IMPROVEMENT OF PREDICTABILITY OF SUBCHRONIC AND CHRONIC TOXICITY STUDIES
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The repeated-dose toxicity studies that are routinely used in industry are based on an omnibus procedure, using large groups of animals of two species, and at least three dose levels of which one is selected to induce overt adverse effects. This approach is contrived to detect indices of general toxicity (e.g. body weight gain, food consumption), selected biochemical changes, mainly those related to disturbances of liver and kidney function, hematological abnormalities and morphological lesions detectable by routine light microscopy.

Although it is possible to demonstrate many adverse reactions, it is evident that the standard toxicological test procedures have failed to detect a variety of toxic effects that are relevant for man. In addition, a considerable number of false positive test results are generated. In order to improve the predictability of repeated-dose toxicity studies, the reasons for the inadequate performance of current methods were discussed. It was illustrated that the usefulness of subchronic and chronic toxicity tests can be improved by addition of supplementary assay methods and by a more careful timing of the laboratory investigations. It was also shown that a number of tests that are routinely performed can be omitted or drastically reduced without jeopardizing the usefulness of the investigations.

Since current toxicological methods neglect, to a large extent, functional organ changes, it is suggested to include more physiological measurements in the toxicological test procedures. In addition, a more careful consideration of the pharmacokinetic characteristics of the test substances is thought be of great importance, in particular for the selection of an optimal dosing schedule and for the ultimate risk assessment. Furthermore, new scientific approaches must be developed to detect adverse effects that are due to idiosyncratic or allergic responses of selected human populations.

It is not considered to be advantageous to include too many measurements and assays into routine repeated-dose toxicity studies, since such activities may interfere with the normal development and the health of the laboratory animals. This is particularly the case for investigations that need invasive assay procedures and for interaction studies. For this reason, it is often better to conduct certain investigations of special satellite groups of animals, or to obtain the necessary information in preliminary pilot or screening tests. Such tests can also include in vitro assays of various types.