Responsibilities in the protection of human health

Lorenzo Tomatis[1]

The main difficulty encountered in primary prevention of cancer due to environmental chemicals is related to the formidable economic interests in most of the chemicals or chemical mixtures that have been identified as, or are suspected to be, human carcinogens. This also holds true for the production and sale of tobacco and tobacco products, an industry like any other chemical industry. Its expansion coincided with the increasing production of synthetic chemicals and massive exploitation of natural chemicals, such as metals and asbestos. Tobacco corporations behave in the same preposterous, devious way, as other chemical industries, in order to protect and increase their profits.

The primary prevention of infectious diseases has progressed on the basis of a wide general consensus and international collaboration. If infectious diseases have not been prevented with the same efficiency throughout the world, it is not because of doubts about the etiological agents of the diseases, but rather as a consequence of the combination of extreme poverty in certain countries, the selfishness of rich countries and the greed of some multinational corporations. In contrast the identification of chemical agents as carcinogenic, has been met with skepticism and often with open hostility from powerful groups which perceive such labeling only from the point of view of jeopardy for their profits and financial interests. It is for this reason that the recognition of some chemicals as carcinogenic has been systematically delayed and that some chemical compounds have been recognized as carcinogenic in certain countries and not in others. Even when a consensus was reached about the carcinogenicity of a compound, the permitted or accepted concentrations varied considerably between countries (1), as if the carcinogenicity disappeared or changed at certain frontiers. A scandalous example of this situation, still with us today, is that of asbestos which has not yet been banned worldwide. Two million tons are still produced by a few countries, including Canada and Russia (2).

Experimental results, which were obscured by the overwhelming predominance of epidemiological findings that began in the late 1960s, have regained their importance and significance in recent years thanks to successes in basic research on mechanisms. Nevertheless, behind the shining shield of basic research which has produced spectacular results in molecular biology and genetics and which has certainly added greatly to knowledge, a negative attitude towards primary prevention is surging. Primary prevention, the argument goes, might become useless in view of the continuous progress in diagnostic capacity and therapeutic efficiency, even though, in spite of such advances, it would seem preferable not to develop a cancer in the first place. Moreover, since measures of primary prevention might impose restrictions on the expansion of industrial production and restraints on consumption, including of medical drugs, they might be considered negative for the economy.

I shall cite only two of the numerous cases in which experimental evidence of carcinogenicity was deliberately ignored. Diethylstilboestrol was shown to cause tumors in mice in the 1930s and in several other animal species in the 1940s and 1950s. This notwithstanding, it became a popular drug for women of reproductive age and during the first period of pregnancy until the1970s, with the known consequences on their offspring (3). In the early 1960s, after a clustering of lung cancer cases was noted among workers involved in the production of bis (chloromethil) ether (BCME), experimental evidence for its carcinogenicity in mice after skin application or subcutaneous injection, first reported in 1968 and confirmed in 1969, was disregarded(4,5). No preventive measures were taken until the 1970s, when rats were reported having developed lung and nasal cavity tumors after receiving BCME by inhalation, the main route by which humans were presumed to be exposed (6-8).

The pretext for ignoring the evidence of carcinogenicity from the first long-term tests on BCME was that the route of exposure and the tumor type induced were different from those in humans. Demonstration of the multipotential carcinogenicity in mice and rats of benzene given orally has shown how irrelevant it is to always require that identical target organs be affected in humans and experimental animals (9).
A recent example of the extent of involvement of powerful economic interests in the choice of measures for primary prevention of disease is provided by the debate on the implementation of REACH, the proposed project of the European Union for the Registration, Evaluation and Authorization of Chemicals.
A correct implementation of REACH would substantially

[1] *Corresponding address: L. Tomatis, International Society of Doctors for the Environment (ISDE) Cave 25/r - 340110 Aurisina (Trieste), Italy; e-mail: ltomatis@hotmail.com*

improve the safety of working procedures, decrease chemical pollution of the environment and of our bodies, and would stimulate safer alternatives in which problematic chemicals were replaced by non toxic or at least less toxic compounds.

The first move made by the powerful chemical industry to dilute or minimize the effects of REACH, was to reduce the number of chemicals under scrutiny from the 30,000 originally proposed to about 12,000. Thereafter it proposed that the production of even dangerous chemicals be authorized if the risk to humans and the environment were adequately controlled, and this proposal is apparently still being discussed. If this proposal is approved it would mean that the release of these chemicals into the environment will not be prevented, and they will therefore continue to accumulate in the environment and absorbed by human beings.

Another move by the chemical industry to defend its interests is an all-out campaign against experimentation in animals and particularly against long-term tests. While there is little doubt that useless or cruel use of animals in toxicity testing should be banned, especially for checking the toxicity of cosmetics, long-term tests still play an important role in predicting possible long-term adverse effects, like cancer, in humans.
Long-term tests are however, relatively costly; industry estimated that the cost of testing all 30,000 chemicals in a complete set of tests in animals would be between 5 and 10 billion dollars. No wonder then that industry has suddenly discovered having a great compassion for animals. This together with a great passion for science has convinced industry to conduct research into alternative methods of toxicity testing, and to sponsor the European Center for the Validation of Alternative Methods (ECVAM) in Ispra, Italy. The cry now is: let toxicity become a respectable scientific discipline.

The question of costs, a part from the combination of human suffering and financial burden that disease imposes on individuals, should also be considered in the light of the fact that, for well over a century, the chemical industry was allowed to introduce chemicals into the environment and expose workers without having to provide evidence for the toxicity of chemicals. The burden of proof that a chemical is harmful to humans laid with the exposed individuals or with the health authorities. Some population groups were exposed to high concentrations of harmful chemicals, for long periods, in closed environments, under conditions that in certain industries closely resembled those of experimental animals in long-term tests. Long-term carcinogenicity tests are vigorously criticized on the basis of the relatively small number of animals, the high doses used and the long duration of administration. Rarely, if ever, however, has the resemblance between certain occupational exposures and animal experimentation been noted (10). Workers exposed to occupational carcinogens were in fact the human counterparts of the laboratory animals. Our society seems to have forgotten that, in the name of the material progress and well being from which we all benefit, generations of workers have been sacrificed without recognition. They even encounter enormous difficulty in obtaining delayed pecuniary compensation for the health damages they have suffered.

Experimental evidence for the carcinogenicity of many chemicals preceded the evidence of their carcinogenic activity in humans. If it had been heeded it would have allowed an earlier implementation of preventive measures (11,12). This was the case for instance with regard to: aflatoxins, 4-aminobiphenyl, 1,3-butadiene, diethylstilbestrol, formaldehyde, melphalan, mustard gas and vinyl chloride.
Dubious or erroneous data have been quoted and used to undermine the relevance of long-term carcinogenicity tests. It is claimed, for instance, that they are “dramatically over predictive”, in that 50% of the results are positive, of which 90% are false positives(13) . Such statements are based largely on the work initiated years ago by Bruce Ames and L.Gold and collaborators to undermine the evidence provided by long-term animal testing for the role of industrial chemicals in the etiology of human cancer.
Unfortunately, the evidence for the carcinogenicity of chemicals in the Carcinogenic Potency Data Bank which they developed is not evaluated critically. A chemical is classified as a carcinogen simply "if it has been evaluated as positive by the author of at least one experiment". This approach is at variance with that adopted by the International Agency for Research on Cancer and by the National Toxicology Program in the USA, in which expert scientific panels carefully and critically assess all the available experimental data before drawing conclusions about the strength of the evidence for carcinogenic risk to humans (14,15).

I am not campaigning in favor of sine die use of long-term animal testing, but the issue should be put under right light and attention should be drawn to the fact that dubious or erroneous data are used to undermine relevance of such testing. By gaining new insights into the mechanisms of carcinogenesis, we might eventually reach a point when we could do without animal tests. At present, however, we should worry more about the increasing use of human beings as experimental animals. It is of some concern that the Environment Protection Agency of the USA has asked the National Academy of Science whether it can be allowed to accept and use the results of research that involves deliberate exposure of human beings to potentially toxic compounds. This rediscovery of elementary ethical principles gives a measure of how far we have gone from the spirit that permeated the World Medical Association when, in Helsinki in 1964, it drew up the principles on which human experimentation should be based. These principles incorporated the “ Nuremberg code”, which, in turn, came from the acts of the Nuremberg trials of Nazi Doctors.

A recent US Congressional report has found that 22 studies in which human beings were intentionally exposed in order

to investigate the possible toxicity of pesticides clearly violated ethical standards. In another case, the well known carcinogen Chromium VI was given orally to volunteers in order to determine whether it is carcinogenic when given by a route other than inhalation. Pharmaceutical companies sponsor studies on so-called volunteers in order to test the toxicity of medical drugs. A recent episode in which several persons became severely ill during a clinical trial has attracted attention because it reached the mass media (16), but the unconstrained use of human beings, is more widespread than a few isolated cases.

The chemical industry claims that it takes the protection of people and the environment very seriously throughout the entire life cycle of its products. Nobody can deny that the industry conducts extensive research and testing on its products, but unfortunately this does not automatically mean that the production of chemicals and their products is thoroughly evaluated and regulated. Industry's priorities do not necessarily coincide with those of public health. The enormous difficulties encountered in the past in promoting efficient preventive measures even after the reporting of cancer occurring in exposed workers, are a good example of the divergence between industry and public health priorities.

One might wonder how much the situation has changed and if multinational corporations can be trusted to care about human health and the protection of the environment. It would be helpful, for instance, to know how many or what percentage of knew compounds or potential medical drugs have been withheld from the market because short term or long-term experimental tests carried out in industry laboratories provided evidence of toxicity. Equally important would be knowing what criteria were used by industry to allow chemicals to start mass production, in particular for those that are later identified as being toxic or as having severe adverse side effects.
While there is little doubt that corporate laboratories are technologically well equipped, often better that national institutions, and that corporate scientific staff are made up of well trained, expert scientists, there is reason to doubt that industry discloses critical information on some of their products. The difficulties encountered in regulating the use of phthalates and bisphenol A, cast further light on the divergence between corporate priorities and those of public health. The company making Teflon and perfluorooctanoic acid (PFOA) apparently withheld from the US EPA the results of a study showing that PFOA can cross the human placenta. Furthermore following a strategy of manufacturing doubt, it was reported to be good for the heart PFOA, while in fact there was evidence instead that it might cause heart disease.
In some cases, in the attempt to influence the scientific establishment, corporations have recruited scientists, openly but often surreptitiously, to carry out studies or to address questions in such a way as to create confusion and to increase the background noise on an otherwise clear-cut evidence of a health risk. To influence public opinion, they have at times avoided mention of health issues and claimed instead that a particular product or industrial process is indispensable in order to protect jobs and maintain an adequate standard of living (17,18). It is hard to accept the statement that appeared in an editorial in The Economist that " if it would not be for the lure of profit" the drugs that various nongovernmental organizations are trying to have made freely available to poor people and in poor countries would not exist. I would prefer to believe that it is not only, and perhaps not even mainly, profit that inspires corporate scientists in their research.

At times we find ourselves facing a choice between adopting an active attitude, such as implementing primary prevention measures in the absence of absolute certainty (which is very rare in biology), and adopting a passive, waiting attitude using etiological uncertainties to justify a disregard for prudent primary prevention. A cautious, prudent attitude is sometimes interpreted as anti-technological and anti-scientific. In fact, those who champion caution are simply recognizing that the capacity for predicting the consequences of technological advances is usually of lesser quality and at a lower level than technological knowledge. Recognition of our limited capacity to predict long-term consequences can only lead to learning more. It therefore represents a stimulus, and not an impediment, to research.
In this context I would like to mention the evidence of adverse effects after prenatal and preconceptional exposures to a variety of chemicals. Experimental and some initial epidemiological observations indicate that such exposures can affect the progeny by crossing the placenta and interacting with fetal tissues, or affect subsequent generations by a mechanism of epigenetic transmission. The finding at birth of DNA translocations typical of leukemia in children that years later developed the disease, in retrospective investigations on cord blood, has been related to the exposure during pregnancy to toxic compounds (19,20), while the presence of ras proto-oncogene mutations in children who developed acute lymphatic leukemia was reported to be associated with maternal exposure to a series of chemicals during pregnancy and paternal exposure before conception (21). It was also reported recently that some endocrine disruptors induce the reprogramming of the male germ line in association with an altered DNA methylation with the consequent persistence of the adverse effects for at least four generations (22,23). These findings emphasizes that our responsibility is not only to protect the present but also the future generations.

By adopting an attitude of responsible caution, we also accept that we have a duty to provide accurate information on possible or potential risks and to prevent ignoring or concealment of relevant data. Only with such an attitude can we avoid use of the entire human species for testing everything technological progress can invent.

Acknowledgements
I thank Elisabeth Heseltine for editing the manuscript

References

1 Carnevale, F.,Montesano, R., Tomatis, L. Comparisons of regulations on occupational carcinogens in several industrialized countries. Am.J.Ind.Med.,1987,12:453-473

2 Ladou, J. The asbestos cancer epidemics. Environ. Health Perspect.,2004,112:265-290

3 IARC Monographs on the Evaluation of the Carcinogenic Risk of chemicals to humans. Sex Hormones. Vol.21. IARC, Lyon 1979

4 Van Duuren, B.L.,Goldschmidt, B.M., Katz, C. et al. Alfa-haloheters: a new type of alkylating carcinogen. Arch.Environ.Health, 1968,16:472-476

5 Van Duuren,B.L.,Sivak,A.,Goldschmidt,B.M., et al. Carcinogenicity of halo-ethers. J.Natl.Cancer Inst., 1069,43:481-486

6 Laskin, S.,Kuschner, M., Drew, R.T., et al. Tumors of the respiratory tract induced by inhalation of bis(chloromethyl)ether. Arch.Environ.Health, 1972,23:135-136

7 Figueroa, W.G., Raszkowski, R., Weiss, W. Lumng can`er in chloromethyl methylether workers. New Eng.J.Med.,1973,288:1096-1097

8 Thiess, W.G.,Hey, W.,Zellwer, H. Zur Toxicologie von Dichlor-dimethylether – Verdacht auf kanzerogene Wirkung auch beim Menschen. Zbl.Arbeitsmed.,1973,23:97-102

9 Maltoni, C., Conti, B.,Scarnato, C. Benzene: a multipotential carcinogen. Result of long-term bioassays performed at the Bologna Institute of Oncology. Am.J.Ind. Med., 1983,4:441-445

10 Tomatis, L. Primary prevention of cancer in relation to science, sociocultural trends and economic pressures. Scand.J.Work Environ. Health, 2005,31:227-232

11 Tomatis, L. The predictive value of rodent carcinogenicity tests in the evaluation of human risks. Ann.Rev.Pharmacol.Toxicol.,1979,19:511-530

12 Huff, J. Chemicals causally associated with cancers in humans and in laboratory animals. In: Waalkes, M.P.,Ward, J.M. Carcinogenesis. Raven Press, New York,1994, pp 25-37.

13 Abbott,A. Animal testing: More than a cosmetic change. Nature, 2005,438:144-146

14 Ames, B.N., and Gold, L.S. Pollution, pesticides, and cancer misconceptions. FASEB J., 1997,11:1041-1052

15 Tomatis, L., Melnick, R., Haseman, J. et al. Alleged 'misconceptions' distort perceptions of environmental cancer risks. FASEB J.,2001,15:195-203

16 Rosenthal, E. When drug trials go horribly wrong. International Herald Tribune, April 8-9,2006

17 Egilman, D.S.,and Bohme, S.R. Overe a barrel: corporate corruption of science and its effect on workers and the environment. Int.J.Occ.Environ.Health, 2005,11:331-337

18 Bohme, S.R.,Zorabedian, J, and Egilman,D.S., Maximizing profit and endangering health: corporate strategies to avoid litigation and regulation Int.J.Occ.Environ.Health, 2005,11:338-348

19 Wiemels, J.L.,Xiao, Z.,Buffler, P.A., et al. In utero origin of t(8:21) SAML1-ETO translocations in childhood acute myeloid leukemia. Blood, 2002,99:3801-3805

20 McHale, C.M.,Smith, M.T. Prenatal origin of chromosomal translocations in acute childhood myeloid leukemia. Am.J.Hematol.,2004,75:254-257

21 Shu, X.O.,Perentesis, J.P.,Wen, W. et al. Parental exposure to medications and hydrocarbons and ras mutations in children with acute lymphoblastic leukemia: a report from the Children's Oncology Group. Cancer Epidemiol.Biomarkers.Prev.,2004,13:1230-1235

22 Anway, M.D., Cupp, A.S., Uzumcu, M.,Skinner, M.K. Epigenetic Transgenerational Actions of Endocrine Disruptors and Male Fertility. Science, 2005,308:1466-1469

23 Weinhold, B. Epigenetics: The science of change. Environ.Health Perspect., 2006,114:A160-167