



Chemical risk assessment is not science

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The Board of Directors has encouraged TAPPI's staff and volunteer leaders to take action to improve awareness and understanding of environmental issues by the individual members of TAPPI. Our industry is facing a tremendous challenge over the next few years in dealing with tightening effluent regulations and the implementation of the requirements of the Clean Air Act. These new regulatory initiatives could result in industry costs of over US\$ 10 billion, and some older, smaller mills may not survive the high cost of compliance.

In setting the new standards, regulators have begun to rely heavily on a technique referred to as "Risk Assessment." The following article, a reprint from the December 1992/January 1993 issue of In Chemistry (Vol. 3, No.2, pp. 23-26), presents a clear and concise description of "risk assessment" and its limitations. Every TAPPI member should read this article carefully and understand how "risk assessment" is being used to set the standards that his or her industry, company, or customers will have to meet. Also, I hope that each of you will spread this understanding to your co-workers, friends, and neighbors. Understanding the scientific basis underlying our regulatory process is an important first step to getting good legislation and regulation.

—Ronald B. Estridge

Everyone knows that some chemicals can cause disease and death. We grow up with chemical risks and have learned to avoid them because our parents said, "That's poison," while pointing to oleanders, rhubarb leaves, bottles of cleaning supplies under the kitchen sink, and other dangers around the house.

Furthermore, we all know about some natural chemicals, such as botulin toxin, that are so toxic that public health officials and industry are charged with protecting us so that we never come into contact with these substances. Even more fearful are some synthetic chemicals, such as nerve gas, which will probably never be released into the environment, except with the specific intention of killing people.

But naturally occurring or household chemicals don't usually come to mind when we think about risky chemicals; rather, we are likely to picture these chemicals as useful products of modern society. I cannot be certain that another person is as interested in my welfare as I am. As a consequence, I'd like to think it over before I let someone expose me to the risk from a commercial chemical. I know that if I am careful I can control the risk from a drain cleaner, and I know immediately if I spill a chemical like that on my hand. But there are other substances I may eat, drink, or breathe without knowing it. These may not pose an immediate risk, but they may cause me trouble in the future.

Risk assessment

Risk assessment is the set of techniques used to calculate risk. Risk management involves measures taken to control or eliminate risks. Federal and state governments, at the urging of citizens, have enacted many laws to regulate or prohibit chemicals in the workplace; in air, water, and soil; and in food and consumer products. In short, governments have set up a process to regulate all components of our environment.

We are healthier now than ever before, as shown by the increases in life expectancies between 1900 and 1990 illustrated in Table I. Even cancer, the disease most often associated with chemical exposure, is decreasing. According to national cancer mortality records from 1933 to the present, age-adjusted cancer rates have remained nearly constant for more than 50 years. Age-adjusted death rates and illness rates control for changes and variations in the age distribution of the population at different times. They decreased for the first time in 1986, continued to decrease through the next two years, and have remained level since then.

To say that overall, age-adjusted cancer rates have declined or remained constant is not to say that rates for every kind of cancer have done so. Some cancers, especially those associated with tobacco use, have increased; others, such as stomach cancer, have decreased. Furthermore, there is evidence that some cancers are more common in people older than 65 years, although part of that increase may be the consequence of steadily decreasing death rates from heart disease and stroke. In the deadly calculus of mortality, some causes of death must go up if others go down.

But overall rates say nothing about specific risks. To assess specific risks, experts have developed a four-step process:

1. **Hazard identification.** This step involves testing animals to see whether exposure to a chemical causes an adverse effect, or studying human populations exposed to a substance to see whether the exposure is associated with increased frequency of disease or death.
2. **Exposure measurement or estimation.** Concentrations of a substance can be determined accurately in air, water, soil, food, or other products, but more often, they are estimated. Frequency and duration of exposure to contaminated materials are determined or estimated for people, such as workers, consumers, and building occupants, who could possibly be exposed.
3. **Dose-response calculation.** If animal testing is used during hazard identification, estimated effects on humans must be extrapolated from the measured effects on animals. This is because animals are usually exposed to very high dosages during testing, but humans almost always experience relatively low exposures. When a hazard has been identified as the result of a human population study, animal-to-human extrapolation is not necessary, but the human populations studied are almost always exposed to higher concentrations than the general population, making it necessary to extrapolate from high to low exposure.
4. **Risk characterization.** At its simplest, this step involves computing risks for the populations of interest. It can include a discussion of the biological plausibility of an effect seen in animals manifested in humans, comments on the shape of the dose-response curve, and consideration of the accuracy of the exposure measurement or calculation.

An examination of dioxin can illustrate the four steps and some of the problems faced in risk assessment. Table II provides two examples illustrating these steps. Various committees of experts have classified dioxin as a probable or possible human carcinogen because it causes cancer in animals, but there is great disagreement about whether it has caused cancer in humans. Some scientists argue that dioxin, at the levels encountered in the general environment, poses no risk, but regulatory agencies have banned products that contain dioxin. In courtrooms, the evidence for dioxin as a probable cause of human cancer has been sufficient to convince some juries that the companies or governments responsible for dioxin exposures should have to compensate sick people or their survivors. Other juries have found the evidence unconvincing and have not awarded compensation.

Given the heated discussions about dioxin and the number of Vietnam War veterans who claim that exposure to dioxin-containing Agent Orange has ruined their health or that of their children, why don't we know whether dioxin is a risk to humans? The answer is simple: We can't. The reason is that risk assessment uses the tools of science, but it is not itself a science.

Science

The single thing that characterizes science, according to Karl Popper (1), is that science permits attempts at falsification. Scientists can develop theories or hypotheses based on observations, measurements, and thoughts. If the theories or hypotheses are scientific, they can be tested. If, after a number of tests, the theory or hypothesis seems to be sound, it is accepted by scientists. If the tests falsify the theory or hypothesis, it is rejected.

For instance, we would like to be able to test whether or not the risks that are calculated from animal tests accurately predict human disease rates. The Environmental Protection Agency (EPA) did a risk assessment for dioxin, but that did not predict how frequently cancer would result from particular exposures. Instead, the risk assessment shows a 95% certainty that a daily exposure of 0.006 picograms of dioxin per kilogram of body weight (pg/kg) increases a person's cancer risk by no more than one in a million. Taken with EPA's statement that the lower confidence limit can include zero, the risk assessment hardly makes a prediction. What it does mean is that any dioxin-related increase in cancer from zero up to one additional incidence of cancer per one million people exposed daily to 0.006 pg/kg is compatible with EPA risk assessment. Even though EPA presents the daily exposure to 0.006 pg/kg as the "95% upper confidence level" for cancer risk from dioxin, that number is often treated as an actual estimate of the dose of dioxin associated with a one in a million risk.

Dioxin is produced by the burning of particular materials, the bleaching of paper, and a number of chemical processes; it is so common that probably all of us are exposed to small or "background" concentrations. The amount of dioxin to which the average person is exposed is unknown, but most people would agree that a daily dose of 1 pg/kg is not too far off. That daily dose is 167 times the dose that EPA equates with a one in a million risk. Therefore, dioxin exposure increases the average person's cancer risk by 0.0167%. The overall risk of cancer in the U.S. population is about 20%. So exposure to dioxin, if it were added onto the overall risk, would increase the risk to 20.0167%. It is not possible for studies of human populations to detect such a small increase in risk or separate out the 0.0167% risk if it is part of the overall risk of 20%.

But wait a minute: We know that some workers have been exposed to much higher levels of dioxin. Can we detect their risks? The highest level of exposure to dioxin for chemical workers has been about 100 times more than that for the average person (2). If risk is proportional to total exposure, those workers would have 100 times the risk of the average person or $100 \times 0.0167\% = 1.67\%$, almost 2% additional risk from dioxin.

Let's assume that 1000 workers were exposed to 100 times the average amount of dioxin. Think about what we might learn from

comparing their cancer rate to the predictions of risk assessment. To do that, we compare the cancer rates of the 1000 exposed workers to the rates in 1000 people who were not exposed to dioxin in an industrial setting. Given that the expected cancer rate is about 20%, we would expect about 200 cancers in the exposed population. If dioxin exposure increased the cancer rate in the exposed population by 2%, we would expect about 220 cancers in the exposed population. Could a study of the two populations detect that difference? Maybe. But since the incidence of cancer fluctuates between different populations—"about 20%" includes numbers like 18% and 22%—it is not certain the 10% increased risk would be ascertained. In fact, studies of the causes of death in about 5000 American chemical plant workers (3) and in about 1600 German chemical workers (4) (exposed to varying amounts of dioxin) revealed a slightly el-

evated cancer death rate in both populations. It has been interpreted that the increase in cancer death rates was caused by dioxin exposure. That conclusion, however, has to be tempered because of other things that are known about the exposed populations. Some of the deaths were from cancers specifically linked to other exposures, such as asbestos. Moreover, the scientists who did the studies were not able to obtain information about smoking and exposure to other carcinogens in either population.

Epidemiologists, the scientists who study the causes and distribution of diseases, make their studies more sensitive by looking at specific cancers in addition to total cancers. For instance, if dioxin were to increase the risk for a particular tumor to 2%, and the average risk for that tumor was 0.2%, then the study of 1000 workers would be an excellent opportunity to detect the increase. In fact, from studies of workers who sprayed dioxin-containing herbicides, and who were exposed to far smaller amounts of dioxin than the American and German chemical workers, some scientists have drawn associations between dioxin and several relatively rare

I. Life expectancies in the United States, 1900 and 1988

	Born in 1900, years	Born in 1988, years	% Change
Black females	33.5	74.5	122
Black males	32.5	66.0	103
White females	48.7	79.3	63
White males	46.6	72.6	56

tumors—soft tissue sarcomas, stomach cancers, and non-Hodgkin's lymphomas. The American and German studies found no evidence of increases in the latter two tumors, and the German study reported no soft tissue sarcomas. Those results seem to weaken the conclusion that dioxin exposure is associated with those rare tumors. On the other hand, the American study reported seven soft tissue sarcomas in a

population where only 0.3 were expected. Surely, here is the evidence—increased numbers of a dioxin-associated tumor in a dioxin-exposed population—that is needed to show that dioxin causes cancer in humans.

However, soft tissue sarcomas are difficult to diagnose. Upon reexamination of the seven tumors, three were found to be different kinds of cancers. Even so, four verified soft tissue sarcomas are clearly more than the expected number. The seven workers with soft tissue sarcomas were not evenly distributed throughout the 12 studied chemical plants. Five employees (three with verified sarcomas and two with misdiagnosed ones) had worked in a single plant. Scientists from the chemical company that owns the plant have stated that exposure to another chemical, which was present only in that plant and not in the other 11, probably caused the soft tissue sarcomas (5). Objections to that interpretation will be raised, but it will have to be considered. In any case, the authors of the American study state, "Excess mortality from . . . soft-tissue sarcoma may result from exposure to TCDD [dioxin], although we cannot exclude the possible contribution of factors such as smoking and occupational exposure to other chemicals."

Perhaps, in time, continuing and careful analysis of the workers in the American study will produce a consensus that dioxin has been a cause of human cancer. Should that happen, we can be certain that the cancers will be detectable only in the heavily exposed industrial populations. Any cancer occurring in populations exposed to minimal amounts of dioxin would be so rare as to

II. Steps in risk assessment, with smoking and dioxin examples

Steps	Examples	
	Smoking	Dioxin
1. Hazard identification	Smokers have higher lung cancer rates.	Most potent cause of cancer tested in animals. Contradictory evidence in humans.
2. Exposure estimation	Interviews to determine when smoking started, duration, and number of cigarettes smoked.	Based on measures of current dioxin levels in exposed humans and models for estimating exposures.
3. Dose-response relationships	Extrapolation from cancer rates in one- to two-pack-a-day smokers who smoked for 20 years to others who smoke less or don't smoke at all.	Extrapolation from effects in animals exposed to high levels to humans exposed to low levels.
4. Risk characterization	Human carcinogen.	Inadequate evidence for carcinogenicity in humans; sufficient evidence for carcinogenicity in test animals.

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go undetected. Therefore, epidemiologic studies cannot answer whether or not a daily dose of dioxin at 0.006 pg/kg increases cancer risk by one in a million.

It is well beyond the wealth and capacity of our society to conduct studies, which are comparable to those completed on dioxin-exposed people, for all chemicals suspected to cause cancer. Moreover, it is not likely that populations of people with high levels of chemical exposure exist for all the chemicals that have been shown to cause cancer in animals, further reducing opportunities to test the predictions of risk assessment. Unless another method is developed for testing predictions of risk assessment, we will have to accept that risk assessment is different from science—its predictions are not falsifiable.

The role of the scientist

Risk assessment is almost certainly going to play a more significant role in our country's politics. For instance, EPA's administrator has called for EPA's priorities to be ordered on the basis of risk. If that order should place cleaning an old mine site in Nevada above providing additional protection for a marsh in New Jersey, some residents of New Jersey are sure to object. When they do, they will enter the political arena by asking EPA for reconsideration and asking their congressional delegation to intercede. As a result of such actions, more and more citizens are going to ask questions about risk assessment.

Many scientists will become involved in risk assessment and work to understand it. They may even conduct risk assessments in their role as citizens. Their training prepares them to understand the quantitative nature of risk assessment, to be able to explain its technical strengths and weaknesses, and to educate others about what it can and cannot do. Involving risk assessment in the political process offers scientists an opportunity to share their talents and education with many people.

Some scientists now have and others will have careers directly related to risk assessment. A few scientists completely disagree with current risk assessment methods. They argue that we know too little about the relationships between biological mechanisms at high doses in animals and at low doses in humans to be able to predict human disease rates. Their objections serve to focus the debate about risk assessment issues. Other scientists work actively in risk assessment, carrying out standard tests, performing epidemiologic studies, or doing the necessary number crunching. Still others work to improve risk assessment methods. The future is impossible to see, but surely the acceptance and improvement of risk assessment will depend on the efforts of scientists who work in or criticize the field. **□**

Literature cited

1. For a short discussion of Popper, see Bondi, H., *Nature* 358: 363(1992).
2. Gough, M., "Dioxin: Can Science Affect Policy?", paper presented at American Society for the Advancement of Science annual meeting, Chicago, February 11, 1992.
3. Fingerhut, M. A., Halperin, W. E., Marlow, D. A., *et al.*, *N. Eng. J. Med.* 324: 212(1991).
4. Manz, A., Berger, J., Dwyer, J. H., *et al.*, *Lancet* 338: 959(1991).
5. Collins, J. J., Strauss, M. E., Levinskas, G. J., *et al.*, *Epidemiology*, 4(1):7(1993).

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