Toxic Chemical Disasters and the Implications of Bhopal for Technology Transfer

BERNARD WEISS
and THOMAS W. CLARKSON

University of Rochester,
School of Medicine and Dentistry

THE METHYL ISOCYANATE THAT SWEPT THROUGH the Indian city of Bhopal on December 3, 1984, producing 2,000 estimated deaths, killed so quickly that it left no ambiguity about either source or consequence. Although many other toxic chemical catastrophes (table 1) preceded Bhopal, they failed to elicit such a dramatic public impact, partly because they emerged more gradually, partly because their sources proved more difficult to identify. Exposures whose sources and consequences are even more ambiguous are correspondingly less likely to claim public or even official attention (table 2). Even in Bhopal it now appears that the acute deaths heralded an even more widespread incidence of chronic, disabling disease whose full extent may not be grasped for decades. In this article we argue that, beyond measures to prevent acute disasters such as Bhopal, we must also consider the potential for delayed, insidious, and subtle toxicity that ultimately may affect vastly more people. Such hazards are especially difficult to recognize and document before they inflict widespread damage. The endpoints are remote in time and often nonspecific: lung cancer from exposure decades earlier, cumulative neurological or kidney damage, an acceleration of aging, a downward shift in intelligence test scores. When such effects take years to detect,

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TABLE 1
Examples of Outbreaks of Mass Human Poisoning from Toxic Chemicals

Date[a]	Location	Chemical	No. affected
1930	U.S.A.	Triorthocresylphosphate	16,000
1934	Detroit	Lead	4,000
1952	London	Air pollutants	4,000
1952	Japan	Parathion	1,800
1955	Moringa (Japan)	Arsenic	12,159[b]
1955	Minamata (Japan)	Methylmercury	1,000
1956	Turkey	Hexachlorobenzene	4,000
1958	Kerala (India)	Parathion	828
1959	Morocco	Triorthocresylphosphate	10,000
1960	Iraq	Ethylmercury	1,022
1964	Niigata (Japan)	Methylmercury	646
1967	Qatar	Endrin	691
1968	Japan	Polychlorinated biphenyls	1,665
1971	Iraq	Methylmercury	50,000
1976	Pakistan	Malathion	7,500
1981	Spain	Toxic oil	12,600
1984	Bhopal	Dimethylisocyanate	2,000[c]

[a] Year of onset.
[b] These were the estimated number of exposed babies. It was stated that several thousand were poisoned and 131 died.
[c] Deaths. The full scale of lingering and permanent morbidity remains unknown.

those exposed cannot easily be identified. The problem of detection is magnified in countries that lack the scope of information resources and scientific and cultural supports available in developed nations, and that may also suffer from high rates of infectious disease, poverty, and malnutrition. Our argument is based on and illustrated by examples from both kinds of societies. Although we review these examples under separate, arbitrary headings, most of them display multiple facets.

We will next examine the policy implications of such examples for the transfer of chemical technology to less-developed countries. We will argue that, beyond the undisputed need for safe designs and proper work practices, absorbing chemical manufacturing facilities into a developing country requires a corresponding assimilation of toxicological points of view and applications, if health protection is

TABLE 2
Examples of Population Exposures Provoking Questions about Delayed or Subclinical Health Effects

Period	Location	Chemical	No. exposed
1900–present	U.S.A. cities	Asbestos	?
1940–present	World cities	Airborne lead	?
1965–?	Vietnam	Agent Orange	?
1973	Michigan	Polybrominated biphenyls	?
1975[a]	Canada	Methylmercury	4,100
1976	Seveso	Dioxin	5,435[b]
1970s	U.S.A.	Indoor air pollutants	?
1981	Buenos Aires	Phenylmercury	12,000

[a] Dated from official recognition of problem.
[b] An additional 31,800 may have been subject to sporadic contamination.

one of the aims of the recipients. These include elements ranging from biological monitoring to the detection of early adverse effects to extrapolation from animal data to the setting of exposure standards. The latter phase is one that depends on the community's social and economic goals, but its formulation must rely on a series of decisions based ultimately on predictions of toxicity.

Categories of Toxic Disasters

Long Latency, Delayed Effects

Although ionizing radiation is a physical agent, its effects ultimately are chemical in form, and it serves as the prototype of other agents whose consequences, after a single or brief exposure without immediate effects, may find expression decades later. Before the risks of radiation exposure and its remote effects were fully appreciated, many infants were subjected to irradiation of the thymus gland in the mistaken belief that an enlarged thymus in the infant was abnormal. The result of that faulty hypothesis was an epidemic of thyroid cancer (because

the thyroid lies in the same region of the neck) beginning over twenty years later (Hempelmann et al. 1975; Shore et al. 1980). Documenting that relationship required careful and intensive epidemiology.

The environmental chemical most closely associated with cancer is asbestos. Even relatively short periods of exposure, as during temporary employment in a shipyard, seem to promote a greatly increased risk of mesothelioma and lung cancer, especially after the passage of 25 years or more (Selikoff and Lee 1978; Selikoff, Hammond, and Seidman 1979). This connection was a laborious one to document, and might still be debated were it not for the extensive employment records maintained by labor unions. It is a useful exercise to imagine whether methyl isocyanate would have been identified as the offender had the Bhopal episode instigated, say, a five-fold cancer increase peaking in the year 2004 instead of immediate death.

Cumulative Effects

Low-level, prolonged exposures to some chemicals may exert detectable adverse effects only after prolonged damage or when enough of the agent has accumulated in body tissues to overwhelm protective or compensatory mechanisms. Tobacco, primarily in the form of cigarette smoking, exemplifies an agent of the former type, and, measured against other mass chemical disasters, exceeds their impact by several orders of magnitude. It also enhances the lung cancer risk of asbestos exposure (Hammond, Selikoff, and Seidman 1979).

Many environmental chemicals are now recognized as carcinogenic. As long ago as the late eighteenth century, Sir Percival Pott noted the high incidence of scrotal cancer among the chimney sweeps of Great Britain, but the association remained ambiguous until the twentieth century, when extracts of soot (coal tar) were discovered capable of inducing cancer in animals. Several classes of industrial chemicals are associated with cancer induction, either in exposed workers or in the laboratory (Ashford 1976). Proof of an epidemiological hypothesis, however, entails exposure assessment because a dose-response relationship is the most cogent basis of such a proof. The difficulties of retrospective exposure assessment for most chemicals are staggering; add such difficulties to those posed by tracing exposed workers after the passage of two or more decades, the assurance that confounding factors such

as smoking habits have been ruled out, that the data base is consistently organized, and that the association between presumed cause and effect makes biological sense, and it is easy to imagine how a large-scale calamity could arise without anyone perceiving a connection.

Cancer is a dramatic event and its victims can be counted, a marked advantage in epidemiological research. Other consequences are even more difficult to detect. Cadmium is a toxic metal found in many industrial processes and products. It is a public health problem because it accumulates in the body, particularly in the kidney, where it may produce damage or impair function (Buchet et al. 1980). For the general population, the main source of cadmium is food, but smokers receive a substantial extra dose. Once absorbed, little cadmium is excreted. Its biological half-life in humans lies between 19 and 38 years (Friberg et al. 1979), meaning that it would take that long for the body to excrete half of its accumulated burden if exposure ceased. The kidney is considered the most sensitive organ, and adverse effects are reflected by excessive urinary excretion of certain proteins, enzymes, and sugar. Consider the implications of the estimate that daily absorption of 10 to 12 micrograms of cadmium (a typical value) for 50 to 70 years eventually produces kidney levels close to the threshold for damage, even in nonsmokers.

Obscured Identity

The heading for this section is meant to convey the problems posed by the uncertain identification of a toxic agent's sources. One striking example was the episode of polybrominated biphenyl (PBB) contamination in Michigan in 1973 (Kay 1977). Dairy farmers in that state began to observe lowered milk production, then severe illness, in previously healthy herds. The epidemic was traced to a fire retardant (Firemaster) that had been blended into the feed instead of a magnesium oxide supplement. The retardant was based on PBBs. That error, compounded by the refusal of key officials to acknowledge a problem, killed 50,000 cows, almost 200,000 chickens, and many herds of other farm animals. The human health consequences of this episode remain blurred. Immunological, neurological, and psychological disorders have been associated with PBB exposure, and the final outcome for the Michigan farmers remains unresolved, but bromohydrocarbons have been identified as carcinogens and the flame retardant Tris (tris

[2,3-dibromopropyl] phosphate), used to treat flammable fabric and apparel, was banned for that reason.

Even with the remarkably lethargic response of Michigan officials, the affected farmers managed to find enough resources and supporters to confirm their suspicions. Moreover, they had maintained healthy, productive herds, so that even a few sick cows were enough to provoke questions. Marginal farmers with marginal herds, exposed to equivalent contamination in developing countries, could not easily make so concrete an inference, nor could they enlist an academic and political network to hear their case.

Hexachlorobenzene (HCB) is a seed-grain fungicide responsible for an outbreak of porphyria cutanea tarda in southeastern Turkey in the 1950s (Peters 1976). The clinical manifestations included several types of skin lesions (Cripps, Gocmen, and Peters 1980), hyperpigmentation, increased body hair in children, coordination deficits, and urine the color of port wine. Since the inhabitants often consumed seed grain when conventional sources proved insufficient, a Turkish physician, aware of the introduction of HCB treatment, hypothesized that it might be the source of the outbreak. Only several years later was the hypothesis confirmed by animal experiments. HCB was banned in 1959, but by that time over 3,000 to 4,000 cases of poisoning, with a mortality rate of 10 percent, had been reported. These figures are likely to be underestimates, especially since cases continued to appear as late as 1961. Another syndrome appeared in the infants of mothers who suffered HCB porphyria or who had consumed bread prepared from the tainted grain. Called pembe yara or "pink sore," it was fatal in 95 percent of the victims. Twenty-five years later, a survey of persons exposed as children or young adults confirmed persistent abnormalities (Peters et al. 1982), including disordered porphyrin metabolism, scarring and hyperpigmentation of the skin, many neurological signs and symptoms, and thyroid gland enlargement, perhaps a precursor of thyroid cancer. HCB was also implicated in an Indian outbreak of epilepsy involving over 250 people (Misra et al. 1985). Again, the source was treated grain.

In the fall of 1980, a pediatrician in Buenos Aires noted an unusual coincidence of three infants suffering from acrodynia or pink disease. Now rare, pink disease is characterized by erythema in the extremities and on the cheeks (Weiss and Clarkson 1982). The infants are photo-

phobic and in considerable discomfort from joint and muscle pains. Pink disease afflicted children in many countries until Warkany and Hubbard (1951) traced it to calomel (mercurous chloride), a common constituent of infant teething powder, a discovery that took approximately one hundred years. One reason the connection remained obscure was that perhaps only one of a thousand exposed infants developed the full syndrome. Incomplete symptoms in the others probably would be ascribed to the usual childhood illnesses.

Fortunately, the pediatricians in Argentina recalled the work of Warkany and Hubbard and began to suspect mercury. If the estimate above was correct, three cases of acrodynia might indicate three thousand exposed infants. Analysis of urine samples confirmed their suspicions. Not only were abnormally high concentrations of mercury found in these three cases, but also in urine samples of many other infants. The source presented a puzzle until a search uncovered a correlation between infants with high urine mercury levels and commercial diaper services serving about 12,000 infants. The diapers were tested and found to contain phenylmercury acetate that had been added as a fungicide during laundering (Gotelli et al. 1985).

This massive (and for a long time unknown) exposure to phenylmercury came close to disaster. The established renal toxicity of mercury led the director of a clinical chemistry laboratory that tested many urine samples to include a new and sensitive test for early subtle changes in kidney function, urinary excretion of the enzyme gamma-glutamyltransferase. The data indicated that phenylmercury exposure did, indeed, affect the kidneys of some of these infants. However, phenylmercury acts only after tissue levels exceed a threshold value that appears to have a fairly narrow range. The threshold for gamma-glutamyltransferase was exceeded by only a few infants. That for a more serious effect, diuresis, lay at higher levels and was exceeded by even fewer infants. Indeed, the sudden appearance of three cases of acrodynia probably arose from a decision by the diaper companies to double the amount of phenylmercury added to the diaper wash.

It is fortunate that phenylmercury acts like a threshold poison, as distinct from the apparent nonthreshold behavior of radiation and some chemical carcinogens, and that, apparently by chance, the diaper companies did not exceed a threshold for serious and irreversible damage. Even at this time, 4 years after the outbreak, it is still not known if more subtle delayed effects may have occurred, and, in

addition to three infants with overt acrodynia, how many others had exhibited signs and symptoms short of the full syndrome.

Subtle Functional Disorders

If exposures are moderate, even clinical manifestations may not be apparent. Behavioral toxicology owes its growth and status as a discipline to that recognition (Weiss 1983a). One focus of the debate about the hazards of leaded gasoline swirls about the evidence that even moderate lead exposure may reduce scores on intelligence tests and other measures of performance and conduct. Findings from different countries and experiments suggest that what used to be considered benign elevations in body stores of lead may reduce I.Q. scores by about five points (Needleman et al. 1979). Such a reduction, about one-third of a standard deviation, might seem trivial, but, if viewed from the standpoint of a total national population and its effect on the entire distribution of intellectual potential, it becomes of major economic, social, and even diplomatic significance. For a population of 100 million, it means a reduction of persons with I.Q. scores above 130 from 2.3 million to 990,000 and a societal disaster in a technologically competitive world. It is worth speculating about how easily these ramifications could be dissected in a country lacking a corps of professional psychologists and their assessment techniques.

Neurotoxicity is one of the most difficult reactions to connect to exposure because its earliest clues tend to be nonspecific and easy to neglect. The outbreak of the syndrome known as "Jamaica ginger paralysis," or "Ginger Jake paralysis," bore such characteristics (Harris 1930; Morgan 1982). It occurred largely in the southeast United States, affected at least 16,000 and perhaps as many as 50,000 people, and was the harbinger of several later toxic epidemics. The first reports began to appear in newspapers in February 1930. They described a peculiar neurological disorder that began with soreness in the calves of both legs. After one or two days, the soreness disappeared, to be succeeded by difficulty in controlling the movements of the feet. With time, these difficulties progressed to a stage at which the victims were forced to rely on canes or crutches to move about.

The agent responsible for this epidemic was triorthocresyl phosphate (TOCP), an organophosphorous compound often added to lubricating

oils and other industrial products. The 1930 victims ingested it as a contaminant of a preparation called "Ginger Jake," an alcohol extract of Jamaica ginger especially popular in the southern United States because it contained 70 to 80 percent alcohol by weight. TOCP apparently entered the formulation when an industrial mixture of oily materials containing tricresyl phosphates was substituted for the previously common castor oil. It took about two months for the extract to be identified as the cause of the outbreak. At least 5,000 men remained paralyzed by the contaminated extract. Another massive outbreak occurred in Morocco in 1959 (Smith and Spalding 1959), this time from cooking oil contaminated with degraded lubricating oil containing almost 3 percent mixed cresyl phosphates. Ultimately, the outbreak claimed about 10,000 victims, a huge burden in a country with 17,000 hospital beds at the time.

TOCP now serves as a model compound with which to investigate the mechanism of organophosphate-induced delayed neurotoxicity, a form of distal axonopathy sometimes called "dying-back" neuropathy. So many of the members of this chemical class, which comprises a range of important insecticides, display this toxic property that new ones are screened routinely for it by standardized animal tests (Cranmer and Hixson 1984).

The identification of potent toxicity is not enough in settings where uneducated, typically rural populations comprise the main users. Jeyaratnam (1985) pointed out that extrapolations by the World Health Organization yield estimates of about 500,000 cases of acute pesticide poisoning annually, with about 9,000 of these resulting in death. Only about 1 percent of these deaths occur in industrialized countries, which, at the same time, consume about 80 percent of world agrochemical production. An outbreak of insecticide poisoning in Pakistan in 1976 illustrates some of the problems that may arise in developing countries. Field workers in a malaria control program were supplied with the insecticide malathion. Of the 7,500 workers employed on the project, about 2,800 experienced some form of toxicity, including seven deaths, and symptoms such as blurred vision, giddiness, nausea, and stomach cramps (Baker et al. 1978). One set of problems arose from improper work practices, such as continuing to wear contaminated clothing and carelessness about dermal exposure. Another set was traced to toxic degradation products in the malathion supplied by two Italian farms.

With such a history, and widespread awareness of organophosphate toxicity, it is surprising that new incidents continue to appear in advanced countries. Workers in a Texas plant that manufactured the organophosphate insecticide leptophos showed evidence of neurological and psychological abnormalities, including diminished muscle tone, ataxia, paresthesias, dizziness, impaired memory, drowsiness, and severe anxiety (Xintaras and Burg 1980). Some of the workers had visited private physicians who attributed their problems to encephalitis or multiple sclerosis. It was only the clustering of such diagnoses in a small group of workers that alerted a medical consultant to the possibility of excessive insecticide exposure. This incident led the investigators to recommend, because of the insidious nature of the effects, that workers exposed to neurotoxic chemicals be monitored by psychological tests. They noted that even workers themselves might remain unaware of slowly progressive functional deficits. The same recommendation could also have emerged from an episode that involved worker exposure to the organochlorine insecticide chlordecone (Cannon et al. 1978). In this instance, the first indication of toxicity was the complaint of nervousness, hardly one that would stir suspicions about an outbreak of poisoning. Organochlorine insecticides are used most heavily in tropical and semitropical developing countries and induce a wide spectrum of behavioral and neurotoxicity problems (Ecobichon and Joy 1982).

Psychological testing of workers has been conducted most often among those exposed to volatile organic solvents such as carbon disulfide, used in the production of rayon. Although recognized as a potent neurotoxicant for over a century, it is only within about the last fifteen years that the more subtle consequences of low-level, chronic exposure have been determined by psychological testing (Hanninen 1971; Grasso et al. 1984). These might be characterized as a general blunting and slowing of reactions, and, in Scandinavia, are embodied in what is termed the organic solvent syndrome.

Susceptible Populations

Identification of an agent as a hazard, or even the arousal of suspicions that the health of a community has suffered, may be impeded when only especially sensitive members of a population respond adversely to an exposure. Several authors have devised schemes to demonstrate how a dose-response function for a general population might obscure

the presence of a hypersusceptible subgroup (Omenn 1984; Weiss 1983b), and the Environmental Protection Agency is studying methods for incorporating such factors into risk assessments. Several types of host factors may modify the response to a toxic agent, including genetic traits, preexisting diseases, behavioral and lifestyle practices, concurrent exposures, and age.

Age is a striking factor in susceptibility. The 4,000 excess deaths in the week-long London smog episode of 1952 (Amdur 1980; Lawther 1958) revealed, incidentally, by retrospective analysis of mortality data, that the four-fold increase in deaths occurred mostly in elderly residents. Recall that the acute phase of the Bhopal disaster cost perhaps 2,000 lives. Elderly, multiparous women were the sole victims of a disease outbreak in Japan attributed to cadmium contamination of rice. Itai-itai ("ouch-ouch") disease describes the main clinical complaint, due to osteomalacia (Tsuchiya 1976). The immature are also often at elevated risk, but it may require careful observation and testing to ascertain, because the manifestations may only become detectable years later, as when the child enters school. The fetal alcohol syndrome is now an accepted consequence of alcohol consumption during pregnancy, but, despite centuries of speculation about the connection, it was not until the 1970s that a definitive link was established, and even later that its more subtle consequences were documented (Streissguth, Barr, and Martin 1984).

The best-documented mass chemical disaster that claimed the developing organism as its prime target was the outbreak of methylmercury poisoning in Iraq in the winter of 1971–1972 (Bakir et al. 1973). It may seem anomalous that a remote pastoral rural area—the Biblical site of the Garden of Eden—should prove to be the site of the greatest known man-made chemical poisoning disaster in history. The wheat fields of Iraq are part of the so-called Fertile Crescent of ancient times and are believed to be where wheat was first domesticated. Wheat production remains the major agricultural activity. In the summer of 1971, drought struck the area and decimated the harvests. The agricultural authorities in Baghdad decided to supplement their ancient strain of wheat with a new tougher variety from Mexico, widely known as Mexipak, that has fueled the "green revolution" in many developing nations. To ensure freedom from fungal infections, they requested that the seed grain be treated with a mercury fungicide. In the process of placing and transmitting the order, a typographical error (a deletion of just one letter) in the commercial name of the

fungicide resulted in a relatively innocuous form of organic mercury being replaced by the deadly methylmercury. Treatment took place in Mexico but the methylmercury came from the United States. Supplies were plentiful as it had just been banned for agricultural and other uses.

The treated wheat amounted to the largest commercial order in history, 78,000 tons, and was delivered to the southern Iraqi port of Basra in the fall of 1971. It was distributed throughout the country to farmers naive in handling toxic materials. In several areas it arrived too late for the planting season, winter was beginning, and food was in short supply. The farmers, all Moslems, were well indoctrinated in the Islamic tenet that the precious wheat should not be wasted but converted to bread. The wheat sacks were labeled with warnings against consumption, but in Spanish. Many of the sacks still had attached to them the original warning labels in English from the U.S. chemical manufacturer and the usual symbol of the skull and crossbones. But Iraqi farmers were not familiar with the Jolly Roger flag of the pirates of the Spanish Main. The wheat was colored with a pink dye, known as a warning to Western farmers that the seeds had been treated with a fungicide. Some farmers' wives washed the wheat, removing the water soluble dye, but leaving the lipid soluble methylmercury fungicide.

Nothing happened immediately to those consuming bread prepared from the treated grain, and nothing was suspected because methylmercury is odorless and tasteless. Its effects are delayed, so that for weeks, even months, no adverse effects appeared. It is possible to consume what later will prove to be a fatal dose without experiencing acute illness. The first symptoms are nonspecific, for example, paresthesia, malaise, or blurred vision. By this time, irreversible damage to the central nervous system may already have occurred. Later, the more devastating effects appear, including ataxia, blindness, deafness, coma, and, for some, death. The pink dye had a bizarre and tragic consequence for at least one village. The inhabitants started to eat the pink loaves. The taste was excellent, the color attractive, and, of course, no adverse effects at first appeared. The supply of pink grain was soon exhausted, so they turned to their stocks of the old (yellow) wheat. Then came the tragic consequence, the first signs and symptoms of methylmercury intoxication. Assuming there must be something wrong with the old wheat, they made efforts, unfortunately successful, to get fresh supplies of the pink grain.

After the first cases were diagnosed at about Christmas 1971, they soon were followed by thousands more. The latent period had ended. By the end of January, over 5,000 cases of severe poisoning had been admitted to hospitals throughout the country. Eventually the total would amount to over 6,000 admissions and some 450 hospital deaths. No precise figures were available for cases not admitted to hospitals. Some estimates place the number of deaths at over 5,000 and the number significantly affected at 50,000 or more.

For adults, the hospital admissions had virtually ceased in March 1972. For those exposed prenatally, the consequences were yet to erupt. During the ensuing years, these effects have been carefully and painstakingly documented. It was discovered that the mother's hair, when measured millimeter by millimeter from the scalp, would accurately recapitulate maternal levels of methylmercury during pregnancy. An exhaustive period of sampling took place in the rural villages and laid the basis for a neurological study of the prenatally exposed children. The most seriously affected children exhibited the classic signs of cerebral palsy. The more subtly impaired were less obvious. At play and at home in their rural villages, these children seemed perfectly normal. Only when they were examined by pediatric neurologists, and exposure confirmed by maternal hair analysis, did it become clear that methylmercury had delayed the achievement of developmental milestones, and had induced seizures and abnormal reflexes. Such data suggested that the fetus may be ten times more sensitive than the adult (Clarkson et al. 1981). The last observations were made in 1978 because the war in that area has halted further work. We still do not know the full extent of this tragedy and, in particular, how these children will adapt to the challenges of adult life, but we can be certain that the dimensions of fetal sensitivity would not have been clarified without precise dosimetry and careful neurological assessment. And, were it not for Iraq, we might still be unaware of the possible hazards posed by maternal consumption of fish with elevated methylmercury concentrations, such as those in lakes subjected to acid deposition (Baker, Clarkson, and Sharpe 1985).

Conclusions

We chose the examples above because they illustrate forcefully our thesis that the most dangerous effects of toxic chemicals arise from

exposures resulting in delayed, cumulative, and insidious onset, especially when the expression of toxicity takes the form of subtle functional disturbances. These are not the kinds of problems that are overcome simply by building manufacturing facilities designed to resist catastrophic accidents more effectively than the plant in Bhopal. In the next section of this article, we examine the policy implications of such examples, focusing particularly on how they might guide the sequence of decisions by which a facility is planned and operated.

Toxicology and Technology in Developing Countries

"Technology transfer" rings with an agreeable bureaucratic and diplomatic resonance, but, especially for chemical technology, it is far from a direct and simple transplanting of technical resources to industrializing countries. The manufacture and distribution of toxic substances require coordination between the primary, or production, or what we will call supratechnology, and the secondary, or support, or infratechnology. For industrial and environmental chemicals, much of the infratechnology embraces toxicology. Although toxicology can be defined succinctly as the science of poisons, we use it in a broader sense to encompass the mechanisms of toxicity, the measurement of adverse effects, the estimate of health risks, the assessment of exposure, and the positing of regulations.

The term "infratechnology" emphasizes its correspondence with "infrastructure," the physical elements such as transportation and communication, and does not imply inferiority. The export of chemical supratechnology, either as facilities or products, without the export of its parallel infratechnology, poses unique problems. The components of a chemical factory can be loaded on ships and transported to the recipient country. Infratechnology must be folded into the social, cultural, educational, and economic practices and resources of that country, a process of impressive, if not revolutionary scope.

Legislation and Regulation

Published articles have noted and objected to United States government policies that encourage, or at least do not restrain, the export of hazardous materials (Shaikh and Reich 1981; Navarro 1984). These current policies contrast with those undertaken during the Carter

administration, which sought to limit and control such exports, and with legislation introduced during that period. But few substances used in chemical production can be considered free of hazard, and many developing countries will continue to strive for indigenous manufacturing facilities, even when such facilities, such as those devoted to asbestos products, pose widely publicized hazards, and, in essence, have been displaced from the advanced industrialized countries because of their dangers (Castleman 1979). Furthermore, how is it possible to export agents that are free of hazard when they are designed, like insecticides, as poisons? Environmental assessment has been adopted by some developing nations, the Agency for International Development (AID) includes environmental assessment in its project evaluations, and President Carter signed legislation in 1976 prescribing such assessments. International registries of toxic substances are available. But these steps fail to address the critical problem.

An instructive hearing, chaired by Senator John Glenn, was held by the U.S. Senate, Committee on Governmental Affairs, Subcommittee on Energy, Nuclear Proliferation, and Federal Services (1979) during the ninety-sixth Congress. It centered on a proposal (Senate document 499) to create a Foundation for International Scientific and Technological Cooperation. Senator Glenn noted in his introductory remarks: "Experience suggests that the benefits of technology transfer to lesser developed countries may best be realized by helping to build a scientific and technological infrastructure in those countries so that they are in a better position to determine the direction of future development themselves." Testimony from the bill's authors, from Frank Press, then Director of the Office of Science and Technology Policy, and from others, emphasized the same points. Press's testimony noted these as follows: Developing countries need help from the industrialized countries in establishing institutional infrastructure and priorities for science and technology; many developing countries have only a marginal capability for acquiring and processing scientific technical information; ready-made scientific and technical solutions cannot be "imported," but, instead, should be supplanted by sustained collaboration between developed and developing countries.

Policy Issues

All participants in the process of technology transfer—source, recipient, and international community—have special roles to play and decisions

to make, depending upon the nature of the transfer. For example, transferring the means of production is a wider issue than shipping a finished chemical product. Although both processes incur possible health and environmental costs, controls for the latter are more easily achieved and narrower in scope since they do not include the same range of effluent production, of long-term waste storage problems and possible diffusion into the communal environment, and of occupational exposures.

Although Bhopal and the ferment it provoked center on accidents and their acute aftermath, most of the crucial decisions in technology transfer are more properly based on long-term health and environmental consequences rather than on short-term benefits (Ashford and Ayres 1985). Long-term planning and protection may incur greater initial costs, but provide a greater final yield. Among the costs of the long-term investment must be included toxicology and its own infrastructure. As Ashford and Ayres note, such costs can be conceived of as the sum of the cost of delay of production plus the cost of establishing toxic protection.

The transfer of technology typically embraces two phases: (1) import the technology, and (2) groom the recipients to assume responsibility for it. For chemical technology, it could be argued that phase 2 should precede phase 1. At the same time, care must be taken in this calculus to weigh economic benefits and their own impact on health against the potential health consequences of possibly unachievable exposure standards. Such factors introduce sequences of alternatives about which choices are required.

Part of this process will be the design of a system for monitoring the health of workers and the community, for assessing the environmental burden, and for providing access to toxicological data. Such a system is part of the long-term costs. Health monitoring requires, in turn, another series of decisions. For example, should it rely on clinical criteria, which are acknowledged to be relatively crude? Or should it turn to advanced techniques for the early detection of hazardous tissue accumulations or of adverse effects, which then would require another set of trained people?

Such questions are facets of a more basic question: How extensively should the approaches based on toxicology be transplanted? Developing countries vary widely among themselves in how readily they can assimilate and exploit such technologies. Applying a uniform criterion of readiness would make no sense. Instead, the introduction of these

approaches is best planned as a series of incrementally advancing steps ranging from simple, even crude, health monitoring to, say, sensitive assays of behavioral function. Each succeeding step would then be paralleled by an increasingly wider distribution of information about toxicological science.

Elements of the Decision

Although the general problems of technology transfer are widely recognized, such recognition is no guarantee of policies that maximize the benefits of the process. Optimal outcomes are achieved only by a careful weighing of different alternatives in policies and actions. Such evaluations may take the form of cost-benefit analysis, a procedure limited in scope, however, because it specifies only monetary values, some rather arbitrarily, and aims primarily to maximize economic efficiency. When elements of the analysis are less tangible than direct monetary values, it suffers a corresponding loss of precision. If loss of life is difficult to specify in monetary terms, consider the challenge of expressing a functional disorder in such terms. Cost-effectiveness analysis suffers from a similar defect because it seeks simply to prescribe a path to a specific goal that minimizes costs.

The transfer of chemical technology is especially vulnerable to uncertainties and ambiguities in policy formulation because the consequences of any particular choice may not appear until many years later, and, even then, may resist unequivocal interpretation. The first section of this article documents such problems many times over. Policy in such a context suffers without an explicit, preferably quantitative, expression of its inherent uncertainty.

Decision analysis is one recognized method for incorporating uncertainty into policy in quantitative terms and tracing the possible outcomes. It combines the concepts of statistical decision theory with systems analysis. Its primary tool is an explicit model representing the implications of various decision sequences, and, most crucial, one that takes direct account of probability when the consequences of a choice are uncertain. It contrasts with what might be called prescriptive policy analysis by eliminating "should."

Decision analysis is particularly suitable for assessing the transfer of chemical technology because it accommodates some of the unique

problems posed by toxicology (National Academy of Sciences 1975): the impact of chronic exposure and the significance of tissue accumulation, the elevated risks to especially susceptible populations, delayed effects both for the individual and for the gene pool, and impaired function or quality of life rather than outright death. All of these embody guesses or extrapolations from toxicological data. Decision models can also incorporate cost-benefit calculations because they integrate information from many diverse sources, including economic ones. Another virtue is that they permit expansion of detail in the time domain, an important aspect for a chemical whose immediate benefits may eventually be overcome by remote adverse effects on the environment and health. They can also be subjected to sensitivity analysis, a technique that allows estimates of how much the uncertainty surrounding a particular decision alternative contributes to the final outcome. Finally, and perhaps most important of all, the discipline of specifying choices and consequences in precise terms enhances markedly the qualitative understanding of different policy courses.

Consider the kinds of decisions that need to be made by a host country in evaluating the feasibility of manufacturing a specific insecticide, especially the degree of control over exposure both in the work place and in the community. Such decisions may not be posed in radically different ways in developed countries, but their consequences may be magnified in countries lacking skilled engineering staffs, toxicological expertise, accessible medical care, and planned waste-disposal facilities. We will list some of these decision nodes, emphasizing those with long-term implications rather than short-term implications such as accident probability and emergency response problems. Ancillary decision sequences would be needed for these.

For such choices to be feasible, the flow of the chemical during manufacture, including its precursors and intermediates, needs to be traced and its eventual disposal, including waste effluent, specified. Its conditions of eventual use, and the health hazards these may represent, form another cluster of problems. For each of those manufacturing steps, exposure estimates are calculated and then extrapolated to health risks. This last step is the crucial one because it typically is the one based on the most ambiguous data and embodies the most sensitive political implications.

Assume that the information available on which to base health risk estimates consists of the following: acute lethality in rodents; a two-

year feeding study in rats; a no adverse-effect level (NOAEL) calculated on the basis of a six-month study and relying on peripheral nerve damage as the endpoint; and scattered epidemiological surveys of exposed workers, none of them large enough to be conclusive. From this information, many questions must then be addressed:

- What kinds of toxicity are expected in the manufacturing process: reversible or irreversible? short or long latencies? functional or tissue damage?
- How great a safety margin should be imposed? For substances that are not carcinogens, current practice typically relies on a figure such as the NOAEL, which is calculated from a dose-damage plot based on animal data, and divides it by a safety factor, such as 100, to provide an exposure level assumed to be free of health risks for the general population. Occupational exposures, however, are not prescribed with safety factors. Instead, a level is derived, from available data, that exerts no adverse effects in most workers (the threshold limit value, or TLV). Safety factors and "most" are flexible values and may depend on the amount of toxicity information available and the nature of the manufacturing process as well as the criteria of toxicity.
- Given a choice of how much toxicity will be tolerated, what exposure controls are then mandated? Are they easy or difficult to achieve?
- What will be the costs of exposure controls? of waste disposal, given predicted biodegradability?
- How much will worker-monitoring cost compared to the cost of treatment for advanced toxicity and reduced earning power?
- What will be the societal costs of impaired community health and impaired environmental productivity for particular exposure choices? Are the very young or very old especially susceptible subpopulations?
- How might certain health, social, and economic benefits of the chemical modify the estimates above? An insecticide, for example, might reduce not only economic pests, but species that transmit disease.

Each of these questions ramifies into other, fractional decision nodes, but for each ramification a cost or probability can be assigned.

The sampling of decision nodes above was chosen to reflect the role of social, economic, and other factors, besides unfettered reliance on dose-damage data, in setting indigenous exposure standards. Although such basic toxicological data are needed to estimate health effects, exposure standards themselves emerge from the community's special requirements and resources. Consider, for example, the use to which quantitative risk analysis (Brown 1985) is put in the United States. On the basis of a particular model, the multistage model of carcinogenesis, the U.S. Environmental Protection Agency (e.g., 1984) calculates what is called a "unit risk estimate" for a particular chemical. It is defined as the incremental risk of cancer in a hypothetical population in which all individuals are exposed continuously, through their lifetimes, to an air concentration of the chemical of 1 microgram per cubic meter. Since the data on which such risk estimates depend typically come from high-dose animal experiments or from epidemiological studies of workers exposed to relatively high concentrations, a method for extrapolation to low concentrations is essential. The linearized multistage model estimates the 95 percent upper bound of the linear slope at low extrapolated doses consistent with the high-dose information. Suppose that the unit risk for a particular chemical for a 70-year lifetime exposure is 5×10^{-4}. But suppose, also, that the probability of living to 70 years of age in the recipient country is 0.10. Does it make sense to impose such a rigorous standard in a country where the introduction of chemical manufacturing or processing facilities elevates living standards? In many instances, even poorly administered factories may be superior to prevailing cottage industries. In parts of India, for example, the traditional method of refining silver exposes workers to high concentrations of lead fumes. The typical workshop is a poorly ventilated room in which unprotected workers boil a mixture of silver and lead on a charcoal fire to refine the silver. In the process, they inhale enormous quantities of lead fumes and experience the signs and symptoms of lead poisoning.

Policy Initiatives

Ashford and Ayres (1985), using the Bhopal accident as their fulcrum, pose in detail the nexus of policy issues entwined around technology transfer. Although the perspective of the article is governed basically by laws and regulations rather than by toxicology, its description of

these issues and its recommendations for policy might easily have derived from toxicology. It notes the need for developing countries to define their goals in acquiring specific technologies, to identify both short- and long-term consequences, and to base decisions on a clear understanding of alternatives. It notes as well the importance of access to information about health effects. Castleman's (1979) main suggestion, based on his survey of relocated production facilities, is to organize a hazard export information service, operated by an international body, to disseminate data about health hazards and to monitor the movements of banned or hazardous materials from one country to another.

Incorporating toxicology into such aims and recommendations will require unique mechanisms because the questions on which it bears are not only complex but politically sensitive. A government of a developing country that adopts standards less stringent than those prevailing in the industrialized countries could find itself either criticized or ridiculed. It might be tempted, like the U.S.S.R., to prescribe rigorous standards and ignore them. To overcome such inherent obstacles in the process requires that toxicological science be incorporated directly into the earliest steps of any decision about technology transfer. In that way, politically based criticisms about decisions may be identified and deflected. We recognize, of course, that most developing countries lack the scientists and scientific institutions that would permit their participation in such decisions. An international effort or mechanism is the most reasonable surrogate, but it must be administered by individuals recognized as scientists. The United States possesses such talents in abundance, as well as institutions recognized for their promotion of science, for example, the National Institutes of Health. One mechanism by which the necessary elements of toxicology could be incorporated into the decision process might be the current network of university Environmental Health Sciences Centers sponsored by the National Institute of Environmental Health Sciences, perhaps acting in concert with the centers sponsored by the National Institutes of Occupational Safety and Health and by the Environmental Protection Agency. These organizations would provide three resources: consultation in the decisions by which a facility is selected and planned and that involve appraisals of potential health risks, a mechanism by which the managers of the facility and the regulators that will oversee it can be familiarized with the health issues and solutions, and an

accessible body of informed scientists who provide a much surer and direct source of reliably evaluated information than a mere bibliography or collection of abstracts. One formal mechanism might be the creation of a technology transfer science advisory board. Although expanding the role of such centers would require increased funds, these could be recaptured from exporters, who stand to profit by the increased confidence in their product that such a program would engender.

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Address correspondence to: Dr. Bernard Weiss, Division of Toxicology, Box RBB, University of Rochester Medical Center, Rochester, NY 14642.