COMMENTARY

Appropriate Models and an Understanding of Carcinogenic Mechanisms - Requirements for Hazard Risk Assessment

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Abstract

Given the immense variety of compounds developed for introduction into the human environment, appropriate carcinogen risk assessment is essential. One of the responsible international bodies recognized as providing a lead in this endeavour is the International Agency for Research on Cancer (IARC), primarily through the Monographs on the Evaluation of Carcinogenic Risks to Humans. However, serious allegations have recently been made that industry now has undue influence on the decisions of the IARC Workshops as to category assignment, especially concerning down-grading of risk. The contention is that too much stress is placed on mechanistic considerations which have not been sufficiently validated. Since avoidance of carcinogens in our environment is clearly of prime importance to cancer prevention, open discussion of how they should be identified is of essential significance to the APOCP. Clearly, decisions should be based solely on scientific evidence and there should be no place for politics or polemic. We have therefore looked, in what we hope is a dispassionate fashion, at the arguments offered in the recent literature, while admitting to a bias towards taking into account all the available knowledge on mechanisms of action of carcinogens and modulating agents. As scientists, generation of an understanding of this area is one of the main reasons why we receive our salaries. To blindly argue that carcinogenicity, for example at high dose in one strain of experimental animal, necessarily implies human risk at normal levels of exposure is obviously untenable. At the same time, precipitous conclusions regarding species-specific mechanisms must naturally be avoided. Both academic and industrial researchers need to apply a balanced judgement and to simply imply that any association with industrial concerns is likely to lead to irresponsible behaviour to the detriment of public health is not tenable. With regard to regulatory decision making, we should be concentrating more attention on mechanisms, rather than less, especially in light of recent findings pointing to hormesis at low doses of carcinogens, which will inevitably generate heated discussion and the charge of bias in favour of industry. The onus is on all members of the scientific community to impartially view all the epidemiological and experimental data which are available in decision-making.

Key Words: Animal models - mechanistic analyses - surrogate markers - hazard risk - hormesis

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IARC Monographs

The importance of the environment and the chemical compounds to which human beings are exposed for cancer development is widely recognized (Doll, 1988) and the need for strict control of agents presenting as carcinogenic risk factors, whether they operate by genotoxic or epigenetic mechanisms, is reflected in the complex regulatory systems which have become established in the developed world. A number of national and international bodies are now active in assessment, including the IARC which has been active in producing Monographs as the result of working group discussion since 1972. A total of 84 volumes have so far been published, with assessment into categories 1-4 (see Table 1) on the basis of biological and epidemiological data which have been published in the openly available peer-reviewed literature. As stressed in the pramble to each of the Monographs, unpublished sources of information may only be used for the sections on chemical and physical properties, on analysis, production and use or occurrence. However, serious allegations have recently been made that category assessment by IARC is excessively influenced by

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Table 1. IARC Monograph Group Categories

1: The agent (mixture) is carcinogenic to humans
2A: The agent is probably carcinogenic to humans
2B: The agent is possibly carcinogenic to humans
3: The agent is not classifiable as to its carcinogenicity to humans
4: The agent is probably not carcinogenic to humans

industry, primarily by Tomatis and Huff (Tomatis, 2002; Huff, 2002) and in a letter addressed to Secretary-General Brundtland of the WHO by a number of concerned individuals with Castleman as their spokesman. The criticism leveled is that there might be a bias towards industrial benefit to the cost of human safety. This issue is clearly important and has received a good deal of press coverage, for example in the Lancet (The Lancet, 2002), Lancet Oncology (Burton, 2003) and OnEarth, the journal of the Natural Resources Defense Council (NRDC) (Luoma 2002). The Director of IARC, Paul Kleihues, has strongly refuted the allegations and an independent consultant commissioned to investigate the disclosure of interest procedure for workshop participants at IARC has confirmed proper use (Burton, 2003). While Huff has expressed a personal view that scientists aligned with industry now account for a disproportionate number of workshop participants, as compared to the period when he was head of the unit responsible (see Table 2), it could be argued that his own figures point to an overwhelming bias during his period of tenure towards those with a 'bias' towards public health. On the other hand, the balance of observers with no voting rights was more equitable. It should be stressed in this context that voting members actually employed by industry account for only a very small number of the voting participants at any of the meetings and that they are never appointed to act as chairpersons.

Table 2. Alignment of Participants at IARC Monographs (percentages after Huff, 2002)

	Voting Members			Observers		
	PH	In	Un	PH	In	Un
Vols 15-22	77	9	14	35	49	16
Vols 62-79*	29	32	38	12	69	20

PH, public health; In, industry; Un, unknown; * Some not included

Table 3. Change in IARC Grading (after Huff, 2002)

	Tomatis et al	Rice et al
Upgraded		
Group 2A to 1	1	1
Group 2B to 2A	33	5
Group 3 to 2B	4	2
	38	8
Downgraded		
Group 2A to 2B	0	1
Group 2B to 3	0	11
	0	12

While there is no doubt about the sincerity of the views expressed by Huff and Tomatis, it might be pertinent here to state that non-partisan perusal of the numbers of compounds upgraded and downgraded during the different periods might in fact lead to the conclusion that a bias existed against appraisal of data pointing to a reduced risk during the previous era (see Table 3). What is the statistical likelihood of 38 compounds necessitating upgrading and zero downgrading, under the circumstances appertaining? Again, it should be stressed that there was no example of downgrading from Group 1 with sufficient evidence of carcinogenicity in humans.

We need to devote particular attention to the major criticism regarding conclusion drawn of reduced risk potential on the basis of mechanisms that might not be expected to operate in humans. This was in fact the subject of a workshop at the recent Society of Toxicology Meeting, entitled 'Mode of Action in Assessing Human Relevance of Animal Tumors: Improving the Framework for Analysis'. Unequivocal identification of mechanisms is naturally very difficult, even under the controlled conditions of animal experimentation, so that 100% certitude in determining operation/non-operation in the human case is impossible. Therefore we should avoid a cavalier attitude, either in favour or against, and look for the most likely scenario. In essence this is what the IARC workshops are set up to do, using the 'best' expertise available. It should be borne in mind that the decisions made will have a bearing on the reactions of the regulatory authorities, for example in the US, Europe and Japan, who have to make the final decisions as to whether compounds should be authorized for use. To generally imply that individual scientists may not be responsible in their behaviour and that industry has no wish to play a positive role in maintaining a safe and productive environment is a very serious charge indeed.

As stated above, we are ourselves 'biased' towards mechanisms as important determinants and essentially concur with the judgements expressed in the Monographs. This is only one example, but to respond (Huff, 2002) to the careful and detailed arguments a-d) from the results reviewed in Lyon for atrazine in volume 73 by statements like'is not accurate', 'make little relevant sense', 'has little meaning' and citing a paper not available in the literature cannot be regarded as appropriate if the aim is to promote debate. Our own feeling is that a better answer is constructive criticism, leading to targeted research to resolve uncertainties where at all possible, focusing on molecular mechanisms.

Models for Carcinogenicity Testing

While traditional long-term test regimens using rodents to detect carcinogenicity are still regarded as the gold standard for risk assessment purposes, they are expensive in terms of financial resources. Moreover, the use of maximum tolerated doses may provide information that can not be extrapolated to the human situation. This is the background to the high priority presently being devoted to establishment of effective alternative animal models which will allow development of more evidence-based approaches. Their utility for carcinogenicity assessment was, in fact, one of the main themes at the Fourth International Conference on Harmonisation, attended by an expert working group responsible for drawing up guidlelines for the regulatory bodies of the European Union, Japan and the USA. It was also the subject of extensive discussion at a special meeting at the International Agency for Research on Cancer in 1997. In vivo models and the end-point parameters which are applied must take into account the large body of information available on mechanisms underlying tumor development, so that the aim of achieving the most reliable results in the shortest period of time may be realised. One focus of attention is on medium-term models which provide results correlating with long-term findings (Ogiso et al., 1985; Hagiwara et al., 1993; Ito et al., 1997) and for which the applicability of surrogate markers (Schatzkin et al., 1996; Einspahr et al., 1997) has been argued (Moore et al., 1998).

The fact that approximately 60% of compounds demonstrating carcinogenicity in long term tests include the liver among their target tissues is of particular significance for risk assessment (IARC Monographs). In particular, the finding that expression of the glutathione S-transferase placental form (GST-P, GST-7-7) goes from essentially nil to a large proportion of the protein production of the cell from very early stages after carcinogen exposure in putative initiated hepatocytes and minifoci (Moore et al., 1987), means that quantitation is simplified, even single altered cells being reliably identifiable (see Figure 1). This has facilitated research into hepatocarcinogen dose dependence, using both genotoxic and non-genotoxic examples (see review by Tsuda et al., 2003). It has thereby been established that hormetic effects are exerted at very low doses by α-BHC, phenobarbital and DDT (Kitano et al., 1998; Maruda et al., 2001; Sukata et al., 2002), with reduction rather than increase in development of preneoplastic foci, in line with the hypothesis of Calabrese and Baldwin (2003), recently proposed in a commentary article in Nature. Hormesis is indeed a well established phenomenon (Calabrese, 2002), and its significance for radiation risk assessment has already been emphasized (Parsons, 2002).

As argued by Calabrese and Baldwin (2003) and Teeguarden et al (2000), the hormetic perspective turns upside down the strategies presently used for risk communication to the public, and if accepted would require

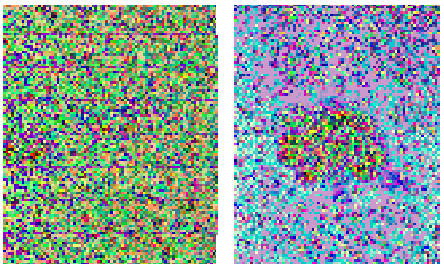

Figure 1. GST-P Positive Foci in Rat Liver

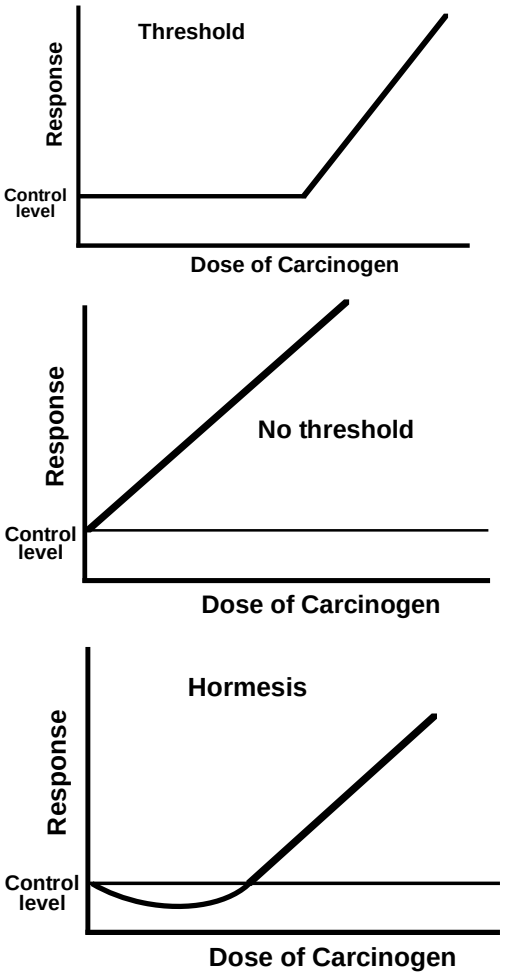

Figure 2. Hypothetical Curves Depicting Threshold, Linear Non-threshold and Hormetic Dose-response Models

a major paradigm shift. This will certainly be resisted by many regulatory and public health authorities as being pro-industry and detrimental to the human environment. The debate about misconceptions as to the importance of environmental pollution will no doubt continue (see Ames and Gold, 1997; Tomatis et al., 2001), with repeated warnings as to the untoward influence of bodies sponsored by industry on international agencies (Watterson, 2001; Ashford et al., 2002), and this is as it should be. However, to repudiate the benefits of mechanistic insights is not a stance that recommends itself to impartial scientists. New strategies for

establishing modes of action as a basis for risk assessment (Cohen and Ellwein, 1991; Butterworth et al., 1995) should continue to be our aim.

Conflict of Interest Statement

None of the authors of this commentary has any personal financial link with any industry which would 'benefit' from relaxation of risk assessment standards and all are in complete agreement with the aim of maintaining the objectivity and credibility of the Monographs Program of the IARC .

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References

Ames BN, Gold LS (1997). Environmental pollution, pesticides, and the prevention of cancer: misconceptions. *FASEB J*, **11**, 1041-52.

Ashford NA, Castleman B, Frank AL, et al (2002). The International Commission on Occupational Health (ICOH) and its influence on international organizations. *Int J Occup Environ Health*, **8**, 156-62.

Burton A (2003) Is industry influencing IARC to downgrade carcinogens? *Lancet Oncol*, **4**, 4.

Butterworth BE, Conolly RB, Morgan KT (1995). A strategy for establishing mode of action of chemical carcinogens as a guide for approaches to risk assessments. *Cancer Lett*, **93**, 129-46.

Calabrese EJ (2002). Hormesis: changing view of the dose-response, a personal account of the history and current status. *Mutat Res*, **511**, 181-9.

Calabrese EJ, Baldwin LA (2003). Toxicology rethinks its central belief. Hormesis demands a reappraisal of the way risks are assessed. *Nature*, **421**, 691-2.

Cohen S, Ellwein LB (1991). Genetic errors, cell proliferation, and carcinogenesis. *Cancer Res*, **51**, 6493-6.

Doll R (1988). Epidemiology and the prevention of cancer: some recent developments. *J Cancer Res Clin Oncol*, **114**, 447-58.

Einspahr JG, Alberts DS, Gapstur SM, et al (1997). Surrogate end-point markers as measures of colon cancer risk and their use in cancer chemoprevention trials. *Cancer Epidemiol Biomarkers Prevent*, **6**, 37-48.

Hagiwara A, Tanaka H, Imaida K, et al (1993). Correlation between medium-term multi-organ carcinogenesis bioassay data and long-term observation results in rats. *Jpn J Cancer Res*, **84**, 237-245.

Huff J (2002). IARC monographs, industry influence, and upgrading, downgrading, and under-grading chemicals: a personal point of view. *Int J Occup Environ Health*, **8**, 249-70.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volumes 1-66. Lyon: IARC (1972-2002)

Ito N, Hasegawa R, Imaida K, et al (1997). Medium-term rat liver bioassay for rapid detection of hepatocarcinogenic substances. *J Toxicol Pathol*, **10**, 1-11.

Kitano M, Ichihara T, Matsuda T, et al (1998). Presence of a threshold for promoting effects of phenobarbital on diethylnitrosamine-induced hepatic foci in the rat. *Carcinogenesis*, **19**, 1475-80 .

Luoma J (Fall 2002). Under the influence. *OnEarth Magazine*, Natural Resources Defense Council.

Masuda C, Wanibuchi H, Otori K, et al (2001). Presence of no-observed effect level for enhancing effcts of the a-isomer of benzene hexachloride (α-BHC) on diethylnitrosamine-initiated hepatic foci in rats. *Cancer Letters*, **163**, 179-85.

Moore MA, Nakagawa K, Satoh K, Ishikawa T, Sato K (1987). Single GST-P positive liver cells - putative initiated hepatocytes. *Carcinogenesis*, **8**, 483-6.

Moore, MA, Tsuda H, Tamano S, et al (1999). Marriage of a medium-term liver model to surrogate markers - a practical approach for risk and benefit assessment. *Toxicol Pathol*, **27**, 237-42.

Ogiso T, Tatematsu M, Tamano S, Tsuda H, Ito N (1985). Comparative effects of carcinogens on the induction of placental glutathione S-transferase-positive liver nodules in a short-term assay and of hepatocellular carcinomas in a long-term assay. *Toxicol Pathol*, **13**, 257-65.

Parsons PA (2002). Radiation hormesis: challenging LNT theory via ecological and evolutionary considerations. *Health Phys*, **82**, 513-6.

Schatzkin A, Freedman LS, Dorgan J, et al (1996). Surrogate end points in cancer research: a critique. *Cancer Epidemiol Biomarkers Prevent*, **5**, 947-53.

Sukata T, Uwagawa S, Ozaki K, et al (2002). Detailed low dose study of 1,1-bis(p-chlorophenyl)-2,2,2-trichloroethane carcinogenesis suggests the possibility of a hormetic effect. *Int J Cancer*, **99**, 112-8.

Teeguarden JG, Dragan Y, Pitot HC (2000). Hazard assessment of chemical carcinogen: the impact of hromesis. *J Appl Toxicol*, **20**, 113-20.

Tomatis L (2002). The IARC monographs program: changing attitudes towards public health. *Int J Occup Environ Health*, **8**,144-52.

Tomatis L, Melnick RL, Haseman J, Barrett JC, Huff J (2001). Alleged misconceptions' distort perceptions of environmental cancer risks. *FASEB J* , **15**, 195-203.

Tsuda H, Fukushima, S, Wanibuchi H, et al (2003). Value of GST-P positive preneoplastic hepatic foci in dose-response studies of hepatocarcinogenesis: evidence for thresholds with both genotoxic and non-genotoxic carcinogens. *Toxicol Pathol*, **31**, 80-6.

Watterson A (2001). Pesticide health and safety and the work and impact of international agencies: partial successes and major failures. *Int J Occup Environ Health*, **7**, 339-47.