VIEWPOINT

The real role of risk assessment in cancer risk management

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Regulatory actions taken to reduce the risk of harmful effects of exposure to chemicals often are not commensurate with the toxicological risk assessment. A number of factors relating to psychology, sociology, economics and politics rather than science and medicine affect the final decision. Werner Lutz and colleagues *illustrate the situation using the leukemia-inducing chemical benzene as an example.*

High-level exposure to benzene in the workplace has been associated with the induction of leukemia, predominantly of the acute non-lymphocytic type. Available data were evaluated in 1982 by the International Agency for Research on Cancer (IARC/WHO) in Lyon (see Ref. 1); the agency considered the epidemiological evidence for carcinogenesis in humans to be sufficient.

The carcinogenic potency at low exposure levels was estimated from ten epidemiological studies[2]. The median probability of developing leukemia from life-long inhalation exposure to 1 μg m^{-3} air was estimated to be nine cases per million lives, on the basis of a linear dose–response relationship. By comparison, the cumulative incidence rate of myeloid leukemia for males in Switzerland is ~0.5 per cent over a 75-year life-span.

Cancer risk from different benzene exposures

Various sources of exposure to benzene exist, and are outlined below. The daily dose and the resulting risk of leukemia has been estimated for the typical adult living and working in a Swiss city (Table I). To compare exposures by different routes, the daily dose resulting from inhalatory exposure to 1 μg benzene m^{-3} is estimated to be 7.5 μg benzene per person (assuming 50% retention of benzene in the lungs, and 15 m^3 air inhaled per person per day).

Benzene in outdoor air

The reported concentrations of benzene in outdoor air range from 0.5 μg m^{-3} to 573 μg m^{-3} (Ref. 1). Measurements of 1–5 μg m^{-3} have been made in rural areas, compared with median concentrations of 10–100 μg m^{-3} in urban areas[3]. In the city of Basel, average benzene concentrations of 3–4 μg m^{-3} were measured in summer 1988, and 8–9 μg m^{-3} were recorded in the winter[4]. The most important source of the contamination of outdoor air with benzene is motor vehicles (80–85%[3]), mainly due to exhaust, but partly due to evaporation of benzene from gasoline during distribution[3].

Benzene in indoor air

Contamination of indoor air is dependent on the quality of outdoor air plus specific indoor sources. In countries where benzene has not been completely banned from building materials, paints, woods, impregnants, glues, cleaning agents, liquid waxes and polishes, the concentration ratio indoor-to-outdoor is greater than one because the indoor sources become more important than the outdoor contaminants[5]. In Switzerland, however, this ratio was found to be close to one (Rothweiler, H., pers. commun.).

Using the unit leukemia risk estimate given above and a mean concentration of 5 μg m^{-3} for outdoor and indoor air, the incidence resulting from air contamination is expected to be 45 cases per million people.

Benzene in cigarette smoke

In tobacco smoke, an average inhaled dose of benzene of 40 μg per cigarette was found[6]. Therefore, smoking twenty cigarettes per day would result in a daily dose of 400 μg (at 50% retention). In a million one-pack-a-day smokers, ~500 additional cases of leukemia would be expected, due to the benzene in cigarette smoke.

Benzene in the workplace

At an average exposure to 24 p.p.m. for a mean period of 8.7 years, the risk of leukemia has been reported to be increased 3.4-fold, relative to the general population[7]. Exposure levels as high as 200–500 p.p.m. were not uncommon and a relative risk of 20 was associated with this exposure. At concentrations around 3 p.p.m., the risk was no longer statistically significantly increased (see Ref. 8 for summary of epidemiological data). In the light of these findings, benzene has been replaced wherever possible as a solvent and reagent in the last decade. In addition, the maximum allowable concentration in the workplace in Switzerland was set to 5 p.p.m. (maximum allowable concentration [MAC]: 16 000 μg m^{-3}). Assuming that average exposure is one tenth of this level (0.5 p.p.m.; 1600 μg m^{-3}), a 30-year worklife with 42 working hours per week could result in 1800 cases of leukemia per million exposed.

Benzene in gasoline

While the number of people exposed to benzene in an industrial setting is small in Switzerland today, a large number of people are exposed to benzene in connection with the production and distribution of gasoline. At

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TABLE I. Risk of leukemia from benzene of different sources

Contamination	Source	Additional cases of leukemia per million exposed	Fraction of population exposed	Preventive measures initiated → Effect
Ambient air	motor vehicle exhausts evaporation from gasoline	~45	all	three-way catalytic converter; vapor recycling in gasoline loading → reduction to about one sixth
Cigarette smoking (1 pack per day)	burning tobacco	~500	40%	no legal action initiated; low tar cigarettes (optional) → reduction up to fivefold
Workplace	production of benzene and industrial use	~1800	small	no further action (marked replacement and reduction in the last decade)
	gasoline vapors at filling stations	~450	considerable	vapor recycling in gasoline loading → marked reduction expected
Hobby and household	misuse of gasoline	risk can be large (>>1000)	??	no action
Mineral water	defective filtration	~0.03	small	withdrawal → no further intake

See text for exposure levels assumed for Switzerland.

gasoline stations, concentrations of up to 10 000 μg m^{-3} air have been reported[1], conditions which carry a substantial cancer risk. With the rather optimistic assumption of a concentration of only 400 μg m^{-3}, a 30-year work-life at a filling station could be responsible for 450 cases of leukemia per million exposed. For the consumer, however, fueling up a car once a week for 5 minutes does not appear to represent a large increase of benzene exposure as long as the general air contamination is at 5 μg m^{-3}.

Most people are not aware of the high concentration of a carcinogen in gasoline. The maximum allowable concentration in the European Community is 5%. In Switzerland in 1988, the average concentration of benzene in unleaded gasoline was 2.2%. Many hobbyists and mechanics misuse the fuel for cleaning purposes and are not aware of a substantial cancer risk when cleaning up spills. 'Washing' the hands with 20 ml gasoline can result in a benzene dose of many milligrams. In comparison with the inhalation exposures estimated above for ambient air (micrograms), it is obvious that regular careless handling of gasoline can represent a very high cancer risk.

Benzene in food and water

Relatively little is known about benzene in food. On the basis of what has been reported (e.g. eggs contained 500–1900 μg kg^{-1}; irradiated beef contained 19 μg kg^{-1}; detectable levels were found in fish, cooked chicken, roasted nuts, various fruits and vegetables), doses of up to 250 μg per person per day have been estimated[1]. This number is probably an upper limit estimate and might include contamination of food items during processing. Few data are available for drinking water. In the USA and Czechoslovakia, benzene concentrations of 0.1–0.3 μg l^{-1} were found.

General contamination of food with benzene is probably due to the air pollution. At benzene concentrations of 1000 μg m^{-3} in the air, equilibrium concentrations of about 500 μg kg^{-1} have been determined in various high-fat food items[9]. Benzene in rainwater (concentration up to 87 μg l^{-1}) can further contaminate agricultural food products. In addition, benzene is a normal constituent of fossil oil-containing sediments which renders contamination of ground water unavoidable to some extent.

Although we are not in a position to give a reliable estimate of dietary intake of benzene in Switzerland, we think that general contamination of food merely reflects the general situation of the air and is unlikely to become a single main source.

Benzene in mineral water

In February 1990, one batch of a well-known mineral water was found to be contaminated with benzene. The concentration found in the mineral water in Switzerland was reported to be ≤15 μg l^{-1} (Ref. 10). Drinking one liter daily for one month (the assumed time until the batch is used up), one would expect 0.03 additional leukemia cases among one million (theoretical) consumers.

Risk management

In view of the fact that the cancer incidence in Switzerland is about 40% in males and 30% in females (cumulative over a life-span of 75 years), an additional cancer risk of 0.0001% (one in one million) from single exogenous factors appears 'acceptable' to most people and is often used as a guideline for regulatory agencies to set exposure limits.

The leukemia risks summarized in Table I are far above this 'acceptable' level, except in the case of the mineral water. It is therefore surprising that the latter issue elicited extensive publicity and preventive measures, while gasoline is still freely available and motor vehicle exhausts may still contain considerable concentrations of benzene.

The concentration of benzene in gasoline motor exhaust can be reduced by a factor of 5–6 with a three-way catalytic converter[3]. In a few years from now, most cars in Switzerland will be equipped with this system and a reduction of benzene emissions is expected. We have to be aware, however, that this measure was not taken primarily to reduce benzene contaminations and that the residual benzene contamination in air still represents a certain cancer risk (Table I). At filling stations, gasoline vapor recycling systems will be installed in the next few years in Switzerland. This measure will result in a marked reduction of the exposure of the people working there.

An uncontrolled, potentially high level exposure to benzene can result from careless handling and use of gasoline for degreasing and cleaning purposes in hobby and household tasks. A 20 µl drop of gasoline may contain up to 1 µl (880 µg) benzene, the equivalent of 20 days of inhalation exposure at 5 $\mu g\ m^{-3}$ air. Authorities show little inclination to inform the population clearly of the high cancer risk associated with regular misuse of gasoline, possibly because the laws would require gasoline to be classified as a carcinogen and withdrawn from the market.

In the light of the risks and hazards described above, the limit of 2 $\mu g\ l^{-1}$ mineral water set by the Swiss authorities in February 1990 appears out of proportion, and driving forces other than toxicological ones must have been involved. One aspect is the demand for purity and quality of a product in general. Other, more psychological aspects, are discussed below.

Risk perception

Opinion research has shown that the overwhelming majority of people use criteria which are not necessarily scientifically based to decide whether or not they consider a given risk objectionable, and whether they will accept or reject regulatory measures (Table II). Slovic[11] has shown that for most people, experience with risks is based on the news media which document mishaps and threats occurring all over the world. The judgement is therefore biased by the amount and type of information provided by the media. The question of whether the risk is run voluntarily or whether it is imposed from outside is of prime importance. People accept risks approximately 1000 times greater from voluntary activities than from involuntary risks[11]. Another important factor is the question of benefit. The acceptance of a risk is roughly proportional to the third power of the benefit derived from the respective activity.

These facts help explain why risks associated with smoking and motor vehicle driving are tolerated much more easily than a risk originating from mineral water. In the latter case, benzene residues represented an involuntary exposure. In addition, the media had a 'new food scandal' with a chemical considered to be of synthetic origin (Table II). The negligible risk was not tolerated, and the company withdrew the contaminated batch immediately to protect their international reputation.

The origin of a chemical is another prime determinant for the perception of risk and benefit. For example, in a study of ~2000 UK adults 70% stated that they believed natural vitamins to be better than laboratory-made ones[12].

The idea that natural products are, almost by definition, healthy is also a common misconception. Nature produces an enormous number of pharmacologically and toxicologically active compounds. Many 'edible' plants also contain numerous toxic chemicals, some of which are responsible for their natural pesticidal activity. When a number of these were tested for carcinogenic potential at near-toxic dose levels, about half were found to be carcinogenic[13].

Ames recently compared the daily dietary intake of natural and synthetic pesticides and concluded that 99.99% (by weight) is of natural origin. This relationship is in strong contrast to the safety requirements. While these are very stringent for synthetic residues, they are practically nonexistent for the natural ones.

Economic and political considerations also influence whether or not preventive measures are taken. Actions have little chance of being pursued if measures to reduce risk associated with a product cost so much that it can no longer be economically sold on the world market or if unemployment is predicted. For politicians, one goal is to be re-elected. If an action is not supported by what people believe should be done, chances are high that elections will be lost.

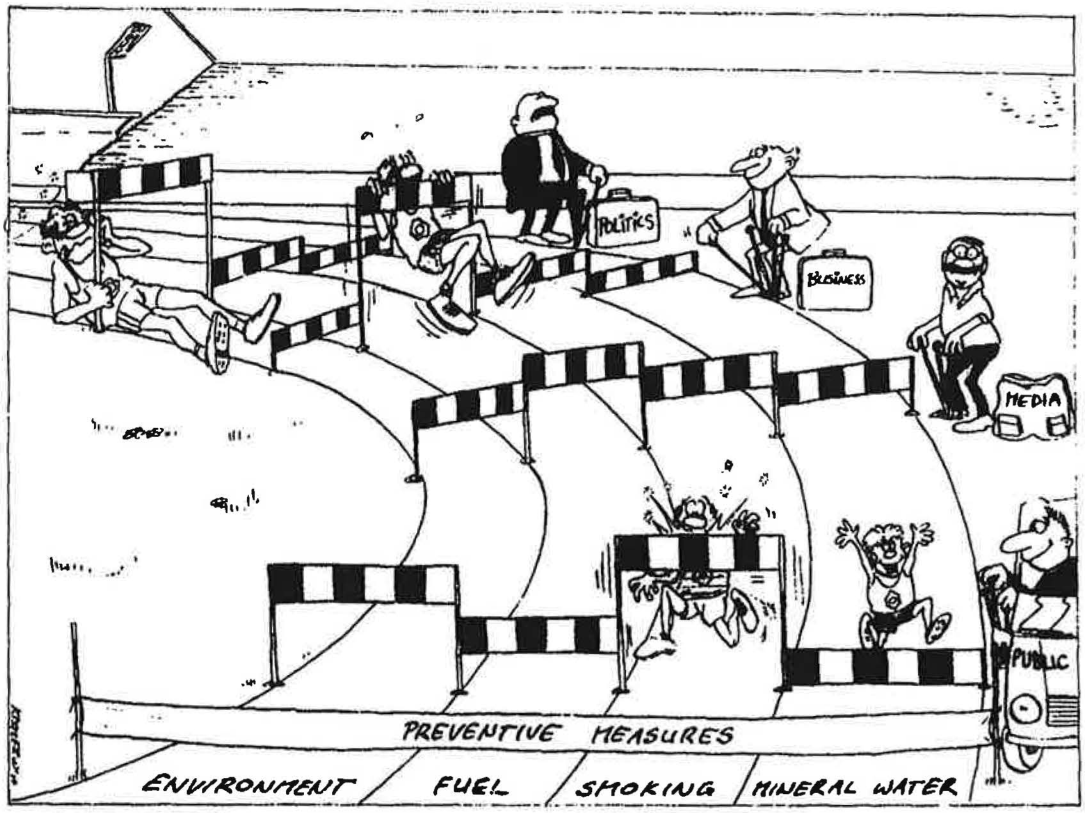
Table II shows a list of questions which govern the reaction of different groups when confronted with a hazardous situation. The cartoon illustrates the concept that preventive measures can only be taken if the hurdles are not set too high by any one of the various groups.

Role of scientists and health authorities

The risk of leukemia at low level exposure to benzene (the unit risk at 1 $\mu g\ m^{-3}$) is used as if there was no doubt about whether this value

TABLE II. Questions which affect the behaviour of different groups of people

Group	Question
Media	Is it of general or only special group interest? Will the headline attract many readers?
Public	Do I run the risk voluntarily? Do I wish to avoid the risk? Do I benefit from running the risk? Do measures reduce my personal freedom? Is it of natural or synthetic origin? Are groups with a bad public image involved (e.g. multinational chemical companies)?
Industry	What is the cost–result relationship of reducing exposure? Are the measures good for the image of my company? What are competitors doing? What is the position of the authorities? What are the chances of costly law suits?
Politics	Is there a consensus among scientists to back me up? How much does it cost? Will we have to raise taxes? Will the measures be accepted? Will I be re-elected if I support taking measures?
Authorities	Is there a legal basis for taking measures? Can the measures be controlled?



is correct. However, low-dose cancer risk assessment is not an exact science and it cannot be made on the basis of human epidemiological data alone. With smaller dose levels, any effect will fall below the level of statistical significance at some point. An understanding of the mechanism of carcinogenesis is crucial for a biologically-based extrapolation below this dose. Carcinogenesis involves all disciplines of the natural sciences; molecular biologists, biochemists, cell biologists, virologists, pharmacologists and medical doctors all feel competent to express an opinion about human risk assessment. It can be difficult for the authorities, therefore, to react firmly if the scientific community expresses opposing assessments.

This problem can also be illustrated with benzene. For the estimation of the leukemia incidence discussed above, proportionality between dose and tumor incidence was used, in accordance with the procedure of most regulatory agencies. However, good evidence to support a sublinear dose–response relationship below 10–30 p.p.m. has been presented[8]. For the present discussion, the shape of the dose–response curve is of minor importance because the ranking of the risks will remain the same. For a comparison with other carcinogens, however, absolute values of risk estimates will be required.

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Our analysis reveals the need for a new function for toxicologists: to educate and inform both health authorities and the public. Health authorities need the best currently available scientific information to support preventive measures in politics, science and industry. The public must be informed especially about the relative risks of different activities. If a well-informed public is able to put a risk into perspective, it will be less reluctant to accept 'unpopular', but necessary, preventive measures.

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