

# Commentaries on the IARC

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Lorenzo Tomatis, former Director of the International Agency for Research on Cancer (IARC), authored a provocative article that appeared in the last issue of IJOEH [Tomatis L. The International Agency for Research on Cancer (IARC) Monographs Program: Changing Attitudes towards Public Health. *Int J Occup Environ Health*. 2002;8:144-152]. Dr. Tomatis persuasively explained that the *IARC Monographs* are losing scientific objectivity and, in turn, their credibility within the public health community. In response to the Tomatis article, Dr. James Huff, a former Chief of the Unit responsible for the *IARC Monographs*, points out in the following article that there has been an unprecedented industry influence on the *Monographs* over the last few years. Huff documents that the downgrading of chemicals by the IARC seems to be done on the basis of little in-depth scientific evidence, and tabulates the names and numbers of chemicals whose evaluations of carcinogenicity have been influenced by “mechanistic” considerations. He leaves no doubt about the source of the IARC’s diminished stature. The integrity of the *IARC Monographs* rests, in part, on the proper implementation of the “Declarations of Interests for WHO Experts,” to be signed by all future participants in the development of *IARC Monographs*. A number of scientists in the following pages add their comments on the importance of protecting the integrity of the IARC, and the scientific validity of the *IARC Monographs*. —EDITOR-IN-CHIEF

## *IARC Monographs*, Industry Influence, and Upgrading, Downgrading, and Under-grading Chemicals

### A Personal Point of View

**JAMES HUFF, PHD**

The first *IARC Monographs* Volume was distributed in 1972, and over the 23 years through 1993, under the leadership of Dr Lorenzo Tomatis, 59 *IARC Monographs* were completed. During 1977–1979 the author was privileged to lead the program for Volumes 15–22, and participated in the pioneering development of the IARC Preamble and Categories of Evidence. During this era other Chiefs of the *IARC Monographs* included Claus Agthe, Harri Vainio, Antero Aitio, and Julian Wilbourn. Since then (starting with Volume 62: 1995), a new attitude seems to have pervaded the *IARC Monographs* program, resulting in an increasing influence of or partiality for industry and a diminishing dedication to public and occupational health and safety concerns, and for primary prevention. Some of this attitude comes from an apparent misguided scientific zest prematurely to endorse purported or hypothetical mechanisms of

chemical carcinogenesis or modes of action of chemicals causing cancer in experimental animals. These speculations are in turn used cavalierly to discount the value of experimental evidence for predicting probable carcinogenicity to humans. Most often this is accomplished by opining that the mechanism(s) of carcinogenicity in animals would not be operative in humans. End of explanation. Examples whereby the IARC has recently “downgraded” or “under-graded” the available evidence of carcinogenicity include: acrylonitrile; atrazine; benzidine-based dyes; 1,3-butadiene, dichloromethane (methylene chloride); di(2-ethylhexyl) phthalate; glass wool insulation; MtBE [methyl tertiary butyl ether]; ochratoxin A; saccharin; sunlamps and sunbeds (use of); trichloroethylene; sulfamethazine; and others more inclusively mentioned in the text and tables. Further impeding or compromising public health, chemicals causing site-specific cancers in animals attendant with calculi/precipitate in the urinary bladder, goiter and thyroid gland, kidney and alpha-2 $\mu$  globulin, peroxisome proliferation and liver tumors, and cell proliferation in general have led the IARC to discount these car-

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cinogenic effects. To stem this tide at the IARC, new leadership, with more objectivity and public health perspective, is needed. *Key words:* International Agency for Research on Cancer; public health; worker health; scientific integrity; *IARC Monographs*; carcinogenicity; industry; standards; primary prevention; National Toxicology Program.

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As a former Chief of the Unit responsible for the chemical carcinogenesis *Monographs of the International Agency for Research on Cancer (IARC)* in Lyon, France, and as a subsequent *Monographs'* participant, I fully agree with and endorse the Commentary by Lorenzo Tomatis,<sup>1</sup> originator of the *IARC Monographs'* program and former Director, IARC. I am certain that it pains and disturbs Dr Tomatis, and previous *Monographs'* Chiefs (Claus Agthe, Harri Vainio, Antero Aitio, Julian Willbourn), as much as it does me and others to witness the *IARC Monographs* lose not only scientific objectivity but also credibility within the public health community. The influence of industry on the *IARC Monographs* over the last few years is unprecedented. More and more industry scientists have been invited to participate in and render influence in the IARC Monographs program either as members of the working groups or as biased industry observers. Even vocal industry advocates/employees have been made part of the IARC secretariat.

In particular, I take specific umbrage at the recent J. Rice/P. Kleihues era of "downgrading" chemicals in general, often using "mechanistic cover-ups," with many of those chemicals/agents being placed unceremoniously into the nebulous category of "unclassifiable as to carcinogenicity." These overt and cavalier actions must be viewed as a concerted effort to appease industry, which then hurts directly public/occupational health by allowing unregulated and increasing exposures to these carcinogens. An equally important negative concept and also a growing recent trend of the *IARC Monographs* is "under-grading" chemicals/agents into categories of lesser public health significance. These downgrading and under-grading issues form the main contents of my personal Commentary. Firstly and briefly mentioned are chemicals/agents that have been upgraded over the

years by IARC due to other relevant information, typically and almost exclusively involving genotoxicity and mutagenicity data. Downgrading or under-grading of chemicals is most often justified by "lack of genotoxicity" or "mechanisms deemed irrelevant" to humans. These chemicals are detailed by quoting from the *IARC Monographs*, followed by my professional comments and opinions regarding the IARC actions.

## IARC MONOGRAPHS

Since 1972 IARC has published 80 *Monographs* volumes, with another few in press, under the direction of several individuals (Table 1). These individuals have significant control over what and when chemicals and exposure circumstances are evaluated for carcinogenic risk, and importantly, who gets invited to the monographs meetings or is allowed to attend. Additionally, such an individual selects both the chairs and vice-chairs of the overall meeting as well as of the subgroups. And throughout the meeting the individual can set the tone of the deliberations and effectuate the outcomes in various ways. Within the *IARC Monographs*, 878 chemicals, agents, or exposure circumstances have been evaluated for evidence of carcinogenicity. The categories of evidence and the numbers of chemicals in each group are given in Table 2. For more background information on the monographs program see the papers by Tomatis<sup>1-5</sup> and one by Huff.<sup>6</sup>

## UPGRADING CHEMICALS BY IARC

Typically, upgrading chemicals from one level of evidence or category to another is based largely on other information in support of the carcinogenicity of that particular chemical: this can include epidemiologic or/and experimental evidence, genotoxicity information comprising both mutagenesis and clastogenesis as well as in-vitro and in-vivo activity, metabolism to another known carcinogen, structural similarity to another carcinogen or belonging to a class of carcinogens such as PAHs or anthraquinones or benzidine-based dyes, forming DNA adducts or other DNA reactivity (especially in humans), and similar tumor target sites in both humans and animals, among others.

Unfortunately, "mechanisms" have been used more often and more recently by IARC influentially to downgrade or under-grade chemicals into lower levels of public health significance. To study this issue and to formulate mechanistic-use guidelines, IARC in 1990 convened a group of 40 experts in carcinogenesis to formulate "mechanisms" standards and strategies for upgrading and to a lesser degree downgrading chemicals in the IARC Monographs program.<sup>7,8</sup> On a less grand scale, the National Toxicology Program (NTP) developed a worded strategy for downgrading or delisting chemicals from one level to the other in their

**TABLE 1. IARC Monographs Published, and Responsible Individuals**

IARC Volumes	Publication Years	Chief of Monographs
1-59	1972-1994	L. Tomatis *
60-61	1994-1994	H. Vainio
62-66	1995-1996	D. MacGregor/ J. Willbourn
67-80	1996-2002	J. Rice
81-84	2002-	(in prep., J. Rice)

\*Chiefs of IARC Monographs program at different periods: L. Tomatis, C. Agthe, J. Huff, H. Vainio, A. Aitio, J. Willbourn.

**TABLE 2. IARC Categories of Overall Evidence of Carcinogenicity and Numbers of Chemicals/Agents/Exposure Circumstances in Each Group**

Evaluation Group	Evaluation Definition/Description	Number of Chemicals	
		Per Group	Cumulative
Group 1	The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans.	87	87
Group 2A	The agent (mixture) is probably carcinogenic to humans. The exposure circumstance entails exposures that are probably carcinogenic to humans.	63	150
Group 2B	The agent (mixture) is possibly carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans.	234	384
Group 3	The agent (mixture, or exposure circumstance) is not classifiable as to carcinogenicity in humans.	493	877
Group 4	The agent (mixture, exposure circumstance) is probably not carcinogenic to humans.	1	878

Reports on Carcinogens (RoC), with no discussion regarding how to use mechanism to upgrade chemicals to “known human carcinogens” with little or no epidemiologic data.<sup>9,10</sup> In other words, only human cancer data can be used in the RoC to declare a chemical or exposure circumstance to be a known human carcinogen. This needs to be updated and changed. Fortunately, and despite this limitation, both IARC and the NTP have upgraded as human carcinogens the same two (and only two) chemicals: ethylene oxide and TCDD.

#### *Upgrading from IARC Group 2A to 1*

Only two chemicals have been upgraded to Category 1 (“carcinogenic to humans”) using other than additional epidemiologic findings and/or carcinogenesis bioassay data: ethylene oxide (IARC Vol. 60; 1994, under H. Vainio) and 2,3,7,8-tetrachlorodibenzo-para-dioxin (Vol. 69; 1997, under J. Rice and P. Kleiheus) (Appendix A). Both chemicals are also considered known human carcinogens by the National Toxicology Program<sup>9</sup>; informatively, within the RoC there are 43 chemicals “known to be carcinogenic to humans” and 175 chemicals considered “reasonably anticipated to be carcinogenic to humans,” for a total of 218 chemicals/agents/exposure circumstances. In my opinion the collective human findings for both chemicals, supported and predated by the animal data, are sufficient in themselves (and especially for TCDD, regardless of purported Ah receptor theory or genotoxic mechanistic information) to place these chemicals into Group 1.<sup>11</sup> For both of these chemicals the evidence in animals preceded that eventually found for humans, and as often happens regarding primary prevention, the animal evidence was unfortunately ignored until more human cancers were found.<sup>5,12-17</sup>

Interestingly, TCDD is not genotoxic.<sup>18, post hoc</sup> And there remains considerable debate in my view regard-

ing whether the Ah receptor is indeed *the* only “carcinogenic” mechanism for TCDD carcinogenesis.<sup>10,19,20</sup> Thus, much of the evidence used to upgrade TCDD centers on the available epidemiologic findings, experimental animal data, supported by mechanistic hypotheses. But additional epidemiologic studies certainly support previous human carcinogenicity findings of TCDD-exposed individuals.<sup>21,22</sup>

Further, in my opinion more chemicals should be considered for upgrading into Group 1 (or as known human carcinogens). I am at a profound and enigmatic loss as to why, almost uniformly and universally, individuals, organizations, and regulatory agencies are much much more prone and apparently comfortable to downgrade or downgrade a chemical regarding human carcinogenic potential rather than take the more protective public health view and upgrade into a more primary preventive level. Perhaps this is the easiest and least challenged direction to take. The rationales for many if not most of these decisions are based on loose and unproven mechanistic speculations and lax information.

#### *Upgrading from IARC Group 2B to 2A*

In the IARC Monographs program, 38 chemicals/substances have been upgraded from Category 2B (“possibly carcinogenic to humans”) to 2A (“probably carcinogenic to humans”) (listed in Appendix B) (see IARC Web site: <<http://193.51.164.11/>>). The primary difference between these two categories reflects the composite confidence of the available information, together with the overall public health implications. Both 2A and 2B groupings are considered hazardous relative to humans, with 2A chemicals being viewed as more hazardous to human cancer risks than are 2B chemicals. The line dividing these two levels is often small, depending on the particular IARC working group, and one

needs to evaluate the actual monographs before assuming that 2B chemicals have lesser carcinogenic risks. Again, unfortunately, some and even many believe that chemicals in Group 2B are relatively safe regarding carcinogenic hazard while those in Group 2A are of some public health concern. Thus industry and those aligned with industry are keenly dedicated to lobbying that “their” chemicals are placed into Group 2B or more preferably into Group 3. Obviously, the same industry strategy holds for the National Toxicology Program’s Report on Carcinogens: at all costs keep chemical carcinogens listed in the “reasonably anticipated” category rather than in the “known to be a human carcinogen” category, or better yet keep chemical carcinogens from being listed in the RoC altogether.

Appendix B shows that 30 of these 38 chemicals were upgraded during the Tomatis et al. era, three during the time of Vainio, whereas only five have been upgraded under Rice (1,2-dimethylhydrazine, etoposide, glycidol, methyl methanesulfonate, teniposide), even though Rice has used the total number of upgrades to indicate that IARC has been balanced in their upgrading and downgrading of chemicals (14 June 2002 letter to J. Sass from P. Kleihues and J. Rice). Without exception these upgrades have been based primarily on genetic toxicology of the individual chemicals. IARC describes all these upgrades with the same generic nondescript, basically uninformative statement in their Web site Internet data file: “(NB: Overall evaluation upgraded from 2B to 2A (or from 3 to 2B) with supporting evidence from other data relevant to the evaluation of carcinogenicity and its mechanisms.)” For more of the latter upgrades there is informational support usually given in the particular *Monograph*. Most if not all upgrades have little or nothing to do with mechanism per se but typically involve simply whether the chemical is genotoxic (mutagenic, clastogenic), or forms DNA adducts, or in some but very few cases activated oncogenes, or a variant or combination of these sorts.

Only the five chemicals upgraded from 2B to 2A during the Rice/Kleihues management are detailed in Appendix C. Each is mentioned individually with the IARC rationale as given in the particular *Monograph*, followed by my comments regarding these upgrades. Those 33 chemicals upgraded from 2B to 2A under the Tomatis leadership are listed in Appendix B, but are not detailed individually. In most of the latter instances upgrading was based largely on other relevant information, as mentioned previously.

### *Upgrading from IARC Group 3 to 2B*

Six agents have been upgraded from Category 3 (“unclassifiable regarding carcinogenic to humans”) to 2B (“possibly carcinogenic to humans”). Appendix D shows that four of these were upgraded during the Tomatis era, whereas two have been upgraded under Rice (aziridine, 1,2-epoxybutane). Almost without

exception, like those from 2B to 2A, these have been upgraded based on genetic toxicology of the individual chemicals. Evaluation details are given for these two chemicals in Appendix E.

The key point is that IARC and others have decided, perhaps unceremoniously and without full experimental and validation proof, that genotoxic chemicals are “more” carcinogenic and more hazardous to humans than are carcinogenic, yet non-genotoxic, chemicals that may even cause the same carcinogenic tumor patterns in experimental animals. This of course is a widely held and continuingly debated, but virtually unproven, hypothesis.<sup>23-26</sup> Some in fact have insisted that we abandon the somatic mutation theory of carcinogenesis,<sup>24</sup> a view I likewise hold. Others<sup>25</sup> also insist that the “gene-centric” approach to cancer occurrence and treatment needs augmentation, whereby they suggest that more focus should be placed on “physiological constraints imposed on the overall tumour system.” And further, “By viewing the tumour system as a whole, the extensive heterogeneity of individual gene expressions is transcended, and unifying principles not deducible from investigations at the genetic level emerge.” Sonnenschein and Soto<sup>24</sup> end their paper by emphasizing that the “available alternatives are thus few and clear: 1) to keep consuming the tranquilizer provided by the somatic mutation theory, 2) to adopt the tissue organization field theory, or 3) to find a worthy option to alternatives 1 and 2.” Folkman et al.<sup>25</sup> suggest more efforts should be directed towards “epigenetic, cell-cell and extracellular influences” as these “are also pivotal to tumour progression.”

For too long we have been held scientifically hostage to the mutagenesis/genotoxic theory of carcinogenesis, whereas in fact close to half of the chemicals evaluated and shown to be carcinogenic experimentally are not genotoxic; all one needs to recall is DES (diethylstilbestrol) and TCDD as being non-genotoxic human carcinogens. Further, a sizable group of genotoxic chemicals are not carcinogenic in experimental animals. These dichotomies have generally been ignored but should be deciphered with respect to mechanism(s) of carcinogenesis. Most believe that genetic events do represent the primary means of tumor development, yet the numbers of different genetic events and of different cancers lead to the realization of multiple mechanisms of environmentally/chemically associated carcinogenic activities. Obviously there are parallel pathways to carcinogenesis, and these can vary widely not only among tumors of the same type but certainly between tumors of different types.<sup>26</sup> Some go so far as to intimate that all chemicals or classes of chemicals could cause tumors by different, or uniquely based, mechanisms or combinations of mechanisms. Clearly we are not going to find a single mechanism of carcinogenesis, that theory was abandoned years ago, and whether the 100–200 diseases we now label cancer

could each have distinct mechanistic attributes remains to be deciphered. [Note: The issue of mechanism in chemical carcinogenesis and evidence of carcinogenic activity relating to predicting human risk of cancer will be covered in more detail in another paper; meanwhile readers may be interested in references 27–34.]

## **DOWNGRADING CHEMICALS/AGENTS BY IARC**

So far, there have been 12 chemicals/agents downgraded by IARC, and all relatively recently under the Rice/Kleihues regime (Appendix F), mainly relegated as such citing mechanistic considerations. The downgrading trend began after H. Vainio left the IARC Monographs program (Volume 61), and D. McGregor became acting head (Volume 62, 1995), and continued until the arrival of J. Rice (IARC Vol. 67, 1996–IARC Vol. 81, 2002). Primarily these have been chemicals/substances shown to be carcinogenic in laboratory animals but have been downgraded or under-graded because Rice et al.<sup>35,36</sup> have encouraged working groups in the belief that the alleged mechanisms are rodent-specific and would not be operative in humans. These are clearly and simply unproven speculations, not yet validated experimentally. The IARC downgrading rationales for these 12 chemicals and my comments are given in Appendix G.

An IARC meeting designed in what I believe was a deliberate attempt to downgrade and to establish a precedent for downgrading multiple chemicals causing tumors at select sites (kidney, thyroid, urinary bladder) was convened in 1998 with overwhelming industry supporters. Melnick and I protested both during and after the meeting, but to no avail [exchange of letters between R. Melnick and J. Huff with J. Rice and J. Wilbourn, 1998].<sup>37,38</sup> By our reckoning, invited to and participating in this IARC meeting were: 12 industry, six “unknown,” and five public health oriented individuals. This is clearly an imbalance of participants. Of course those I have suggested as being aligned with industry don’t necessarily have industry addresses, but nonetheless in my opinion they are allied in that direction. IARC has routinely cited in their Preamble, since the early days of Tomatis, that “Each participant who is a member of a working group serves as an individual scientist and not as a representative of any organization, government or industry.” Plainly, this is not what happens in reality; few of us are as objective as we strive to be. And some are less objective than others. Nonetheless, attendees at this meeting decided these mentioned chemically-induced organ cancer sites were typically irrelevant to humans; these decisions have little bases in fact, or credible scientific truth. Industry influence at this meeting was blatant. Thus, chemicals causing tumors at these sites (kidney, thyroid, urinary bladder) will receive intense scrutiny to render them rodent-specific cancers not pre-

dictive of cancers in humans exposed to the same chemicals. However, the ultimate biologic proof for this speculation remains so far absent.

Significantly, no chemicals/agents suffered this downgrading fate during the first 30 years of the IARC Monographs program. Importantly, however, “mechanistic” considerations have been influential and used cautiously over the years in the overall evaluations—genotoxicity, metabolism (e.g., to known carcinogens), structure relationships to experimental or known carcinogens—and more formal mechanistic guidelines were introduced in 1992 under the leadership of L. Tomatis and H. Vainio.<sup>7,8</sup> Also over the years, carcinogenicity evaluations have been changed as new information has become available, such as additional or new experimental or epidemiologic findings. In almost all cases these new data would tend to upgrade chemicals, not downgrade them. That is, a “new” negative experimental or epidemiologic carcinogenicity study would not under virtually all circumstances overturn a previous positive carcinogenicity outcome. During the Tomatis years there was a greater scientific scrutiny and scientific skepticism about whether a posed mechanism was or was not rodent-specific, and in no case was a mechanistic speculation used to downgrade a chemical.

The current attitude of IARC seems to reflect an uncritical acceptance of “mechanism” or “mode-of-action” hypotheses to downgrade or under-grade carcinogens into categories of lesser public health importance. Of the 12 chemicals downgraded, one chemical was downgraded from 2A to 2B (acrylonitrile; although this chemical is not signaled as a downgrade in the IARC Web site data system), whereas the other 11 were downgraded from 2B (“possibly carcinogenic to humans”) to 3 (“not classifiable as to its carcinogenicity to humans”) (Appendix F). These actions, taken prematurely in my view, would thus allow unfettered and higher permissible workplace and consumer exposures to these chemicals simply because chemicals in Group 3 are typically ignored regarding standard setting or safety precautions. Each of these 12 downgraded chemicals/agents is discussed in some detail in Appendix G. Of course, each of these chemical-specific commentaries must be brief, and thus one is encouraged to delve further into these issues.

## **OVERALL SUMMARY OF UPGRADING AND DOWNGRADING CHEMICALS**

The numbers of chemicals either upgraded or downgraded are recorded in Table 3. These actions were taken purportedly most often using “mechanistic” information, based largely if not exclusively on genetic toxicology information. Of the 46 chemicals that have been upgraded by the IARC over the course of 80 *Monographs* volumes, 38 were during the leadership of L. Tomatis (along with C. Agthe, J. Huff, H. Vainio, A.

**TABLE 3. Cumulative Data on Upgrading and Downgrading of Chemicals/Agents/Exposure Circumstances\***

	Numbers of Chemicals Upgraded/Downgraded		
	Total	During Years of	
		Tomatis et al.	Rice et al.
<b>Upgraded</b>			
From Group 2A to Group 1	2	1	1
From Group 2B to Group 2A	38	33	5
From Group 3 to Group 2B	<u>6</u>	<u>4</u>	<u>2</u>
TOTAL	46	38	8
<b>Downgraded</b>			
From Group 2A to Group 2B	1	0	1
From Group 2B to Group 3	<u>11</u>	<u>0</u>	<u>11</u>
TOTAL	12	0	12

\*There may be more of these chemicals that have been downgraded, but only those identified on the IARC Web site are counted here; acrylonitrile is perhaps an example of such an exception, not being designated as "downgraded."

Aitio, J. Wilbourn), with eight being upgraded under the management of J. Rice. Of course these numbers may be relative because more volumes were produced under Tomatis (59, plus the two under H. Vainio) than under Rice (15, plus five under MacGregor/Wilbourn and a few in press). On the other side, 12 chemicals have been downgraded by IARC, all of which happened during the term of Rice. Several of these chemicals were downgraded following the hasty mechanism-based precedent set forth previously by IARC, as discussed above.<sup>35,36</sup>

As an arbitrary separation into categories of opined evidence for downgrading, *three* were downgraded because of the "thyroid theory of carcinogenesis"; one was downgraded because of the "kidney mechanistic speculation"; *two* were downgraded because of the "urinary bladder precipitate hypothesis"; *two* were downgraded because of the "non-genotoxic reduced hazard theory"; and *four* were downgraded because of "re-evaluation" of epidemiologic findings. Additionally the "peroxisome proliferation speculation" was a major reason for downgrading DEHP. For the "particulates," e.g., fiberglass, the findings appear to be based on reevaluation of evidence, and the theory of biologic persistence. For all of the downgraded chemicals, less carcinogenic risk is suggested by IARC's actions, and thus permits higher worker and consumer exposures. If proposed changes are based on solid scientific evidence, then by all means we should correct or adjust any previous misplacements of chemicals as we discover them and move them into the appropriate groups. However, in these cases I do not consider the stated rationales for downgrading to be good science, and certainly not good public health. As Tomatis has so rightfully warned "If (subsequent experimental) tests show these hypotheses to be incorrect, or if they do not account adequately for the wide range of susceptibility in humans, serious consequences for public health may follow."<sup>1</sup>

## UNDER-GRADED CHEMICALS/AGENTS

Another important evaluation issue long ignored or simply overlooked centers on placing chemicals in categories/groupings of lesser risk characterization than the available evidence would suggest. Ergo, there appear to be many chemicals that have been under-graded (examples are given below). For some of these under-graded chemicals new data have become available since the particular monographs were prepared, and thus updates are needed. For others I hold the view that they were graded lower than the available information suggested or warranted. The reasons for undergrading are often ephemeral and not easily quantifiable, but the influence of industry on the handling of these apparently economically important chemicals plays a key role. This is true especially for these selected and highlighted chemicals, as examples: benzidine-based dyes; 1,3-butadiene; chloroform; dichloro-methane; formaldehyde; gasoline; methyl tert butyl ether; ochratoxin A; phenacetin; sunlamps and sunbeds; trichloroethylene; vinyl halides. I had initially prepared a tabular listing of chemicals I considered under-graded, but abandoned that exercise because the listing was not complete nor did I have sufficient time to fully review the available information. Again, this partial list rests on my professional and scientific opinion, and my having been a Unit Chief for the *IARC Monographs* and a Group Leader for the *NTP Chemical Carcinogenesis Bioassay Reports*.

Alternatively, and as examples of under-grading, two of the chemicals are summarized hereinafter: 1,3-butadiene and MtBE (methyl tert butyl ether). As with the rest of the views in this paper, these are my opinions and should in no way reflect unfavorably on those who hold different opinions, nor should they be taken to mean my colleagues or Institute would hold the same opinions.

*1,3-Butadiene* (IARC Vol. 39, 1986; Suppl. 7, 1987; 54, 1992; 71, 1999) is probably the prime example of the

overt influence of industry on the *IARC Monographs* process. This chemical remained in Group 2A (probably carcinogenic) rather than being upgraded into Group 1 (human carcinogen) because more than one “final” vote (some say three) was taken, apparently until the desired outcome was achieved. Note that, unlike the NTP’s procedures and policies in formulating their *Bioassay Technical Reports* and their *Reports on Carcinogens*, vote tallies are not recorded. Most importantly, the IARC epidemiology subgroup at that meeting voted to list 1,3-butadiene as a human carcinogen, and the first votes of the entire working group were in favor of Group 1. Yet in the industry-influenced plenary session (with chemists and in-vitro experts and toxicologists) the third vote ended with Group 2A, apparently after alleged overnight lobbying by industry and reportedly by IARC staff. Also, one or two individuals left the meeting in advance of the “final” vote.

Of course, one must ask who better should evaluate epidemiology findings than epidemiologists? One can only wonder how chemists and toxicologists and pathologists could overturn the key subject-related advice and conclusions of the epidemiologists at that IARC meeting? Conversely, the NTP has placed 1,3-butadiene into their listing of “known to be carcinogenic to humans.”

In my view, the experimental evidence is patently clear that 1,3-butadiene is a potent multi-site, multi-strain, multi-species, and genotoxic chemical, causing cancers resulting from as little as 13 weeks of exposure and at concentrations 150 times lower than the OSHA standard of 1,000 ppm (recently lowered to 3 ppm).<sup>39-41</sup> This unequivocal and overwhelming evidence alone seems to me to be enough to place butadiene in Group 2A. Additionally, the epidemiologic evidence is equally unequivocal, whereby 1,3-butadiene causes tumors of the lymphohematopoietic system, similar to those induced in animals. Further, and mechanistically, both major metabolites of butadiene are genotoxic and carcinogenic in animals. Thus, collectively one could hardly consider butadiene to be other than a human carcinogen.

Regarding the IARC designation of Group 2A, I am convinced that the economically important 1,3-butadiene was placed into this grouping because of industry interests and intense lobbying efforts. According to the NTP, “1,3-Butadiene is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic information, which indicate a causal relationship between occupational exposure to 1,3-butadiene and excess mortality from lymphatic and/or hematopoietic cancers.” For IARC to not consider 1,3-butadiene as a human carcinogen places undue and unnecessary risks on workers in the butadiene industries.

*MtBE (methyl tert butyl ether)* (*IARC Vol 73, 1999*), the soon-to-be-banned (phased out in the United States) gasoline additive, is another under-graded chemical

placed into IARC Group 3 (unclassifiable), whereby in this case the published carcinogenicity findings are both under-interpreted and misrepresented in the *Monographs*. All the available experimental data were apparently not used to make the evaluation, and also some of the studies were “discounted” or considered of lesser importance by industry influence because they unfairly impugned the reputation of the investigators (who were not at the meeting) who conducted and reported multiple-site MtBE-induced carcinogenesis from their long-term carcinogenesis studies.

IARC stated that “Methyl tert-butyl ether was tested for carcinogenicity in a non-standard protocol [see below] in rats by gavage. The incidences of Leydig-cell tumours of the testis in males and of lymphomas and leukaemias combined in females were increased. Methyl tert-butyl ether was tested by inhalation in one experiment in mice and in one experiment in rats. It increased the incidence of hepatocellular adenomas in female mice and that of renal tubular tumours in male rats in a non-dose-related manner. tert-Butyl alcohol, a metabolite of methyl tert-butyl ether, marginally increased the incidence of follicular-cell adenomas of the thyroid in female mice.”

IARC did not mention in their summary that the interstitial cell tumors of the testes were increased in the inhalation experiments as well, confirming the same site in the oral studies. Further, no mention was made of an increase in sarcomas of the uterus in the low-dose group in the oral studies.

The so-called non-standard protocol led IARC to this comment: “The Working Group noted that the dosing schedule was unusual, that the animals were allowed to live out their normal lifespan and that mortality-adjusted analyses were not performed; therefore, estimates of effective group numbers and tumor incidences were difficult to analyse.” This protocol has been used for years by the Ramazzini Foundation and accepted universally. Likewise, there is nothing “wrong” with exposing animals on Monday, Tuesday, Thursday, Friday; does this mean also that seven days’ exposure (other than dietary) would also be “unusual”? Additionally, allowing animals to live out their life mimics more closely the human situation and allows for late-appearing tumors, or regression of preneoplastic lesions or even tumors.<sup>42,43</sup> And the numbers of animals are indeed given in the publications from this laboratory, and the numbers of animals are given as the effective number remaining after the first tumor of interest was observed, also not an uncommon practice. So to qualify these experiments and carcinogenicity findings as “unusual” is misleading and incorrect.

Moreover, IARC under-reported the NTP results on tert-butyl alcohol, the major metabolite of MtBE in both humans and animals and relevant to the overall evaluation of MtBE. IARC mentions only follicular cell adenomas of the thyroid in female mice, which they

called a “marginal increase,” when in fact the NTP evaluated this increase as “some evidence of carcinogenicity.” The NTP did evaluate the increase of these tumors in male mice as “equivocal evidence.”\* A key supporting point is that increases in these thyroid gland tumors were observed in both sexes. Further, tert-butyl alcohol also caused increases in renal tubular cell adenomas/carcinomas in male rats. The NTP indicated that although the signs of alpha 2μ-globulin were observed in male rats (no histochemical measurements were made), “the increased severity of nephropathy also seen in females suggests that the mechanism for renal cytotoxicity was not limited to an increased accumulation of alpha 2μ-globulin.”

Interestingly, IARC discounts the kidney tumors induced by MtBE by opining that “In male rats, methyl tert-butyl ether-induced kidney lesions were associated with alpha 2μ-globulin nephropathy, a male rat-specific response.” This IARC decision despite what the NTP indicated for the metabolite t-butyl alcohol-induced renal tumors, and the facts that 1) this so-called mechanism has not been uniformly accepted as scientific truth,<sup>29,33,34,37</sup> and 2) as with all these speculative hypothetical mechanisms, one should not expect the same tumor target site responses among different species exposed to the same chemical, and 3) thus among different species or even carcinogenic organ sites, there is the clear possibility of different mechanisms’ prevailing.

Other examples of under-grading (and downgrading) include those chemicals causing tumors of the thyroid, tumors of the urinary bladder, and tumors of the kidney.<sup>35,36</sup> These are typically relegated to Group 3 (unclassifiable).

Regarding the NTP and MtBE, the four MtBE review committees of the NTP voted cumulatively with 14 for listing in the *Report on Carcinogens* and 20 for not listing in the RoC. A majority was for not listing, yet with a sizable number who considered the carcinogenetic findings convincing for listing. The NTP Board of Scientific Counselors were 5 to 6 for listing. In my minority opinion, MtBE should have been listed in the RoC.

## WORKING GROUP PARTICIPANTS, BIASES, AND PREDISPOSITIONS

Of course one might counter my singular views with the opinion that working groups are independent, and they collectively have a more “weighted” balance (versus me as an individual) to place these chemicals in the most appropriate and reasoned groups. Having been Chief of

the IARC Monographs program, I recognize that there is some validity to that notion of purity, but not that much, especially in recent times. I have been there, as well as being the leader of the NTP bioassay evaluation program for the years of the David Rall regime (1979–1990). And I was part of the small team (with Hans Falk) and the later larger team that decided on the selection rationale and chemical entries for the NTP *Report on Carcinogens* (Volumes 1–10).<sup>10</sup>

Most IARC (and NTP or other organizations) attendees have their individual biases, and one knows about them either before a meeting or shortly therein. That is why it is vitally important and imperative to have well-balanced working groups to help decide in what categories to place the individual chemicals. Only in this way can the *Monographs* be relevant and objective. Also, and obviously, the secretariat indeed has considerable influence before the meetings by selecting the participants (and the chair and vice-chair) and at the meeting on the eventual outcomes of the votes for particular chemicals. The secretariat wields considerable “power” during (and before) the *Monographs* meetings, as many/most participants often and typically follow/defer to the secretariat not only on format and policy issues but on evaluation opinions as well. Additionally, for many chemicals the available data are fairly clear relative to which groupings they rightfully belong, as the data are straightforward and unequivocal. However, there are important and economically profitable chemicals (such as those mentioned) that can be and have been placed into or downgraded into categories/groups below those in which they justly belong.

Thus as an exercise, I examined the lists of participants at relatively recent *Monograph* meetings (in particular, those for Volumes 62 to the latest one, Volume 80), and divided the participants into these groups: public health, industry, and “unknown.” For the latter grouping this meant I did not know the particular individual or in some cases was not aware of the individual’s philosophical or historical views on public health or industry interests. Table 4 gives the numbers per grouping for these monographs, divided by participants and observers, and from my perspective it seems clear that the influence of industry at the *IARC Monographs* meetings is quite pervasive and obvious. In all but one of the *Monographs* meetings those aligned with industry “outnumbered” those aligned with public health. Overall, the numbers aligned with public health equal about 76 (or 29%), those aligned with industry were 83 (32%), and unknown were 99 (38%). The observers were even more aligned with industry than were the invited participants, and these clearly have considerable influence at the meetings by participating fully in discussions and subgroup deliberations, but do not “vote” on final evaluations: 69% industry; 12% public health; 20% unknown. Combining these two categories gives 118 individuals aligned with industry

\*NTP definitions: “Some Evidence of Carcinogenic Activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined); “Equivocal Evidence of Carcinogenic Activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.”

**TABLE 4. Alignment of Participants Attending IARC Monographs Meetings Resulting in Volumes 62 through 80: Divided and Placed into Categories of Attendee Alignment**

Monograph Volume, Year, Title*	Alignment According to the Author†					
	Public Health	Industry	Unknown	Observers		
				PH	I	Un
62: 1995; Wood dust and Formaldehyde	6	4	9	0	3	1
63: 1995; Dry cleaning, Some Chlorinated Solvents and Other Industrial Chemicals	9	4	4	1	4	1
65: 1996; Printing Processes and PrintingInks, Carbon Black and Some Nitrocompounds	4	5	8	0	3	1
66: 1996; Some Pharmaceutical Drugs	5	4	8	1	2	0
68: 1997; Silica, Some Silicates, Coal Dust and para-Aramid Fibrils	6	9	4	2	4	1
69: 1997; Polychlorinated Dibenzo-para-Dioxins and Polychlorinated Dibenzofurans	9	4	11	1	3	1
71: 1999; Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide	12	6	13	0	6	2
72: 1999; Hormonal Contraception and Postmenopausal Hormonal Therapy	2	3	20		none	
73: 1999; Some Chemicals that Cause Tumors of the Kidney or Urinary Bladder in Rodents, and Some Other Substances	4	14	4	0	3	1
76: 2000; Some Antiviral and Antineoplastic Drugs, and Other Pharmaceutical Agents	4	5	8	0	0	1
77: 2000; Some Industrial Chemicals	11	13	5	0	4	1
79: 2001; Some Thyrotropic Agent	4	12	5	1	3	0
TOTAL						
Number	76	83	99	6	35	10
Percentage	29%	32%	38%	12%	69%	20%
Chairs	5	6	1			
Vice-Chairs	7	2	0			

\*Participants at the following meetings were not tabulated because the *Monographs* topics and attendees were outside the author's sphere of knowledge: 64: 1995; Human Papillomaviruses; 67: 1996; Human Immunodeficiency Viruses and Human T-Cell Lymphotropic Viruses; 70: 1997; Epstein-Barr Virus and Kaposi's Sarcoma Herpesvirus/Human Herpesvirus 8; 74: 1999; Surgical Implants and Other Foreign Bodies; 75: 2000; Ionizing Radiation, Part 1: X- and Gamma (g)-Radiation, and Neutrons; 78: 2001; Some Internally Deposited Radionuclides; 80: 2002; Non-Ionizing Radiation, Part 1: Static and Extremely Low-Frequency (ELF) Electric and Magnetic Fields.

†The designations and placements into three categories (aligned to public health, industry, or unknown) result from my personal opinions and observations; moreover, addresses or affiliations do not always represent where or how an individual aligns.

(38%); 109 unknown (35%); 99 public health (26%). Thus, for IARC to state that "The number from industry involved in any one meeting has never been more than one or two out of usually 25 members of a Working Group and they are never appointed as chairs of subgroups or of the meetings as a whole" is clearly not accurate (correspondence to B. Castleman from P. Kleiheus, Director, IARC, 14 June 2002).

Of course, those under the "aligned unknown" category could be added to either grouping, and perhaps change the balance one way or the other. Again, this is my opinion, and for some of the individuals I could be wrong about their "leanings" or professional and scientific alignments, but this is indeed my opinion. Even within the secretariat in recent years there have been

individuals from industry, and one recently, apparently on leave from the oil industry. Others may have been, are, or planned to be part of the *IARC Monographs* team in the future. This is clearly a conflict of interest and inappropriate.

## COMMENTS AND FURTHER OPINION

Historically the *IARC Monographs* have represented the most authoritative and scientific series of chemical carcinogenesis information used internationally for primary prevention of cancer. This long-held value has diminished in my opinion due to the increasing influence of those aligned with the industry point of view regarding chemicals and their inert hazards to public

and occupational health. The current regime at IARC holds responsibility for this decline in objectivity and scientific neutrality and public health integrity. To opine that science drives the decision-making process is not being forthright. Significantly, the secretariat decides on the invited participants and further selects the chair and vice-chair for each meeting, rendering significant pre-meeting influence or alignment on the eventual outcome of the deliberations. Granted there are times when an objective unbiased balance of participants is not easy or even possible. However, the current management seems to pointedly select those who have views favoring the industry positions on key items of economic interest (Table 4).

Moreover, this is where the necessity for clear identification of any conflicts of interest must be declared; where those with self-identified conflicts should not be allowed to “vote” on an evaluative grouping for a chemical or exposure circumstance; where observers and industry representatives are not allowed during the meetings to enter the scientific and public health debates; where the conflict-of-interests declarations must be announced at the opening of the meeting and should be made available/known to the public [see letters to WHO’s Dr. Brundtland, on pages 271 and 279 of this issue of *IJOEH*]; where those with known alignments should be balanced with opposite alignments; and where public, environmental, and occupational health must once more be a primary influencing factor in IARC evaluations.

A shift in balance and an alignment with industry can be seen clearly in Table 4. Similarly, observers and representatives attending these *IARC Monographs* meetings likewise favor an industry perspective significantly. And as we all know, just because someone is from academia or from government does not mean he or she aligns automatically with public health or does not align with industry. So to imply that only scientists from industry align with industry is of course a naïve and unfortunate position. Where people work does not identify either their politics or their views on public health. The long-espoused notion that academics are for some reason more scientifically pure and objective than either government or industry scientists is far from reality. In my experience, most often industry scientists are indeed industry, whereas government and academic scientists might typically fit any of the three categories in Table 4. Often, scientists at a public health governmental facility align typically with the public health position, but not near always. At times I have had more argumentative “scientific” debates with “public health servants” than I have had with industry scientists. Of course, those that are demarcated into black or white often get unanimous consensus, but many issues, including chemical carcinogenesis information, are often not that clear-cut. This is especially true when mechanistic hypotheses are viewed as truth

rather than as speculations. It has been said that the longer or more often a theory is expressed the better chance it has of becoming truth, even when no additional data have become available.<sup>44</sup>

Frequently one hears the comment “I am on the fence on this issue,” and to me that means when the vote is taken that person will inevitably align with the more conservative point of view (read industry). From personal observation in these situations, I find it amusing that “fence sitters” rarely if ever topple to the liberal or public health side of an issue. Time and again the so-called sitters take the “chemical” side of the debate; that is, vote in favor of a lower level of likely risk. Many seem more comfortable with declaring “false positives” and hence assigning lower levels of significance than they are with “false negatives,” which are the ones I and others worry most about. I am prone to find this activity both perplexing and droll, but not being a psychologist I wonder why this “falling-off-the-fence” response is habitually so predictable and consistent. Sometimes I am fooled when I guess the outcomes, but not a lot. That is not to say that fence sitters who topple on the conservative side are uncaring or malicious; what I think is that the easier path to take is no path at all, the one with the least number of obstacles or controversy.

As an illustration, in my experience of evaluating nearly 300 long-term chemical carcinogenesis bioassays, I can not recall a time when there was any serious consideration or protest made that negative study results could be wrong. Conversely, when results are positive, especially for an economically important chemical, we have been bombarded with arguments decrying the bioassay results, with often flagrant misstatements and outright untruths that the carcinogenesis findings are wrong or meaningless or that the mechanism is not relevant to humans or that (despite no epidemiology studies being done) the chemical has been used for decades and no cancers have been observed in humans. And the list of frequently and frivolously trumped-up disagreements goes on: humans are not rodents; exposures are unrealistically high; humans don’t have that organ (e.g., forestomach or Zymbal glands); mouse liver tumors are irrelevant because the occurrence of cancer of the liver is relatively low in the United States; that exposure route is not the relevant one for humans; durations are too long; and so forth.<sup>45-50</sup>

The most serious imbalance of participants occurred in the meetings resulting in IARC Volumes 73, 77, and 79. For each of these, the issues from a public health point of view were critical, and yet these three had the most unbalanced alignments with industry attendees (Table 4), both among participants and among observers. Two of these *Monographs* were heavily geared toward the “mechanism” or “mode-of-action” concept (see the following paragraph). Interestingly, the balance appears to have been weighted toward the

public health view for Volume 71, but this is hard to tell (in any *Monograph*) because of the large number of “unknowns”; of course, there were four observers from industry. Again, the industry category held the most overall attendees. This simply means that I or several colleagues who helped me with this placement did not know the individuals, and this “unknown” grouping came about largely because many of these scientists were in the fields of chemistry and general toxicology; ones with which I am less familiar.

Further and wrongly, the participants from the non-cancer subgroups can and often do outvote the participants from the more relevant experimental carcinogenesis and cancer epidemiology subgroups (1,3-butadiene is a major example). Perhaps IARC ought to reconsider how the working groups are established (obviously more public health-aligned scientists should be invited and non-industry representatives as observers) and how voting should be structured and allowed, to better reflect the direct purpose of the vote outcomes establishing the carcinogenic risks of chemicals to humans. That is, with all due respect, a chemist or a teratologist might not know the issues or the carcinogenesis data well enough to render an informed decision. In these cases, perhaps IARC should inform the participants that each member does not necessarily need to vote, especially if he or she is not knowledgeable enough to be comfortable with voting. I am not proposing that non-cancer experts should be denied voting, just that the issues are often so important that an errant or uninformed vote can tip the balance away from public health (again, witness 1,3-butadiene where one or two “swing” votes made the difference between Group 2A and more exposures or Group 1 and fewer exposures).

In the observers category, there is the largest imbalance towards industry, with nearly 6+ times more industry than public health representatives (Table 4). This may reflect the difficulty for public health people to get the money to attend these meetings, because observers are not sponsored by IARC as are the invited participants. Typically, however, industry does have the funds to send representatives to these meetings, and for obvious reasons. None of this should be taken to mean that industry people should not be invited or even serve as observers or representatives. The message here is 1) that conflicts of interest (regardless of each person’s address) should be more cogently identified and affected individuals should not be permitted to vote or to enter into debates about chemicals in which they have vested interests. And 2) more scientists with known alignment to public health should be invited to these meetings.

Importantly, at the meetings that resulted in the 12 monographs completed under Rice, considered in this part of the discussion, none of the participants, not one, was invited from a public interest group or from an environmental advocacy group. None attended as

an observer either. There is a chance I might perhaps have missed one, but more likely probably not. This is in stark contrast to the numbers of industry participants invited by IARC and the numbers of industry observers/representatives permitted to attend. This IARC policy too should change. Does this mean, from IARC’s view, that there are no scientists from these public health advocacy groups who are expert in chemical carcinogenesis? I hope not. And names could be given to IARC if they are unable to find any.

For the chairs selected for these meetings, there were six industry, four public health, two unknown. In one monograph meeting, both the chair and the vice-chair were aligned toward industry, and in another both were aligned with public health. Those picked as vice-chairs were aligned mainly toward public health (six), with three being industry. For three monographs there was no vice-chair listed. In meetings to decide the import of future monographs it would be considerably useful to identify in the listings of participants who had chaired/co-chaired the subgroups (experimental carcinogenesis; epidemiology; other data including the genetic toxicology; chemistry; other subgroups) and also to key the names of the subgroup members in the listings in the fronts of the monographs. This would be very informative to the users of the monographs. In my opinion the most influential and expert-knowledgeable subgroups regarding eventual carcinogenicity evaluations are and should be those dealing with the epidemiology and experimental carcinogenesis information. This is not to downplay or besmirch the value of the other subgroups, simply to state the fact, and to place into perspective when chemists and toxicologists might combine perhaps unwittingly to outvote epidemiologists and experimental carcinogenesis experts. IARC should certainly avoid situations like this from occurring.

To be more objective and fair about the analysis in Table 4, I went back to the eight *Monographs* for which I was chief of the program (IARC Volumes 15 through 22) and did the same exercise as was done for the 12 IARC Volumes in Table 4. In selecting experts for IARC working groups we gave first priority to specific expertise in particular areas of carcinogenesis related to hazard evaluation, taking into account the chemicals, agents, and exposures to be evaluated. If there was a bias from our side, it may be expressed as follows: at equal levels of expertise we preferred scientists who had records of independence and autonomy. About a year in advance of the meeting, lists of names were prepared and discussed among IARC staff, and clearly biased individuals were either placed in secondary groupings or taken from the list. The list was further pared to a reasonable number, with more emphasis given to those with public health or worker health attitudes. This is reflected very well in the alignment distributions of the attendees invited to these earlier eight monograph meetings (Table 5): 77% aligned with public health; 9%

**TABLE 5. Alignment of Participants Attending IARC Monographs Meetings Resulting in Volumes 15 through 22: Divided and Placed into Categories of Attendee Alignment**

Monograph Volume, Year, Title*	Alignment According to the Author†					
	Public Health	Industry	Unknown	Observers		
				PH	I	Un
15: 1977; Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals	12	2	3	1	0	2
16: 1978; Some Aromatic Amines and Related Nitro Compounds - Hair Dyes, Colouring Agents and Miscellaneous Industrial Chemicals	9	1	5	0	0	1
17: 1978; Some N-Nitroso Compounds	13	1	1	2	2	0
18: 1978; Polychlorinated Biphenyls and Polybrominated Biphenyls	12	1	1	2	2	0
19: 1979; Some Monomers, Plastics and Synthetic Elastomers, and Acrolein	12	1	2	3	5	0
20: 1979; Some Halogenated Hydrocarbons	14	2	2	1	3	0
21: 1979; Sex Hormones (II)	9	1	3	2	3	2
22: 1980; Some Non-Nutritive Sweetening Agents	12	2	0	2	3	1
TOTAL						
Number	93	11	17	13	18	6
Percentages	77%	9%	14%	35%	49%	16%
Chairs	8	0	0			
Vice-Chairs	6	2	0			

\*These eight IARC Monographs resulted from the tenure of J. Huff/L. Tomatis.

†The designations and placements into three categories (aligned to public health, industry, or unknown) result from my personal opinions and observations; moreover, addresses or affiliations do not always represent where or how an individual aligns.

industry; 14% unknown. Observers showed the industry to be dominant at 49%, whereas if industry is present at all, this is where they should be, as nonvoting observers. For the chairs and vice-chairs of these eight meetings, only two of the 16 aligned with industry. Some might argue that we were biased in the direction of public health, and I would agree. We still believe that is the way it should be: human health comes before economic and industry health. Personally I believe there should be no compromise regarding human health. None.

Going forward a bit more, and to be more certain that the members in Table 5 were not uniquely aligned toward public health, I selected four other monographs at random to further analyze attendee patterns of the Tomatis era: IARC Volumes 30, 40, 50, and 60. Here, too, the numbers of scientists invited to these meetings show higher percentages of individuals having independence and public health and worker safety alignment; the detailed tabular data are not given but the results show 53% public health, 13% industry, 35% unknown. As observers, more were from industry (49%) than from public health (35%) or unknown (16%). If industry is to be involved in the Monographs process, this is where they should settle, as observers. Thus the history of the Tomatis era of the IARC Monographs clearly shows a more public health

attitude compared with the Rice years, which show an overwhelming industry influence.

Likewise, it seems to me, regulatory agencies in the United States have also fallen dupe to speculative and self-indulged “mechanisms” and “modes-of-action” theories being rampantly bandied about to discount both experimental and epidemiologic data. What have we come to? What happened to public health concerns? And worker safety? Over the last decade and a half or so the emphasis has shifted away from public/occupational health toward chemical and economic-influenced positions. Witness the current draft of the EPA’s carcinogenesis guidelines. The EPA was the first organization of note to unabashedly embrace prematurely and wrongly the alpha 2u-globulin theory for discounting chemically induced male rat kidney cancer. Woe is us.

The IARC Monographs over the last few years have apparently embraced wholeheartedly albeit prematurely the ideas of mechanism and mode of action to influence the grouping of chemicals, and in particular, it appears, to downgrade chemicals from one group designation to another. In almost every situation in which mechanism (other than genotoxicity) has been evoked, the result has been to downgrade a chemical (see Appendixes F and G and Table 3). Then, of course, there is the less obvious “under-grading” of chemicals (listing and data

not shown), which has the same effect as downgrading: allowing continued and unregulated exposures. Certainly whether a chemical is under-graded is an individual opinion (in this case mine) and can be debated. Some under-graded chemicals are simply in need of reevaluation and likely upgrading, whereas others have been under-graded using poor judgment.

Atrazine is yet another proof-example of the mechanistic hoax charade being perpetuated by those who turn speculations into reality just by wishing it, and IARC (and the EPA as well) has not only participated in this anti-public health endeavor, but as an international agency of historical stellar repute, has in fact taken the lead in an blatant effort to endorse unproven mechanisms and modes of action. IARC has used these as a means to both downgrade chemicals from one level of risk to a lower level of risk and as, or even more, importantly, has under-graded many more risks of hazardous chemicals. The latter effort is much harder to discover and divulge because one has to devote considerable energy and time to critically study each and every evaluation coming from IARC to ascertain the truth. The list of under-graded chemicals is long, and becoming longer, yet it continues to be quite difficult to reverse or widely renounce the IARC published evaluations. The scientific process of attempting this one chemical at a time (e.g., atrazine, butadiene) is slow and laborious, but necessary from a public health and especially from a worker safety point of view.

## AFTERWORD

To finish this commentary with candor, I remain proud and honored to have worked at the IARC for nearly three years, completing eight monograph volumes, under the leadership of Lorenzo Tomatis. Over the years after leaving the IARC I remained proud of and supported fully the IARC Monographs program, until these recent years. IARC is also where I became so excitedly involved in public health advocacy and in the philosophy and content of the *Monographs* and especially in bioassay conduct and results evaluations that I changed my field of interest from pharmacology/toxicology to chemical carcinogenesis. This then led to my joining the National Institute of Environmental Health Sciences/National Toxicology Program under the leadership of David P. Rall, another pioneer and champion of public, environmental, and occupational health.<sup>51</sup>

One of the "little" things about the *IARC Monographs* that I am truly proud of is changing the title of the *Monographs* between volumes 16 and 17 from "carcinogenic risks to man" to "carcinogenic risks to humans." There was some unexpected opposition to this change, but the trade was made and remains today. Of course, being involved in establishing the "modern" Preamble and creating and formulating the initial levels or categories of evidence of carcinogenicity are most significant for me.

Perhaps times were different then regarding the importance of and dedication to the *Monographs* work we were doing. Clearly the emphasis on public and worker health and the importance of the *Monographs* for primary prevention of cancer and other diseases were considerably more in the forefront of our thinking than they appear to be today. That is a pity. I only hope that the *Monographs* will become reoriented toward public and worker health, that is, "topple" on the side of "humans" rather than on purported mechanisms or chemicals or delaying public health decisions until "we have more data." Lastly, the role of the IARC and the NTP is simple: protect human health. Nothing else is as important. Further, their role is not to "guess" about mechanisms or to guess about whether this chemical carcinogen or that chemical carcinogen will be "safe" or to guess about the economic, regulatory, and political consequences of a particular carcinogenic evaluation, but to always judge the information and articulate the overall assessment from the viewpoint of public health and safety. Period. To do otherwise is unworthy.

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APPENDIX A

*IARC Agents and Exposure Circumstances Upgraded Using "Mechanism" from 2A ("probably carcinogenic to humans") to 1 ("carcinogenic to humans")*

See page 251 for comment

**Two Agents**

- Ethylene oxide (75-21-8) (Vol. 60; 1994).  
“(NB: Overall evaluation upgraded from 2A to 1 with supporting evidence from other data relevant to the evaluation of carcinogenicity and its mechanisms.)”  
“In making the overall evaluation, the Working Group took into consideration the following supporting evidence. Ethylene oxide is a directly acting alkylating agent that: (i) induces a sensitive, persistent dose-related increase in the frequency of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes and micronuclei in bone-marrow cells of exposed workers; (ii) has been associated with malignancies of the lymphatic and haematopoietic system in both humans and experimental animals; (iii) induces a dose-related increase in the frequency of haemoglobin adducts in exposed humans and dose-related increases in the numbers of adducts in both DNA and haemoglobin in exposed rodents; (iv) induces gene mutations and heritable translocations in germ cells of exposed rodents; and (v) is a powerful mutagen and clastogen at all phylogenetic levels.”
- 2,3,7,8-Tetrachlorodibenzo-para-dioxin (1746-01-6) (Vol. 69; 1997).  
“(NB: Overall evaluation upgraded from 2A to 1 with supporting evidence from other data relevant to the evaluation of carcinogenicity and its mechanisms.)”  
“In making the overall evaluation, the Working Group took into consideration the following supporting evidence: (i) 2,3,7,8-TCDD is a multi-site carcinogen in experimental animals that has been shown by several lines of evidence to act through a mechanism involving the Ah receptor; (ii) this receptor is highly conserved in an evolutionary sense and functions the same way in humans as in experimental animals; (iii) tissue concentrations are similar both in heavily exposed human populations in which an increased overall cancer risk was observed and in rats exposed to carcinogenic dosage regimens in bioassays.”

APPENDIX B

*IARC Agents and Exposure Circumstances Upgraded Using "Mechanism" from Group 2B ("possibly carcinogenic to humans") to Group 2A ("probably carcinogenic to humans")*

**38 Chemicals/Agents**

IARC Volumes	No. Chemicals Upgraded	Person Responsible
1-59	30	L. Tomatis*
60-61	3	H. Vainio
62-66	0	D. MacGregor/J Wilbourn
67-80	5	J Rice

\*Chiefs of IARC Monographs Programme at different periods: C. Agthe, J. Huff, H. Vainio, A. Aitio, J. Wilbourn

*Note:* The following statement, used as the basis for upgrading, appears for each chemical on the IARC URL database that has been updated. Readers wishing more information on the older upgrades need to approach each Monograph for the upgrade rationale; in many cases the information is either not stated specifically as a rationale for upgrading or is sketchy or absent.

“(NB: Overall evaluation upgraded from 2B to 2A with supporting evidence from other data relevant to the evaluation of carcinogenicity and its mechanisms)”.

*Key:* Chemical name (CAS #) (IARC Monographs Volume No., year of publication)

**Chemicals/Agents upgraded from Group 2B to Group 2A under L. Tomatis (no details given)**

- Adriamycin (23214-92-8) (Vol. 10, 1976; Suppl. 7, 1987).
- Azacitidine (320-67-2) (Vol. 50, 1990).
- Benz(a)anthracene (56-55-3) (Vol. 32, 1983; Suppl. 7, 1987).
- Benzidine-based dyes (Suppl. 7, 1987).
- Benzo(a)pyrene (50-32-8) (Vol. 32, 1983; Suppl. 7, 1987).
- Captadol (2425-06-1) (Vol. 53, 1991).
- Chloramphenicol (56-75-7) (Vol. 50, 1990).
- 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) (13010-47-4) (Vol. 26, 1981; Suppl. 7, 1987).
- Chlorozotocin (54749-90-5) (Vol. 50, 1990).
- Cisplatin (15663-27-1) (Vol. 26, 1981; Suppl. 7, 1987).
- Dibenz(a,h)anthracene (53-70-3) (Vol. 32, 1983; Suppl. 7, 1987).
- Diethyl sulfate (64-67-5) (Vol. 4, 1974; Suppl. 7, 1987; Vol. 54, 1992; Vol. 71, 1999). *Note:* this chemical was already in Group 2A in Suppl. 7, 1987.
- Dimethylcarbamoyl chloride (79-44-7) (Vol. 12, 1976; Suppl. 7, 1987; Vol. 71, 1999). *Note:* this chemical was already in Group 2A in Suppl. 7, 1987.
- Dimethyl sulfate (77-78-1) (Vol. 4, 1974; Suppl. 7, 1987; Vol. 71; 1999). *Note:* this chemical was already in Group 2A in Suppl. 7, 1987.
- Epichlorohydrin (106-89-8) (Vol. 11, 1976; Suppl. 7, 1987; Vol. 71; 1999). *Note:* this chemical was already in Group 2A in Suppl. 7, 1987.
- Ethylene dibromide (106-93-4) (Vol. 15, 1977; Suppl. 7, Vol. 71; 1999). *Note:* this chemical was already in Group 2A in Suppl. 7, 1987.
- N-Ethyl-N-nitrosourea (759-73-9) (Vol. 1, 1972; Vol. 17, 1978; Suppl. 7; 1987).
- IQ (2-Amino-3-methylimidazo(4,5-f)quinoline) (76180-96-6) (Vol. 56; 1993).
- 5-Methoxypsoralen (484-20-8) (Vol. 40, 1986; Suppl. 7; 1987).
- 4,4'-Methylene bis(2-chloroaniline) (MOCA) (101-14-4) (Vol. 4, 1974; Suppl. 7, 1987; Vol. 57; 1993).
- N-Methyl-N'-nitro-N-nitrosoguanidine (MNNG) (70-25-7) (Vol. 4, 1974; Suppl. 7; 1987).
- N-Methyl-N-nitrosourea (684-93-5) (Vol. 17, 1978; Suppl. 7; 1987).
- N-Nitrosodiethylamine (55-18-5) (Vol. 17, 1978; Suppl. 7; 1987).
- N-Nitrosodimethylamine (62-75-9) (Vol. 17, 1978; Suppl. 7; 1987).
- Procarbazine hydrochloride (366-70-1) (Vol. 26, 1981; Suppl. 7; 1987).
- Tris(2,3-dibromopropyl) phosphate (126-72-7) (Vol. 20, 1979; Suppl. 7, 1987; Vol. 71; 1999). *Note:* this chemical was already in Group 2A in Suppl. 7, 1987.
- Ultraviolet radiation A (Vol. 55, 1992).
- Ultraviolet radiation B (Vol. 55, 1992).
- Ultraviolet radiation C (Vol. 55, 1992).
- Vinyl bromide (593-60-2) (Vol. 19, 1979; Vol. 39, 1986; Suppl. 7, 1987; Vol. 71; 1999). *Note:* this chemical was already in Group 2A in Suppl. 7, 1987.

**Chemicals/Agents upgraded from Group 2B to Group 2A under H. Vainio (no details given)**

- Acrylamide (79-06-1) (Vol. 60, 1994).
- Clonorchis sinensis (infection with) (Vol. 61, 1994).
- Styrene-7,8-oxide (96-09-3) (Vol. 11, 1976; Vol. 19, 1979; Vol. 36, 1985; Suppl. 7, 1978; Vol. 60; 1994).

**Chemicals/Agents upgraded from Group 2B to Group 2A under J. Rice (see Appendix C for details and comments)**

1. 1,2-Dimethylhydrazine (540-73-8) (Vol. 4, 1974; Suppl. 7, 1987; Vol. 71; 1999).
2. Etoposide (33419-42-0) (Vol. 76; 2000).
3. Glycidol (556-52-5) (Vol. 77; 2000).
4. Methyl methanesulfonate (66-27-3) (Vol. 7, 1974; Suppl. 7, 1987; Vol. 71; 1999).
5. Teniposide (29767-20-2) (Vol. 76; 2000).

APPENDIX C

*IARC Agents and Exposure Circumstances Upgraded Using “Mechanism”*

**Five Chemicals Upgraded in IARC Monographs 67 – 80 from Group 2B (“possibly carcinogenic to humans”) to Group 2A (“probably carcinogenic to humans”)**

For each of the five chemicals, the IARC rationale is given followed by my comments. The conclusions made by IARC involve a Working Group, and my commentaries should be viewed as mine only.

1. *1,2-Dimethylhydrazine (IARC Vol 4, 1974; Suppl. 7, 1987; Vol 71, 1999)*

“In making the overall evaluation, the Working Group took into account that 1,2-dimethylhydrazine is consistently mutagenic in a wide range of test systems and gives rise to a similar pattern of DNA damage in human and animal tissues *in vitro*.” It is not genotoxic in bacteria. Regarding the experimental cancer findings: “Whatever the route of administration, 1,2-dimethylhydrazine, if given at an appropriate dosage, produced in mice and rats a high incidence of adenomas and adenocarcinomas of the colon and, to a lesser extent, of the small bowel. When given with drinking water or by gavage at low single doses, it produced a high incidence of vascular tumours.” “In some experiments in rats, it produced ear duct papillomas and carcinomas, hepatocarcinomas, kidney adenomas, carcinomas and fibrosarcomas. When given to rats at very high single doses, it produced high incidences of nephroblastomas.” “In some strains of mice, it produced a high incidence of hormone-dependent angiosarcomas of the kidney capsule (males only), uterine sarcomas or vascular tumours and tumour-like lesions of the ovary.”

*Comment:* One could easily deduce that based on the experimental data of multiple target site cancers and single-exposure carcinogenesis this chemical belonged in group 2A, supported by but not solely dependent on the genotoxicity information. For many years, this chemical has been used as a standard for inducing and studying tumors of the large intestine.

2. *Etoposide (IARC Vol 76, 2000)*

“In reaching this conclusion, the Working Group noted that etoposide causes distinctive cytogenetic lesions in leukaemic cells that can be readily distinguished from those induced by alkylating agents. The short latency of these leukaemias contrasts with that of leukaemia induced by alkylating agents. Potent protein-masked DNA breakage and clastogenic effects occur in human cells *in vitro* and in animal cells *in vivo*.” Importantly, as with most cancer chemotherapeutic agents, IARC further stated that “Etoposide in combination with cisplatin and bleomycin is carcinogenic to humans (Group 1)” “causing acute myeloid leukemia.”

*Comment:* Interestingly, IARC did report that “In the patients with Langerhans cell histiocytosis, a strongly increased risk for acute myeloid leukaemia of the promyelocytic type was found after treatment with etoposide alone”; and continued on to speculate that “however, the possibility could not be ruled out that such patients have an inherently increased risk for acute promyelocytic leukaemia.” Further, “one cohort study of patients with Langerhans cell histiocytosis and several cohort studies of patients with germ-cell tumours or lung cancer treated with etoposide-containing chemotherapy showed increased risks for acute myeloid

leukaemia.” One could easily question why the IARC did not consider etoposide a Group 1 human carcinogen, given that IARC decided on “limited evidence in humans for the carcinogenicity of etoposide” and if one adds to that the combined therapy has been classified as Group 1, and adding mechanistic considerations then Group 1 is certainly realistic. IARC states that “treatment with etoposide alone” associates strongly with an “increased risk for acute myeloid leukaemia.” One can only wonder why such hesitation to place this DNA topoisomerase II inhibitor in Group 1!

3. *Glycidol (IARC Vol 77, 2000)*

“In making the overall evaluation, the Working Group took into consideration that glycidol is a direct-acting alkylating agent that is mutagenic in a wide range of *in-vivo* and *in-vitro* test systems.”

*Comment:* Surely this chemical belongs in 2A based on the experimental carcinogenicity data alone, given that glycidol caused tumors in both male and female rats and mice in a total of 16 different organs/tissues. Additionally, the exposure concentrations used for the two-year studies were relatively low: 37.5 and 75 mg/kg for rats and 25 and 50 mg/kg for mice. For IARC to indicate this chemical has been upgraded based on its alkylating activity seems a bit unnecessary, because of the magnitude of the carcinogenic responses and because all chemicals should be judged on the totality of the evidence. In this, and other recent cases, is IARC implying that without knowing the alkylating activity (or genotoxicity) of glycidol (or other chemicals), this chemical might have been placed in Group 2B, or perhaps even Group 3? I tend to think not.

4. *Methyl methanesulfonate (IARC Vol 7, 1974; Suppl 7, 1987; Vol 71, 1999)*

“In making the overall evaluation, the Working Group took into consideration that methyl methanesulfonate is a direct-acting methylating agent which is mutagenic in a wide range of *in-vivo* and *in-vitro* test systems.” As summarized in the *IARC Monograph*: “Methyl methanesulfonate was tested in rats by inhalation exposure and by subcutaneous and intraperitoneal administration, producing nasal tumours, tumours of the nervous system and tumours at the injection site. In rats, it was carcinogenic after administration of a single dose as well as following prenatal exposure. Following instillation into the bladder of rats, it potentiated the effect of N-methyl-N-nitrosourea. In one study, following oral administration in mice, it increased the incidence of lung tumours and of lymphomas.”

*Comment:* From these findings (especially being carcinogenic following a single exposure and prenatally as well) one would expect this chemical to have been placed into 2A based on these carcinogenic findings alone, without having to invoke that MMS is a “methylating agent.” Of course this methylating activity was well known long before 1999, and MMS is a “standard” laboratory carcinogen. MMS is another relatively unique chemical that causes lung cancers when given orally.

5. *Teniposide (IARC Vol 76, 2000)*

In reviewing the human data, IARC states that “One large, well-conducted cohort study of acute lymphoblastic leukaemia in the USA and one case-control study of childhood cancer in United Kingdom found strong positive associations between the incidence of acute myeloid leukaemia and treatment with teniposide. A dose-response relationship was found in the case-control study. In both studies, teniposide was administered with other cytotoxic drugs. Although some of the other agents may have contributed to the positive association seen in the cohort study, use of these agents has not been associated with acute myeloid leukaemia in other large studies of childhood cancer. “Further, to upgrade to 2A, “In reaching this conclusion, the Working Group noted that teniposide causes distinctive cytogenetic lesions in leukaemic cells that can be readily distinguished from those induced by alkylating agents. The short latency of these leukaemias contrasts with that of leukaemia induced by alkylating agents. Potent protein-masked DNA breakage and clastogenic effects occur in human cells *in vitro* and animal cells *in vivo*.”

*Comment:* The same rationale as used for etoposide, mentioned above, is used for teniposide as well. And for this cancer chemotherapeutic agent the epidemiologic evidence would appear adequate to place teniposide in IARC Group 1.

#### APPENDIX D

*IARC Agents and Exposure Circumstances Upgraded Using "Mechanism" from Group 3 ("unclassifiable regarding carcinogenicity to humans") to Group 2B ("possibly carcinogenic to humans")*

##### Six Agents

IARC Volumes	No. Chemicals Upgraded	Person Responsible
1-59	4	L. Tomatis*
60-61	0	H. Vainio
62-66	0	D. MacGregor/J. Wilbourn
67-80	2	J. Rice

\*Chiefs of IARC Monographs program at different periods: C. Agthe, J. Huff, H. Vainio, A. Aitio, J. Wilbourn.

*Note:* The following statement, used as the basis for upgrading, appears for each chemical on the IARC URL database that has been updated. Readers wishing more information about the older upgrades need to approach each *Monograph* for the upgrade rationale; in many cases the information is either not stated specifically as a rationale for upgrading or is sketchy or absent.

"(NB: Overall evaluation upgraded from 3 to 2B with supporting evidence from other data relevant to the evaluation of carcinogenicity and its mechanisms.)"

*Key:* Chemical name (CAS #) (*IARC Monographs* Volume No., year of publication)

##### Chemicals/Agents upgraded from Group 3 to Group 2B under L. Tomatis (no details given)

1. Bleomycins (11056-06-7) (Vol. 26, 1981; Suppl. 7; 1987)
2. Styrene (100-42-5) (Vol. 19, 1979; Suppl. 7, 1987; Vol. 60; 1994; Vol. 82, 2002 in press). *Note:* this chemical was already in Group 2B in Suppl. 7, 1987.
3. Diesel fuel, marine (Vol. 45; 1989). *Note:* Monograph should be updated as there is new information.
4. Gasoline (Vol. 45; 1989). *Note:* Monograph should be updated as there is new information.

##### Chemicals/Agents upgraded from Group 3 to Group 2B under J. Rice (see Appendix E for details and comments)

#### APPENDIX E

*IARC Agents and Exposure Circumstances Upgraded Using "Mechanism"*

##### Two Chemicals Upgraded in IARC Monographs 67-80 from Group 3 ("unclassifiable regarding carcinogenicity to humans") to Group 2B ("possibly carcinogenic to humans")

For each of these chemicals, the IARC rationale is given followed by my comments.

1. *Aziridine* (*IARC Vol. 9, 1975; Suppl 7, 1987; Vol. 71; 1999*)

"In making the overall evaluation, the Working Group took into consideration that aziridine is a direct-acting alkylating agent which is mutagenic in a wide range of test systems and forms DNA adducts that are promutagenic." According to IARC, "Aziridine produces genetic damage in bacteria, insects and mammalian cells in culture, as well as dominant lethal effects in mice." Regarding carcinogenicity, "Aziridine was tested for car-

cinogenicity in mice by oral administration, producing an increased incidence of liver-cell and pulmonary tumours. Subcutaneous injection of single doses in suckling mice produced an increased incidence of lung tumours in males. In one experiment in rats it increased the incidence of tumours at the injection site following injection in oil."

*Comment:* Importantly, lung tumors were induced following both oral and SC injection (single doses), not a typical finding using these routes of exposures. One might wonder if the genotoxic data were unavailable would IARC have kept this chemical in Group 3? Of course the totality of the available information demands this chemical being placed into Group 2, and maybe 2A would be more appropriate, especially if one considers that the genotoxicity information is mechanistically based. This chemical could have been placed into Group 2 in Supplement 7.

2. *1,2-Epoxybutane* (*IARC Vol. 47, 1989; Vol. 71, 1999*)

"In making the overall evaluation, the Working Group took into consideration that 1,2-epoxybutane is a direct-acting alkylating agent which is mutagenic in a range of test systems." According to IARC, "1,2-Epoxybutane induced morphological transformation, sister chromatid exchanges, chromosomal aberrations and mutation in cultured animal cells; however, in a single study, it did not induce unscheduled DNA synthesis in rat primary hepatocytes. It induced sex-linked recessive lethal mutations and translocations in *Drosophila melanogaster*, mitotic recombination in yeast, and mutations in yeast and fungi. 1,2-Epoxybutane induced DNA damage and mutations in bacteria." Regarding carcinogenicity, "1,2-Epoxybutane was tested for carcinogenicity by inhalation exposure in one study in mice and in one study in rats, producing nasal papillary adenomas in rats of both sexes and pulmonary alveolar/bronchiolar tumours in male rats. Oral administration of trichloroethylene containing 1,2-epoxybutane to mice induced squamous-cell carcinomas of the forestomach, whereas administration of trichloroethylene alone did not."

*Comment:* Again one might wonder what IARC would have done without having any genotoxicity information. In the only two bioassays reported, 1,2-epoxybutane caused tumors of the nose and tumors of the lung in rats. No carcinogenic effects were seen in the mice. In an oral chemical combination study with TCE in mice, 1,2-epoxybutane caused a few forestomach tumors. Thus, this chemical apparently induced application-site tumors. However, in one limited dermal exposure experiment (77 weeks) no skin tumors were reported. Perhaps this latter experiment should be repeated.

#### APPENDIX F

*IARC Agents and Exposure Circumstances Downgraded Using "Mechanism" from Group 2B ("possibly carcinogenic to humans") to Group 3 ("not classifiable as to its carcinogenicity to humans")*

(*Note:* one chemical in this Table was downgraded from 2A to 2B: acrylonitrile.)

##### 12 Agents

IARC Volumes	No. Chemicals Upgraded	Person Responsible
1-59	0	L. Tomatis*
60-61	0	H. Vainio
62-66	0	D. MacGregor/J. Wilbourn
67-81	12	J. Rice

\*Chiefs of IARC Monographs program at different periods: C. Agthe, J. Huff, H. Vainio, A. Aitio, J. Wilbourn.

*Note:* The following statement, used as the basis for downgrading, appears for each chemical on the IARC URL database that has been downgraded. Readers wishing more information need to approach each *Monograph* for the downgrade rationale.

Also, some chemicals may have been downgraded but have not been designated as such.

“(NB: Overall evaluation downgraded from 2B to 3 with supporting evidence from other data relevant to the evaluation of carcinogenicity and its mechanisms.)”

*Key:* Chemical name (CAS #) (IARC Monographs Volume No, year of publication)

#### One Chemical downgraded from Group 2A to Group 2B (see Appendix G for details and comments)

1. Acrylonitrile (107-13-1) (Vol. 19, 1979; Suppl. 7, 1987; Vol. 71, 1999)

*Note.* This chemical was evaluated as 2A in Suppl. 7, 1987, and was downgraded to 2B in Vol. 71, 1999. A statement such as given below does *not* appear with this listing in the IARC Web site listing of chemicals (whether more chemicals/agents would fit this category needs further study): “(NB: Overall evaluation downgraded from 2A to 2B with supporting evidence from other data relevant to the evaluation of carcinogenicity and its mechanisms.)”

#### Eleven Chemicals/Agents downgraded from Group 2B to Group 3 (see Appendix G for details and comments)

1. Amitrole (61-82-5) (Suppl. 7, 1987; Vol. 79, 2001)
2. Atrazine (1912-24-9) (Vol. 53, 1991; Vol. 73, 1999)
3. Di(2-ethylhexyl) phthalate (117-81-7) (Vol. 29, 1982; Suppl. 7, 1987; Vol. 77, 2000)
4. Ethylenethiourea (96-45-7) (Suppl. 7, 1987; Vol. 79, 2001)
5. Glass wool, insulation (Vol. 43, 1988; Vol. 81, 2002). *Note.* Volume in press.
6. d-Limonene (5989-27-5) (Vol. 56, 1993; Vol. 73, 1999). *Note.* This downgraded statement is attached to d-limonene on the IARC Web site but is incorrect because it was already a Group 3 in Vol. 56, 1993.
7. Melamine (108-78-1) (Vol. 30, 1986; Suppl. 7, 1987; Vol. 73, 1999). *Note.* This downgraded statement is attached to melamine on the IARC Web site but is incorrect because melamine was already a Group 3 in Suppl. 7, 1987.
8. Rock (stone) wool (Vol. 43, 1988; Vol. 81, 2002) See glass wool in text.
9. Saccharin (81-07-2) and its salts (Vol. 22, 1980; Suppl. 7, 1987; Vol. 73, 1999).
10. Slag wool (Vol. 43, 1988; Vol. 81, 2002) See glass wool in text.
11. Sulfamethazine (57-68-1) (Vol. 79, 2001).

### APPENDIX G

#### IARC Agents and Exposure Circumstances Downgraded Using “Mechanism”

#### Twelve Chemicals/Agents Downgraded in IARC Monographs 67–81

#### One Chemical Downgraded from Group 2A (“probably carcinogenic to humans”) to Group 2B (“possibly carcinogenic to humans”)

For each of these chemicals, the IARC rationale is given followed by my comments.

##### 1. Acrylonitrile (IARC Vol. 71, 1999)

Downgraded from 2A (Suppl. 7, 1987) to 2B. According to IARC, “Acrylonitrile forms adducts with proteins and glutathione. It also forms DNA adducts in vitro, but only after cytochrome P450 bioactivation, most likely through its epoxide metabolite (cyanoethylene oxide), which is also formed in vivo. Acrylonitrile-haemoglobin adducts have been detected in exposed workers. Acrylonitrile is mutagenic in vitro; in *Salmonella* systems, bioactivation (to cyanoethylene oxide) is required, but in *Escherichia coli* and in rodent systems, bioactivation by an added microsomal system is not required. The results of genotoxicity experiments in vivo have in most cases been negative, although acrylonitrile is mutagenic in *Drosophila*.” Thus, acrylonitrile is

genotoxic both in vitro and in vivo, and causes adducts in humans. Regarding carcinogenicity, “Acrylonitrile has been tested for carcinogenicity in one study in rats by inhalation with pre- and postnatal exposure. This study confirmed the findings of increased incidences of glial cell tumours of the central nervous system found in several previous studies that had not been fully reported and also found increases in malignant mammary tumours, Zymbal gland carcinomas, benign and malignant hepatocellular tumours and extrahepatic angiosarcomas.” Thus five organ/tissue sites of carcinogenesis.

*Comment.* More recent information from the National Toxicology Program, and subsequent to the IARC evaluation, confirms and extends the acrylonitrile tumor patterns in experimental animals. The NTP two-year gavage studies in mice showed “clear evidence of carcinogenic activity” that acrylonitrile caused forestomach and harderian gland neoplasms in male and female B6C3F1; neoplasms of the ovary and lung in female mice may have been related to administration of acrylonitrile. The NTP did not study this chemical in rats. Furthermore, supporting “Nonneoplastic lesions of the forestomach and harderian gland in males and of the forestomach and ovary in females were associated with administration of acrylonitrile by gavage for 2 years.” Thus, a total of nine organ/tissue sites of acrylonitrile-associated tumor induction.

IARC does not give specifics for why this chemical was downgraded, but they opine “On balance and given the largely unresponsive findings from the other (human) studies, the evidence from this one (positive human) study was not considered to be sufficiently strong to conclude that there was a credible association between acrylonitrile and lung cancer. Thus, the earlier indications of an increased risk among workers exposed to acrylonitrile were not confirmed by the recent, more informative studies.” Nonetheless the positive study remains, and the experimental studies clearly identify a multi-species/strain and multi-site carcinogen, including brain. And acrylonitrile adducts have been found in workers. Thus, together with the animal cancer findings and the genetic toxicology data (mutagenic, clastogenic, adducts in humans) would seem to have been fully adequate to keep acrylonitrile in 2A. This is supported further by the human and animal evidence regarding concordance in lung cancer.

#### Eleven Chemicals/Agents downgraded from Group 2B (“possibly carcinogenic to humans”) to Group 3 (“not classifiable as to its carcinogenicity to humans”)

##### 2. Amitrole (IARC Vol. 79, 2001): IARC

“In making its evaluation, the Working Group concluded that amitrole produces thyroid tumours in mice and rats by a non-genotoxic mechanism, which involves interference with the functioning of thyroid peroxidase, resulting in a reduction in circulating thyroid hormone concentrations and increased secretion of thyroid-stimulating hormone. Consequently, amitrole would not be expected to produce thyroid cancer in humans exposed to concentrations that do not alter thyroid hormone homeostasis. An additional consideration of the Working Group, based on the lack of genotoxicity of amitrole, was that the liver tumours in mice and benign pituitary tumours in rats were also produced by a non-genotoxic mechanism. Evidence from epidemiological studies and from toxicological studies in experimental animals provide compelling evidence that rodents are substantially more sensitive than humans to the development of thyroid tumours in response to thyroid hormone imbalance.”

*Comment.* In 1987 (Suppl. 7:92-93), IARC evaluated the information available on amitrole and decided this herbicide exhibited “inadequate evidence of carcinogenicity to humans” and “sufficient evidence of carcinogenicity to experimental animals,” placing it in Group 2B. Between this 1987 evaluation and the later 2001 IARC evaluation there was no additional experimental or epidemiologic carcinogenesis information.

Thus, to hypothesize that amitrole will not cause thyroid tumors, liver tumors, or pituitary tumors in humans because of “non-genotoxic mechanisms” seems to place considerably more

confidence in these speculations than one should, especially considering worker exposures to this and other herbicides, pesticides, fertilizers, and additional chemicals in general. Importantly, to stress that these carcinogenic sites in animals would not be operative in humans stands on at least two false and glaring pretentious and posturing factors: there is no unequivocal edict to expect exact site-for-site concordance among various species (strains) of mammals, including humans, and the adoption of these “mechanisms” as unequivocal on the one side and that they would not operate in humans is disingenuous. Further, IARC concludes unconvincingly that “Consequently, amitrole would *not be expected* [emphasis mine] to produce thyroid cancer in humans exposed to concentrations that do not alter thyroid hormone homeostasis.” One wonders if this “mode-of-action” regarding both animals and humans has been adequately tested. How does one know that humans with or without thyroid dysfunction will not get cancer from amitrole exposures? Obviously, the implication of “would not be expected” is not good enough when human health is at risk. In their view IARC dismisses the relevance of the thyroid tumors, but IARC does not adequately mention the other carcinogenic organ sites induced by amitrole, albeit simply that they are induced by non-genotoxic mechanisms.

### 3. Atrazine (IARC Vol 73, 1999)

In 1991 IARC (IARC Vol. 53, 1991) placed atrazine in Group 2B based largely on experimental bioassay findings. “Atrazine was tested for carcinogenicity in one experiment by oral administration to rats, producing increased incidences of mammary tumours (mainly benign) in males and of uterine adenocarcinomas and tumours of the haematopoietic system in females. It was also tested by intraperitoneal administration to mice; it was stated in a preliminary report to have produced an increase in the incidence of lymphomas.” And mechanistically, “In making the overall evaluation, the Working Group took into consideration the following supporting evidence. The increased risks for tumours that are known to be associated with hormonal factors, which were observed in studies of both animals and human beings, are consistent with the known effects of atrazine on the hypothalamic–pituitary–gonadal axis.”

*Comment.* This 1991 evaluation and rationale was overturned in 1999, when atrazine was downgraded to Group 3: “In making its overall evaluation, the Working Group concluded that the mammary tumours associated with exposure to atrazine involve a non-DNA-reactive, hormonally mediated mechanism. In reaching the conclusion, the following evidence was considered: (a) Atrazine produces mammary tumours (fibroadenomas, adenocarcinomas) only in intact female Sprague-Dawley rats (not in Fischer 344 rats, CD-1 mice or ovariectomized Sprague-Dawley rats) and does not increase the incidences of other tumour types. (b) Atrazine affects neuroendocrine pathways of the hypothalamus to accelerate the onset of reproductive senescence in female Sprague-Dawley but not Fischer 344 rats. (c) Atrazine does not have intrinsic oestrogenic activity. (d) There are critical interspecies differences in the hormonal changes associated with reproductive senescence. Therefore, there is strong evidence that the mechanism by which atrazine increases the incidence of mammary gland tumours in Sprague-Dawley rats is not relevant to humans. Atrazine is not classifiable as to its carcinogenicity to humans (Group 3).”

These hypotheses are just that: speculation. One might even say audacious speculation. Further, (a) above is not accurate, (b) and (d) make little relevant sense, and (c) has little meaning. Thus, the second IARC Working Group (Vol 73, 1999) seems to have ignored the other carcinogenic observations: uterine adenocarcinomas and tumors of the hematopoietic system and lymphomas, as well as total malignant tumors. In another study tumors of the pituitary gland and mammary glands were increased. IARC, citing industry studies and hypotheses, discounted increases in testicular tumors in male rats apparently because the high-dose group lived longer and because the incidence rate in the high dose group fits within the historical range.

However, the most proper comparison is between the exposed groups and the concurrent control group, since these are randomly allocated from the same litters and represent greater contemporary sameness than do historical groups, which may “change” over time. Thus, if the control group is “low” for interstitial cell tumors, then logically so are the other groups; likewise, if the lower doses did not produce a carcinogenic effect on the reproductive organs in males then these too may be considered “like controls” since their rates were also below the historical incidence (interestingly, epithelial hyperplasia of the prostate was increased in rats, an uncommon event).

A recent epidemiological study by industry shows increases in prostate cancer in workers exposed primarily to atrazine.<sup>52</sup> The analysis of data reported for the actively employed plant workers whose exposure histories were longest indicated that 11 were diagnosed as having prostate cancer, versus 1.2 expected, based on Louisiana statewide comparison (SIR = 918; C.I. = 458-1,642). Syngenta’s report further acknowledged that “(t)he overall study group (employees and contract workers) had more than expected cancers of the buccal cavity (3/2.1 obs/exp), esophagus (2/0.7), stomach (2/0.9), urinary bladder (3/1.6), thyroid glands (2/0.6) and lymphohematopoietic system (7/4.5).” Clearly these findings discredit the rationale used by IARC to discount the experimental data showing carcinogenic responses in several organs. Further, for IARC 1999 to use the same “hormonal mechanism” to overturn IARC 1991, who considered this hormonal effect to be relevant to the evaluation, seems strange indeed

### 4. Di(2-ethylhexyl) phthalate (IARC Vol. 29, 1982; Suppl 7,1987; IARC Vol. 77,2000)

In all three evaluations IARC decided: “There is inadequate evidence in humans for the carcinogenicity of di(2-ethylhexyl) phthalate. There is sufficient evidence in experimental animals for the carcinogenicity of di(2-ethylhexyl) phthalate.” In the first two *Monographs* the IARC concluded for Group 2B, whereas in the latter case IARC downgraded to Group 3. No epidemiologic study has been reported on the potential carcinogenicity of DEHP, and cancer epidemiologic studies of hypolipidemic fibrate drugs (peroxisome proliferators) are inconclusive. Always amusing to me is when industry emphasizes that DEHP (or phthalates or any other chemicals) has “not produced a single cancer in workers over the last so-many years” when in fact they fail or neglect to mention that no epidemiologic study has every been done or reported on the particular chemical they indicate is safe.

The carcinogenicity of DEHP in experimental animals is unequivocal: dose-related tumors of the liver were observed in both male and female rats and mice in several strains. The first reported evidence of carcinogenicity was by the NTP, and these findings stimulated a massive effort toward ascertaining a mechanism(s) of carcinogenic activity. Unfortunately, this research on DEHP (and gasoline and d-limonene and melamine and saccharin and others) appears to have been by a vested interest to show that the carcinogenic responses in animals were not relevant to humans. These hypotheses have yet to be proven.<sup>53</sup>

IARC (Vol. 77,2000) continues: “In making its overall evaluation of the carcinogenicity to humans of di(2-ethylhexyl) phthalate, the Working Group took into consideration that (a) di(2-ethylhexyl) phthalate produces liver tumours in rats and mice by a non-DNA-reactive mechanism involving peroxisome proliferation; (b) peroxisome proliferation and hepatocellular proliferation have been demonstrated under the conditions of the carcinogenicity studies of di(2-ethylhexyl) phthalate in rats and mice; and (c) peroxisome proliferation has not been documented in human hepatocyte cultures exposed to di(2-ethylhexyl) phthalate nor in the liver of exposed non-human primates. Therefore, the mechanism by which di(2-ethylhexyl) phthalate increases the incidence of hepatocellular tumours in rats and mice is not relevant to humans.” Again, a too-strongly worded-endorsement of a non-universally endorsed hypothesis.<sup>28,31,53,54</sup> There is likewise considerable debate about the reliability of the DEHP–human liver *in vitro* studies, especially regarding the experimental design and

the viability of the human liver samples. Melnick<sup>53</sup> indicates that “the mechanism of liver cancer induction by DEHP and other peroxisome proliferators is not understood.” And that peroxisome proliferation is not an obligatory precursor step in DEHP carcinogenicity. Tomatis<sup>1</sup> strongly cautioned that workers and consumers would likely be exposed to unrestricted use of DEHP based on the IARC downgrading, and this could be catastrophic if adequate testing of these speculative mechanisms proved them to be incorrect.

5. *Ethylene thiourea (Suppl. 7:207;1987; IARC Vol 79:659; 2001*

In 1987, IARC reviewed ETU for the first time and “In three studies, ethylene thiourea produced high incidences of follicular carcinomas of the thyroid in rats after its oral administration; animals of each sex were affected, although male rats had a higher incidence. Lower doses produced thyroid follicular hyperplasia. In mice, oral administration of ethylene thiourea produced liver tumours; the thyroids of these animals were not examined. In dosed rats, either shortened survival due to thyroid tumours or altered body weights may have obscured a potential carcinogenic effect on the liver due to administration of ethylene thiourea. A feeding study in hamsters showed no effect.” IARC placed ETU in Group 2B, with sufficient evidence of carcinogenicity in experimental animals.

In 2001, IARC summarized the available animal data (human data were considered inadequate) as “Ethylenethiourea was tested for carcinogenicity by oral administration in two studies in three strains of mice, with perinatal exposure in one study. It was also tested in five studies in rats by oral administration, with perinatal exposure in one study. In mice, it produced thyroid follicular-cell tumours and tumours of the liver and anterior pituitary gland. In rats, it consistently produced thyroid follicular-cell adenomas and carcinomas. Ethylenethiourea did not cause neoplasms in one strain of hamsters.” This time, however, and despite “sufficient evidence of carcinogenicity in animals,” IARC decided “Ethylenethiourea is not classifiable as to its carcinogenicity to humans (Group 3).” Because they claim “In making its evaluation, the Working Group concluded that ethylenethiourea produces thyroid tumours in mice and rats by a non-genotoxic mechanism, which involves interference with the functioning of thyroid peroxidase resulting in a reduction in circulating thyroid hormone concentrations and increased secretion of thyroid-stimulating hormone. Consequently, ethylenethiourea would not be expected to produce thyroid cancer in humans exposed to concentrations that do not alter thyroid hormone homeostasis. An additional consideration of the Working Group, based on the lack of genotoxicity of ethylenethiourea, was that the liver tumours and benign pituitary tumours in mice were also produced by a non-genotoxic mechanism. Evidence from epidemiological studies and from toxicological studies in experimental animals provide compelling evidence that rodents are substantially more sensitive than humans to the development of thyroid tumours in response to thyroid hormone imbalance.” Another common experimental mistake is to base these speculations on very-short-term (at times single exposures) studies and extrapolate the findings to the two-years exposure condition studies as if they would be the same. Not true. Unless the mechanistic information is gathered under the same conditions as the cancer bioassay is carried out, the findings are not exchangeable. For example, the whole issue of the role of cell proliferation in chemical carcinogenesis is another well-studied mechanistic issue that clearly shows that data collected from short-term exposures do not predict or mimic long-term bioassay exposures, data or cancer outcome.<sup>32</sup>

*Comment.* Surely the use of and IARC reliance on “rodents are substantially more sensitive” needs scientific proof before one dismisses these carcinogenic effects. This of course is the same wording and rationale used to downgrade amitrole, and I predict this will be used to downgrade all “non-genotoxic” chemicals causing tumors of the thyroid in animals. Again, IARC dismisses the carcinogenic activity of ETU in both the liver and pituitary glands because purportedly they “were also produced by a non-genotoxic

mechanism.” IARC further seems to ignore the well-known endocrine disruptor activity of atrazine as being likely related to the hormonally mediated carcinogenesis.

Two key (and repetitive) factors are necessary. To opine that so-called nongenotoxic mechanisms in animals make exposures to the same chemicals in humans safe has no credibility whatsoever: we know many non-genotoxic human carcinogens (e.g., DES; TCDD) that cause cancer in humans. And to discount these other tumor sites (liver and pituitary glands) with the same argument makes one more reluctant to take these claims seriously when human health is at stake. To accept this edict one must believe that all three tumor sites arise by the same “mechanism.” Not true. Also, IARC uses the qualifier as if to make those individuals exposed to this “vulcanization accelerator in the rubber industry . . . (and) degradation product of and an impurity in ethylenbisdithiocarbamate fungicides” feel safe: “ethylenethiourea **would not be expected** (emphasis added) to produce thyroid cancer in humans exposed to concentrations that do not alter thyroid hormone homeostasis.” This again is a hypothesis yet to be tested or demonstrated in human populations exposed to these ETU chemicals. Further, humans, unlike experimental animals, are exposed to many and myriad chemicals, and often live in substandard socioeconomic conditions while working with these chemicals on farms and in produce units. I know of no study whereby ETU in combination with other chemicals was tested for co-carcinogenic or promotional effects. The IARC conclusion does not claim that humans are non-responsive, only that they are less sensitive. Is that an adequate reason to downgrade, and profess safety for human exposures?

6. *Glass wool, insulation (IARC Vol. 43; 1988; IARC Vol. 81; 2002; in press)*

IARC first evaluated glass wool (or fiberglass) and other “man-made mineral fibres” in 1988, and considered glass wool in Group 2B: “possibly carcinogenic to humans,” based largely on “sufficient evidence of carcinogenicity in experimental animals” and “inadequate evidence in humans.” While some thought this evaluation was lower than the human evidence indicated,<sup>55,56</sup> the second evaluation from IARC in October 2001 (IARC Web) was clearly unexpected: “the more commonly used vitreous fibre wools including insulation glass wool, rock (stone) wool and slag wool are now considered not classifiable as to carcinogenicity to humans (Group 3).” IARC insists that “Epidemiologic studies published during the 15 years since the previous *IARC Monographs* review of these fibres in 1988 provide no evidence of increased risks of lung cancer or of mesothelioma (cancer of the lining of the body cavities) from occupational exposures during manufacture of these materials, and inadequate evidence overall of any cancer risk” (IARC Web site).

The “mechanistic” thesis put forth here by IARC settles on the notion that glass wool has little or no persistence in vivo, and thus will not lead to cancer in humans. The evidence for this hypothesis in humans is sketchy at best, with no valid study reported on dissolution rates or persistence. Further, “Glasswool induced numerical and structural chromosomal alterations but not sister chromatid exchanges in mammalian cells in vitro. It caused morphological transformation in rodent cells in vitro; transformation was found to be dependent on fibre length and diameter. Glasswool did not induce mutation in bacteria” (IARC Vol. 43:39; 1988). Showing cell transformation in Syrian hamster embryo cells, Oshimura et al.<sup>57</sup> suggested that the “physical characteristics of the fibers determine their ability to induce cell transformation and their ability to induce chromosome mutations, suggesting a possible mechanistic relationship.” Thus, to downgrade glass wool from “possibly carcinogenic to humans” to “unclassifiable” puts a greater health risk burden on glass wool workers and insulation installers. The evidence of carcinogenicity in animals and the clastogenicity in SHE cells clearly demonstrate the ability of glass wool fibers to present carcinogenic hazards to humans. Further, an independent evaluation of the epidemiologic data support continuing to have glass wool in at least Group 2B, or more appropriately, in Group 2A.<sup>55,56</sup>

These findings and others were evaluated by Infante et al.,<sup>55,56</sup> who reached the conclusion that "From our comprehensive review of the available information, we conclude that fibrous glass materials are carcinogenic, and . . . Our review then examines the carcinogenic potency of glass fibers to humans in comparison with asbestos fibers and concludes that on a fiber-per-fiber basis, glass fibers may be as potent or even more potent than asbestos."

Conversely, the 2002 IARC indicated that "Epidemiologic studies published during the 15 years *since* the previous IARC *Monographs* review of these fibres in 1988 provide no evidence of increased risks." Others differ with this latest IARC evaluation of the available human and animal data,<sup>55,56</sup> and the NTP<sup>9</sup> lists glass wool (respirable size) as being "reasonably anticipated to be a human carcinogen."

7. *d-Limonene* (Vol. 56, 1993; Vol. 73, 1999)

*Note.* This downgraded statement is attached to d-limonene on the IARC Web site but is incorrect because it was already a level 3 in Vol. 56, 1993, the first time d-limonene was evaluated.

Nonetheless, IARC in Vol. 73 opined that "In making its overall evaluation of the carcinogenicity to humans of d-limonene, the Working Group concluded that d-limonene produces renal tubular tumours in male rats by a non-DNA-reactive mechanism, through an  $\alpha$ -2u-globulin-associated response. Therefore, the mechanism by which d-limonene increases the incidence of renal tubular tumours in male rats is not relevant to humans." In any event, the experimental carcinogenesis data support d-limonene in Group 3 (single organ in a single sex and single species response) regardless of the mechanistic rationale put forth by IARC.

*Comment.* In fact, this overconfident and hasty rationale is speculation at best.<sup>23,28,29,33,34,37</sup> Even if one were certain of a mechanism of carcinogenesis in animals (which we are not) that would not necessarily mean the same exact mechanism or mechanisms would be functioning singularly or exactly in another species.<sup>27,28,30,32</sup> We have seen, for example, different target sites and likely different mechanisms of carcinogenesis in various animal species, including humans. Why would we not expect this?

8. *Melamine* (Vol. 30, 1986; Suppl. 7, 1987; Vol. 73, 1999)

"(NB: Overall evaluation downgraded from 2B to 3 with supporting evidence from other data relevant to carcinogenicity and its mechanisms.)" *Note.* This downgraded statement is attached to melamine on the IARC web site but is incorrect because melamine was already a level 3 in Suppl. 7, 1987.

Nevertheless, IARC remarked that "In making its overall evaluation, the Working Group noted that the non-DNA-reactive mechanism by which melamine produced urinary bladder tumours in male rats occurred only under conditions in which calculi were produced."

*Comment.* The difficulty with statements such as this is that the evidence to support them is nothing more than empirical: calculi or "stones" or urolithiasis is present in the urinary bladder of an animal that also has a tumor of the urinary bladder. In the case of melamine there were adenocarcinomas of the urinary bladder in eight male rats and an additional male rat with a papilloma, with seven of the nine having a stone. Thus, two male rats did not have a stone and, importantly, two melamine female rats had transitional cell tumors of the urinary bladder without stones. Further, nearly half the rats had nephropathy and most melamine females had chronic inflammation. One also wonders how IARC is so certain of a "non-DNA-reactive mechanism"?

Significantly, in the NTP study, "Acute and chronic inflammation and epithelial hyperplasia of the urinary bladder were found in increased incidence in dosed male mice. The incidence of bladder stones in dosed male mice was increased relative to controls (control, 2/45, 4%; low dose, 40/47, 85%; high-dose, 41/45, 93%); however, there was no evidence of bladder tumor development in this species. Also, four high-dose female mice had bladder stones without any tumors."<sup>58,59</sup> Thus, overall there were considerably more animals with stones in the urinary bladder without having tumors of the urinary bladder than there were with stones

having tumors. If "stones" were to unequivocally turn out to be "the" mechanism, then why didn't the mice have tumors as well? One wonders why the female rats had no stones? Much more work needs to be done before assigning with such adamancy this empirical mechanism to the induction of tumors of the urinary bladder. This should pertain to the theory of saccharin-associated tumors of the urinary bladder as well (see below).

9. *Rock (stone) wool* (Vol. 43, 1988; Vol. 81, 2002; *in press*)  
See glass wool, no. 6.

10. *Saccharin and its salts* (IARC Vol. 22, 1980; Suppl. 7, 1987; Vol. 73, 1999)

In 1987 IARC placed saccharin in Group 2B based on "sufficient evidence in experimental animals." In 1999, IARC, "In making its evaluation, the Working Group concluded that sodium saccharin produces urothelial bladder tumours in rats by a non-DNA-reactive mechanism that involves the formation of a urinary calcium phosphate-containing precipitate, cytotoxicity and enhanced cell proliferation. This mechanism is not relevant to humans because of critical interspecies differences in urine composition." One can only ask: what does that statement mean? "Urine composition"? IARC concluded that "There is sufficient evidence in experimental animals for the carcinogenicity of sodium saccharin." But then IARC goes on to ignore these findings, downgrading saccharin to Group 3.

IARC summarizes the genotoxicity data as "Sodium saccharin was mutagenic in host-mediated and body fluid assays and caused DNA single-strand breaks in hepatic and renal cells of mice; however, bile from rats exposed to sodium saccharin was not mutagenic. Sodium saccharin did not cause DNA damage and did not bind covalently to DNA of rat liver or bladder. It induced genotoxic effects in human and rodent cells and in *Drosophila* and yeast. It was not mutagenic to bacteria."

"The positive results for genotoxicity found with sodium saccharin in mammalian cells *in vitro* have been hypothesized to result from increased osmolality (i.e. nonspecific ionic effects). This hypothesis would appear to explain some but not all of the findings of sister chromatid exchange, chromosomal aberrations and gene mutations *in vitro*. The few positive results seen in mice treated with sodium saccharin *in vivo* would not be readily explained by ionic influences." And yet IARC moved in favor of the "precipitate" mechanism, when in fact there are mutagenic and clastogenic activities. IARC of course has most often in the past used this type of genotoxic information to upgrade chemicals from one Group to another. In this case IARC seems to make an exception. Some studies have shown that exposure to saccharin does not increase the urinary pH and osmolality. Furthermore, saccharin causes bladder cancer not only in male rats but also female rats, whose urine has lower levels of protein and a higher pH.

Further, these IARC phrases from the above paragraph do not give much confidence in allowing unregulated saccharin exposures (workers) and consumption (consumers): "have been hypothesized to result from"; "hypothesis would appear to explain some but not all"; "would not be readily explained by."

Unfortunately, the NTP has removed saccharin from their Report on Carcinogens (RoC) using the same guise of mechanism. (NTP Web site): "Saccharin has been removed from the 9th edition (of the RoC). The Calorie Control Council nominated saccharin for delisting, which led to a new review of the carcinogenicity data for saccharin. Saccharin had been listed in the RoC as "reasonably anticipated to be a human carcinogen" since 1981. The basis for this listing was sufficient evidence of carcinogenicity in experimental animals. Saccharin was removed from the RoC after this extensive review determined that the rodent cancer data are not sufficient to meet the current criteria to list this chemical in the RoC as a "reasonably anticipated human carcinogen." This is based on the determination that the observed bladder tumors in rats arose from a mechanism that is not relevant to humans."

*Comment.* Interestingly and importantly, four separate "expert" groups evaluated saccharin for the NTP regarding whether or not

to delist from the RoC. The composite “voting” was 22 to delist and 12 not to delist, far from overwhelming agreement on an important public health issue. Significantly, the NTP Board of Scientific Counselors (nongovernment scientists), after less than adequate discussion, nevertheless voted in the majority (4 to 3) not to delist. Additionally, 5–6 experts in chemical carcinogenesis were asked the same question and again the majority “vote” was for not to delist. And of course most of the delist evaluation centered on consumer exposures, whereas equal or more concern should have been devoted to saccharin workers, who receive larger and longer exposures, in particular now that both the IARC and NTP have “delisted” the risk of saccharin.

Thus, IARC and the NTP are taking mechanism to the next level of obfuscation and sheer speculation. Apparently, this “precipitate” does not occur in female rats with tumors of the urinary bladder, and clearly this can not be used to explain the significant increase in liver tumors in mice. There is some but limited evidence of tumors of the thyroid in mice. Increases in other organ tumor sites have been reported as well. So here we have a purported “mode of action” that makes little sense (including the fact that not all male rats with this precipitate get tumors of the urinary bladder), does not explain the “different” mechanism in female rats (which apparently do not exhibit this “urine composition and precipitate” of male rats, and who have lower levels of urinary proteins), and yet “another” mechanism for mouse liver tumors (and the other tumors associated with saccharin exposure). Further, there are exposure concentrations used in male rats that caused tumor formation with no precipitate. Also, the “precipitate mechanism” does not account for the promoter and co-carcinogenic activity of saccharin. Perhaps an NTP-type “modern” bioassay should be done with saccharin to settle this issue.

Additionally, a study by the National Cancer Institute reported that a cohort of women taking saccharin had an increased incidence of tumors of the urinary bladder (obviously the same site as in rats exposed to saccharin and thus more than relevant), which should not be ignored. IARC reports on these thusly: “In spite of the fact that three studies showed high, statistically significant relative risks for small subsets of consumers of very large amounts of artificial sweeteners, the finding was limited to men in one study and to women in the other two.” I wonder if this should bring comfort to those individuals in the “small subsets” of women who had cancer of the urinary bladder?

Overall, with the available carcinogenesis information in animals and humans, with the evidence of carcinogenicity in female rats, with the evidence of liver tumors, with the evidence of thyroid tumors, with the evidence of other tumor sites, with the evidence of co-carcinogenicity, genotoxicity, and in particular clastogenicity, perhaps the saccharin issue needs to be revisited.

11. *Slag wool* (IARC Vol. 43, 1988; Vol. 81, 2002; in press)  
See glass wool above, no. 6.

12. *Sulfamethazine* (IARC Vol. 79, 341; 2001)

As this is the first time that sulfamethazine was evaluated by IARC, one wonders how it could be considered downgraded from 2B to 3? No explanation is given in the *Monograph* for this IARC Web site designation listing it as such. Is this simply “deception” whereby IARC evaluates the data as Group 2B and at the same meeting downgrades it to Group 3 based on a mechanistic hypothesis?

IARC considers that “Sulfamethazine produces thyroid tumours in mice and rats by a non-genotoxic mechanism, which involves inhibition of thyroid peroxidase resulting in alterations in thyroid hormone concentrations and increased secretion of thyroid-stimulating hormone. Consequently, sulfamethazine would be expected not to be carcinogenic to humans exposed to doses that do not alter thyroid hormone homeostasis.”

“Evidence from epidemiological studies and from toxicological studies in experimental animals provide compelling evidence that rodents are substantially more sensitive than humans to the development of thyroid tumours in response to thyroid hormone imbalance.”

*Comment.* Where and what is this “compelling evidence that rodents are substantially more sensitive than humans to the development of thyroid tumours in response to thyroid hormone imbalance”? How does one determine this sensitivity imbalance? This is also the same mechanistic/speculative rationale that is used to downgrade both amitrole and ethylene thiourea. Does this mean that any chemical that induces tumors of the thyroid in animals will be immediately downgraded, and thus one labels all thyroid carcinogens “safe”?

Of course, these IARC reasons are speculative on the notion that only genotoxic chemicals may be carcinogenic to humans, when in fact this is not the case; e.g., DES, TCDD, others. This IARC rationale also presumes that this and other thyroid-active chemicals cause tumors only when thyroid gland homeostasis is disturbed. Because lots of humans have thyroid hormonal imbalances/dysfunctions, might one wonder whether these people, and more importantly, workers exposed to sulfamethazine (or amitrole or ETU) would be at increased risk of cancer of the thyroid? Or other organs? Further, if this were the mechanism should one would expect more or all animals in these studies to develop tumors of the thyroid? And they do not. For example, diffuse and focal follicular-cell hyperplasias were observed in the three highest concentrations in male mice and in the top two levels in female mice, yet tumors were observed only in the highest-dosed group of each sex. Should this give us pause from embracing this mechanistic hypothesis of “complete safety”? The authors also reported a marginal increase in liver tumors, but IARC apparently discounted these.