BIO-MEDICAL RESEARCH
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Dow research shows way out of chemical carcinogen problems

THAT chemical companies worldwide are urgently researching short-term toxicology tests (such as that developed by Bruce Ames of California University) indicates the significance of the "chemical carcinogen problem" and partly reflects the requirements of legislation coming into force in the US and being formulated in Europe.

Although still at an early stage of development the tests are already being incorporated into new legislation (such as the UK Health and Safety Commission's notification scheme) as a means of quickly screening compounds and as an indicator of whether animal tests should be carried out.

The techniques will be the major topic of discussion at an industrial toxicology conference being held at Surrey University next week, but they are indeed only short-term and not entirely reliable indicators as to whether a chemical is likely to be a carcinogen, however desirable a substitute they may be for long-term feeding trials.

One of those who hold reservations about the true value of these techniques and who is more concerned with the broader problem of how to deal with carcinogens once they have been identified is Dow's head of toxicological research Perry Gehring. He will be speaking at the Surrey conference on the need for an understanding of the mechanisms of action of carcinogens before any extrapolation on the results of high-dose animal tests to humans is carried out (in this case examining vinyl chloride).

This reflects work done at Dow Chemical's Michigan laboratories which is helping to overcome one of the biggest theoretical obstacles to a rational approach to chemical carcinogens—the fact that it has never been possible to show that there exist any safe exposure levels, although such "threshold" levels of exposure have been long accepted for substances which are simply toxic.

By understanding the detoxification or excretion processes which can allow man and animals to cope with small doses of carcinogens, but which are overwhelmed by large doses, Dow Chemical has shown that the normal statistical extrapolation of high-dose results, to produce an indication of cancer incidence resulting from real-life exposure, leads to great overestimations. Gehring doesn't suggest that this means an early introduction of a "threshold" concept for all carcinogens, but there is already evidence, he says, that high doses of some compounds overwhelm natural detoxification processes, this being so with vinyl chloride, styrene, carbon disulphide, β-naphthylamine and 1,4-dioxane.

This is one reason why *in vitro* or short-term tests are so divorced from the real situation, notes Gehring. Because the cell cultures used to detect whether a compound causes mutation represent an artificial environment, the situation excludes the natural excretion and repair processes.

The detoxification processes occur in different ways, sometimes involving excretion of the chemical itself or sometimes action on the active metabolite (the adduct, between the carcinogen and a macromolecule, which is usually the true carcinogenic agent).

In the case of vinyl chloride, he says, the detoxification process involves a substance produced in the liver (glutathione) which is only in limited supply, and it is therefore not surprising that the process proceeds faster at lower doses. It would require unrealistic numbers of test animals to show a no-effect level experimentally in feeding trials, but Gehring's work characterizing the dose-response data of VCM-induced angiosarcoma in rats has encouraged him to venture estimates of levels of exposure which he regards as likely to result in no greater occurrence of human angiosarcoma than would be expected to occur spontaneously. Gehring suggests around 25ppm as being such a level.

Neglecting the possibility that a threshold level might exist and the fact that rats have been shown to be 5-50 times more susceptible to VCM-induced tumours than humans, Gehring's calculations based on rat data show that chronic exposure to VCM at the 1ppm level would be expected to result in one case of angiosarcoma in 100m. subjects —lower than the spontaneous occurrence.

Acrylonitrile, which has more recently come under scrutiny as a carcinogen, is already characterized by Gehring as combining directly with the basic life molecule DNA, rather than via a metabolite, like VCM.

According to the evidence from Dow's long-term rat-feeding trials which first raised the suspicion about acrylonitrile, the compound is also more potent because it causes tumours in the brain, where detoxification processes do not operate. But the fact that an excess of brain tumours was not revealed by Du Pont's recent epidemiological study at its plant at Camden, South Carolina, leads Gehring to be suspicious of that study's validity, and he waits to see better evidence that it is a carcinogen.

This lack of correlation with animal results he suspects, despite the common suggestion that humans don't necessarily exhibit the same effects as test animals. Asbestos, VCM and β-naphthylamine, have all shown good correlation in this respect, he notes.

Nevertheless, Gehring believes that a threshold effect will be detected with acrylonitrile, with detoxification processes operating in the blood and lungs.

Duplicated Legislation

These rapid developments in the state of the toxicological art come at a time when the chemical industry is being criticized for not detecting such chemical hazards earlier, although the means have not been available to allow such an understanding.

In contrast, the US legislature's answer to the problem, the Toxic Substances Control Act, according to Gehring has only duplicated existing legislation which has never been implemented.

Although incidents such as the kepone pollution at Hopewell, Virginia, were cited as indications of the need for such new law, it simply reflected the result of ineffective implementation of existing laws, according to Gehring.

Gehring maintains that 90 per cent of the new law's aims could be achieved with existing legislation, the only neglected area having previously been law controlling disposals of solids on land.

The strength of Dow's belief in this led not just to efforts to modify its contents, Gehring admits, but to try and prevent its ever reaching the statute book.

What makes Dow's toxicological work so important is not legislation but the rate at which industrial chemicals are being labelled carcinogenic, often as a result of the massive-dose techniques which Gehring calls "solid state toxicology".

Thus the US National Cancer Institute's bioassay programme, originally conceived a decade ago to examine highly bioactive compounds, particularly pesticides, is now committed to reporting animal test data on more than 200 suspect chemicals at the rate of three a week. The "Chemical carcinogen of the year" phenomenon of the recent past, notes Gehring, threatens to become the "Chemical carcinogen of the week" in the near future.

What can the industry do to put new evidence in perspective and ensure a fair "trial by media" in such cases? The recent release by the NCI of test data linking perchlorethylene with liver cancer in mice provides an illustration of Dow's efforts. The fact that Dow

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