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Cancerous Contradictions: The Mis-Regulation of Human Carcinogens Based on Animal Data

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ABSTRACT

The regulation of human exposures to potential carcinogens constitutes society's most important use of animal carcinogenicity data. However, for environmental contaminants of greatest U.S. concern, we found that in most cases (58.1%; 93/160) the U.S. Environmental Protection Agency (EPA) considered the animal data inadequate to support a classification of probable human carcinogen or non-carcinogen.

The World Health Organisation's International Agency for Research on Cancer (IARC) is a leading international authority on carcinogenicity assessments. For chemicals lacking human exposure data (the great majority), IARC classifications of identical chemicals were significantly more conservative than EPA classifications ($p<0.0001$), indicating that: (i) the EPA is over-reliant on animal carcinogenicity data, (ii) as a result, it tends to over-predict carcinogenic risk, and (iii) the true predictivity for human carcinogenicity of animal data is even poorer than indicated by EPA figures alone. EPA policy erroneously assuming that tumours in animals are indicative of human carcinogenicity is implicated as the greatest source of these errors.

* Summarised from the poster *Animal carcinogenicity studies: poor human predictivity* by Andrew Knight, Jarrod Bailey and Jonathan Balcombe, which received the Animal Welfare Poster Award from Deutscher Tierschutzbund (the German Animal Welfare Federation) at the 5th World Congress on Alternatives and Animal Use in the Life Sciences, Berlin, 25 August 2005. Reproduced with permission from the complete paper: Knight, A., Bailey, J., Balcombe, J. (2006). Animal carcinogenicity studies: 1. poor human predictivity. *Alternatives to Laboratory Animals 34(1*), 19-27.

INTRODUCTION

Since the first animal carcinogenicity test in 1915, when Yamagiwa and Ichikawa showed that coal tar applied to rabbits' ears caused skin carcinomas, several thousand carcinogenicity bioassays have been conducted, with the objective of determining human carcinogenic risks for the great majority of chemicals lacking human exposure data (Huff, 1999). However, animal carcinogenicity testing remains a controversial area of research.

Proponents claim that all known human carcinogens that have been studied in sufficient animal species have produced positive results in one or more species (Wilbourn et al., 1986; Tomatis et al., 1989; Rall, 2000). Critics respond that if enough animal testing is conducted, carcinogenesis will eventually occur in *some* species, regardless of human cancer risk. A study published in *Mutagenesis* found that of 20 human *non*-carcinogens, 19 produced carcinogenic effects in animals (Ennever et al., 1987).

The most important use of animal carcinogenicity data lies in the regulation of human exposures to potential carcinogens. The U.S. Federal agency most responsible for regulating exposures to environmental contaminants is the Environmental Protection Agency (EPA, undated a), and the chemicals of greatest public health concern (EPA, undated b) are listed within its Integrated Risk Information System (IRIS) chemicals database, along with their animal toxicity data and consequent human carcinogenicity assessments (EPA, undated c).

To assess the utility of animal carcinogenicity data in deriving human carcinogenicity assessments, we surveyed the IRIS chemicals database. To assess the reliability of the EPA carcinogenicity assessments obtained from animal test data, we compared them with those of a leading world authority, the World Health Organization's International Agency for Research on Cancer (IARC).

METHODS

The 543 chemicals catalogued in the EPA's IRIS chemicals database (as of January 1, 2004; EPA, undated d) were examined to determine the proportion for which the EPA was able to derive classifications of "probable human carcinogen" or "probable human non-carcinogen" based primarily on animal carcinogenicity data. The relatively few classifications of "definite human carcinogen" relied primarily on available human exposure data. The remaining classifications of "unclassifiable" or "possible human carcinogen" were not considered substantially useful for risk assessment or regulatory purposes. They are excluded from the U.S. National Toxicology Program annual *Report on Carcinogens* (NTP, 2002).

Of the 177 chemicals considered by the EPA to possess at least limited human or animal data, 128 were assigned human carcinogenicity classifications by both the EPA and the IARC. Of these 128, 17 were considered by the EPA to possess at least limited human data, while 111 were primarily reliant on animal data.

The consistency of classifications between the EPA and the IARC was examined for these two groups by comparing the carcinogenicity classification proportions within each group by chi-square tests, 1 and also by comparing the individual classifications of the 111 chemicals primarily reliant on animal carcinogenicity data.

Chi-squared tests provide statistical calculations of the probability that two data sets, such as EPA and IARC human carcinogenicity classifications, are samples from the same underlying data population, and that any observed differences are simply due to random sampling variation. Large chi-squared (X2) values reflect increased probabilities that observed differences are due to real differences in underlying data populations.

RESULTS

EPA human carcinogenicity classifications

Of the 543 chemicals catalogued in the EPA's IRIS chemicals database, 235 had been assigned human carcinogenicity classifications. Of these, 17 were classified as definite (A) or probable (B1) human carcinogens on the basis of their human carcinogenicity data. Of the remaining 218 chemicals lacking even limited human data, 160 were deemed to possess animal carcinogenicity data, primarily sourced from the biomedical literature (B2, C, subset of D, and E; tab. 1).

The human utility of animal carcinogenicity data based on EPA figures

Of the 160 EPA chemicals lacking even limited human data (A or B1) but having animal data (B2, C, subset of D, and E), 64 were considered probable human carcinogens (B2), and three were considered probably not carcinogenic to humans (E). The remaining 93 chemicals were considered possible human carcinogens (C; 40) or unclassifiable as to their human carcinogenicity (D; 53) based on animal data considered inadequate to support a stronger classification (tab. 1).

In sum, of those 160 chemicals lacking even limited human data but having animal data, the EPA considered the animal data inadequate to support the substantially useful classifications of probable human carcinogen or probable human non-carcinogen in the majority of cases (93/160; 58.1%, 95% CI: 50.4-65.5)[2].

Comparison of EPA and IARC human carcinogenicity classifications

Of those 177 chemicals considered by the EPA to possess human or animal data (A, B1, B2, C, D with animal data, or E), 128 were also assessed by the IARC. Of these, 17 were considered by the EPA to possess at least limited human data (A or B1), and the remaining 111 EPA carcinogenicity classifications were primarily reliant on animal data.

For those 17 chemicals considered by the EPA to possess at least limited human data, overall EPA classifications were not found to differ significantly from those predicted by IARC classifications (p = 0.5896, X2 = 0.291, 1 df, tab. 2)[3].

However, for those 111 chemicals considered by the EPA to lack even limited human data, but to possess animal data, EPA and IARC classifications were very significantly different overall (p < 0.0001, X2 = 215.548, 2 df; fig. 1)[4].

The EPA was much likelier than the IARC to assign carcinogenicity classifications indicative of greater human hazard. The EPA classified 60 chemicals as probable human carcinogens and 51 in all other categories, which was very significantly different from the IARC figures of 12 and 99, respectively (p < 0.0001, X2 = 215.273, 1 df). Similar disparities were found for possible human carcinogens (X2 = 19.771, 1 df, p < 0.0001) and unclassifiable chemicals (p < 0.0001, X2 = 24.378, 1 df).

Comparison of the individual classifications of these 111 chemicals revealed that 67 (60.4%) were assigned an EPA carcinogenicity classification indicative of greater human hazard, 38 (34.2%) were assigned an equivalent classification, and 6 (5.4%) were assigned a classification indicative of lesser human hazard than the corresponding IARC classification of the same chemical.

DISCUSSION

Based on EPA figures alone, the predictivity of animal carcinogenicity data for human hazard, and hence its utility in deriving substantially useful human carcinogenicity classifications, is clearly poor. Of those 160 IRIS chemicals lacking even limited human data but possessing animal data, the EPA considered the animal data inadequate to support substantially useful human carcinogenicity classifications in the majority (58%) of cases.

However, IARC assessments of the same chemicals reveal that the human utility of animal carcinogenicity data is probably even lower than indicated by EPA figures. EPA and IARC carcinogenicity classifications were similar only for those chemicalswith human data. For those with only animal data, the EPA

was much likelier than the IARC to assign carcinogenicity classifications indicative of greater human hazard. Given that the IARC is recognised as a leading international authority on human carcinogenicity classifications (Tomatis et al., 1993; IARC undated), the very significant differences in classifications of identical chemicals between the IARC and the EPA indicate that:

- (i) in the absence of significant human data the EPA is over-reliant on animal carcinogenicity data,

- (ii) as a result, the EPA tends to over-predict carcinogenic risk, and

- (iii) the true human predictivity for human carcinogenicity of animal data is even poorer than indicated by EPA figures alone.

EPA human carcinogenicity classifications appear to be less scientifically-based than those of the IARC, due to: 1) the varying depth of EPA assessments, due to resource constraints; 2) the less rigorous standards required of data incorporated into EPA assessments; and, in particular, 3) EPA public health-protective policy, which errs on the side of caution by assuming that tumours in animals are indicative of human carcinogenicity (Knight et al. 2006).

Our findings corroborate those of previous investigators. In response to a 2000 Congressional directive, the EPA undertook an evaluation of the data variability and uncertainty within its IRIS assessments. A representative sample of 16 IRIS assessments was subjected to in-depth evaluation by a panel of six independent experts, who concluded that despite being advertised as quantitative science-based classifications, some were, in fact, more grounded in EPA policy favouring classifications indicative of greater human risk (Hogan, 2000).

EPA carcinogenicity assessments may be no more suspect than those of other U.S. regulatory agencies, however. In their survey of 350 representative chemicals, Viscusi and Hakes (1998) found that the carcinogenicity assessments of other U.S. regulatory authorities, particularly the Food and Drug Administration and the Occupational Safety and Health Administration, are even less reflective of actual human risk than those of the EPA. Poor human predictivity of animal carcinogenicity studies was also demonstrated by Tomatis and Wilbourn (1993) and Haseman (2000), and further described by Rall (2000), Ashby and Purchase (1993), Fung et al. (1995) and Ennever and Lave (2003).

CONCLUSIONS

By 1998, only about 2,000 (2.7%) of the 75,000 industrial chemicals in use and listed in the EPA's Toxic Substances Control Act inventory had been tested for carcinogenicity (Epstein, 1998). The cost of testing these 2.7% of industrial chemicals was millions of animal lives (Monro et al., 1998; Gold et al., 1999),

millions of skilled personnel hours (Gold et al., 1999), and hundreds of millions of dollars (Greek et al., 2000; Stephens et al., 1998).

The most important use of the animal data thus derived is in the regulation of human exposures to potential carcinogens by governmental agencies such as the EPA. However, our results demonstrate that the human predictivity of animal carcinogenicity data was inadequate for the EPA to derive substantially useful human carcinogenicity classifications for the majority (58.1%) of chemicals of greatest public health concern.

Profound differences in human carcinogenicity classifications of identical chemicals between the EPA and the IARC reveal an over-reliance on animal carcinogenicity data by the EPA. The result is that the EPA over-predicts carcinogenic risk. Hence the true human predictivity of animal carcinogenicity data is even poorer than indicated by EPA figures alone.

The sensitivity of the traditional rodent bioassay in detecting human carcinogens for *some* sex-species combinations is not in question. However, its very poor human specificity severely limits its utility for identifying human carcinogens, and its subsequent use in regulating exposures to them. The implementation by regulatory authorities of alternative assays with superior human predictivity is clearly necessary.

Table 1. EPA human carcinogenicity classifications of IRIS chemicals

EPA human carcinogenicity classification (with basis for classification)	# of chemicals	% of Total
A: Human carcinogen (convincing human data)	11	4.7
B1: Probable human carcinogen (limited human data)	6	2.6
B2: Probable human carcinogen (sufficient animal data)	64	27.2
C: Possible human carcinogen (animal data inadequate for stronger classification)	40	17.0
D: Unclassifiable (animal data inadequate for stronger classification)	53	22.6
D: Unclassifiable (no animal or human data)	58	24.7
E: Probable human non-carcinogen (sufficient animal data)	3	1.3
TOTAL	**235**	

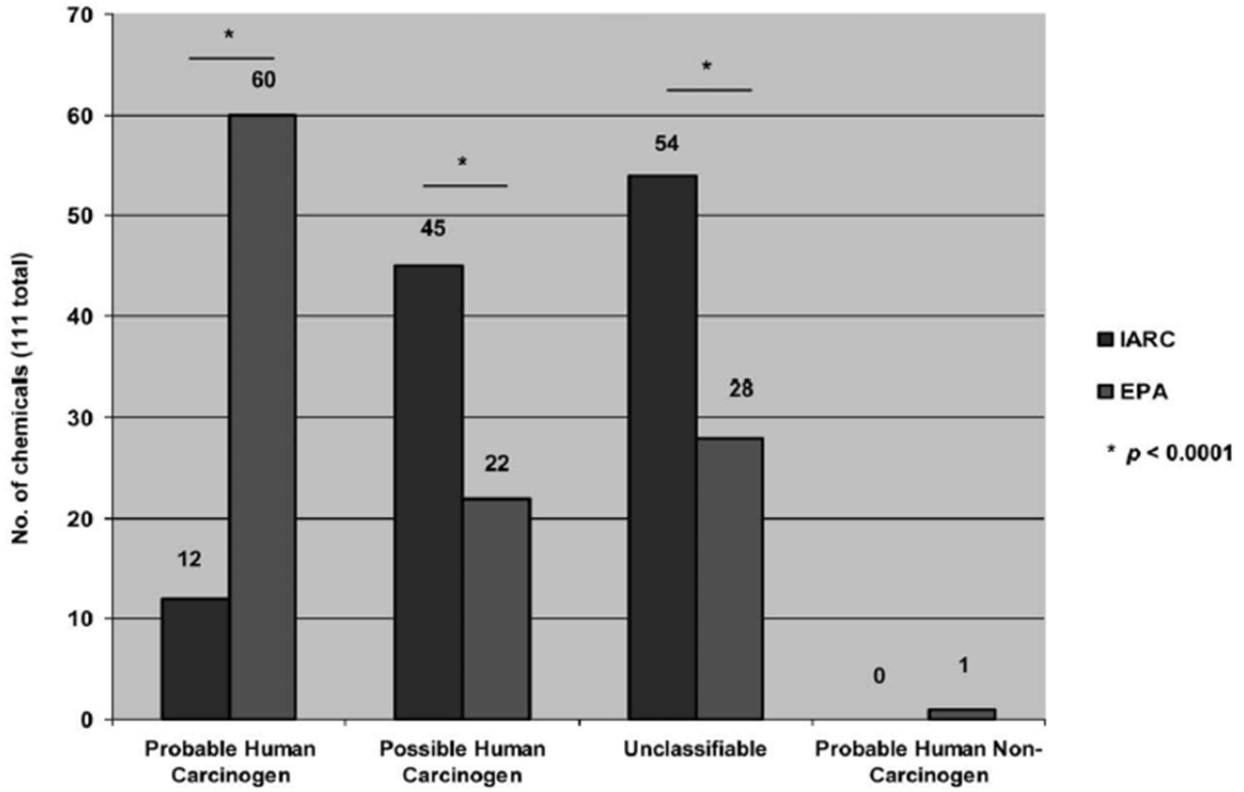
160 chemicals lacking in human data had received a human carcinogenicity assessment primarily on the basis of their animal data.
Data source: EPA Integrated Risk Information System database, 1 January 2004.

Table 2. IARC classifications of EPA chemicals possessing significant human data (EPA categories A or B1)

Human carcinogenicity classification	EPA	IARC
Human Carcinogen (A)	11	12
Probable Human Carcinogen (B1)	6	4
Possible Human Carcinogen	0	1
Total	**17**	**17**

Data sources: The EPA Integrated Risk Information System database, 1 January 2004, and the IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans, Volumes 1-82, 1 January 2004.

Figure 1. EPA and IARC human carcinogenicity classifications of chemicals considered by the EPA to lack human data but to possess animal data.



Data source: IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans, and the EPA Integrated Risk Information System database, Jan. 1, 2004.

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[1] Chi-squared and two-tailed p values were derived from the online statistical calculators available at www.graphpad.com/quickcalcs/index.cfm.

[2] Confidence interval derived via the modified Wald method described by Agresti et al. (1998) as being more accurate than the so-called "exact" method commonly used.

[3] Chi-squared analysis does not allow comparison when one category lacks any data, hence acrylonitrile, assessed as the only possible human carcinogen by IARC, but as a probable human carcinogen (B1) by the EPA, was excluded, yielding a more conservative result.

[4] To allow chi-squared analysis, methacrylate, assessed as unclassifiable by IARC, but as the only probable human non-carcinogen by the EPA, was excluded, yielding a more conservative result.

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