Appendixes

Contents

Appendix Am—A Comparison of the National Cancer Institute's and the International Agency for Research on Cancer's Evaluation of Bioassay Results

A working group assembled by the International Agency for Research on Cancer (IARC) reevaluated data about 354 chemicals previously evaluated and described in the first 20 IARC monographs (185,186). The working group developed the following criteria for grading evidence about carcinogenicity. The first three categories are essentially the same as those used in earlier IARC compilations (344), and two new categories were added:

> *Sufficient evidence* of carcinogenicity indicates that there is an increased incidence of malignant tumours: (a) in multiple species or strains; (b) in multiple experiments (preferably with different routes of administration or using different dose levels); (c) to an unusual degree with regard to incidence, site or type of tumour, or age at onset. Additional evidence may be provided by data concerning dose-response effects, as well as information on mutagenicity or chemical structure.
>
> *Limited evidence* of carcinogenicity means that the data suggest a carcinogenic effect but are limited because: (a) the studies involve a single species, strain, or experiment, *or* (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting, or (c) the neoplasms produced often occur spontaneously or are difficult to classify as malignant by histological criteria alone (e.g., lung and liver tumours in mice).
>
> *Inadequate evidence* indicates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect.
>
> *Negative evidence* means that within the limits of the tests used, the chemical is not carcinogenic. The number of negative studies is small, since in general, studies that show no effect are less likely to be published than those suggesting carcinogenicity.
>
> No *data* indicates that data were not available to the working group (185).

IARC (185) made the following statement about the value of bioassay results:

> . . . in the absence of adequate data in humans it is reasonable, for practical purposes, to regard chemicals for which there is *sufficient evidence* of carcinogenicity (i. e., a causal association) in animals as if *they presented a carcinogenic risk for humans.* The use of the expressions "for practical purposes" and "as if they presented a carcinogenic risk" indicates that at the present time a correlation between carcinogenicity in animals and possible human risk cannot be made on a scientific basis, but rather only pragmatically, with the intent of helping regulatory agencies in making decisions related to the primary prevention of cancer. (Emphasis in original.)

The largest single testing effort is the National Cancer Institute's (NCI)'s Carcinogenesis Testing Program (now a part of the National Toxicology Program (NTP)). Griesemer and Cueto (146) analyzed the results of NCI's testing 190 chemicals and placed each tested chemical into one of nine classifications (see table A-l). Ninety-eight of the 190 were judged to be carcinogenic (classifications 1 through 5); 28 were equivocal (classification 6); and 64 were noncarcinogenic (classifications 7 through 9). The NCI results had earlier been reviewed by a panel of governmental and nongovernmental experts and Griesemer and Cueto drew on that review in their compilation.

A significant difference between the data analyzed by Griesemer and Cueto (hereafter referred to as the "NCI list") and by IARC is that all the NCI experiments were carried out according to a standard protocol (331). The IARC evaluations consider experiments carried out under a variety of protocols including those done by NCI.

Thirty-three chemicals appearing on the IARC list of 354 also appear in the NCI list. In table 39, such chemicals are listed in the class to which they were assigned by Griesemer and Cueto. For instance, the chemical chloroform appears in the NCI class 1, and it is also present on the IARC list. Following each listed chemical is an S, L, or 1, The letters indicate IARC's classifications of sufficient, limited, or inadequate evidence for carcinogenicity. In some cases, additional data that became available between the compilation of the 1978 (185) and 1979 (344) IARC lists changed a chemical from I or L to S; these changes are reflected in the table.

Comparisons between the NCI and IARC lists are not direct because different criteria were used, but the following scheme may be useful.

Evidence	*IARC classification*	*NC] classification*
Strongly positive	Sufficient evidence (S)	Classes 1, 2
Positive	Limited evidence (L)	Classes 3, 4, 5
Not Positive	Inadequate evidence (I)	Classes 6, 7, 8, 9

Agreement is good about the strongly positive chemicals, Seven of the 12 NCI class 1 chemicals were found to have "sufficient evidence" for carcinogenicity by IARC. Of the remaining five, some are likely to be reevaluated by IARC. For instance, reserpine was classified in the "inadequate evidence" group by IARC before the results of the NCI bioassay

Table A-1 .—National Cancer Institute (NCI Analysis of the Results of Testing 190 Chemicals[a] and the International Agency for Research on Cancer (IARC) Analysis of Chemicals[b c] That Appear on the NCI List

NCI Group A: Five categories of results showing increased tumor incidence, ordered with most convincing category being number 1.

Very strong evidence in 2 species.
317 chemicals

Chemicals among the 31 that appear on the IARC lists	Evidence for carcinogenicity, IARC 1979[c]	1978[b]
Chlorodecone (kepone)	S[d]	—
Chloroform	S	I
2,4-diaminoanisole	—	I
2,4-diaminotoluene	S	L
Dibromochloropropane (DBCP)	S	S
1,2-dichloroethane	S	—
1,4-dioxane	S	S
5-nitroacenaphthene	S	S
Phenoxybenzamine hydrochloride	—	L
Reserpine	I[e]	I
Selenium sulfide (IARC entry is selenium compounds)	—	I
Ortho-toluidine hydrochloride	—e	I

Very ***strong evidence in 1 species,***
sufficient evidence in 2d species.
9 chemicals

None of the 9 chemicals appears on the IARC lists.

Very strong evidence in 1 species,
no evidence in 2d species.
35 chemicals

Chemicals among the 35 that appear on the IARC lists		
4-amino-2-nitrophenol		I
Aniline hydrochloride (IARC entry is aniline)		I
Azobenzene	—	L
Chlordane	L	—
Chlorobenzilate	—	L
Cinnamyl anthranilate		I
Heptachlor	L	I
Lasiocarpine	S	S
Oestradiol mustard (IARC entry is estradiol mustard)	—	L
Trichloroethylene	—	L
Toxaphene	S	—
4-chloro-ortho-toluidine hydrochloride (IARC entry is parachloro-ortho-toluidine hydrochloride)		I

Sufficient evidence in 2 species.
4 chemicals

None of the 4 chemicals appears on the IARC lists.

Sufficient evidence in 1 species,
no evidence in 2d species.
19 chemicals

Chemicals among the 19 that appear on the IARC lists		
Aldrin	—	I
Ethyl tellurac	—	I

NCI Group B: One category showing insufficient evidence to lead to a conclusion about carcinogenic it y.

Table A-1 .—National Cancer Institute (NCI) Analysis of the Results of Testing 190 Chemicals[a] and the International Agency for Research on Cancer (IARC) Analysis of Chemicals[b c] That Appear on the NCI List (Continued)

	Evidence for carcinogenicity, IARC 1979[c]	1978b
Equivocal evidence in 1 or 2 species.		
28 chemicals		
Chemicals among the 28 that appear on the IARC lists		
Phenacetin (tested by itself by I ARC; tested in combination with aspirin and caffeine, APC, by NCI)	L	—
Styrene	L	—
NCI Group C: Three categories showing no evidence of carcinogenicity.		
No ***evidence in limited experiments.***		
51 chemicals		
Chemicals among the 51 that appear on the IARC lists		
Dieldrin	L	
Endrin	—	
Ethionamide	—	
Lindane	—	
Methoxychlor.	—	
No ***evidence in 1 species.***		
10 chemicals		
1 chemical among the 10 appears on the IARC lists		
Anthranilic acid	—	
No ***evidence in 2 species.***		
3 chemicals		
None of the 3 chemicals appears on the IARC lists.		

[a] Griesemer and Cueto, 1979.
[b] Tomatis, et al., 1978; Tomatis, 1979.
[c] IARC, 1979; IARC, 1980.
[d] S Indicates "sufficient evidence of carcinogen icity."
L Indicates "limited evidence of carcinogenicity."
I indicates "Inadequate evidence of carcinogen icity."
'See text

of that drug were available, and ortho-toluidine hydrochloride is being reevaluated by IARC. Both NCI and IARC found that phenoxybenzamine hydrochloride is carcinogenic. Therefore the lists may only differ significantly over two chemicals, and those differences, too, may disappear as more data become available.

Agreement is not as good about chemicals that are less positive. NCI's classes 3, 4, and 5 roughly correspond to IARC's L group, but 5 of the 11 NCI class 3 compounds common to both lists were put in the "in adequate evidence" category by IARC. Additionally, NCI found no evidence for carcinogenicity for any chemical in classes 6 through 9, but IARC found "limited evidence" for carcinogenicity for five of the eight chemicals that it reviewedin those classes.

As was mentioned, the data considered by IARC and NCI are not independent of each other; IARC considers NCI results in addition to all others. The differences in classification may result from the different criteria used by the two organizations, as well as from IARC considering other results.

Comparison of the *1978* and 1979 IARC listings shows that the evidence for the carcinogenicity of some chemicals became more positive. The progression to more-significant-evidence classes ma, be important to the contention that repeated testing increases the chances that a chemical will be determined to be a carcinogen.

Neither the IARC nor the NCI list include reviews of all chemicals of interest. For instance, neither saccharin nor sodium nitrite appears on either list, but

both compounds have been much discussed by regulators and potentially regulated industries.

The last sentences of the Griesemer and Cueto (146) paper draw attention to the importance attached to positive results.

> Those compounds for which evidence for carcinogenicity was not found. . . cannot necessarily be considered as noncarcinogens since the tests were conducted under a limited set of circumstances. It is possible that evidence for carcinogenicity might be found if, for example, a different strain of animal or a different route of exposure were used.

The quote illustrates the impossibility of proving a negative, and in a more immediate sense, it also shows that rules are not established to allow classifying a chemical as safe. A workable approach to allow making a decision that a chemical should be regarded as safe rather than as a potential risk may be necessary to separate important problems from minor and nonexistent ones. In fact, Griesmer and Cueto's group C which includes four grades of negative evidence shows that conclusions can be drawn that chemicals were found not to be risky under conditions of the tests.