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Current issues of dose response assessment in chemical risk assessment −focusing on the application of animal data−

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ABSTRACT— A major objective of combination toxicology is to establish whether a mixture of chemicals will result in an effect similar to that expected on the basis of additivity. This requires understanding of the basic concepts of the combined toxicological action of the compounds of the mixture: simple similar action (dose addition), simple dissimilar action (effect or response addition), and interaction (synergism, potentiation, antagonism). The number of possible combinations of chemicals is innumerable, and in vivo testing of these mixtures is unattainable from an ethical, economical, or pragmatic perspective. Prediction of the effect of a mixture based on the knowledge of each of the constituents requires detailed information on the composition of the mixture, exposure level, mechanism of action, and receptor of the individual compounds. Often, such information is not or is only partially available and additional studies are needed. Research strategies and methods to assess joint action or interaction of chemicals in mixtures such as whole mixture testing, physiologically based toxicokinetic modeling and isobologram and dose response surface analyses are discussed. Guidance is given for risk assessment of both simple and complex mixtures. We hypothesize that, as a rule, exposure to mixtures of chemicals at (low) non-toxic doses of the individual constituents is of no health concern. To verify the hypothesis is a challenge; to timely detect exceptions to the rule is the real challenge of major practical importance.

KEYWORDS: isoboles, response surface analysis, physiologically based toxicokinetic modeling, weight of evidence approach, complex mixtures, simple mixtures, combination toxicology.

1. INTRODUCTION

For most chemical mixtures data on exposure and toxicity are fragmentary, and roughly over 95% of the resources in toxicology is still devoted to studies of single chemicals [1], [2]. Concurrent or sequential human exposure to a multitude of chemicals (e.g., food additives, pesticides, indoor and outdoor air pollutants, and occupational environments) dictates the necessity of exposure assessment, hazard identification, and risk assessment of chemical mixtures. Moreover, public concern regarding exposure to chemical mixtures and the interest of scientists and regulators in this challenging vanguard of toxicology have increased. Topics of continuous debate are concepts of similar joint action and independent joint action vs. interaction of chemicals, design of experimental studies, and analysis of the results, including the use of statistical methods, dose response relationships and lowdose extrapolation, mechanisms of toxicokinetic and toxicodynamic interactive effects, and, last but not least, the lessons learned from risk assessment of real-life examples of exposure to chemical mixtures [3- 9]. It is important that the right parameters are used for summation of the effects of the individual compounds in assessing joined effects. For example, the addition of 1 l water to 1 l ethanol will result in a volume that is less than 2 l. In this case the parameter weight rather than the parameter volume should have been used. Another example, given by Steel and Peckham, [10] is the amalgamation of two spherical balls of clay. The sum of the radii of each single sphere is dissimilar to the radius of the newly formed spherical ball. In this case the volume or the

weight should be used to predict the result of the amalgamation. These examples illustrate the paramount importance of the use of the appropriate parameters and evaluation models to predict the hazard of a mixture relative to its constituents.

Complex chemical mixtures consist of tens, hundreds, or even thousands of compounds. Their composition is qualitatively and quantitatively not fully known and may change. Examples are wood smoke, diesel exhaust, welding fumes, fly ash, food, and occupational and environmental settings. Often adequate testing of such mixtures is impossible because they are virtually unavailable for testing and a sufficient number of dose levels cannot be applied. Moreover, highdose levels of the mixture may have different types of effects than low-dose levels, and low-dose extrapolation may be meaningless [7], [11]. In some cases (diesel exhaust, coal dust), testing of complex mixtures as a whole has been shown to produce relevant toxicological information. For all of the aforementioned reasons, one of the main interests of scientists in the field of combination toxicology is to find out whether the toxicity of a mixture is different from the sum of the toxicities of the single compounds; in other words, will the toxic effect of a mixture be determined by additivity of dose or effect or by supra-additivity (an effect stronger than expected on the basis of additivity) or by infra-additivity (an effect less than expected on the basis of additivity)? The toxic effect of a mixture appears to be highly dependent on the dose (exposure level), the mechanism of action, and the target (receptor) of each of the mixture constituents. Thus, information on these aspects is a prerequisite for predicting the toxic effect of a mixture. In this article the basic concepts of similar and dissimilar action of chemicals and of toxicological interactions between chemicals in a mixture are briefly discussed. Furthermore, strategies are described for studying both simple and complex mixtures.

2. OBJECTIVE

Scientists and risk assessors are well aware that toxicity can be modified by exposure to multiple environmental agents [7]. There is substantial evidence, for example, that simultaneous exposure to tobacco smoke and asbestos or radon increases the risk of lung cancer multiplicatively compared to the additive effects of the individual agents combined. Likewise, the risk of hepatocellular carcinoma is increased by the interactive effects of hepatitis B infection and exposure to aflatoxin-contaminated food, toxicity to aquatic organism is increased by interactions between polycyclic aromatic hydrocarbons and ultraviolet light, risks of hearing loss are potentiated by exposure to both noise and toluene, and children of parents experiencing stress are more susceptible to viral infections. However, most of the available scientific evidence involves relatively simple interactions between comparatively few constituents, so that application of cumulative risk assessment to real-world mixtures is hindered or precluded by a scarcity of appropriate data, paucity of mechanistic understanding, and shortage of verified analytical frameworks [4], [7].

3. RESULTS

It has been observed that there has been an upsurge in consciousness of quality during the past decade. Initially, herbal medicines were used as food and there were no quality requirements. Presently they are classified into different categories such as drugs, health products, nutritional substances (neutraceuticals), cosmetics, and so on according to the laws of various countries. The status of herbal products is also changing due to the incorporation of modern science. To maintain quality control over the products, some countries have published pharmacopoeias of herbs and herbal products (eg, UK, India, United States, EU) prescribing specific monographs of the herbs used (Table 1). Several other countries are in the process of developing monographs (eg, Brazil). Some countries are using pharmacopoeias of other countries to standardize their products. The number of monographs varies in different pharmacopoeias and also from one edition to another (Tables 2 and 3) [5– 8]. A recent survey of WHO member countries has shown that 34 countries have a national pharmacopoeia and 104 countries do not possess their own pharmacopoeia [4].

Quality requirements also vary. For example, pharmacopoeial specification for Andrographis paniculata is not less than 1% andrographolide in the Indian Pharmacopoeia (IP) 2007, 0.5–0.9% andrographolide in the Indian Herbal Pharmacopoeia (IHP), 6% andrographolide in the WHO specification, not less than 0.8% andrographolide in the Pharmacopoeia of the People's Republic of China (CP), and so on. India has seven volumes of Ayurvedic Pharmacopoeia and recently published two volumes of Ayurvedic Pharmacopoeia of India (Formulations), two volumes of Herbal Pharmacopoeia, two volumes of Ayurvedic Formulary, and eight volumes of Homeopathic Pharmacopoeia.

4. CONCLUSION

From a public health point of view, it is most relevant to answer the question whether chemicals in a mixture interact in a way that results in a reduced or increased overall response when compared with the sum of the responses to the individual chemicals in the mixture, or indeed in an effect that is simply a summation of the expected effects. By and large, regulatory actions and industrial practices are based on the use of dose-addition as the default assumption addition has been stated most explicitly for assessing carcinogenic risks. Although, in general, this is a prudent practice, this assumption may usually overestimate risk and sometimes underestimate risk. Approaches for dealing with risk assessment of mixtures rely heavily on some form of additivity model unless data are adequate for a direct risk assessment of the mixture of concern. Although the previously described additivity models are mathematically simple, they require assumptions about the mechanisms and the mode of action. The number of mixtures to which direct risk assessment or risk assessment using the relative potency method have been devoted is limited. The theoretical considerations in risk assessment of chemical mixtures should be verified by simple case studies as published recently. The usefulness of a method for hazard identification and risk assessment of a complex mixture very much depends on the context in which one is confronted with a complex mixture and also on the information that is available on the chemistry and toxicity of the mixture. The way to approach a complex mixture of which the components are largely known but whose hazard is almost unknown is different from the way to approach a complex mixture whose hazard has been established but the chemical composition of which is largely unknown. The development of decision trees to tackle complex mixtures has been suggested and should be pursued. The weight-of-evidence approach might prove to be very useful in evaluating simple defined mixtures.

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