covered by Ms Partensky and Dr Grosse. Overall, at each level there are the same numbers of key personnel as before. The following table summarizes these changes.

| Role | 2000 | Current (May 2004) |
|---|---|---|
| Principal investigator | J Rice[1] | VJ Cogliano[2] |
| Responsible officers | D McGregor**,[1]<br>J Wilbourn[1]<br>RA Baan**,[3] | RA Baan**<br>K Straif**,[2]<br>Y Grosse |
| Scientists | C Partensky[1]<br>Y Grosse**,[3]<br>(vacancy)**,[4] | B Secretan**,[2,3]<br>F El Ghissassi**,[2,3]<br>(vacancy)[5] |

**Salary covered by NCI funds
[1] Retired
[2] Recruited
[3] Temporary (11-month) contract
[4] Vacancy from retirement in 1999 filled by K Straif in 2001
[5] Vacancy from retirement of C Partensky in 2003

An unfortunate development during the current project period has been a series of published criticisms alleging industry influence and lack of transparency in the *IARC Monographs*. Some changes were undertaken in 2003 to make it clear that the *IARC Monographs* are highly resistant to

and not influenced by outside pressures. A new category of meeting participant was created, the *Invited Specialist*, to codify the principle that a meeting participant with a conflict of interests would be recused from critical activities such as serving as chair, writing text for a *Monograph*, or participating in the final evaluations. New *Ethics Guidelines for Observers* put into writing IARC's long-standing intention that working groups be free from lobbying and inappropriate offers and attempts to influence. The new requirement that each participant submit a *Declaration of Interests (WHO 2004)* at the time of invitation and update it at the meeting gives greater visibility to the serious attention that IARC attaches to this matter. With publication of these changes soon in *Environmental Health Perspectives*, the scientific community should find it easy to know IARC's procedures and have confidence in the *IARC Monographs*.

## c.2. *IARC Monographs* developed or printed during the current project period

**Volume 77: *Some industrial chemicals.*** This volume includes evaluations of several chemical intermediates or additives to which large numbers of workers are exposed. Studies on three chemicals had used genetically modified mice, and these evaluations were guided by a recent IARC scientific publication on the use of such animals in carcinogenicity evaluations *(IARC Scientific Publication 146, 1999)*. Three other chemicals cause peroxisome proliferation in mice or rats, and these evaluations were guided by an IARC technical publication on the role of peroxisome proliferation in a mechanism of carcinogenesis *(IARC Technical Report 24, 1994)*. A working group of 28 scientists from 12 countries met in February 2000 to develop the following evaluations.

| | | |
|---|---|---|
| 2,2-Bis(bromomethyl)propane-1,3-diol | 2B | *Possibly carcinogenic to humans* |
| 4-Chloro-*ortho*-toluidine | 2A | *Probably carcinogenic to humans* |
| 5-Chloro-*ortho*-toluidine | 3 | *Not classifiable* |
| Cinnamyl anthranilate | 3 | *Not classifiable* |
| Coumarin | 3 | *Not classifiable* |
| 2,3-Dibromopropan-1-ol | 2B | *Possibly carcinogenic to humans* |
| Diethanolamine | 3 | *Not classifiable* |
| Di(2-ethylhexyl) adipate | 3 | *Not classifiable* |
| Di(2-ethylhexyl) phthalate | 3 | *Not classifiable* |
| Ethylbenzene | 2B | *Possibly carcinogenic to humans* |
| Glycidol | 2A | *Probably carcinogenic to humans* |
| Nitromethane | 2B | *Possibly carcinogenic to humans* |
| *N*-Nitrosodiethanolamine | 2B | *Possibly carcinogenic to humans* |
| Pyridine | 3 | *Not classifiable* |
| *Ortho*-Toluidine | 2A | *Probably carcinogenic to humans* |
| Triethanolamine | 3 | *Not classifiable* |

**Volume 78: *Ionizing radiation, part 2: Some internally deposited radionuclides.*** Internal sources of radiation result from radioactive fallout from nuclear weapons tests or nuclear power accidents, radiotherapy for malignant and non-neoplastic conditions, and some occupational exposures. (Volume 75 had addressed external sources of ionizing radiation.) A working group of 23 scientists from 8 countries met in June 2000 to develop the following evaluations.

| | | |
|---|---|---|
| Phosphorus-32, as phosphate | 1 | *Carcinogenic to humans* |
| Plutonium-239 and its decay products (may contain | | |

| | | |
|---|---|---|
| plutonium-240 and other isotopes), as aerosols | 1 | *Carcinogenic to humans* |
| Radioiodines, short-lived isotopes, including iodine-131, from atomic reactor accidents and nuclear weapons detonations (exposure during childhood) | 1 | *Carcinogenic to humans* |
| Radionuclides, *alpha*-particle-emitting, internally deposited | 1 | *Carcinogenic to humans* |
| Radionuclides, *beta*-particle-emitting, internally deposited | 1 | *Carcinogenic to humans* |
| Radium-224 and its decay products | 1 | *Carcinogenic to humans* |
| Radium-226 and its decay products | 1 | *Carcinogenic to humans* |
| Radium-228 and its decay products | 1 | *Carcinogenic to humans* |
| Radon-222 and its decay products | 1 | *Carcinogenic to humans* |
| Thorium-232 and its decay products, administered intravenously as a colloidal dispersion of thorium-232 dioxide | 1 | *Carcinogenic to humans* |

**Volume 79: *Some thyrotropic agents.*** Many chemicals in common use produce thyroid tumours in rats and mice. These chemicals have diverse uses: as pharmaceuticals, sedatives, diuretics, antifungal agents, antibacterial agents, pesticides, food additives, hair dyes, and industrial chemicals. New understanding of mechanisms of thyroid carcinogenesis had become available *(IARC Scientific Publication 147, 1999)* and was used by a working group of 22 scientists from 8 countries, who met in October 2000 to develop the following evaluations.

| | | |
|---|---|---|
| Amitrole | 3 | *Not classifiable* |
| Chlordane/heptachlor | 2B | *Possibly carcinogenic to humans* |
| 2,4-Diaminoanisole | 2B | *Possibly carcinogenic to humans* |
| *N,N'*-Diethylthiourea | 3 | *Not classifiable* |
| Doxylamine succinate | 3 | *Not classifiable* |
| Ethylenethiourea | 3 | *Not classifiable* |
| Griseofulvin | 2B | *Possibly carcinogenic to humans* |
| Hexachlorobenzene | 2B | *Possibly carcinogenic to humans* |
| Kojic acid | 3 | *Not classifiable* |
| Methimazole | 3 | *Not classifiable* |
| Methylthiouracil | 2B | *Possibly carcinogenic to humans* |
| Phenobarbital | 2B | *Possibly carcinogenic to humans* |
| Propylthiouracil | 2B | *Possibly carcinogenic to humans* |
| Spironolactone | 3 | *Not classifiable* |
| Sulfamathazine | 3 | *Not classifiable* |
| Sulfamethoxazole | 3 | *Not classifiable* |
| Thiouracil | 2B | *Possibly carcinogenic to humans* |
| Thiourea | 3 | *Not classifiable* |
| Toxaphene | 2B | *Possibly carcinogenic to humans* |

**Volume 80: *Non-ionizing radiation, part 1: Static and extremely low-frequency (ELF) electric and magnetic fields.*** This is the first in a series of two volumes to consider various kinds of

non-ionizing radiation in the frequency range below that of visible light. A working group of 21 scientists from 10 countries met in June 2001 to develop the following evaluations.

| | | |
|---|---|---|
| Electric fields (extremely low-frequency) | 3 | *Not classifiable* |
| Electric fields (static) | 3 | *Not classifiable* |
| Magnetic fields (extremely low-frequency) | 2B | *Possibly carcinogenic to humans* |
| Magnetic fields (static) | 3 | *Not classifiable* |

**Volume 81: *Man-made vitreous fibres.*** Man-made vitreous fibres in the form of synthetic wools are widely used in thermal and acoustic insulation and in other manufactured products. A working group of 19 scientists from 11 countries met in October 2001 to re-evaluate the carcinogenic hazards of the following airborne vitreous fibres.

| | | |
|---|---|---|
| Continuous glass filament | 3 | *Not classifiable* |
| Insulation glass wool | 3 | *Not classifiable* |
| Refractory ceramic fibres | 2B | *Possibly carcinogenic to humans* |
| Rock (stone) wool | 3 | *Not classifiable* |
| Slag wool | 3 | *Not classifiable* |
| Special-purpose glass fibres | 2B | *Possibly carcinogenic to humans* |

**Volume 82: *Some traditional herbal medicines, some mycotoxins, naphthalene and styrene.*** This volume considered three diverse topics. Traditional herbal medicines, which encompass a diverse group of preparations that originate from many different cultures, have become widely marketed in developed countries for novel uses such as weight loss or athletic performance. Mycotoxin contamination of staple food is a serious public health concern in several developing regions. Naphthalene and styrene are commercially important chemicals to which humans are exposed from several uses. A working group of 29 scientists from 15 countries met in February 2002 to develop the following evaluations.

| | | |
|---|---|---|
| Aristolochic acids (naturally occurring mixtures of) | 2A | *Probably carcinogenic to humans* |
| Herbal remedies containing plant species of the genus *Aristolochia* | 1 | *Carcinogenic to humans* |
| 1-Hydroxyanthraquinone | 2B | *Possibly carcinogenic to humans* |
| Madder root (*Rubia tinctorum*) | 3 | *Not classifiable* |
| Riddelliine | 2B | *Possibly carcinogenic to humans* |
| Aflatoxins (naturally occurring mixtures of) | 1 | *Carcinogenic to humans* |
| Fumonisin $B_1$ | 2B | *Possibly carcinogenic to humans* |
| Naphthalene | 2B | *Possibly carcinogenic to humans* |
| Styrene | 2B | *Possibly carcinogenic to humans* |

**Volume 83: *Tobacco smoke and involuntary smoking.*** The major cause of lung cancer, the most common fatal cancer in the world, is tobacco smoking. Involuntary (or passive) smoking involves inhaling carcinogens and other toxic components that are present in tobacco smoke. Tobacco smoke had previously been known to cause cancer of the lung, bladder and renal pelvis, oral cavity, pharynx, larynx, oesophagus (squamous cell), and pancreas. This new evaluation

determined that tobacco smoke also causes cancer of the kidney, stomach, oesophagus (adenocarcinoma), liver, nasal cavities and sinuses, and uterine cervix, plus myeloid leukaemia. A working group of 29 scientists from 12 countries met in June 2002 to develop the following evaluations.

| | | |
|---|---|---|
| Tobacco smoke | 1 | *Carcinogenic to humans* |
| Involuntary smoking | 1 | *Carcinogenic to humans* |

**Volume 84: *Some drinking-water disinfectants and contaminants, including arsenic.*** Drinking-water, whether obtained from large public systems or small private wells, may include some level of contamination, including by-products of the drinking-water disinfection process. A working group of 23 scientists from 13 countries met in October 2002 to develop the following evaluations.

| | | |
|---|---|---|
| Arsenic in drinking-water | 1 | *Carcinogenic to humans* |
| Chloral hydrate | 3 | *Not classifiable* |
| Chloramine | 3 | *Not classifiable* |
| Dichloroacetic acid | 2B | *Possibly carcinogenic to humans* |
| 3-chloro-4-(dichloromethyl)-5-hydroxy-2[5H]-furanone (MX) | 2B | *Possibly carcinogenic to humans* |
| Trichloroacetic acid | 3 | *Not classifiable* |

**Volume 85: *Betel-quid and areca-nut chewing and some related nitrosamines.*** Betel-quid and areca-nut chewing are widely practised in many parts of Asia and in Asian-migrant communities elsewhere in the world. There are hundreds of millions of users worldwide. A working group of 16 scientists from 7 countries met in June 2003 to develop the following evaluations.

| | | |
|---|---|---|
| Areca nut | 1 | *Carcinogenic to humans* |
| Betel quid with tobacco | 1 | *Carcinogenic to humans* |
| Betel quid without tobacco | 1 | *Carcinogenic to humans* |
| 3-(Methylnitrosamino) proprionaldehyde (MNPA) | 3 | *Not classifiable* |
| 3-(Methylnitrosamino) proprionitrile (MNPN) | 2B | *Possibly carcinogenic to humans* |
| N-nitrosoguvacoline (NGL) | 3 | *Not classifiable* |
| N-nitrosoguvacine (NGC) | 3 | *Not classifiable* |

**Volume 86: *Cobalt in hard-metals and cobalt sulfate, gallium arsenide, indium phosphide and vanadium pentoxide.*** This volume includes evaluations of some metal compounds, plus metallic cobalt and cobalt compounds, to which workers in the hard-metal industry are exposed. A working group of 17 scientists from 10 countries met in October 2003 to develop the following evaluations.

| | | |
|---|---|---|
| Cobalt metal with tungsten carbide | 2A | *Probably carcinogenic to humans* |
| Cobalt metal without tungsten carbide | 2B | *Possibly carcinogenic to humans* |
| Cobalt sulfate | 2B | *Possibly carcinogenic to humans* |
| Soluble cobalt (II) salts | 2B | *Possibly carcinogenic to humans* |
| Gallium arsenide | 1 | *Carcinogenic to humans* |
| Indium phosphide | 2A | *Probably carcinogenic to humans* |
| Vanadium pentoxide | 2B | *Possibly carcinogenic to humans* |

**Volume 87:** ***Inorganic and organic lead compounds.*** Human exposure to lead is universal, and all humans carry a body burden of lead. Since the use of lead in pipes, paints, and gasoline has been or is being phased out in many countries, the predominant use of lead is now in batteries and, to a lesser extent, in construction materials and lead-based chemicals. Lead has long been of concern for its adverse health effects other than cancer, in particular, its neuro-developmental effects on the foetus, infants, and children. Nonetheless, there is a history of epidemiologic and experimental investigations attempting to determine whether exposure to lead is associated with the development of some forms of cancer. A working group of 20 scientists from 11 countries met in February 2004 to develop the following evaluations.

| | | |
|---|---|---|
| Inorganic lead compounds | 2A | *Probably carcinogenic to humans* |
| Organic lead compounds | 3 | *Not classifiable* |

**c.3.** ***IARC Monographs*** **scheduled for the remainder of the project period**

**Volume 88:** ***Formaldehyde, 2-butoxyethanol and propylene glycol mono-t-butyl ether.*** Formaldehyde is one of the most widely studied potential carcinogens in the workplace and in the environment. Glycol ethers are solvents that have a wide variety of industrial and consumer uses. New cancer studies and mechanistic information have become available for several of these compounds, to which there is widespread human exposure. A working group of 26 scientists from 10 countries will meet in June 2004 to develop evaluations of the following compounds.

Formaldehyde
2-Butoxyethanol
Propylene glycol mono-t-butyl ether

**Volume 89:** ***Smokeless tobacco and some related nitrosamines.*** A working group tentatively consisting of 18 scientists from 7 countries will meet in October 2004 to develop evaluations of the following agents.

Smokeless tobacco
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)
N'-nitrosoanabasine (NAB)
N'-nitrosoanatabine (NAT)
N'-nitrosonornicotine (NNN)

**Volume 90:** ***Human papilloma viruses.*** A working group will meet in February 2005 to evaluate the new evidence of carcinogenicity for human papilloma viruses. The specific viral agents to be evaluated will be determined by the working group, which is being selected as this application is being prepared.

**Volume 91.** The last working group to be convened during the project period will meet in June 2005. The topic and working group will be selected soon after the June 2004 meeting is finished.

## c.4. Scientific Publications related to the *IARC Monographs*, 2000-2005

***Mechanisms of carcinogenesis: Contributions of molecular epidemiology*** (IARC Scientific Publication 157, 2004). Molecular epidemiology is the study of the distribution and determinants of disease in human populations using techniques of molecular biology and epidemiology. Molecular epidemiology has found many domains of application, in particular cancer epidemiology, environmental epidemiology, and infectious disease epidemiology. During the last two decades, molecular epidemiology has become an important discipline in cancer research. The early contributions of molecular epidemiology came from the application of markers of exposure, such as measurements of adducts in blood and urine, in population-based studies. The investigation of aflatoxin exposure markers in cohorts at high risk of liver cancer remains a paradigm of the potential of the new approaches. Over the years, molecular cancer epidemiology has evolved towards the development, validation and application of markers of susceptibility and, more recently, markers of mechanisms of cancer development.

This IARC Scientific Publication originates from a workshop co-sponsored by IARC and held in Lyon during November 2001. The workshop was devoted to providing guidelines for use of molecular techniques in cancer epidemiology, in particular with respect to the study of cancer mechanisms. Molecular cancer epidemiology is often defined in terms of biomarkers, which are found internally within biological systems as indicators of exposure, or effects or susceptibility to disease. However, the traditional distinction of biomarkers of exposure, effect, and susceptibility is no longer necessary. For example, DNA adducts are markers that integrate exposure, effect and susceptibility. The new IARC Scientific Publication covers from an interdisciplinary perspective the contribution of molecular epidemiology to the understanding of mechanisms of carcinogenesis, and represents a further contribution to the development of molecular epidemiology as a mature scientific discipline.

***Management of mycotoxins in foods and feeds for improving public health*** (IARC Scientific Publication 158, in preparation). Following a recommendation of the Working Group for *IARC Monograph* volume 82 (*Some herbal medicines, some mycotoxins, naphthalene and styrene*), a separate, comprehensive document on strategies for remediation of mycotoxin-infested crops is being developed in collaboration with WHO (Geneva) and the Food and Agriculture Organization (FAO, Rome). A group of 15 scientists from 14 countries convened in Lyon to prepare the outline and develop chapters for this IARC Scientific Publication on methods and strategies to prevent, limit, and control infection of foods and feeds by mycotoxin-producing fungi. Several participants came from regions where mycotoxin contamination of staple food is a serious concern. The document will:

(a) Focus on five types of mycotoxin (aflatoxins, ochratoxin A, fumonisins, deoxynivalenol and ergot) that are generally considered to be most important on a worldwide basis.
(b) Provide information on all species of fungi known to produce these toxins, with clear emphasis on those that affect crops of commercial importance. Co-occurrence and super-infection by more than one species should be mentioned as well.
(c) Provide physical and chemical data on the mycotoxins, describe analytical methods and review the toxic effects in food-producing animals and humans.
(d) Discuss the major and the minor crops known to be affected by these toxins, as well as crops unlikely to be affected, and indicate the times (pre- or post-harvest) when crops are likely to become contaminated.
(e) Outline strategies that may be used to limit the production of toxins before or immediately after harvest of the major crops, including during transport and storage.

(f) Discuss methods to reduce existing toxin in crops involving improved farm management practise (crop rotation, weed control and irrigation, row spacing, etc.); cleaning; analysis and segregation; colour and UV sorting; roasting (for peanuts); and by chemical means, notably ammoniation to produce animal feeds.

The publication will also describe the choice of practical approaches to deal with mycotoxin contamination and will include discussion of risk perception, risk communication, and risk management. A set of illustrative case studies will review specific questions, past experience, and particular needs in relation to contamination of crops with mycotoxins encountered in developing countries.

## c.5. Advisory Groups convened related to the *IARC Monographs*, 2000-2005

**Biological agents.** In April 2001 an Advisory Group met in Annecy, France, to recommend biological agents and infectious processes that should be evaluated in future *IARC Monographs*. Based on this Advisory Group's recommendation, the topic of human papilloma viruses has been scheduled for evaluation in volume 90 in February 2005.

**Chemical agents and mixtures.** In February 2003 an Advisory Group of 12 scientists from 10 countries met in Lyon to develop a list of priorities for future evaluations of chemical agents. Prior to the meeting, nominations had been solicited from scientists at major national cancer research centres and at other national and international organizations. Nominations also had been solicited through the Internet. The Advisory Group identified more than 20 chemical agents, mixtures, or exposures as high priorities for future evaluation or re-evaluation.

Industrial chemicals: carbon black; 2-butoxyethanol and some related glycol ethers; formaldehyde and other aldehydes; lead and lead compounds; organic fibres (*para*-aramid, cellulose, polyvinyl alcohol); titanium dioxide.

Complex mixtures: bitumen; diesel engine exhaust and gasoline engine exhaust.

Lifestyle factors: alcoholic beverages; smokeless tobacco including moist oral snuff and nicotine-derived nitrosamines (NNN, NNK).

Pharmaceuticals: oral contraceptives and hormone replacement therapy; treatment regimens related to acid peptic disease; primidone (an anti-epileptic); salicylazosulfapyridine (an anti-inflammatory).

Food additives and contaminants: urethane (with alcoholic beverages); acrylamide.

Naturally occurring substances: nitrate, nitrite, and endogenous nitrosation; ptaquiloside and bracken fern.

Environmental contaminants: air pollution, including sulfur dioxide; microcystins and blue-green algae.

These will be considered for *IARC Monographs* to be developed during the period 2004-2008. (All three meetings scheduled for 2004 are devoted to evaluating agents and exposures on this list of high priorities.)

In some cases, the Advisory Group recognized that the topics were complex and would require a planning meeting before evaluations could be scheduled.

Air pollution: A meeting to plan a series of monographs on outdoor and indoor air pollution.

Nitrate, nitrite, and endogenous nitrosation: A meeting to define the scope of this monograph.

In addition, the Advisory Group also discussed several strategic issues. The result was a recommendation to convene broad, scientific meetings to discuss important strategic developments.

Meeting to consider revising the *Preamble*.
- — Discuss the relationship of IARC evaluations with those of other organizations.
- — Discuss relationship to public health principles and implementation.
- — Discuss development of mechanistic criteria for re-evaluating agents.
- — Describe procedure for selecting meeting participants.
- — Discuss bias and conflict of interests.
- — Discuss listing target sites, with a specific format, for Groups 1 and 2A.
- — Discuss limitations of exposure and risk statements.
- — Emphasize that new studies be sent to IARC after an evaluation.

Mechanisms of metal carcinogenesis, to discuss the potential for combined evaluation of some metals, in the absence of metal-specific data on carcinogenicity in epidemiological studies and in experimental animals.

Meeting to discuss quantitative risk assessment at IARC (perhaps as an adjunct programme separate from the *IARC Monographs*).

# d. RESEARCH DESIGN AND METHODS

The *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* is an international expert-consensus approach to carcinogen hazard identification. The long-term objective is to critically review and evaluate the published scientific evidence for all carcinogenic hazards to which humans are exposed. These include chemicals, complex mixtures, occupational exposures, lifestyle factors, and physical and biological agents. Each *IARC Monograph* is the product of an international, interdisciplinary working group of expert scientists, who meet for a week at IARC to finish their critical review of the scientific literature and to develop a consensus evaluation of evidence for each agent being considered.

The following description of the methods used in developing the *IARC Monographs* is organized according to the following topics: how agents are selected for evaluation (section d.1), how the working group is selected (section d.2), procedures for addressing conflicts of interests (section d.3), scientific literature considered by the working group (section d.4), the contents of each *IARC Monograph* (section d.5), how the *IARC Monographs* are developed (section d.6), and the different categories of participants at *IARC Monograph* meetings (section d.7).

## d.1. Selection of agents and exposures for evaluation

Agents are selected for evaluation based on (1) evidence of human exposure and (2) some evidence or suspicion of carcinogenicity. Agents and exposures can be re-evaluated if significant new data become available.

Periodically, IARC convenes Advisory Groups to advise on priorities for future evaluation or re-evaluation. These Advisory Groups consist of scientists from national and international health agencies and research institutions, striving to include scientists from many countries. Seeking such advice is meant to ensure that the *IARC Monographs* reflect the current state of scientific knowledge and remain relevant to national health agencies and to the research and public health communities. In the interim, additional guidance may be received from IARC's Scientific Council and IARC's Governing Council.

During each year of the project period, IARC will convene three separate working groups on different agents or exposures suspected of causing cancer in humans. (The NCI funding being requested will support two of these working groups each year.) The topics generally will be selected from the list of high priorities for future evaluations recommended by an *IARC Monographs* Advisory Group in February 2003. These are listed in section c.5. Among these, based on the availability of published data, the most urgent topics that may be scheduled for evaluation in 2005-2007 include:

- Diesel engine exhaust and gasoline engine exhaust.
- Bitumen.
- Carbon black, titanium dioxide, and ultra-fine particles
  (to follow the planning meeting on air pollution, see section c.5).
- Some indoor air pollutants
  (to follow the planning meeting on air pollution, see section c.5).
- Some biological agents, including ptaquiloside, bracken fern, microcystins, blue-green algae.
- Acrylamide.

Additional topics will be scheduled as significant new scientific information becomes available or as national health agencies identify an urgent public health need related to human cancer. In particular, the last in the series of four volumes on radiation, which will evaluate radiofrequency fields and radar, will be scheduled as soon as the major IARC study on cellular telephones is completed, perhaps in 2006.

## d.2. Selection of *IARC Monograph* working groups

Two principles govern the selection of *IARC Monograph* working groups: (1) to invite the best-qualified experts and (2) to avoid real or apparent conflicts of interests. Consideration is given also to demographic diversity. Members are chosen on the basis of knowledge and experience, which can come from research into the specific agents to be evaluated or from general experience in conducting or evaluating epidemiological or experimental studies.

The working groups are international in nature, with the typical working group consisting of approximately 20-25 expert scientists from 8-12 countries. To promote consistent evaluations and efficient meetings, some effort is made to include a few scientists who have had prior experience in the *IARC Monographs* Programme. These scientists are invited to serve as chair for the meeting as

a whole and for the subgroups on exposure, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data.

### d.3. Addressing conflicts of interests

All participants at *IARC Monograph* meetings must complete a *Declaration of Interests* that covers financial interests, employment interests, and research support *(WHO 2004)*. Potential working group members must complete their *Declaration* before a formal invitation can be extended. IARC supplements the information provided by potential working group members by asking the heads of the IARC epidemiology and laboratory groups, who themselves represent a broad cross-section of the international cancer research community, whether they know of any potential conflicts among the list of working group members being considered. In addition, "Acknowledgements" in published papers are reviewed and Internet searches are performed to acquire additional information pertinent to potential conflicts of interests.

IARC assesses this information to determine whether there is a real or apparent conflict that warrants some limitation on participation. In some cases, an expert with both critical knowledge and a conflicting interest can be invited to participate in a limited capacity, recused from serving as meeting chair or subgroup chair, from drafting text that discusses cancer data or that contributes to the evaluations, and from participating in evaluation discussions.

Each participant updates the *Declaration of Interests* at the opening of the meeting. Interests pertinent to the subject matter of the meeting are disclosed to the meeting participants and in the published *IARC Monograph*.

### d.4. Studies considered in the *IARC Monographs*

Each *IARC Monograph* considers all pertinent scientific articles published or accepted for publication. Reports and documents from national and international government agencies are considered if they are publicly available. Consensus reports in the published literature are also considered, subject to the same scrutiny as other articles, including consideration of the composition and balance of the panel that produced the consensus. Research that is not publicly available, including articles in preparation, is not considered.

IARC has extensive capabilities for retrieving any pertinent scientific paper. Since IARC was established in 1965, the IARC Library has subscribed to the major scientific journals related to cancer research. The use of on-line databases for rapid retrieval of scientific papers has been increasing. The IARC Library has agreements with other scientific libraries to facilitate timely retrieval of hard-to-obtain papers, often on an overnight basis. IARC's multilingual scientific staff can assist with on-the-spot translation and interpretation of papers published in virtually any language used for modern scientific publications.

### d.5. Contents of the *IARC Monographs*

The *IARC Monographs* are published as a series of *volumes*. Each volume contains one or more *Monographs*, which can cover either a single agent or a group of related agents. Each *Monograph* includes the following *sections*.

1. Exposure data
2. Studies of cancer in humans
3. Studies of cancer in experimental animals
4. Other data relevant to an evaluation of carcinogenicity and its mechanisms
5. Summary of data reported and evaluation
6. References

Sections 1-4 provide a *critical review* of the pertinent, peer-reviewed scientific literature. The critical review includes a brief, separate, factual synopsis of each study, summarizing the study's design and results. Following each study synopsis is a separate assessment by the working group of the study's strengths and limitations. These comments provide insight into the working group's reasoning by revealing the factors that might affect their interpretation or evaluation of that study.

Section 5 includes the *evaluation* developed by the working group. For each agent, one of the descriptors *sufficient evidence*, *limited evidence*, *inadequate evidence*, or *evidence suggesting lack of carcinogenicity* is chosen for the evidence of cancer in humans and for the evidence of cancer in experimental animals. These two partial evaluations are combined into a preliminary default evaluation that the agent is either:

*Carcinogenic to humans* (Group 1)
*Probably carcinogenic to humans* (Group 2A)
*Possibly carcinogenic to humans* (Group 2B)
*Not classifiable as to its carcinogenicity to humans* (Group 3)
*Probably not carcinogenic to humans* (Group 4)

Then the mechanistic and other relevant data are considered to determine whether the default evaluation should be modified, upwards or downwards. The final overall evaluation is a matter of scientific judgement, reflecting the weight of the evidence derived from studies in humans, studies in experimental animals, and from mechanistic and other relevant data. In considering the relevant scientific data, the working group may assign the agent to a higher or lower group than the default would indicate. This stepwise evaluation process provides insight into the working group's reasoning by revealing the weight given to each line of evidence.

The goal is a consensus evaluation by the working group. The evaluation includes a synopsis that discusses the rationale for the conclusions. If the working group is not able to reach consensus, the overall evaluation is determined by majority vote. In this case, the synopsis will present the differing scientific positions, the data that support or are inconsistent with each position, and the rationale for the majority position. The evaluation can identify research needed to test different hypotheses, especially those that have not received adequate attention.

The *Preamble* to the *IARC Monographs (IARC 2004)* opens each volume. The *Preamble* discusses the principles and procedures used in developing *IARC Monographs*, including the scientific criteria that guide the evaluations. The written *Preamble* promotes consistency of evaluations developed by different working groups on different topics.

## d.6. Development of the *IARC Monographs*: *IARC Monograph* meetings

Each *IARC Monograph* volume, which may contain one or more *Monographs*, is developed by a working group at an *IARC Monograph* meeting. Each year, IARC generally convenes three separate working groups on different topics.

Before each meeting, IARC staff searches and collects the pertinent scientific literature and makes it available to the working group. Working group members critically review the literature and write first drafts of sections 1-4 on exposure, cancer in humans, cancer in experimental animals, and other relevant data, respectively. IARC collects and formats these first drafts for review at the meeting.

The objectives of the meeting are review and consensus. The first days of the meeting are devoted to subgroup work. Four subgroups, each responsible for one section (see d.5), peer-review the individual members' drafts and develop a joint revised draft, then they write the summaries that become section 5. The subgroup on cancer in humans also proposes a partial evaluation of the human evidence on each agent, choosing one of the descriptors *sufficient evidence*, *limited evidence*, *inadequate evidence*, or *evidence suggesting lack of carcinogenicity*. Similarly, the subgroup on cancer in experimental animals proposes a partial evaluation of the animal evidence, choosing from the same set of descriptors. The subgroup on mechanistic and other relevant data characterizes the mechanistic evidence using terms such as "weak", "moderate", or "strong" and discusses whether the mechanisms of tumour formation in experimental animals are likely to be operative in humans.

The final days of the meeting see the subgroups come together in plenary session. The entire working group peer-reviews and reaches consensus on the critical reviews in sections 1-4 and discusses and reaches consensus on the summaries and partial evaluations proposed by the subgroups. Then the working group as a whole develops and reaches consensus on an overall evaluation of each agent as either *carcinogenic to humans*, *probably carcinogenic to humans*, *possibly carcinogenic to humans*, *not classifiable as to its carcinogenicity to humans*, or *probably not carcinogenic to humans*.

After the meeting, IARC scientists review all data cited by the working group in their final draft to ensure their scientific accuracy and clarity. IARC*Press* then publishes and distributes the finished volume.

## d.7. Categories of participants at *IARC Monograph* meetings

There are five categories of participants at *IARC Monograph* meetings: Working Group Members, Invited Specialists, Observers, Representatives of national and international health agencies, and the IARC Secretariat.

Working Group ***Members*** are responsible for the content of the *IARC Monographs*. They are expert scientists selected for their knowledge and experience. Most have published research papers on the specific agents being evaluated, others have general experience in conducting or evaluating epidemiological or experimental studies. Working Group Members are selected to chair the meeting and the subgroups and are the only participants who vote on the overall evaluations, if a vote is needed. Working Group Members are invited to serve in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated.

An ***Invited Specialist*** is an expert with critical knowledge and experience who is recused from certain activities because of a real or apparent conflict of interests. These activities include serving as meeting chair or subgroup chair, drafting text that discusses cancer data or contributes to the evaluations, and participating in evaluation discussions. The category of Invited Specialist is a new one, allowing the meeting to include the best-qualified experts without allowing conflicting interests to influence the critical activities of the meeting. Invited Specialists are available during the subgroup and plenary discussions to contribute the benefit of their knowledge and experience. Invited Specialists also agree to serve in their individual capacities as scientists and not as representatives of any organization or interest. In this way, the meeting can include the best-qualified experts, and the evaluations are developed and written by experts with no real or apparent conflict of interests.

Scientifically qualified ***Observers*** are welcome to attend *IARC Monograph* meetings. Consideration is given to admitting Observers from different constituencies with differing interests. The main role of Observers is one of transparency, to serve as sources of first-hand information from the meeting to the organizations that sponsor them. Observers can play a valuable role in ensuring that all published information and scientific perspectives are considered. Observers do not serve as meeting chair or subgroup chair, draft any part of an *IARC Monograph*, or participate in the evaluations. Observers are asked to agree to ethics guidelines that include a requirement not to lobby Working Group Members, both before and during the meeting. Working Group Members have assumed the responsibility to safeguard the integrity of their work by resisting any attempt at interference. To aid them in this responsibility, Working Group Members are reminded not to discuss the subject matter of the meeting with those outside the meeting and are asked to report all attempts at interference.

***Representatives*** of national and international health agencies (for example, the U.S. National Cancer Institute) often attend and provide independent assurance and guarantee of the integrity of the *IARC Monographs*. Representatives may participate in all discussions but do not vote on the evaluations.

The ***IARC Secretariat*** consists of scientists employed by IARC. The Secretariat hosts the meeting and drafts text or tables when requested by the Chair or subgroup Chair. To facilitate consistency across different *IARC Monographs*, the Secretariat serves as rapporteurs and answers questions about IARC principles and procedures discussed in the *Preamble*. The Secretariat participates in all discussions but does not vote on the evaluations, thus the evaluations are determined by Working Group Members only.

### d.8. Scientific meetings related to the *IARC Monographs*

As the importance of mechanistic understanding has continued to increase, the Programme has become an integrated and balanced activity that combines regular development of new *IARC Monographs* with special scientific workshops on pertinent issues involving mechanisms of carcinogenesis. Like the *IARC Monographs*, the workshops bring together international, interdisciplinary working groups of expert scientists. Each workshop seeks to determine whether scientific knowledge has accumulated to develop a consensus in a particular area. The results of these workshops are published as IARC Scientific Publications and distributed to the scientific research community.

(NCI funds will not be used for these scientific workshops; they are mentioned here for the sake of completeness in describing the overall Programme.)

### d.9. Advisory Group meetings related to the *IARC Monographs*

To ensure that the *IARC Monographs* remain relevant to the needs of government health agencies and the scientific research community, the Programme periodically seeks advice from scientists at national health agencies and leading research institutions. Advisory Groups have been convened approximately every 5 years (1979, 1984, 1989, 1993, 1998, 2003) to recommend chemical agents for evaluation or re-evaluation. In addition, Advisory Groups have been convened to recommend physical agents (1998) and biological agents (2001) for future evaluation. The Advisory Groups also provide useful information about major studies in progress that, when published, will make a new evaluation timely.

A particularly important Advisory Group that will be convened soon is a meeting to discuss broad, strategic issues and to consider revisions to the *Preamble*, which discusses the principles and procedures used in developing the *IARC Monographs* (see section c.5).

(NCI funds will not be used for the these Advisory Group meetings; they are mentioned here for the sake of completeness in describing the overall Programme.)

### d.10. Plan for data sharing

Wide dissemination of the information developed in the *IARC Monographs* is an important objective. Each volume is printed in 2500 or more copies, many of which are distributed free of charge to libraries, government agencies, and interested scientists. The U.S. National Cancer Institute manages distribution throughout the United States and Canada, and IARC manages distribution to the rest of the world. Individual copies can also be purchased from IARC*Press* (Lyon, France) or the World Health Organization Distribution and Sales Service (Geneva, Switzerland).

Lists of all evaluations developed to date, summaries of each *IARC Monograph*, and a discussion of the principles used in developing the evaluations are available through the Programme's website (http://monographs.iarc.fr). As new evaluations are developed, the summary is placed on the website within a few weeks. New evaluations of great importance or widespread interest are announced immediately through a press release or press conference.

To make the *IARC Monographs* even more accessible, a complete and searchable electronic version of all volumes published to date is available, both in CD-ROM format and on-line through the Internet. These have been updated yearly and are made available by subscription through GMA Industries, Inc. (Annapolis, Maryland) and through IARC*Press*.

## e. HUMAN SUBJECTS RESEARCH – Not applicable

## f. VERTEBRATE ANIMALS – Not applicable

## g. LITERATURE CITED

IARC (1972) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, vol 1. Lyon: IARC*Press*.

IARC (1979) Chemicals and industrial processes associated with cancer in humans: IARC Monographs , Volumes 1 to 20. *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans,* suppl 1. Lyon: IARC*Press*.

IARC (1987) Overall evaluations of carcinogenicity: An updating of *IARC Monographs* Volumes 1 to 42. *IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans,* suppl 7. Lyon: IARC*Press*.

IARC (2003) World Cancer Report. Eds: Stewart BW, Kleihues P. Lyon: IARC*Press*.

IARC (2004) *Preamble* to the *IARC Monographs*. Lyon France: International Agency for Research on Cancer; http://monographs.iarc.fr.

NTP (2002) *Report on Carcinogens*, tenth edition. Washington DC: U.S. Department of Health and Human Services; http://ntp-server.niehs.nih.gov.

WHO (2004) Declaration of interests for WHO experts. Geneva Switzerland: World health Organization; http://www.who.int/pcs/ra_site/docs/Declaration_of_interest.pdf.

**Recent *IARC Monographs***

IARC (2000) Some industrial chemicals. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* vol 77. Lyon: IARC*Press*.

IARC (2001) Ionizing radiation, part 2: Some internally deposited radionuclides. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, vol 78. Lyon: IARC*Press*.

IARC (2001) Some thyrotropic agents. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* vol 79. Lyon: IARC*Press*.

IARC (2002) Nonionizing radiation, part 1: Static and extremely low-frequency (ELF) electric and magnetic fields. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* vol 80. Lyon: IARC*Press*.

IARC (2002) Man-made vitreous fibres. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* vol 81. Lyon: IARC*Press*.

IARC (2002) Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* vol 82. Lyon: IARC*Press*.

IARC (2004) Tobacco smoke and involuntary smoking. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* vol 83. Lyon: IARC*Press*.

IARC (in preparation) Some drinking-water disinfectants and contaminants, including arsenic. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* vol 84.

IARC (in preparation) Betel-quid and areca-nut chewing and some related nitrosamines. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* vol 85.

IARC (in preparation) Cobalt in hard-metals and cobalt sulfate, gallium arsenide, indium phosphide and vanadium pentoxide. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* vol 86.

IARC (in preparation) Inorganic and organic lead compounds. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans,* vol 87.

**Related IARC Scientific Publications and Technical Reports**

IARC (1992) Mechanisms of carcinogenesis in risk identification. IARC Scientific Publication 116. Lyon: IARC*Press*.

IARC (1995) Peroxisome proliferation and its role in carcinogenesis. IARC Technical Report 24. Lyon: IARC*Press*.

IARC (1996) Mechanisms of fibre carcinogenesis. IARC Scientific Publication 140. Lyon: IARC*Press*.

IARC (1999) The use of short- and medium-term testes for carcinogens and data on genetic effects in carcinogenic hazard evaluation. IARC Scientific Publication 146. Lyon: IARC*Press*.

IARC (1999) Species differences in thyroid, kidney and urinary bladder carcinogenesis. IARC Scientific Publication 147. Lyon: IARC*Press*.

IARC (2003) Predictive value of rodent forestomach and gastric neuroendocrine tumours in evaluating carcinogenic risks to humans. IARC Technical Report 39. Lyon: IARC*Press*.

IARC (2004) Mechanisms of carcinogenesis: Contributions of molecular epidemiology. IARC Scientific Publication 157. Lyon: IARC*Press*.

IARC (in preparation) Management of mycotoxins in foods and feeds for improving public health. IARC Scientific Publication 158.

***IARC Monographs* Advisory Group Reports**

IARC (1998) Report of an ad-hoc *IARC Monographs* Advisory Group on physical agents. IARC internal report 98/002; http://monographs.iarc.fr.

IARC (2003) Report of an *ad-hoc IARC Monographs* Advisory Group on priorities for future evaluations. IARC internal report 03/001; http://monographs.iarc.fr.

## h. CONSORTIUM/CONTRACTUAL ARRANGEMENTS - None

## i. CONSULTANTS – None anticipated

Principal Investigator/Program Director (last, First, Middle): Cogliano, Vincent James

## CHECKLIST

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

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

☐ SBIR Phase I ☐ SBIR Phase II: SBIR Phase I Grant No. _____ ☐ SBIR Fast Track

☐ STTR Phase I ☐ STTR Phase II: STTR Phase I Grant No. _____ ☐ STTR Fast Track

☐ REVISION of application number: _____

*(This application replaces a prior unfunded version of a new, competing continuation, or supplemental application.)*

☒ COMPETING CONTINUATION of grant number: CA33193-24

*(This application is to extend a funded grant beyond its current project period.)*

INVENTIONS AND PATENTS *(Competing continuation appl. and Phase II only)*

☐ No ☐ Previously reported

☐ SUPPLEMENT to grant number: _____ ☐ Yes. If "Yes," ☐ Not previously reported

*(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: _____

☒ FOREIGN application or significant foreign component.

**1. PROGRAM INCOME** ***(See instructions.)***

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

| Budget Period | Anticipated Amount | Source(s) |
|---|---|---|
| | | |

**2. ASSURANCES/CERTIFICATIONS** ***(See instructions.)***

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 are provided in Section III. If unable to certify compliance, where applicable, provide an explanation and place it after this page.

•Human Subjects; •Research Using Human Embryonic Stem Cells• •Research on Transplantation of Human Fetal Tissue •Women and Minority Inclusion Policy •Inclusion of Children Policy• Vertebrate Animals• •Debarment and Suspension; •Drug- Free Workplace *(applicable to new [Type 1] or revised [Type 1] applications only)*; •Lobbying; •Non-Delinquency on 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); •Recombinant DNA and Human Gene Transfer Research; •Financial Conflict of Interest (except Phase I SBIR/STTR) •STTR ONLY: Certification of Research Institution Participation.

**3. FACILITIES AND ADMINSTRATIVE COSTS (F&A)/ INDIRECT COSTS.** See specific instructions.

☐ DHHS Agreement dated: _____ ☐ No Facilities And Administrative Costs Requested.

☐ DHHS Agreement being negotiated with _____ Regional Office.

☒ No DHHS Agreement, but rate established with J. W. Berry, Accountant, DHHS Date October 18, 1983

CALCULATION* *(The entire grant application, including the Checklist, will be reproduced and provided to peer reviewers as confidential information.)*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| a. Initial budget period: | Amount of base $ | 760,564 | x Rate applied | 13.00 | % = F&A costs | $ | 98,873 |
| b. 02 year | Amount of base $ | (b)(5) | x Rate applied | (b)(5) | % = F&A costs | $ | (b)(5) |
| c. 03 year | Amount of base $ | | x Rate applied | | % = F&A costs | $ | |
| d. 04 year | Amount of base $ | | x Rate applied | | % = F&A costs | $ | |
| e. 05 year | Amount of base $ | | x Rate applied | | % = F&A costs | $ | |
| | | | | | TOTAL F&A Costs | $ | |

*Check appropriate box(es):

☐ Salary and wages base ☐ Modified total direct cost base ☒ Other base *(Explain)*

☐ Off-site, other special rate, or more than one rate involved *(Explain)*

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

Rate applied to total direct costs

**4. SMOKE-FREE WORKPLACE** ☒ Yes ☐ No *(The response to this question has no impact on the review or funding of this application.)*