Is there a carcinogen threshold limit?

Everyone who is anyone in cancer research discussed issues like threshold limits, mutagenic screens and correlation of animal test data to human exposures in sometimes heated sessions at last week's Conference on Origins of Human Cancer at the Cold Spring Harbor, N.Y., laboratory of James D. Watson of DNA fame.

Watson would sometimes rush forward with a piercing question for a speaker. But the limelight was most often on such titans as Irving Selikoff, Cesare Maltoni, Bruce Ames, John Weisburger, Umberto Saffiotti and Samuel Epstein. Failure of regulatory agencies and inadequacy of test data were the most common topics. And revelations of new evidence implicating such chemicals as polychlorinated biphenyls and chloroprene created the biggest stirs.

Against this lineup the effort of Dow's toxicology research lab director Perry Gehring to develop a threshold limit concept for known carcinogens met with some opposition.

With evidence on dose-response changes for animal testing of vinyl chloride and 1,4-dioxane, Gehring proposed to "get rid of the usual definition" of threshold limits and begin to "examine what's happening on both sides of the latency period inflection points so we can begin to make decisions we apparently can't make today."

Limits on Threshold: The National Cancer Institute's Saffiotti described attempts to establish protocols to test and regulate chemical carcinogens.

"We still don't know how to establish a safe exposure level," he said: "Methods we now use give us only qualitative indications." Moreover, Saffiotti proposed that a "truly realistic" approach should take into account multiple-source exposure. He noted that tests at NCI had shown that when two chemicals, neither of which had any cancer-causing indications, had been used jointly on animals there had been a marked increase in tumors.

But, according to Saffiotti, no data "allows us to establish a threshold for carcinogens." This view was upheld earlier in the week by Cesare Maltoni, who said that his Institute of Oncology and Tumor Center (Bologna, Italy) was "unable to detect a safe dose of vinyl chloride" (*C&EN, Sept. 15, p. 47*).

But using Maltoni data as well as Dow's own test results, Gehring says that the "fate of VCM changes with the dose . . . because the primary pathway for the metabolism of VCM is saturated at high doses or exposures."

Latency Link: Latency-period data also point up the dose-response relationship, according to Gehring. He notes that Maltoni's data indicate latency periods in a relatively narrow range of 64-79 weeks for exposures from 10,000 ppm. down to 250 ppm. But at 50 ppm. the latency period suddenly zooms to 135 weeks. And that rate was for rats that died of other causes. Gehring concludes that "exposure to 50 ppm. VCM four hours/day is in the threshold transition zone for tumor induction."

Moreover, studies of VCM metabolism demonstrate that the reaction involves nonprotein sulfhydryl groups. Dow postulates that depletion of these groups frees the VCM to attack DNA and lipids and perhaps start a cancer reaction. Measuring the hepatic nonprotein sulfhydryl groups, Dow found no depression in their content for exposures of 10 ppm. of VCM for seven hours. Conclusion: there is a threshold of exposure in rats where the ability to replace sulfhydryl groups is not overwhelmed.

Dow has developed test data indicating these kinds of dose-dependent rates for many chemicals, including 1,4-dioxane, styrene, ethylene, glycol, aniline and benzopyrene. "It is likely that as more compounds are evaluated, dose-dependent rate will be found to be the rule rather than the exception," says Gehring.

He adds: "Translation of the data for maximum tolerated dose (below levels where toxic effects occur) to predict hazard of low-level exposure is presumptuous guesswork at best."

Chemicals Cautioned: Despite Gehring's caution, projections continued to be made, linking high-dose exposure data to some low-level human exposures to chemicals.

The issue of carcinogenicity of PCBs is still up in the air, despite some cases of increased incidences among exposed workers (*C&EN, Sept. 8, p. 26*). Monsanto, sole U.S. maker of the heat-transfer fluid, said it had seen "nothing to date indicating a link between PCBs and cancer."

But Ijkeshi Hirayama, of Japan's National Cancer Center Research Institute, told the conference of increased incidence of liver cancer among the 1,200 residents of Yusho, Japan, who consumed rice accidentally contaminated with several thousand parts per million of PCB in 1968.

Hirayama's report of two definite and three possible cases of liver cancer among those who ate the rice suggests a "high possibility" that PCBs caused the liver cancer.

Monsanto says it had no prior knowledge of the report and until the data is reviewed, the company would have no comment on it. But Monsanto states that it has no evidence of any liver cancer in its own employees. It says more study is needed.

More study is needed of chloroprene also, according to Peter Infante of the National Institute for Occupational Safety and Health. "After 45 years of experience with this large commodity chemical, not one epidemiological or animal study has been completed," says Infante. But some partially completed studies indicate the material may be mutagenic.

The paucity of test data was also decried by Lehn Goldberg, head of the new Chemical Industry Institute of Toxicology (Research Triangle, N.C.). "It's amazing how little long-term testing of building-block chemicals has been done," he says.

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J.R. Withey of Canada's Bureau of Chemical Safety says toxicological testing has been done on only 400 of 7,500 chemicals used in making plastics. And Lorenzo Tomatis of the International Agency for Research on Cancer (Lyon, France) says his agency's survey indicates that 89 laboratories in 19 countries are presently engaging in toxicological testing of some 828 chemicals.

The message for the chemical industry is clear: a lot more long-term testing of new and old chemicals is in the offing. But interpretation of the test results into some meaningful and practical regulations apparently is as far off as ever.

MONS 035238