Misgivings over a 'consensus' on carcinogenesis

In the war against cancer, federal laws passed since 1952 for hazardous substances hardly reflect a uniform view of cancer or of the role that hazardous substances play in the incidence of cancer. In fact, according to the Office of Science and Technology Policy (OSTP), directed by George A. Keyworth II, science advisor to the President, a study of the laws shows "that each reflects the scientific views existing at the time of enactment." Now, OSTP has completed the comment period on a policy statement that paints, in broad strokes, "a view of carcinogenesis that scientists generally hold in common today."

Broad as that sounds, comments last week by chemical groups indicate concern that OSTP's statement, as it stands, could subtly tilt the scales against producers in the current regulatory reviews of formaldehyde and negotiated testing agreements for the Environmental Protection Agency (EPA). Further, the organizations fear that the document, if not changed, could skew federal policy on risk assessment, a highly controversial area.

OSTP's objective in drafting the document was to compose a series of general principles useful for setting specific guidelines for assessing carcinogenic risk. The statement comes in two parts. Part I states 31 general scientific principles, including points on risk assessment (*table*). Part II focuses on the current status of cancer research, noting advances in assessing gene damage and repair.

Risk. In general, chemical groups give OSTP high marks for the effort. Nevertheless, they are worried about the ground rules covering how regulators assess the risk of a chemical, since it is the first step on the road to a possible ban (*CW, May 9, p. 26*).

One key criticism of Part I, which sets down the 31 principles, is that it fails to make unmistakably clear that several items are actually "science policy" principles, not "scientific" principles. For instance, the Chemical Manufacturers Assn. (CMA), in a 71-page analysis, warns that Principle 8, which would define the term carcinogen broadly in interpreting long-term tests, may actually be too inclusive. CMA contends that the principle could be read to suggest that an agent that increases the incidence of only benign neoplasms can be termed a carcinogen. And that, the organization says, is "a controversial issue of science policy that should not be reflected as an established principle."

Another key policy choice, CMA says, lies in Principle 11, which covers the use

A federal statement could tilt the scales against chemical makers in regulatory review ...

of high test doses in animals, at levels that generally exceed human exposure levels. The principle calls for use of the maximum tolerated dose (MTD) in such tests. In Part I, says CMA, "This is one of the primary science policy decisions."

Distinction. Distinguishing between risk assessment and risk management is also a matter of science policy, says the American Industrial Health Council, which coordinated its response with the Formaldehyde Institute. The distinction, it says, is that scientific choices on risk assessment are "analogous to the choice of medical procedures by a doctor," while risk management decisions are guided by social values, such as "costs, benefits, technology and the need for conservatism."

In risk assessments, as EPA Administrator William D. Ruckleshaus has pointed out, researchers can stack conservative assumptions "on top of one another." But what the regulator needs, in deciding whether to ban a product or to restrict it, is some idea of how much confidence to place in the estimates of risk and an idea of how likely it is that the substance will cause real damage.

Courts have already determined that better risk assessment methods are required. In the case of the attempted ban on urea-formaldehyde foam insulation, eventually a federal court set aside a decision to ban by the Consumer Product Safety Commission, which relied solely on one model that predicted an upper boundary of risk.

CMA is in complete accord with OSTP on Principle 31, which says that risk assessments should consist of numbers and an explanation of the numbers. "Risk assessment," CMA says, must not degenerate into a sterile mathematical exercise." In some cases—dichloromethane, for one—the interpretation "may indicate that there is no scientifically justifiable basis for calculating a human cancer risk for the agent at all."

CMA says that some chemicals, such as formaldehyde, have been shown to be carcinogenic in animal tests. But it adds that "the epidemiological evidence and our knowledge of mechanisms of

Keyworth: Obsolete science yields obsolete law.

action and interspecies differences indicate that the agent can be suspected of being only a weak human carcinogen."

Linearity. Indeed, CMA comes down particularly hard on parts of Principle 26, covering assessing risk by extrapolating results from high-dose tests to obtain low-dose data. Principle 26 favors using models incorporating low-dose linearity in cases where information is limited—"the usual case, says CMA"—and where scientists are uncertain about the mechanism of carcinogenic action. CMA calls this "an unjustifiably strong and unqualified endorsement" of such models, pointing out that for formaldehyde,

models based on low-dose linearity were inconsistent with the biological and biochemical evidence on the mechanism of action.

Because of the controversy over using such high doses in animal testing, CMA suggests adding a caution that the high dosages themselves could help induce malignant tumors. In addition, CMA would like to see language to the effect that "a properly conducted test must include doses lower than the MTD," which would help validate the response observed at that high dose and help develop a dose-response curve.

Another factor. In a similar vein, the Chemical Industry Institute of Toxicology (CIIT) points out that the chemical makeup of the substance may not be the only consideration in determining carcinogenicity. It observes, for example, that "bladder tumors can be produced in rats by placing glass beads in the bladder," yet it is reasonably certain that the beads do not act directly on the genome. And, CIIT adds, "the same can be said for sarcomas produced by placing inert material in muscle."

It's also important to differentiate be-

...and blur the distinction between risk assessment and risk management

tween exposure to a substance and its absorption, says (CIIT), which was the first to report nasal cancer in rats from chronic high doses of formaldehyde. The researchers point out that low-dose linearity models measure exposure by administered dose, which is an external measure, as for example, the concentration of formaldehyde in air for an inhalation study. Delivered dose, by contrast, is the concentration of the chemical, such as formaldehyde, in specific target tissues. According to the CIIT researchers, if the delivered-dose concept is taken into account when performing low-dose extrapolations, there is "a unilateral reduction in estimates of cancer risks associated with exposure to low airborne concentrations."

Not surprisingly, the chemical industry's arguments do not persuade the Natural Resources Defense Council (NRDC), which says that while the models predict an abrupt decrease in the slope of the dose-response relationship at low-dose levels—a "hockey stick" curve—the models should not be confused with true threshold models.

The key level, the council says, is where "absolutely no increase in cancer incidence is attributable to the carcinogenic agent at exposures below the threshold dose." NRDC notes that, while there is a sharp decrease, the dose-response curve, although very shallow, shows a figure that is "nonzero, meaning that there is a finite probability of the toxic event occurring and no real threshold." In particular, the NRDC study says, use of a hockey stick threshold model to assess formaldehyde, as advocated by some chemical industry researchers, is fraught with problems, such as the difficulty in gathering a set of parameters. It should not be used, NRDC maintains, as a general method of risk assessment.

For its part, the Chemical Specialties Manufacturers Assn. (CSMA) agrees with CMA on the need to distinguish between risk assessment and risk management. In addition, the association calls for independent scientific peer review of risk assessment data. In fact, CSMA states, the peer review committee's meetings should be public, limited only enough to protect confidential business data. It feels, too, that a regulatory agency should "respond publicly when their policy decisions are contrary to the peer review group's advice and counsel." CSMA adds that the National Academy of Science and other groups

Principles of cancer assessment

Epidemiology

15. The strength of the epidemiological method is that it is the only means of assessing directly the carcinogenic risk of environmental agents in humans; however, primary reliance is often placed on animal testing.
16. Descriptive epidemiological studies are useful to generate and refine hypotheses, or provide supporting evidence, but rarely provide information allowing a practical causal inference.
17. Well-designed case control or cohort epidemiological studies can provide the basis for practical causal inferences especially useful for public health decisions.
18. Elements in interpreting the above studies include the magnitude of the risk estimates and the reproducibility of the findings.
19. A high quality negative epidemiological study, while useful, cannot prove the absence of an association between chemical exposure and human cancer.

Exposure assessment

20. Exposure routes used in animal studies of health effects should be comparable to those in human studies.
21. There is no single general procedure for a complete exposure assessment.
22. Exposure assessments should be tailored to provide the data to support analytical needs.
23. An exposure assessment should describe the strengths and limits of the data, and indicate the assumptions for the exposure estimates.
24. In general, a range of exposure values is preferable to a single numerical estimate.

Risk assessment

25. Decisions on carcinogenicity should be based on a weight-of-evidence approach, taking into account positive or negative responses, and should use sound biological and statistical principles.
26. No single mathematical procedure is recognized as the most appropriate for low-dose extrapolation in carcinogenesis. However, when data is limited, and there is great uncertainty about the mechanism of carcinogenic action, models that incorporate low-dose linearity are preferred.
27. Quantification of the sources of uncertainty can be as important as projection of the risk estimate itself.
28. Differences in human susceptibility suggest that there are subpopulations at greater-than-average risk.
29. A full evaluation of risk to humans should include a written consideration of the strengths and weaknesses of the hazard and exposure data, in addition to numerical estimates.

Source: Office of Science and Technology Policy

have already advocated such measures.

CSMA raises other objections. On risk evaluation, it believes that Principle 25 forces scientific evaluators to be biased on the conservative side. The principle, the group says, "appears to give overwhelming weight to 'positive' carcinogenic evidence without consideration of its scientific validity. Thus positive evidence must always outweigh negative." The principle, CSMA adds, would lead to "a poor animal study being given preference over a well-designed and well-conducted human epidemiology study." In addition, CSMA recommends adding a principle to the list that would "emphasize the importance of using quality assurance procedures."

One of the main complaints of its members, though, CSMA says, is that the draft implies that synthetic chemicals are a major cause of cancer or are responsible for the increase in certain types of cancer. But it points out that "recent studies by Higginson and Doll and Peto indicate that, at most, 10% of all cancer may be associated with man-made chemicals and pollution." As a result, CSMA concludes that reference to those studies in Part II's epidemiology chapter "would provide a better balance for the final document." □

Celanese Canada consolidates

Canadian textile and fiber producers for the garment industry are slowly being hemmed in by bolting apparel imports. As a result, the country's major man-made fiber producers have pulled up their stakes in certain segments of the business over the last several years and have consolidated. And in the latest of these amalgamations, Celanese Canada says that it will restructure its textile group. In addition to phasing out a weaving plant and shedding certain lines from its product mix, the company last week said that it had arranged to sell a polypropylene fiber and yarn plant to Amoco Fabrics Ltd., the Canadian fibers arm of Amoco Chemical.

When the trimming is complete, Celanese Canada—56.4%-owned by Celanese (New York City)—will indeed be thinner. Its chemical group, which makes acetic acid, acetic anhydride, vinyl acetate, methanol and formaldehyde at a sprawling complex at Edmonton, Alta., will remain untouched. But only two of four plants will remain in its textile group: a polyester facility at Millhaven, Ont., and an acetate fabric and fiber unit at Drummondville, Que. In addition, the company says that it will "sharply reduce" its product menu, manufacturing pure acetates and polyesters rather than blends.

Senseless. The planned shutdown of Celanese's weaving facility at Coaticook, Que., when completed in March 1985, will furlough 170 workers. The plant, already fully depreciated, will be sold to the town for $1; select looms from the operation will be integrated with existing facilities at Drummondville. "It didn't make sense to run Coaticook," says a spokesman for Celanese Canada, explaining that operating rates at both weaving facilities had languished to about 70% of capacity.

As for the polypropylene fibers and yarns unit at St.-Jean-sur-Richelieu, Que., it will be sold, according to the spokesman, because "Celanese doesn't have the technology base to be a world leader in this area." The sale represents the final exit by Celanese Canada from the carpet business. The spokesman explains that fibers and yarn from the St. Jean plant, in addition to supplying the handicraft industry, had been channeled to Celanese Canada's carpet manufacturing business until its sale in 1981.

While polypropylene fibers may be a misfit for Celanese, it may well be a trump card for Amoco Fabrics, which now operates three plant in Ontario. Amoco Chemical, says a company spokesman, is already leader of the pack of polypropylene fabrics, fibers and yarns suppliers. The new facility is not only expected to broaden the Canadian arm's penetration of the domestic home furnishings market, but will vault it into first place among Canadian polypropylene fibers suppliers. The company's U.S. affiliate, notes Amoco Fabrics Ltd. President Kenneth M. Thompson, now holds that title for North America.

Fibers boom. The carpet fibers business, says Du Pont Canada—lead domestic supplier of nylon to that market—is indeed booming. And that is a boon to Du Pont Canada, which has bitten the bullet during the last few years on several of its fibers ventures.

Although Du Pont has since cut its reliance on the textile industry, it once was susceptible to rising apparel imports. In 1973, explains a Du Pont Canada spokesman, the company—encouraged by what then seemed to be a thriving market for polyester—built a multi-million-dollar polyester plant in Coteau du Lac, Que., but delayed and delayed startup because of teeming polyester imports. Even during the two years of its operations—until Du Pont Canada backed out of the business in 1982—the plant "never made a profit," recalls the source. That defeat followed a similar, yet less severe, blow the year before, when Du Pont shut a small acrylic fibers plant at Maitland, Ont., again because of "competitive pressures," the source notes.

Meanwhile, says the Du Pont source, "the Canadian apparel industry is having trouble surviving." Last year, notes the Celanese spokesman, imports had a grip on 40% of the Canadian garment market. In the last 10 years, he adds, the textile and clothing workforce in Canada has been whittled a little more than 20%, to 165,000 employees. □

(news continues on p. 14)