Introduction

Due to a paucity of human exposure data, the regulation of human exposures to chemicals by regulatory authorities such as the U.S. Environmental Protection Agency (EPA) relies heavily upon animal carcinogenicity data. However, our survey of the 160 IRIS chemicals lacking significant human data for these 160 IRIS chemicals. The systems most commonly affected were the liver (66.3%), the lung (31.7%), and the kidney, skin and stomach (all 13.2%). Figure 1).

Species used

Up to 43 organ systems were found to exhibit neoplastic lesions, with up to 11 jointly affected for each chemical. The three species most commonly used were mice (92.4%), rats (86.7%), and hamsters (14.6%) (Figure 1).

Methods

Of the 160 IRIS chemicals contained within the EPA’s IRIS database, as of Jan. 1, 2004, 160 lacked significant human exposure data but possessed animal data, and had received human carcinogenicity assessments. For each of these we determined the species and route(s) of administration used, and the organ systems affected.

Results

Species

At least 10 different species were used, namely: chickens, dogs, guinea pigs, hamsters, mice, min, primates (one macaque, three unspecified “monkey” species, baboon, vervet, and chimpanzee). The three species most commonly used were mice (49.4%), gavage (49.4%), and oral: food, subcutaneous, surgical implantation, and subcutaneous. Those most commonly used were food (49.4%), gavage (49.4%), and oral: food, subcutaneous, surgical implantation, and subcutaneous.

Route of administration

The three species most commonly used were mice (92.4%), rats (86.7%), and hamsters (14.6%) (Figure 1).

Discussion

A wide variety of doses were used, with rodents being predominant; a wide variety of routes of administration were used, and a particularly wide variety of organ systems were affected. Key biological and mathematical attempts to describe extrapolation of human carcinogenicity from such animal data.

Discordance between mice and rats

Large-scale studies have shown that human carcinogenicity in mice are not as robust as in rats, and that only about a quarter of rodent carcinogens are consistently carcinogenic across all sex-species groups. Even within the same sex-species group, many chemicals yield inconsistent results.

Discordance between rodents and primates

Inherent biological and environmental differences exist between rodents and primates, including differences in their immune systems, responses to stress, and hormonal regulation. Immune responses between species vary, due to differences in evolutionary history, species-specific adaptations, and genetic differences. In addition to these differences, there are also differences in the routes of administration used, which can influence carcinogenicity.

Carcinogenesis predisposition of stressful routes of administration

Stressful routes of administration can induce a number of biological changes that can influence carcinogenicity. For example, chronic stress can lead to changes in the immune system, endocrine system, and other biological systems, which can influence carcinogenicity. In addition, stress can also lead to changes in the metabolism of chemicals, which can influence their bioavailability and toxicity.

Conclusions

The high carcinogenesis predisposition of stressful routes of administration undermines its human predictivity. To investigate the reasons for this inadequacy, we examined the animal test results for these 160 IRIS chemicals. However, our survey of the 160 IRIS chemicals lacking significant human data for these 160 IRIS chemicals.

Acknowledgements

We gratefully acknowledge the assistance of the Physicians Committee for Responsible Medicine, Washington DC, and Dr. Steven Alexander, London, for their invaluable contributions to this work.