SECTION III

EXTRAPOLATION OF DATA

EXTRAPOLATION OF EXPERIMENTAL ANIMAL DATA TO HUMANS

by
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For new chemical compounds being introduced, or planned to be introduced into practical use, animal studies provide basic information on their toxicity, including toxic doses and concentrations, types of injury and mechanism of toxic action. Studies with laboratory animals also provide data which may be utilized to estimate human risk and to establish new or correct existing environmental exposure limits for humans. The practical use of animal toxicity studies is based on the fundamental assumption that the results make the prediction of the toxic effects of chemicals in humans possible. This assumption is based on the similarities in the anatomy and physiology of mammalian species. For most substances, the pathogenesis of poisoning is the same in humans and other mammals; therefore, the signs of intoxication are also analogous. Qualitative effects of the toxic action of chemicals in humans can usually be inferred from animal studies with a high degree of certainty. On the other hand, the accuracy and reliability of a quantitative prediction of toxicity in humans depend on a number of conditions - choice of animal species, design of the experiment and methods of extrapolation.

Species Differences

Qualitative differences in the sensitivity of humans and other animals are exceptional. No poison with a selective action on humans alone has yet been found. However, the problem exists that some effects are difficult to measure in experimental animals: for example, intelligence and the more esoteric behavioural changes. Social factors, so important to humans, cannot be evaluated in experimental animals.

The most difficult problem in the extrapolation of animal data to humans is the presence of quantitative differences in toxic responses between humans and other animals and among various animal species. As far as lethal doses are concerned, man is considered to be rather more sensitive than certain laboratory animals to lethal doses, but many

cases exist where certain animal species are more sensitive than are humans. For example, the lowest lethal dose of methanol for humans is about 10-20 times lower than that for the rabbit, dog and monkey (1). However, the dog is more sensitive to hydrocyanic acid than are humans (2). The most significant differences in sensitivities between humans and other animals are observed for alkaloids. The human is 100-350 times more sensitive for atropine, morphine and nicotine than are laboratory animals.

Sensitivity to the toxic action of chemicals varies among different species of animals. Smaller or greater differences in lethal doses may be observed even among the rodents commonly used in toxicity evaluation. The difference in sensitivity to the chronic action of chemicals may also be observed. For example, the mouse is more sensitive than the rat, developing chronic toxic and/or cancerogenic effects from vinyl chloride, vinylidene chloride, perchloroethylene and chloroform (3,4). On the other hand, aflatoxin is more carcinogenic to rats than to mice (5). Sensitivity to toxic and cancerogenic actions of chemicals may also depend on the strain of animals used in experiments.

Species differences in sensitivity of toxic chemicals can often be explained by differences in the fates of the chemicals in the organism, particularly by quantitative and qualitative differences in biotransformation and also by differences in the rates of absorption, transport, distribution and elimination of chemicals. In general, absorption and distribution of xenobiotics in the organism might be expected not to show a great variation among species because the most significant species differences are in the qualitative pathways and kinetic characteristics of metabolism (6-12). Thus, species differences in sensitivity to toxic chemicals seem to be mainly related to routes and rates of their biotransformation. For example, species differences in the carcinogenicity of 2-acetylaminofluorene have been attributed to the rate of metabolism of an ultimate carcinogen, N-hydroxyderivative (13). Higher sensitivity of mice than rats to the cancerogenic action of chloroform, perchloroethylene and vinylidene chloride has been related to the greater extent of metabolism of these chemicals by the mouse (4,14). Based on the well-known rule that large animals metabolize chemicals more slowly on a body weight basis than do smaller animals, Ramsey &

Gehring (4) have recently formulated the general concept that "whether a larger animal species will be more or less sensitive to a chemical than a smaller species is dependent on whether metabolism of the chemical constitutes a detoxication or an intoxication process, respectively".

Strain differences in metabolism may also influence toxicity, as exemplified by methoxyflurane. A high rate of methoxyflurane metabolism to inorganic fluoride, together with increased susceptibility to the nephrotoxic effects of inorganic fluoride, results in renal lesions in Fischer rats, which are not developed in the other strains of rat (15).

Obviously, differences in metabolism in humans and other animals should be considered when experimental animals are selected. Unfortunately, metabolic information is usually not available for new chemicals at the time they undergo toxicity testing.

Methods of Extrapolating Animal Data to Humans

The extrapolation of animal data to humans is confronted with two fundamental problems: low-dose extrapolation, which would enable an extrapolation from a known dose-response range to an unknown range of great practical importance (16), and interspecies extrapolation of projected response from laboratory animals to humans. Low-dose extrapolation is the subject of a separate lecture; in this paper, some views and practices in extrapolation from one animal species to another and, finally, to humans will be presented.

Species differences in sensitivity to chemicals make the application of a species conversion factor, when extrapolating animal data to humans, reasonable. No definite, generally accepted rule for the species conversion factor exists, and the problem is still under discussion. If the extrapolation of data is based on the most sensitive species tested, some toxicologists use a factor of 1 (17), but others recommend a factor as large as 10 (18).

To eliminate the problem of species differences, the calculation of the dose of substances per unit or surface area approximately equivalent to the weight raised

to the power two thirds has been suggested (19,20). Ramsey & Gehring (4) have recently proposed separate interspecies conversion formulae for direct-acting toxins and for toxins requiring metabolic activation:

I. Direct-acting toxin

$$P_{man} = P_{test} \times \frac{\text{Body Wt}_{man}}{\text{Body Wt}_{test}}^{1/3}$$

II. Metabolic activation required

$$P_{man} = P_{test} \times \frac{\text{Body Wt}_{test}}{\text{Body Wt}_{man}}^{1/3}$$

Using Formula II for chloroform, from which toxicity is most probably due to the production of reactive metabolites, these authors found that the relative carcinogenicity of chloroform in rats predicted from the mouse data is in reasonable agreement with the observed tumour incidence in rats. When Formula I was applied according to the procedure of the Carcinogen Assessment Group of EPA, inconsistent results were obtained.

Another method for quantitative extrapolation from one animal species to another and from other animals to man has been suggested by Krasovskij (21). The so-called "body weight rule" is based on an established relationship between the indices of acute toxicity and body weight for different animal species. For 80-85% of the total number of 700 substances analysed, the logarithms of toxicity indices in laboratory mammals show a linear regression to the logarithms of body weight. The regression coefficient for individual substances ranges from 0.1 to 5.5.

For most substances, the values of the coefficient are between 0.9 and 0.5, which means that the sensitivity of the animals to those poisons increases as a linear function of body weight. The extrapolation coefficient from experimental animals to humans can be calculated or read from a special nomogram (11). To calculate the extrapolation coefficient for a compound, at least four species of laboratory animals must be studied.

Understanding among toxicologists is growing that the comparison of metabolic pathways and toxicokinetic parameters of a chemical in different species of other animals can provide a valuable, scientifically based tool for extrapolation of animal toxicity data to humans (4,10,11,18,22-27). Ideally, the most appropriate animal species should be selected to predict human response on the basis of comparative consideration of metabolism in a broad understanding of the balance of toxication and detoxication reactions. However, many unpredictable differences emerge in the quantitative and qualitative details in metabolism, and metabolic studies in humans are limited for ethical reasons. Conducting detailed metabolic and toxicokinetic studies of the thousands of chemicals that are, or will be, introduced into practical use is not possible. One way to overcome this problem may be to develop simple in vitro systems to provide information on metabolic pathways and their kinetic characteristics which, together with existing knowledge, would enable the prediction of toxicokinetics in intact animals, including humans. Attempts to develop such models have been described in literature (11).

Apart from differences in sensitivity between laboratory animal species and humans for low-dose extrapolation, some other uncertainties are also involved in the estimation of human risk from animal experiments, including: extrapolation from a small group of genetically homogeneous laboratory animals to sometimes large, genetically highly heterogeneous human populations, which include genetically predisposed individuals with increased susceptibility; synergistic effects of other environmental chemicals and factors; and great variation in human health, including subclinical pathology. To provide for existing uncertainties in extrapolating from laboratory animals to humans, the introduction of a safety factor is common practice. No precise guidelines have been drawn for deciding the appropriate size of such a factor, although some calculation methods have been proposed by Russian toxicologists.

Kagan (28) proposed to relate size of the safety factor to accumulative properties of chemicals. Sanockij & Sidorov (29) calculated the distribution of safety factors for 240 industrial chemicals on the basis of the coefficient of accumulation. For about 90% of the chemicals tested, appropriate safety factors do not

exceed 20. The formula offered by Sanockij & Sidorov includes values of several toxicometric parameters:

$$K = A \cdot Z_{CH} \cdot \frac{W}{Z_{AC}}$$

Where:

K = safety factor

A = coefficient which depends on the types of chemical compound

Z_{CH} = coefficient of chronic effects =

$$\frac{\text{Threshold of acute effects}}{\text{Threshold of chronic effects}}$$

E_{AC} = coefficient of acute effects =

$$\frac{CL_{50} \text{ or } DL_{50}}{\text{Threshold of acute effects}}$$

W = coefficient of hazard of inhalation poisoning =

$$\frac{\text{Max. conc. at } 20^{\circ}C}{\text{Threshold of chronic effects}}$$

Sidorenko & Pinigin (30) proposed to relate size of the safety factor to parameters of the concentration-time dependence curve established in animal experiments. The classification of hazard according to these parameters is presented in Table 1. The authors suggest that, for industrial chemicals, the minimal safety coefficient, equal to five, be established for substances at the boundary of moderate and highly hazardous substances where the angle of the concentration-time dependence curve is equal to 137°. From this value of the coefficient, it increases 25-fold and more, both in the case of increasing and of decreasing hazard of poisoning. The authors state that their approach has been confirmed by a comparison of epidemiological data and levels of maximum admissible concentrations (MAC) for substances that are widely distributed and have been relatively well studied, by a

Table 1. Classification of hazard from substances according to parameters of the concentration-time curve (30)

Class of hazard	Parameters of curve		Decrease in concentration of substance	Increase in time for occurrence of effect
	Angle of incidence	Tangent of angle of increase		
1st: extremely hazardous	155°	0.475	10 x	3 x
2nd: highly hazardous	155-137°	0.475-0.950	10 x	3-9 x
3rd: moderately hazardous	137-125°	0.950-1.425	10 x	9-27 x
4th: slightly hazardous	125°	1.425	10 x	27 x

comparison of existing proposals for determining safety factors in the field of occupational hygiene and a comparison of the predicted MAC with the MAC for the same substances in atmospheric air. None of the calculation methods presented has been generally accepted, even in the USSR.

In general, the value of the safety factor depends on:

- the nature of the toxic effect;
- the nature of the dose-response curve;
- the size and type of population to be protected; and
- the quality of toxicological information.

In industrial hygiene, safety factors usually range from 2 to 10, sometimes reaching 50. Safety factors have also been proposed for carcinogenic chemicals, ranging from 10 (31,32) up to 5000 (22), but they have not been generally accepted. At the Institute of Occupational Medicine in Lodz, the practice is to set safety factors for industrial exposures up to 10.

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