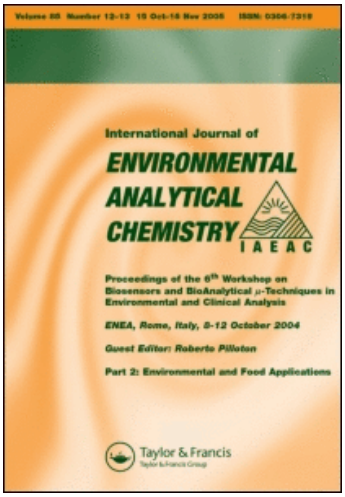

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An IARC Manual Series Aimed at Assisting Cancer Epidemiology and Prevention. "Environmental Carcinogens: Selected Methods of Analysis"

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An IARC Manual Series Aimed at Assisting Cancer Epidemiology and Prevention. "Environmental Carcinogens: Selected Methods of Analysis"†

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Since 1975, the IARC has been preparing a series of volumes entitled "Environmental Carcinogens: Selected Methods of Analysis" (IARC Manual series) of which the purposes are to assist analysts, epidemiologists and regulatory authorities in planning or performing exposure measurements that are truly comparable between different studies. The Manual series provides expert information within each volume on multimedia sampling, methods of analyses and some background of epidemiology, metabolism, use/occurrence for a group of known or suspect carcinogens. So far, eleven volumes have been published or are in preparation on the following subjects: (1) *N*-nitrosamines, (2) vinyl chloride, (3) PAH, (4) aromatic amines, (5) mycotoxins, (6) *N*-nitroso compounds, (7) volatile halogenated hydrocarbons, (8) metals, (9) passive smoking, (10) benzene and alkylated benzenes, (11) dioxins, PCDFs and PCBs.

The presentation will discuss needs and priorities for use of analytical chemistry in estimating exposures of apparently greatest relevance to cancer causation, i.e. the

†Presented at the 16th Symposium on the Analytical Chemistry of Pollutants, Lausanne, Switzerland, March 17–19, 1986.

approach to developing this series. Indications from epidemiology, evaluations of carcinogenic risk to humans, and recent developments in total exposure assessment are that new methods and matrices need more emphasis, e.g. as with biochemical dosimetry, exhaled breath, and in indoor air.

INTRODUCTION

Cancer exacts substantial costs in treatment and preventative measures on a world-wide scale,[1] as well as causing immeasurable human suffering. Taken together it has been inferred,[2] that environmental causes contribute to the majority of cancers and this emphasises the potential benefits of environmental detection and preventative measures. While some progress has been made in associating some agents, e.g., tobacco, alcohol, asbestos, with cause or risk, there is much more progress needed. Among the various goals in the whole field of environmental research, the approximately 20% cancer mortality in developed countries therefore raises cancer-related aspects to the highest priority.

The International Agency for Research on Cancer aims at these aspects by undertaking an extensive programme for cancer epidemiology, experimental research and education, part of which is to publish the title series that includes not only selected sampling/analysis procedures but also provides the substance-related background of epidemiology, use/occurrence and special features aimed at exposure. Expertly selected methods are needed to give best possible data and also permit comparisons between different studies. Since sampling/analysis in collaboration with biological testing and epidemiology appears to be a potentially most fruitful future direction, the purpose of this presentation is to briefly describe background development of this series and to discuss some critical directions for analytical work.

THE CANCER PROBLEM AND ENVIRONMENTAL INFLUENCES

Descriptive epidemiology has shown that the incidences of cancers vary greatly not only with country, culture and climate[3] but also with time and in otherwise homogeneous regions for which many

studies attempt to attribute cause. A detailed study[2] to estimate potentially avoidable cancer in the USA found that 85% of cancers might arise from environmental causes and that, of those avoidable, about half may be attributable to dietary influences. Earlier, Higginson and Muir[4] estimated that the total proportion of cancers in Birmingham, UK and Bombay, India that could be attributed to environmental factors were 85% and 79% respectively. However, the multi-stage and multi-factorial nature of cancer has been experimentally demonstrated with many substances found in the environment that can act as initiators,[5] promoters[6] or modifiers of such processes. Nevertheless, a powerful approach is the comparison of environmental exposures in populations at greatly different cancer risk; variation in cancer risk is 300-fold for cancers of the oesophagus and the least variation is 7-fold for cancers of the breast, bladder or ovaries.

As evaluated in the IARC Monograph series on the Evaluation of Carcinogenic Risk of Chemicals to Humans,[7,8] many substances, complex mixtures, or occupational exposures are known to be carcinogenic to humans at differing levels of certainty (Table I). Most striking is that the numbers of substances, associated in some manner with carcinogenic risk, increase sharply with the lessening degree of certainty to be involved in human cancer; often the missing

TABLE I

Degree of certainty in classifying chemicals, groups of chemicals, complex mixtures or occupational exposures as being causally related to human cancer[8]

Degree of certainty[a]	Number of chemicals, complex mixtures or occupational exposures
A. As human carcinogen	
Group 1 (Sufficient evidence)	39
Group 2A (Probably carcinogenic)	17
Group 2B (Probably carcinogenic)	51
Group 3 (Unclassifiable)	69
B. Sufficient evidence in experimental animals, no human data	214

[a]As evaluated by international working groups in vols 1–38 of IARC Monograph series.

information is on human exposure which frequently occurred many years ago or for which there is absolutely no epidemiologic data in relation to some potent mutagens/animal carcinogens. Given the difficulties created by both the multi-stage, multi-factorial nature of cancer and the dependence of epidemiological techniques on absence of confounders, accurate recall and sufficient statistical power, it is now particularly appreciated that there is a need for use of appropriate sampling/analysis methods in biochemical epidemiology[9,10] and exposure assessment.

Especially appropriate goals for environmental analysis are the identification of hitherto-unknown genotoxic agents, and the exploration of relatively uninvestigated matrices or body fluids using short-term tests for DNA-damaging agents and complementary development of biochemical dosimetry. Listed in Table II are some recent examples that widened the perspectives of environmental cancer research. Carefully chosen strategies may help resolve the present scenario where, simultaneously, there are (a) many animal carcinogens and mutagens as yet unassociated with human cancers (Table I), (b) possible human carcinogens for which definite exposure

TABLE II

Examples of recently discovered mutagens/carcinogens or indications of substances in recently investigated body fluids that may be associated with human cancer

Substance	Exposure or body fluid	Ref.
Protein pyrolysates from cooking	Diet	11
Opium pyrolysates	Narcotic use	12
Nitro-PAH	Diesel exhaust	13
Nitro-PAH	Photocopy toners	14
Many volatile carcinogens	Indoor air	15
Methylglyoxal	Coffee	16
Radon and radon daughters	Indoor air	17
Side-stream cigarette smoke	Indoor air	18, 19
Aquilide A	Bracken fern	20
Dioxins, PCBs	Human milk	21
Nitrosoproline	Urine	21, 22
Fecapentaenes	Faeces	23
Many volatile carcinogens	Breath	24

data is lacking (Table I) and, of course, (c) the large majority of human cancers as yet unassociated with any specific cause.[1,2,4]

THE IARC MANUAL SERIES

Consequent upon both the IARC Monograph evaluations of published data and the aforementioned epidemiological approaches, is the need to promote environmental studies that can most efficiently yield exposure data comparable with other studies; the IARC Manual series has this aim not only for analysts but also epidemiologists and regulators who are frequently responsible for designing or commissioning such work. The list of volumes published or in preparation (Table III) shows a wide range of both substances and matrices which have already been covered, and that both environmental analysis and biological monitoring methods are being presented. Each volume is chosen by an eminent Editorial Board and then designed, authored and reviewed by experts in the specific area, with special attention given to providing complete and clear experimental procedures. Carcinogenic risk factors are included irrespective of degree of certainty for humans or their role in the multi-stage process.

The design of future volumes incorporates sampling/analytical procedures for recently-investigated sources or recently-identified mutagens/carcinogens (including some examples from Table II). All analytical sciences are covered and future volumes will include biochemical dosimetric procedures, for example, ultra-sensitive methods[25] able to detect a few DNA-adducts per cell in human tissue. The presently-available volumes have been well received in developing countries which not only lack resources to develop methods but often have substantially different patterns of cancer.[26]

EXPOSURE ASSESSMENT, BIOLOGICAL MONITORING AND MOLECULAR EPIDEMIOLOGY

Probably the most direct and appropriate approach to exposure assessment is via biological monitoring since, by integrating exposures from all sources and via all routes, it precludes many of the

TABLE III

IARC manual series[a]					
Volume number	Subject (short title)	Matrices covered[b]	Number of methods described	Chairman Review Board	Publication appeared
1.	Nitrosamines	F	11	R. Preussmann	1978
2.	Vinyl chloride	F, A, W, CP	12	D. C. M. Squirrell	1978
3.	PAH	F, A, W, SM, CP	8	P. Bogovski	1979
4.	Aromatic amines	F, A, BF, CP	17	L. Fishbein	1981
5.	Mycotoxins	F	20	L. Stoloff	1982
6.	*N*-nitroso compounds	F, A, W, BF, SM, CP	28	R. Preussmann	1983
7.	Halogenated hydrocarbons	F, A, W, BF, CP	30	L. Fishbein	1985
8.	Metals; As, Be, Cd, Cr, Ni, Pb, Se, Zn	F, A, W, BF	29	P. Schuller	1986
9.	Passive smoking	A, BF, SM	19	D. Hoffmann	1986
10.	Benzene, etc.	A, BF	9	L. Fishbein	1987?
11.	Dioxins, etc.	F, SM, BF, CP, S	17	C. Rappe	1988?
12.	Indoor air	A, SM			
13.	Biological monitoring	BF			

[a]For details, contact the International Agency for Research on Cancer, 150 cours Albert Thomas, 69732 Lyon Cedex 08, France.
[b]F = food; A = air; W = water; BF = biological fluids; CP = commercial products; S = soils; SM = smoke and exhausts.

unsubstantiatable assumptions in extrapolating from environmental point concentrations. Biological monitoring is in rapid development,[9,27] and is increasingly emphasised in IARC Manual volumes; however, for trace-level specific analyses of carcinogen metabolities or indicators of DNA damage, it often makes demands on analytical sciences that are unfulfillable at present. By contrast, the sensitivity of existing methods for many established carcinogens *in the environment* (Table IV) is generally adequate, and scarce resources should not be diverted in attempts to lower environmental detection levels. Table IV also exemplifies carcinogens for which sensitive biological monitoring has eventually become possible. All the examples quoted in Table II relate to environmental exposures and for some of them it may never be practicable to use biological monitoring although, for some endogenously-formed substances like fecapentaenes and *N*-nitroso compounds, the internal environment of the human gastro-intestinal tract is all-important.

Thus, analytical measurement procedures should have a critical role in molecular epidemiology and exposure regulation, as well as environmental monitoring as summarized in Figure 1. The importance of correct study design in relation to exposure assessment is emphasized by the over-abundance for substances listed in Table IV of point concentration data in concert with sometimes untenable extrapolations forced on those assessing population-wide exposures. Recent work on total exposure assessment,[15] on air pollution,[31] on *N*-nitroso compound exposure[32] illustrates how erroneous have been old assumptions on exposure sources from which vast numbers of analytical data have since been generated. Measurement of the biologically effective doses of carcinogenic substances being the real

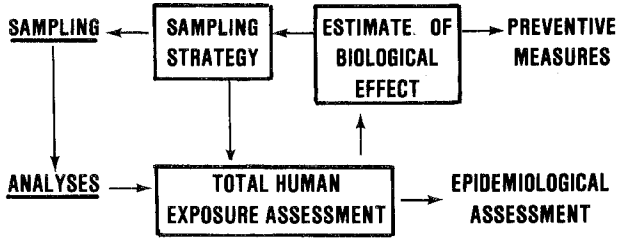

FIGURE 1 Activity network common to environmental analysis, molecular epidemiology and exposure regulation.

TABLE VI

Analytical techniques and their sensitivities in relation to estimated (inadvertent) exposures for some human and animal carcinogens

Substances and IARC classification as carcinogens	Estimated exposures[d] (μg/day) and sources		Environmental samples		Human Samples	
	General population	Most exposed group	Analytical technique commonly used	Sensitivity (matrix)	Technique	Sensitivity (ng/ml) (matrix)
Asbestos[a]	0.01–0.1; air	1,000; work-place	Microscopy	1 fibre/m^3 air	Not available	
Aflatoxins[b]	0.01; food	10; food	Thin layer chromatography fluorescence	2 μg/kg food	Enzyme immunoassay	0.1[e] urine
Arsenic[a] compounds	60; food	500; work-place	Spectrophotometry	0.8 μg/kg food	Spectrophotometry	100 (urine)
Benzene[a]	300; tobacco, air	20,000; work-place	Gas chromatography (GC)	0.3 μg/m^3	Mass spectrometry	—[e] (breath)

Cadmium[b] compounds	14–17; food, tobacco	200; work-place	Atomic absorption spectrophotometry (AA)	2 μg/kg food	AA	0.1 (urine)
N-nitroso[c] compounds	4; food, tobacco	600; chewed tobacco	GC-Thermal Energy Analyser (GC-TEA)	0.1 μg/kg food	GC-TEA	0.5 urine
Formaldehyde[b]	1,100; air	10,000; work-place	Spectrophotometry	120 μg/m^3 air	Not available	
Tobacco smoke[a]	50,000; tobacco	$>10^6$; tobacco	—	—	Radioimmunoassay (cotinine)	0.1 urine
PAH[b,c]	4; food, tobacco	50; work-place	GC	0.05 μg/kg food	RIA	0.1[e] urine
Benzidine[a]	—	—	GC	3 μg/kg food	GC	1 urine

[a]Human carcinogen.

[b]Probable human carcinogen.

[c]Many animal carcinogens included in this group of substances.

[d]Estimates are for Finnish total population (including smokers) and work-places[28] except for elevated aflatoxin exposures,[29] elevated *N*-nitroso compounds from tobacco chewing,[30] and elevated tobacco tar from heavy smoking (60 cig./day) of high yield (20 mg tar/cig.) cigarettes.

[e]Recently described in literature and thus regarded as under development at time of writing.

aim of environmental analysis for carcinogenic risk factors, requires (a) interaction with biological tests,[33] (b) more detailed knowledge of "normal" background levels to permit contrast between different cancer cohorts, (c) an appreciation of the likely range of effect that an environmental level has on the target organ/macromolecule.

SUMMARY

Rapid development of analytical measurements on the external or internal human environment, as part of biochemical epidemiology or exposure regulation, appears to be an indispensable part of cancer etiology and control. The IARC Manual series is intended to be as effective as possible and all suggestions are welcome in development of this programme.

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