

## Glossary

***Ah receptor (AhR):*** Aryl hydrocarbon receptor, a protein receptor in cells that binds dioxins at low concentration and mediates dioxin toxicity.

***carcinogenic potency:*** An estimate of the lifetime daily dose-rate of a chemical that will give tumors to a specified percentage of animals in a cancer test. (See  $TD_{50}$ ,  $LTD_{10}$ , and  $q_1^*$  for three measures of carcinogenic potency.)

***Carcinogenic Potency Database (CPDB):*** A widely used and easily accessible resource on the standardized results of chronic, long-term animal cancer tests. See <http://potency.berkeley.edu>. Analyses are presented of 5,152 experiments on 1,298 chemicals reported in the published literature and include results sufficient for many investigations into carcinogenesis.

***case-control study:*** An epidemiological study design in which individuals are selected based on the presence (case) or absence (control) of disease. Well-designed case-control studies require that the two groups be derived from the same population.

**Chinese herb nephropathy:** Kidney disease associated with consumption of the medicinal herb *aristolochia*.

**chronic bioassay:** An experiment to investigate the effects of a substance when administered chronically for life at the maximum dose that is predicted to be tolerated by test animals for a lifetime.

**cohort study:** An epidemiological study design in which individuals with known characteristics (occupational exposure, smoking, exercise, etc.) are enrolled and followed over time for specific outcomes. The rate of cancer (or other disease) in the exposed is compared to that in the unexposed. Relative rates of disease in people exposed to the variable of interest (e.g. fruit and vegetable consumption) are compared to the unexposed or the less exposed.

**confounding factor:** Confounding occurs because behavior-related variables of interest tend to cluster. An exposure (e.g., vegetable consumption) may be of interest in protecting against a particular cancer. However, if smokers eat fewer vegetables than non-smokers (they do), we may falsely attribute a risk reduction to vegetables that is really due to the fact that a higher proportion of vegetable eaters are non-smokers. Smoking, here, is a confounder of the association between vegetables and cancer. It can be controlled for by separating the smokers and the non-smokers and asking whether the vegetable-cancer association is seen in both groups (or by more sophisticated, but conceptually similar, statistical techniques).

**CPDB:** See Carcinogenic Potency Database

**deficiency:** Defined here as the dietary intake of a vitamin or mineral at a level <50% of the RDA, as distinguished

from acute deficiency such as acute vitamin-C deficiency causing scurvy.

**epidemiology:** The study of patterns and causes of human health outcomes in a specified population.

**HERP:** An index of possible cancer hazard (Human Exposure/Rodent Potency, reported as a percent), which compares the dose of chemical to which humans are exposed vs. the estimate of the dose that gives tumors to half of test animals in a lifetime experiment.

**inducibility:** Ability to cause the synthesis of.

**IQ:** (2-amino-3-methylimidazo[4,5-*f*]quinoline), a mutagenic chemical formed naturally when meat, chicken, or fish is cooked at high temperatures. This heterocyclic amine is carcinogenic in rodent and monkey experiments.

**LTD<sub>10</sub>:** The lower 95% confidence limit on the dose estimated to produce an extra lifetime cancer risk of 10% in an animal cancer test.

**MeIQx:** (2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline), a mutagenic chemical formed naturally when meat, chicken, or fish is cooked at high temperatures. This heterocyclic amine is carcinogenic in rodent experiments.

**mitochondria:** The organelles in all cells that produce chemical energy (ATP) by removing electrons (burning or oxidizing) from fat or carbohydrate fuel and adding the electrons to oxygen.

**NCI:** United States National Cancer Institute

**NTP:** United States National Toxicology Program

**oxidative damage:** Damage from oxidants.

**oxidative DNA lesions:** Damage products in DNA from oxidants.

**oxidative mutagens:** Agents damaging DNA by removing electrons.

**oxidative stress:** Toxicity due to oxidants.

**PDR:** *Physician's Desk Reference*, the standard reference in the United States for prescription drugs.

**PhIP:** (2-amino-1-methyl-6-phenylimidazo[4,5-*b*]-pyridine), a mutagenic chemical formed naturally when meat, chicken, or fish is cooked at high temperatures; this heterocyclic amine is carcinogenic in rodent experiments.

**$q_1^*$ :** The measure used by the US EPA for carcinogenic potency of a substance in an animal cancer test; a plausible 95% upper-bound estimate of the probability of cancer during a lifetime per unit dose.

**recall bias:** This can occur if individuals are describing events (exposures, diseases, pregnancy outcome, etc.) in the past in a non-comparable manner. It is primarily a problem in case-control studies when the presence of the disease in one group (cases) may result in differential recall (e.g. of alcohol consumption or dietary behavior) from that of controls.

**$TD_{50}$ :** If there are no tumors in control animals, then  $TD_{50}$  is that chronic dose-rate in mg/kg body wt/day that would induce tumors in half the test animals at the end of a standard lifespan for the species. The average daily

dose-rate estimated to halve the probability of remaining tumor-free throughout a lifespan experiment in test animals. The measure of carcinogenic potency in the CPDB.

**TDS:** The Total Diet Study of the United States Food and Drug Administration, which provides estimates of the total consumption of pesticide residues and other chemicals via food for specified age and gender groups. Conducted annually for more than 20 years.



## **Appendix—Method for calculating the HERP index**

The HERP index takes into account both human exposures and the carcinogenic dose to rodents and compares them. HERP values indicate what percentage of the rodent carcinogenic daily dose (mg/kg/day) for 50% of test animals that a person receives from an average daily exposure (mg/kg/day).

For example, methyleugenol is a chemical that is carcinogenic in rats and mice and has a HERP value of 0.004% for average daily US exposure in food from its natural occurrence, and 0.0006% for average daily US exposure as a synthetic food additive. Below is an example of the HERP calculation for methyleugenol that occurs naturally (see table 5 at HERP = 0.004%). Data are available indicating that average naturally occurring methyleugenol consumption in the US is 46.2 µg/day (Smith & al. 2002). The calculation of HERP from the values in table 5 for methyleugenol is as follows:

- (1) Human dose of rodent carcinogen is:  
 $46.2 \mu\text{g/day} / 70 \text{ kg body weight} = 0.66 \mu\text{g/kg/day}$   
(=0.00066 mg/kg/day);
- (2) Rodent potency: the TD<sub>50</sub> is 18.6 mg/kg/day in mice;

(3) Possible hazard (HERP) is:

$$\frac{0.0006 \text{ mg/kg/day human exposure}}{18.6 \text{ mg/kg/day TD}_{50}} = 0.00004; 0.00004 \times 100 = 0.004\%$$

The TD<sub>50</sub> values used in HERP are averages for rats and mice separately, calculated by taking the harmonic mean of the TD<sub>50</sub> values from positive experiments. For methyleugenol, the TD<sub>50</sub> in rats is 19.7 mg/kg/day and in mice 18.6 mg/kg/day. Since the mouse TD<sub>50</sub> is lower (more potent), this value is used in HERP. Experiments in the CPDB that do not show an increase in tumors are ignored in HERP.

The TD<sub>50</sub> value for rats or mice in the HERP table is a harmonic mean of the most potent TD<sub>50</sub> values from each positive experiment.

The harmonic mean (T<sub>H</sub>) is defined as:

$$T_H = \frac{1}{\frac{1}{n} \sum_{i=1}^n \frac{1}{T_i}}$$