FORUM

Rodent Tumors of Urinary Bladder, Renal Cortex, and Thyroid Gland in IARC Monographs Evaluations of Carcinogenic Risk to Humans

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In the absence of adequate human cancer data, it is biologically plausible and prudent to regard agents for which there is sufficient evidence2 of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans. However, the possibility that an agent causes cancer in animals through a mechanism that does not operate in humans must be taken into account. During recent years, evidence has developed that certain neoplasms, commonly seen in bioassays for carcinogenicity in rodents, can, in some cases, develop through such mechanisms. These neoplasms include urinary bladder carcinomas associated with urolithiasis, microcrystalluria, and certain urinary precipitates; renal cortical neoplasms arising specifically in male rats in association with α2-urinary globulin (α2u) nephropathy; and thyroid follicular-cell tumors associated with imbalances in thyroid stimulating hormone (TSH) levels. All of these conditions involve persistent hyperplasia in specific cell types from which neoplasms arise. Tumors can arise in all three organ sites in rodents, in response to exposure to various clearly genotoxic carcinogens, but histologically similar neoplasms also may develop in response to certain non-genotoxic agents.

To consider how rodent tumors of the urinary bladder, renal cortex, and thyroid gland should be treated within the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, a scientific advisory group3 of invited experts met in Lyon in November, 1997. This meeting addressed the comparative pathology, biology, and natural occurrence of these neoplasms in rodents and in humans. A consensus was reached on criteria for evaluating agents that are associated with tumors at these organ sites (Capen et al., 1999). These criteria for tumors of kidney and urinary bladder were recently applied to the evaluation or re-evaluation of certain chemicals at the October 1998 IARC Monographs Working Group4 meeting (IARC, 1999). Full summaries of the published literature supporting the development of these criteria appear in Capen et al., 1999. This report summarizes the findings of the November 1997 advisory meeting. It also summarizes some of the evaluations that were made by the October 1998 Working Group that were based in part on those findings.

Carcinoma of the Urinary Bladder

Many agents that clearly act through genotoxic mechanisms (notably, certain aromatic amines) are known to cause urinary bladder carcinoma in humans and to cause cancers in rodents at various sites that do not always include the urinary bladder. In rodents (especially rats), and to some extent in humans, non-genotoxic mechanisms can also contribute to pathogenesis of urinary bladder neoplasia.

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2 For definitions of terms and of the IARC classification scheme for carcinogenic risks to humans, see the Preamble to the IARC Monographs, which is printed at the beginning of each volume in the series and is also available on the Internet in the IARC Monographs Database at http://www.iarc.fr/.
3 IARC Advisory Group on Species Differences in Thyroid, Kidney and Urinary Bladder Carcinogenesis, Lyon, 3–8 November 1997: J. B. Beckwith (USA), A. Blair (USA), C. C. Capen (USA), S. M. Cohen (USA), W. Dekant (Germany; unable to attend), E. Dybing (Norway), S. Franceschi (Italy), S. Fukushima (Japan), A. Fusco (Italy), G. Hard (USA), J. Huff (USA), C. La Vecchia (Italy), L. Lehman-McKeeman (USA), R. M. McClain (USA), A. Mellemgaard (Denmark), R. L. Melnick (USA), R. Oyashu (USA), T. Sanner (Norway), J. A. Swenberg (USA), B. Terracini (Italy), G. A. Thomas (UK), and D. Williams (UK).
4 IARC Monographs Working Group, Volume 73, 13–20 October 1998. Members: S. J. Borghoff (USA), G. Brambilla (Italy), T. E. Bunton (USA), C. C. Capen (USA), S. M. Cohen (USA), L. Fishbein (USA), S. Fukushima (Japan), M. Gerin (Canada), G. C. Hard (USA), J. K. Haseman (USA; unable to attend), M. Hayashi (Japan), R. J. Kavlock (USA), B. G. Lake (UK), L. D. Lehman-McKeeman (USA), S. Olin (USA), J. H. Olsen (Denmark), T. Paratanen (Finland), T. Sanner (Norway), R. Schulte-Hermmann (Austria), B. Terracini (Italy), S. Vamvakas (Germany, unable to attend), J. M. Ward (USA), M. D. Waters (USA), J. Whysner (USA). Observers: R. H. Adamson and R. M. David (American Industrial Health Council), J. Foster (European Centre for Ecotoxology and Toxicology of Chemicals, ECETOC), and E. Vavasour (Canadian Food Directorate).
There is evidence that urinary tract calculi are associated with an increased risk of urinary bladder cancer, in humans as well as in rodents. For chemicals that cause calculus formation in the urinary bladder in rodents, and that also induce urinary bladder neoplasms under the same conditions, the Advisory Group thus concluded that such a tumor response is indeed relevant to evaluations of carcinogenicity to humans (i.e., qualitative hazard identification). However, large quantitative differences in susceptibility exist among species and between the sexes, and these must be considered in carcinogenic risk assessments, which are quantitative in nature. Microcrystalluria is often associated with calculus formation, but its relevance to interspecies differences in carcinogenic mechanisms could not be assessed.

Amorphous precipitates of various compositions that can form in the urine may also be associated with bladder carcinogenesis in rats. Amorphous urinary precipitates that contain calcium phosphate, such as those resulting from administration of high doses of some organic sodium salts, can also lead to production of urinary bladder tumors in this species. There is evidence that this sequence cannot occur in humans. Therefore the Advisory Group concluded that production of bladder cancer in rats, under such conditions, is not predictive of carcinogenic hazard to humans, provided that the agent fulfills all criteria that were defined for carcinogenic activity exclusively involving calcium phosphate-containing precipitates. The most important of these criteria is that thorough testing for genotoxic activity should have been conducted, with consistent and convincingly negative results. In cases where an agent also induces tumors at other sites in rats or in other species, evidence for tumorigenicity at non-bladder sites should be evaluated independently of tumors of the urinary bladder, taking into account the various modes of action of the agent. Following are the criteria for establishing that an agent which induces renal cortical tumors in male rats does so through an α2u globulin-associated response:

- The agent and its metabolites lack genotoxic activity, based on an overall evaluation of in-vitro and in-vivo data.
- Renal tumorigenicity and associated nephropathy are specific to male rats.
- Induction of the characteristic sequence of histopathological changes is demonstrated in short-term studies; of these changes, protein droplet accumulation in the cytoplasm of renal tubular cells is obligatory.
- The protein that accumulates in renal tubule cells is identified as α2u globulin.
- Binding of the chemical or metabolite to α2u globulin is reversible.
- Sustained increased cell proliferation in the renal cortex is induced.
- Dose-response relationships for tumor development and for histological end-points characteristic of α2u globulin nephropathy (protein droplets, α2u globulin accumulation, cell proliferation) are similar.

Renal Cell Carcinoma

The pathology and genetics of the various forms of renal carcinoma in humans are complex, and few chemical exposures are convincingly associated with causation of renal cancer in humans. Humans lack the α2u globulin that is abundantly secreted by male rats and that is associated with a specific form of nephropathy, persistent renal tubule hyperplasia, and renal-cell tumor formation in male rats in response to chronic exposure to certain chemicals. Criteria were developed to identify a carcinogen that acts solely through α2u globulin nephropathy.

In the opinion of the Working Group, the induction of renal-cell tumors alone, and in male rats only, by agents that fulfill these criteria (among which the most important is clear evidence that the agent is not genotoxic) is not predictive of a carcinogenic hazard to humans. If a renal carcinogen also causes tumors at other sites in rats or in other species, evidence regarding these other responses should be evaluated independently of the kidney tumors, taking into account the various modes of action of the agent. Following are the criteria for establishing that an agent which induces renal cortical tumors in male rats does so through an α2u globulin-associated response:

- The agent and its metabolites lack genotoxic activity, based on an overall evaluation of in-vitro and in-vivo data.
- Renal tumorigenicity and associated nephropathy are specific to male rats.
- Induction of the characteristic sequence of histopathological changes is demonstrated in short-term studies; of these changes, protein droplet accumulation in the cytoplasm of renal tubular cells is obligatory.
- The protein that accumulates in renal tubule cells is identified as α2u globulin.
- Binding of the chemical or metabolite to α2u globulin is reversible.
- Sustained increased cell proliferation in the renal cortex is induced.
- Dose-response relationships for tumor development and for histological end-points characteristic of α2u globulin nephropathy (protein droplets, α2u globulin accumulation, cell proliferation) are similar.

Thyroid Follicular-cell Neoplasms

No non-radioactive chemical exposure is known to cause tumors of thyroid follicular epithelium in humans, although a small excess of thyroid cancer mortality has been recorded in one cohort of individuals exposed to polychlorinated-para-dibenzodioxins (IARC, 1997). In contrast, such tumors are readily induced in rodents by both genotoxic and non-genotoxic agents, including goitrogens. The Advisory Group concluded that agents that cause thyroid neoplasia through an adaptive hormonal mechanism belong to a different category from those acting through genotoxic effects or mechanisms
involving pathological responses to tissue injury. To define an agent as causing thyroid follicular-cell neoplasia in rodents, solely through hormonal imbalance, the agent and its metabolites must lack genotoxic activity. This should be based on an overall evaluation of in vivo and in vitro data, and persistent hormonal imbalance must have been demonstrated under the conditions of the carcinogenicity assay. Such agents also usually interfere with thyroid homeostasis in humans, if given at a sufficient dose for a sufficient time, but they can be expected not to be carcinogenic in humans at exposure levels that do not lead to alterations in thyroid homeostasis. When tumors are observed for carcinogenicity, both in the thyroid and at other sites in bioassays, tumors at other sites should be evaluated separately, taking into account the various modes of action of the agent in different tissues. Following are the criteria for identification of agents that cause thyroid follicular-cell tumors in rodents solely through hormonal imbalance:

- Lack of genotoxic activity by both the agent and its metabolites, based on an overall evaluation of in-vitro and in-vivo data.
- Hormone imbalance occurs, and has been demonstrated under the conditions of the carcinogenicity bioassay.
- The mechanism whereby the agent leads to hormone imbalance has been defined.

**Application of These Criteria to Re-evaluations of Carcinogenic Risk**

As part of a continuing effort to selectively update and, where appropriate, re-evaluate agents that had been reviewed by the IARC Monographs Programme more than 5 years previously, the October 1998 *IARC Monographs* Working Group reviewed 25 compounds for which published literature had become available since the previous evaluations. These included several agents to which considerations of mechanisms underlying carcinogenicity to kidney and urinary bladder were relevant. Two compounds not previously evaluated, meta-dichlorobenzene and methyl tert-butyl ether (MTBE), were also reviewed. A complete list of compounds reviewed, with the previous and revised evaluations, is presented in Table 1. The remainder of this paper addresses the evaluations of several chemicals that illustrate the application of mechanistic considerations to overall evaluations of carcinogenicity to humans by the *IARC Monographs*, in the absence of adequate data from epidemiological studies.

Neoplasms of the urinary bladder in rodents, and the carcinogenic mechanisms by which they developed, were considered in re-evaluations of several chemicals including melamine, saccharin and its salts, and sodium ortho-phenylphenate. For all of these, epidemiological evidence of carcinogenicity to humans was considered inadequate, or no epidemiological data existed. Evaluations were therefore based on animal tumor data from bioassays, on laboratory studies on genetic effects, and on other relevant data including biotransformation pathways and mechanisms of carcinogenesis.

Melamine, which does not undergo biotransformation and is not genotoxic, produced carcinomas of the urinary bladder and ureter in male rats, but only urinary bladder hyperplasia in male mice. The occurrence of urinary bladder tumors in male rats correlated strictly with exposure to high doses of melamine and calculus formation, and concomitant administration of sodium chloride to increase urinary output resulted in a decreased tumor yield. Calculus formation was not observed in mice. Urinary bladder tumors in male rats exposed to high doses of melamine appear to be produced by a non-DNA-reactive mechanism involving epithelial hyperplasia secondary to the presence of melamine-containing bladder stones. Consequently, bladder tumors would not be expected in any species except at doses that produce bladder calculi. The Working Group considered that there was sufficient evidence in experimental animals for the carcinogenicity of melamine under conditions in which it produces bladder calculi, but reached an overall evaluation that melamine is not classifiable as to its carcinogenicity to humans (Group 3).

Sodium saccharin (but not its conjugate acid) produced tumors of the urinary bladder when fed to rats, but only when exposure began prenatally or very early in postnatal life, and only at very high doses—on the order of 5% of the diet. Saccharin and its salts are not biotransformed and are generally not genotoxic, and available evidence does not support a mechanism for the induction of urothelial tumors of the bladder in rats that involves direct interaction of sodium saccharin with DNA. Sodium saccharin does fulfill the criteria for a urinary bladder carcinogen that acts through the formation of a calcium phosphate-containing urinary precipitate. The Working Group agreed that sodium saccharin produces urothelial tumors in rats by a non-DNA-reactive mechanism that involves the formation in the urine of a calcium phosphate-containing precipitate that causes cytotoxicity and increased urothelial cell proliferation. The Working Group concluded that this mechanism is not relevant to humans because of critical interspecies differences in urine composition. It evaluated saccharin and its salts as not classifiable with regard to carcinogenicity to humans (Group 3), in spite of there being sufficient evidence of the carcinogenicity of sodium saccharin to experimental animals.

Sodium ortho-phenylphenate, although also the sodium salt of an organic acid and selectively carcinogenic to the urinary bladder in rats, does not fulfill the criteria listed above. Notably, it does undergo biotransformation, and there are data that suggest the possibility of a genotoxic contribution to its mechanism of action. Therefore, its overall evaluation as possibly carcinogenic to humans cannot be modified by the consider-
Tumors of the renal cortex in male rats contributed to the evaluation of several agents, including d-limonene, methyl tert-butyl ether (MTBE), and para-dichlorobenzene. There are no epidemiological data on cancer in humans resulting from exposures to these chemicals.

d-Limonene was tested for carcinogenicity by oral gavage in mice and rats and in several 2-stage experiments with multi-organ carcinogens. It significantly increased the incidence of

<table>
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<tr>
<th>Compound: (previous volume, year)</th>
<th>Previous evaluation</th>
<th>Volume 73 Evaluation</th>
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<tbody>
<tr>
<td></td>
<td>Human</td>
<td>Animal</td>
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<td><strong>Compounds with changes in evaluations</strong></td>
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<tr>
<td>Atrazine (Vol. 53, 1991)</td>
<td>I</td>
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<td>Butyl benzyl phthalate (Vol. 29, Suppl. 7, 1987)</td>
<td>I (ND)</td>
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<td>Chlorothalonil (Vol. 30, Suppl. 7, 1987)</td>
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<td>Cyclamates (Vol. 22, Suppl. 7, 1987)</td>
<td>I (ND)</td>
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<tr>
<td><em>ortho</em>-Dichlorobenzene (Vol. 29, Suppl. 7, 1987)</td>
<td>I (ND)</td>
<td>I</td>
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<td><em>para</em>-Dichlorobenzene (Vol. 29, Suppl. 7, 1987)</td>
<td>I (ND)</td>
<td>S</td>
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<tr>
<td>Hexachloroethane (Vol. 20, Suppl. 7, 1987)</td>
<td>I (ND)</td>
<td>L</td>
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<td>d-Limonene (Vol. 56, 1993)</td>
<td>I (ND)</td>
<td>L</td>
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<td>Melamine (Vol. 39, Suppl. 7, 1987)</td>
<td>I (ND)</td>
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<td>Paracetamol (Acetaminophen) (Vol. 50, 1990)</td>
<td>I (ND)</td>
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<tr>
<td><em>ortho</em>-Phenylphenol (Vol. 30, Suppl. 7, 1987)</td>
<td>I (ND)</td>
<td>I</td>
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<tr>
<td>Saccharin (Vol. 22, Suppl. 7, 1987)</td>
<td>I</td>
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<td><em>Saccharin and its salts</em></td>
<td>I</td>
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<td><em>Sodium saccharin</em></td>
<td>S</td>
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<tr>
<td><em>Saccharin (acid form) and calcium saccharin</em></td>
<td>I</td>
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<tr>
<td>Simazine (Vol. 53, 1991)</td>
<td>I</td>
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**Compounds with no changes in evaluation**

| Allyl isothiocyanate (Vol 36, Suppl. 7, 1987) | I (ND) | L       | 3       |
| *ortho*-Anisidine (Vol. 27, Suppl. 7, 1987) | I (ND) | S       | 2B      |
| Chloroform (Vol. 20, Suppl. 7, 1987)        | I      | S       | 2B      |
| Hexachlorobutadiene (Vol. 20, Suppl. 7, 1987) | I (ND) | L       | 3       |
| Nitriloacetic acid and its salts (Vol. 48, 1990) | I (ND) | S       | 2B      |
| Potassium bromate (Vol. 40, Suppl. 7, 1987) | I (ND) | S       | 2B      |
| Quercetin (Vol. 31, Suppl. 7, 1987)          | I (ND) | L       | 3       |
| Sodium *ortho*-phenylphenate (Vol. 30, Suppl. 7, 1987) | I (ND) | S       | 2B      |

**New compounds**

| meta-Dichlorobenzene               | I (ND) | I       | 3       |
| Methyl tert-butyl ether            | I (ND) | L       | 3       |

*Note. I, inadequate evidence; ND, no data; L, limited evidence; S, sufficient evidence; ESL, evidence suggesting lack of carcinogenicity; 2B, possibly carcinogenic to humans; 3, not classifiable as to carcinogenicity to humans.

* Data regarding mechanisms of carcinogenesis were taken into account in making the overall evaluation.

No epidemiological data on cancer in humans resulting from exposures to these chemicals.
renal tubule tumors (adenomas and carcinomas) and induced atypical renal tubule hyperplasia in male rats, which normally synthesize α2u globulin in the liver, but not in female rats or in mice of either sex. It consistently enhanced renal tubule tumor incidence and atypical renal tubule hyperplasia initiated by renal carcinogens in 2-stage renal carcinogenesis assays in male rats of a strain conventionally used in bioassays, but not in a strain (NBR) that lacks hepatic synthesis of α2u globulin. It did not increase the incidence of tumors at any other site. d-Limonene is biotransformed to various metabolites in mammals, but the available data indicate that neither the parent compound nor its 1,2-epoxide metabolite is genotoxic. d-Limonene is the prototype compound causing male rat-specific α2u globulin nephropathy and sustained cell proliferation in renal proximal tubule cells, and the dose-response relationships for histopathological endpoints including enhanced cell proliferation and for tumor outcome are similar. Female rats, male rats of a strain that does not express this protein and other species are not susceptible to the nephrotoxic action of d-limonene. d-Limonene fulfills the criteria for a renal carcinogen that acts through an α2u globulin-associated response. The Working Group concluded that there is inadequate evidence in humans, but sufficient evidence in animals for the carcinogenicity of d-limonene. Additionally, d-limonene produces renal tubular tumors in male rats by a non-DNA-reactive mechanism through an α2u globulin-associated response, which is a mechanism that is not relevant to humans. d-Limonene was placed in Group 3, as being unclassifiable as to its carcinogenicity to humans.

MTBE, which is not genotoxic in experimental systems, was tested for carcinogenicity by inhalation exposure in one experiment in mice. It increased the incidence of hepatocellular adenomas in female mice, and, in one experiment in rats, increased the incidence of renal tubule tumors in males in a non-dose-related manner. The renal lesions in male rats were associated with α2u globulin nephropathy. When MTBE was given to rats by gastric instillation, Leydig-cell adenomas of the testis in males and lymphomas and leukemia in females were increased; no effect on the kidney was noted. A metabolite of MTBE, tert-butyl alcohol, marginally increased the incidence of follicular-cell adenomas of the thyroid in female mice. The Working Group considered the evidence for carcinogenicity of MTBE to experimental animals to be limited, because none of the positive findings have been shown to be reproducible, and it placed MTBE in Group 3 without invoking mechanistic evidence.

Para-Dichlorobenzene was tested by oral administration and inhalation in mice and rats. After oral administration, it produced an increase in adenomas and carcinomas of the liver in male and female mice and of renal tubule carcinomas in male rats. Para-Dichlorobenzene causes male-rat-specific α2u globulin nephropathy; and along with its major metabolite, 2,5-dichlorophenol, it binds reversibly to α2u globulin. The parent compound causes sustained cell proliferation in proximal renal tubule cells, and the dose-response relationships for tumor outcome, enhanced cell proliferation, and other histopathological endpoints typical of α2u globulin nephropathy are similar. Female rats, male rats of a strain that does not express this protein, and mice are not susceptible to the nephrotoxic action of para-dichlorobenzene. While no conclusion could be drawn from the few data on genotoxicity in vivo, there is weak evidence for the genotoxicity of para-dichlorobenzene in mammalian cells in vitro. The Working Group agreed that the renal tumors could be attributed to an α2u globulin-associated response, and are not predictive of human carcinogenic hazard. But, on the basis of the liver tumors in male and female mice, and the less than satisfactory evidence that the mechanism by which they were produced was nongenotoxic, the Working Group maintained the previous evaluation of sufficient evidence of carcinogenicity in animals, and the overall evaluation of Group 2B: possibly carcinogenic to humans.

Comments

In the IARC Monographs, separate evaluations are first made of the strength of the evidence for cancer in humans caused by exposure to an agent, and for carcinogenicity of that agent to animals in bioassays. These are then combined to reach a final, overall evaluation. Other data, particularly including those considered relevant to mechanisms of carcinogenesis, can be applied to the final, overall evaluation and may result in a change from the default classification.

When human data are inadequate, but bioassay data are sufficient (that is, adequately designed and conducted studies have yielded positive and reproducible results), the default IARC classification is Group 2B—possibly carcinogenic to humans. When animal bioassay data are considered less than sufficient, and human data are inadequate for evaluation or do not exist, the usual classification is Group 3—the agent cannot be evaluated as to carcinogenicity to humans. The Preamble to the IARC Monographs was revised in 1992 to codify the use of mechanistic evidence in carcinogenic hazard evaluation (IARC, 1992). Exceptionally, since then, agents for which the evidence of carcinogenicity is inadequate in humans but sufficient in experimental animals, may be placed in Group 3 when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans. The October 1998 Working Group was the first to use mechanistic evidence in this way.

In the case of saccharin and its salts, this criterion was applied in a straightforward way by the Working Group to reach a revised classification of Group 3. Some salts of saccharin produce tumors in experimental animals, but only in the urinary bladder and only under certain conditions, which recent evidence indicates do not occur in humans. The evidence of carcinogenicity to animals is reproducible and has been considered sufficient since the first evaluation of saccharin by the IARC Monographs in 1979 (IARC, 1980). When the present
system of classification was introduced in 1987, saccharin was placed in Group 2B, on the basis of demonstrated carcinogenicity to animals but inadequate evidence for cancer in humans (IARC, 1987). It is the sufficiency of bioassay results that allowed mechanistic evidence to be applied to the overall evaluation of saccharin by the October 1998 Working Group.

For \(d\)-limonene, only one positive bioassay in rats had been published when that chemical was first evaluated in 1992. Although the selective carcinogenicity of \(d\)-limonene to the renal cortex of male rats was revealed by that study, and had been confirmed by one additional 2-stage experiment, in 1992 this was considered less than sufficient confirmation of the carcinogenicity of the compound. Evidence of carcinogenicity of \(d\)-limonene to animals was therefore judged to be limited at that time (IARC, 1993). The resulting overall evaluation was Group 3, solely on the basis of limited animal data, and mechanistic evidence played no specific role in that evaluation. In 1998, with the subsequent publication of additional, confirmatory 2-stage carcinogenicity studies, evidence for carcinogenicity in animals was judged to have become sufficient. This allowed mechanistic evidence regarding the role of \(\alpha_{\text{s}}\) globulin nephropathy to be considered in reaching the same overall evaluation as before (Group 3), but by quite different reasoning.

For MTBE, only one of the several published bioassays available to the October 1998 Working Group reported renal tumors in male rats. The inconsistency of the results from the available bioassays led to an evaluation of limited evidence of carcinogenicity in animals, and a Group 3 evaluation in which mechanistic evidence played no role.

\(\text{para-}\)Dichlorobenzene presents the case of what is sometimes called a “trans-species carcinogen,” which causes tumors in more than one species and, in this case, in more than one target organ. For \(\text{para-}\)dichlorobenzene, the Working Group decided to accept the evidence that the rat renal tumors result from an \(\alpha_{\text{s}}\) globulin-related mechanism, and should be excluded from the overall evaluation of carcinogenicity. But after prolonged discussion, the Working Group decided to retain the previous overall evaluation of “possibly carcinogenic to humans” (Group 2B) on the basis of the mouse liver tumors. This was because there was limited evidence that in mice, a genotoxic component to the mechanism of carcinogenic action may exist, and the Working Group felt that this evidence could not be disregarded. This decision emphasizes the fundamental importance of a complete and consistent database indicating a lack of genotoxic activity, to support any proposal to discount evidence of carcinogenicity in a second species and in other organ systems.

The use of evidence regarding mechanisms of carcinogenicity is becoming widespread in carcinogenic hazard evaluations and in risk assessments made by many governmental and intergovernmental authorities, not only for the organ sites and mechanisms discussed here, but for others as well. It cannot be emphasized too strongly that such evaluations must be done cautiously and by application of the most rigorous scientific criteria. It is a mistake to attempt to apply mechanistic considerations to a carcinogenic hazard evaluation when insufficient data are available to fulfill all established criteria for a given mode of action. Premature application of concepts not yet adequately tested or widely accepted by the scientific and public health communities should be avoided.

The 3 organ sites discussed here all exist in both humans and laboratory animals, and site-specific epidemiological and biological findings for tumors of these sites in humans can be compared directly to the corresponding neoplasms in rodents. For other organ sites and other tumor types in rodents that do not correspond exactly to any human counterpart, other approaches to an evaluation are necessary. These will be addressed by future expert advisory groups to be convened by the IARC Monographs Programme.

**REFERENCES**


