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EDITORIAL

Risk Assessments of Low-Level Exposures

In cancer-risk assessments employed by the U.S. Environmental Protection Agency assumptions are made that exaggerate risks by large factors. Among these is an important but unproven hypothesis that results obtained by administering huge doses of substances are predictive of effects of minuscule doses.

To calculate effects of small doses, a linear extrapolation from large doses to zero is employed. The routine use of this procedure implies that pathways of metabolism of large doses and small doses are identical. It implies that mammals have no defense against effects that injure DNA. It implies that no dose, however small, is safe. Examples of instances in which these assumptions are invalid are becoming numerous.

Linear extrapolation of effects from high to lower doses is often not valid. In a third or more of instances in which a maximum tolerated dose elicited extra tumors in rodents, one-half that dose did not. Bruce Ames and others have pointed out that huge doses of non-genotoxic substances are accompanied by toxicity, cell death, and cell replacements. This creates conditions favorable for growth of tumors. At doses in which cellular death does not occur, tumors would not be produced by non-genotoxic substances. The majority of chemicals are not genotoxic, nor does metabolism of them give rise to genotoxic intermediates. Thus the linear extrapolation is not applicable to the majority of chemicals.

Recently, short-term experiments have measured extent of damage to linear DNA caused by different levels of doses of test substances. In one example, 11 chemicals known to cause cancer at high doses were administered at low levels. With 8 of 11 substances, the minimum amounts of damaged DNA were found not in controls but in the animals that received an amount intermediate between zero and a high dose. Instead of damaging the DNA of the rodents' livers, the low doses were apparently beneficial to them. In another study, female rats administered 0.001 μg/kg per day of dioxin had fewer breast, uterine, pituitary, and liver tumors and fewer tumors overall than did controls. When doses of 0.01 μg/kg per day were administered, the incidence of liver tumors exceeded that of controls, but breast, uterine, pituitary, and total tumors, were markedly fewer than in controls. In the above instances, safe (diminished cancer) levels of exposure exist for substances known to cause cancer at higher doses.

The use of linear extrapolation from huge doses to zero implies that "one molecule can cause cancer." That assertion disregards the fact of natural large-scale repair of damaged DNA. Natural chemical and physical lesions of DNA are caused by thermal and oxidative insults. Metabolic processes employ reactive oxygen species including peroxides and OH.* Natural kinds of injury to DNA include depurination, depyrimidination, deamination, single-strand breaks, double-strand breaks, base modification, and protein-DNA crosslinks. Mammalian cells on average undergo about 10,000 measurable DNA modification events per cell per hour. Adult humans are internally exposed to about 500 g per day of oxygen—a relentless known destroyer of DNA. In contrast, hypothetical insults from anthropogenic sources are usually from substances present in microgram quantities.

Creatures ranging from micro-organisms to mammals could not survive if they did not have mechanisms to respond to challenges from their environments. During exposure to a somewhat elevated temperature, living forms synthesize a host of different proteins that enable them to endure even higher temperatures. This phenomenon has been noted in experiments with cadmium, mercury, copper, zinc, polychlorinated biphenyls, and insecticides. Studies using x-rays show that a large total instantaneous dose is fatal while the same total dose spread over time is not. Repair of DNA occurs. Studies have shown that DNA-damaging agents induce a substantial number of responses, including production of proteases, DNA repair agents, oncogenes, and chromatin changes.*

The current mode of extrapolating high-dose to low-dose effects is erroneous for both chemicals and radiation. Safe levels of exposure exist. The public has been needlessly frightened and deceived, and hundreds of billions of dollars wasted. A hard-headed, rapid examination of phenomena occurring at low exposures should have a high priority.

Philip H. Abelson

* BELLE Newsletters, University of Massachusetts; telephone 413-545-1239.