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COMPLEX MIXTURES
Methods for In Vivo Toxicity Testing

Committee on Methods for the
In Vivo Toxicity Testing
of Complex Mixtures
Board on Environmental Studies and Toxicology
Commission on Life Sciences
National Research Council

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:abl narily to studies of target
;eneral systemic toxicity. This re-
ıammals, particularly humans, to
the larger issues involved in envi-
ecology. It recommends that such
c group, and it suggests that more
:hanisms of toxicity in nonmam-

ılable scientific problem. The key
s and planning of the strategy or
ture of testing should be guided
what needs to be learned. Selec-
ed strongly to questions related to
interest, and to the likely use and

effects of a mixture, the strategies
re itself. The first step should be a
ixture, because this will provide
ıd the physical and chemical char-
y the types of anticipated effects.
ss: samples must reflect as closely
sed to; they must be suitable to the
ust be maintained at all points, as
an situation. Questions regarding
:ause different components age or
unc inty about what is actually
exp d to. Established and em-
or evaluating complex mixtures as

lack of animal or cellular models
:spiratory disease). Therefore, the
pment of animal models that per-
rch for exposure-related effects in
esulting information must be inte-
ls in toxicology.
ith complex mixtures is related to
:ific health effects. The strategies
ily on the integration of toxicology
the complexity and diversity of
ıcterization of every sample under

not used for single agents, is the
ioassays of fractions derived from

mixtures are used to identify which fractions need chemical characterization; the most toxic fractions are quickly identified.

In dealing with the ability to predict adverse effects of mixtures, the committee distinguished between factors related to effects and factors useful in modeling. The predictive value of an effects strategy centers on the ability to use data from tests of one mixture to predict the likely effects of exposure to a new but similar mixture. Among the effects strategies, comparative-potency studies and matrix testing were designed for such prediction. (Matrix testing involves the identification and manipulation of several variables that are arrayed in a two-dimensional matrix, such as boiling range and aromaticity.) The predictive value of a model strategy is related to the toxicity of components of simple mixtures whose components are all known. In such a case, if the toxicity of each component is known or can readily be determined, it might not always be necessary to test the whole mixture. (This model-driven prediction is described in Chapter 3.)

Simple mathematical models have been used to assess the toxicity of simple mixtures, particularly binary mixtures. Those models suggest that interactions that might be observed at a high dose, such as an experimental dose, do not necessarily occur at lower doses; hence, models might play an important role in permitting the extrapolation of toxicity to lower doses. Although a concentrated effort has been made to define the role of models in assessing the toxicity of more complex mixtures, it is clear that further work is needed to test the validity of models against experimental and epidemiologic data.

Consistency of analytic results between mixtures implies an increase in the predictability of their effects. The more similar two mixtures are chemically, the more similar their toxicologic properties are expected to be. However, even mixtures that are relatively well characterized sometimes have unexpected toxic effects. One must be prepared to look for unexpected results of exposure to complex mixtures, because of the potential disjunction between chemical analysis and biologic effect. Complex chemical mixtures are more likely to produce unexpected results than are individual chemical substances, for several reasons. Mixtures are composed of various substances, exposure to which can be expected to be associated with different toxicities. The constituents of a mixture sometimes combine chemically to produce new compounds with different toxicities. The presence of some materials might mask, dilute, or increase the toxicity of other materials. Such phenomena, referred to as interactions, can amplify or reduce anticipated effects. Moreover, different doses of separate materials might increase the bioavailability of materials that are otherwise nontoxic at the doses present in the mixture.

On the basis of theoretical considerations and its examination of some epidemiologic studies, the committee noted that effects of exposures to agents with low response rates usually appear to be additive. The only examples of interaction that were considered greater than additive occurred in humans exposed to

agents, such as cigarette smoke, that alone produced a high incidence of effects. Current quantitative models used to assess cancer risks support these results. However, the committee did not thoroughly review the toxicologic data on additivity assumptions.

The committee recognizes that several important related issues are not discussed in its report. Its discussion of the testing of complex mixtures deals largely with strategies, rather than with detailed testing methods.