Misconception 2—Synthetic chemicals at environmental exposure levels are an important cause of human cancer

Studies of cancer rates around the world indicate that the major avoidable causes of cancer primarily reflect lifestyle or other environmental factors that can be modified to reduce cancer risk (i.e. factors that are not genetic) (Armstrong & Doll 1975; Doll & Peto 1981). The main evidence for this conclusion is that rates of cancer in specific organs differ markedly in different countries; when people migrate to other countries their cancer rates change and within a few generations usually resemble the rates in their new countries. Additionally, rates change over time in a given country.

Neither ***epidemiology*** nor toxicology supports the idea that exposures to synthetic industrial chemicals at the levels at which they are generally found in the environment are important as a cause of human cancer (Ames & al. 1995; Devesa & al. 1995; Gold & al. 1992).

Instead, other environmental factors have been identified in epidemiological studies that are likely to have a major effect on lowering cancer rates: reduction of smoking, improving diet (e.g. increased consumption of fruits and vegetables), hormonal factors (some of which are diet-related), and control of infections (Ames & al. 1995).

Few epidemiological studies find an association between the risk of cancer and low levels of industrial pollutants or pesticide residues; the associations are usually weak, the results are often conflicting, and the studies usually do not address individual pesticides (Dich & al. 1997). Moreover, the studies often do not correct for potentially large ***confounding factors*** such as composition of the diet (Ames 1998; Ames & al. 1995; Doll & Peto 1981; Gold & al. 2001a, http://monographs.iarc.fr/monoeval/crthgr01.html; International Agency for Research on Cancer 1971–2001). Epidemiological studies on the risk of breast cancer have found no association with pesticide residues (Gammon & al. 2002; Grodstein & al. 1997; Hunter & al. 1998). The most recent ***case-control study*** measured residues in blood of DDT, DDE, dieldrin, and chlordane and found no association with breast cancer (Gammon & al. 2002).

From the toxicological perspective, exposures to synthetic pollutants are at very low levels and, therefore, rarely seem plausible as a causal factor, particularly when compared to the background of natural chemicals in the diet that are carcinogenic in rodents in high-dose tests (i.e. rodent carcinogens) (Ames & al. 1990a; Gold & al. 1997b; Gold & al. 1992). Even if one assumes that the worst-case risk estimates for synthetic pollutants are true risks, the proportion of cancer that the United States Environmental Protection Agency (EPA) could prevent by regulation would be tiny (Gough 1990). Historically, some high occupational exposures to some industrial chemicals have caused human cancer, though estimating the proportion of all cancers that are due to occupational exposures has been a controversial issue: a few percent seems a reasonable estimate (Ames & al. 1995; Doll & Peto 1981), and much of this is from asbestos in smokers. Exposures to synthetic chemicals or industrial mixtures in the workplace can be much higher than the exposure to chemicals in food, air, or water. Past occupational exposures have sometimes been

high, and about half the agents that have been evaluated as human carcinogens by International Agency for Research on Cancer (IARC) were identified by workplace exposures. Since occupational cancer is concentrated among small groups with high levels of exposure, there is an opportunity to control or eliminate risks once they are identified. In the United States, Permissible Exposure Limits in the workplace are sometimes close to the carcinogenic dose in rodents (Gold & al. 1994a) and, thus, require priority attention. See **Misconception 7** (p. 43).

Aging and cancer

Cancer is due, in part, to normal aging and increases exponentially with age in both rodents and humans (Ames & al. 1993b). To the extent that the major avoidable risk factors for cancer are diminished, cancer will occur at later ages and the proportion of cancer caused by normal metabolic processes will increase. Aging and its degenerative diseases appear to be due in part to ***oxidative damage*** to DNA and other macromolecules (Ames & al. 1993b; Beckman & Ames 1998). By-products of normal metabolism—superoxide, hydrogen peroxide, and hydroxyl radical—are the same ***oxidative mutagens*** produced by radiation. ***Mitochondria*** from old animals leak oxidants (Hagen & al. 1997): old rats have been estimated to have about 66,000 ***oxidative DNA lesions*** per cell (Helbock & al. 1998), although methods to measure such lesions are improving and may change the number somewhat. DNA is oxidized in normal metabolism because antioxidant defenses, though numerous, are not perfect. Antioxidant defenses against oxidative damage include vitamin C (Rice-Evans & al. 1997) which comes from dietary fruits and vegetables, and vitamin E (Rice-Evans & al. 1997), which comes from nuts, vegetable oils, and fat. In addition, mitochondria, the organelles in the cell that generate energy and are the main source of oxidants, may need different antioxidants (Hagen & al. 2002; Liu & al. 2002a; Liu

& al. 2002b). Increasing antioxidant intake in those persons with low intakes may help to prevent cancer but it is difficult to disentangle dietary intake of individual vitamins or minerals in epidemiological studies (Ames & Wakimoto 2002).

Smoking

In Canada, smoking contributes to 27% of cancer deaths and about 45,000 premature deaths per year (American Cancer Society 2000; Makomaski Illing & Kaiserman 1999; National Cancer Institute of Canada 2000; Ries & al. 2000). Overall, 21% of deaths from the three leading causes of death (cancer, heart disease, and cerebrovascular disease) are attributable to smoking (Makomaski Illing & Kaiserman 1999). Tobacco is a cause of cancer of the lung, mouth, pharynx, larynx, esophagus, bladder, pancreas, stomach, kidney, uterine cervix, and myeloid leukemia (International Agency for Research on Cancer 1986; International Agency for Research on Cancer 2002, in press). Smoke contains a wide variety of mutagens and substances that are carcinogenic in rodents. Smoking is also a severe ***oxidative stress*** and causes inflammation in the lung. The oxidants in cigarette smoke—mainly nitrogen oxides—deplete the body's antioxidants (Lykkesfeldt & al. 2000). Thus, smokers need to ingest more vitamin C than non-smokers to achieve the same level in blood but they tend not to do so: an inadequate concentration of vitamin C in plasma is more common among smokers (Lykkesfeldt & al. 2000). A recent Danish study indicated that smokers consumed fewer fruits and vegetables than nonsmokers (Osler & al. 2002). Additionally, people who take supplements of vitamins and minerals are less likely to be smokers (Patterson & al. 2001).

Men with inadequate diets or who smoke may damage the DNA in all cells of the body, including their sperm. When the level of dietary vitamin C is insufficient to keep vitamin C in the seminal fluid at an adequate level, the oxidative lesions in sperm DNA are increased 2.5 times (Ames

& al. 1994; Fraga & al. 1991; Fraga & al. 1996). Male smokers have more oxidative lesions in sperm DNA (Fraga & al. 1996) and more chromosomal abnormalities in sperm (Wyrobek & al. 1995) than do nonsmokers. It is plausible, therefore, that fathers who smoke may increase the risk of birth defects and childhood cancer in offspring (Ames & al. 1994; Fraga & al. 1991; Woodall & Ames 1997). Some epidemiological studies suggest that the rate of childhood cancers is increased in offspring of male smokers (Ji & al. 1997; Sorahan & al. 1995).

Involuntary (environmental) exposure to tobacco smoke (i.e. "second-hand smoke") has also been evaluated as a human carcinogen (International Agency for Research on Cancer 2002, in press; US Department of Heath and Human Services 1986; US Environmental Protection Agency 1992b), and is estimated to increase the risk of lung cancer by 20% to 30%. In comparison, smokers have an increased risk of lung cancer of 2000% (International Agency for Research on Cancer 2002, in press), i.e. 600 to 1000 times greater risk than from involuntary smoking.

Diet

Dietary factors have been estimated to account for about one third of cancer deaths in the United States (American Cancer Society 2000; Ames & al. 1995; Doll & Peto 1981; Ries & al. 2000) and specific dietary factors are slowly being clarified, although epidemiological research on diet has many complexities and confounding factors. Low intake of fruits and vegetables is associated with increased cancer incidence in many case-control studies (Block & al. 1992; World Cancer Research Fund 1997); results from several recent ***cohort studies***, however, have been less consistent (Willett 2001). (See **Misconception 3**, p. 15). Excessive consumption of alcoholic beverages is associated with cancers of the breast, oral cavity (primarily in smokers), and liver (International Agency for Research on Cancer 1988; Willett 2001).

There has been considerable interest in calories (and dietary fat) as a risk factor for cancer, in part because caloric restriction markedly lowers the cancer rate and increases life span in rodents (Ames & al. 1995; Hart & al. 1995b; Turturro & al. 1996; Vainio & Bianchini 2002). For two common cancers, breast and colon, international comparisons in incidence suggested a role for fat intake; however, combined analyses of many studies do not support such an association (Hunter & al. 1996; Willett 2001). Higher intake of dietary fiber does not appear to protect against colon cancer, although some earlier case-control studies suggested that it did (Willett 2001). Current scientific attention has focused on body weight (obesity), weight gain among adults, and inadequate physical activity as risk factors for cancer (Caan & al. 1998; Giovannucci & al. 1995; Huang & al. 1997; Vainio & Bianchini 2002; Willett 2001). A recent report by IARC states:

> Taken together, excess body weight and physical inactivity account for approximately one fourth to one third of breast cancer, cancers of the colon, endometrium, kidney (renal cell) and oesophagus (adenocarcinoma). Thus adiposity and inactivity appear to be the most important avoidable causes of postmenopausal breast cancer, endometrial cancer, renal cell cancer, and adenocarcinoma of the oesophagus, and among the most important avoidable causes of colon cancer. (Vainio & Bianchini 2002)

Lack of regular physical activity contributes independently to risk of colon (Giovannucci & al. 1995; Giovannucci & al. 1996; Martinez & al. 1997; Platz & al. 2000; Willett 2001) and breast cancer (Bernstein & al. 1994; Rockhill & al. 1999; Willett 2001).

Hormonal factors

Endogenous reproductive hormones play a large role in cancer, including that of the breast, prostate, ovary, and

endometrium (Henderson & Feigelson 2000; Henderson & al. 1991), contributing to about 20% of all cancer. Many life-style factors such as reproductive history, lack of exercise, obesity, and intake of alcohol influence hormone levels and therefore affect risk (Ames & al. 1995; Henderson & Feigelson 2000; Henderson & al. 1991; Hunter & Willett 1993; Kelsey & Bernstein 1996; Writing Group for the Women's Health Initiative Investigators 2002). The mechanisms for postmenopausal breast cancer may involve changes in hormone metabolism: e.g. earlier menstruation and postmenopausal release of estrogen from body fat, never having a child, giving birth for the first time over age 35, or hormone replacement therapy. Recent results of a clinical trial in the study by the Women's Health Initiative indicate that hormone-replacement therapy (estrogen and progestin) increases the risk of postmenopausal breast cancer (Writing Group for the Women's Health Initiative Investigators 2002).

Chronic inflammation

Chronic inflammation results in the release of oxidative mutagens from white cells and other sentinel cells of the immune system, which combat bacteria, parasites, and viruses by destroying them with potent, mutagenic oxidizing agents (Ames & al. 1995; Christen & al. 1999). These oxidants protect humans from immediate death from infection but they also cause oxidative damage to DNA, chronic killing of cells with compensatory cell division, and mutation (Shacter & al. 1988; Yamashina & al. 1986); thus, they contribute to cancer. Anti-inflammatory agents, including some antioxidants, appear to inhibit some of the pathology of chronic inflammation. Chronic infections such as hepatitis B and C, viruses and liver cancer, *Helicobacter pylori* and stomach cancer that give rise to chronic inflammation are estimated to cause about 21% of new cancer cases in developing countries and 9% in developed countries (Pisani &

al. 1997). Obesity is associated with a systemic chronic inflammation, which suggests that it may play a role in cancer risk (Das 2001).

Other factors

Other causal factors in human cancer are excessive exposure to the sun, viruses (e.g., human papillomavirus and cervical cancer), and pharmaceuticals (e.g. phenacetin, some chemotherapy agents, diethylstilbestrol, estrogens). Genetic factors affect susceptibility to cancer and interact with life-style and other risk factors. Biomedical research is uncovering important genetic variation in humans that can affect susceptibility.