The Relative Importance of Mutagens and Carcinogens in the Diet

Werner K. Lutz[1] and Josef Schlatter[2]

[1]Institute of Toxicology, ETH and University of Zürich, [2]Division of Food Science, Swiss Federal Office of Public Health, CH-8603 Schwerzenbach, Switzerland

Abstract. Known mutagens and carcinogens in the diet were compiled and the risk of cancer was estimated on the basis of average exposure levels in Switzerland and carcinogenic potencies from rodent bioassays. The analysis showed that, except for alcohol, the sum of all known dietary carcinogens could only explain a few percent of the cancer deaths attributed by epidemiologists to dietary factors. The discrepancy was explained by a "carcinogenicity" of excess macronutrients. This hypothesis was based on an evaluation of dietary restriction experiments in rats and mice, where a dramatic reducing effect on spontaneous tumour formation was seen. From these experiments, a "carcinogenic potency" was deduced for food in excess (TD_{50} approximately 16 g/kg per day). Overnutrition in Switzerland was converted into excess food intake and the cancer risk estimated on the basis of the TD_{50} value. The resulting risk of 60,000 cases per one million lives would allow to explain by overnutrition almost all "diet-related" cancer deaths in humans.

Geographical variation in cancer incidence rates is often attributed to differences in the diet. It is estimated that about one third of the cancer deaths in Western countries are due to dietary factors (Doll, 1992; Doll & Peto, 1981). No attempt has so far been made, however, to sum up the cancer risk from the total exposure to all known specific dietary carcinogens and compare the result with epidemiological predictions. In view of a total cancer mortality of about 25 percent, the one third attributed to the diet would result in about 80,000 cancer cases per 10^6 lives. In this communication, we try to close this gap and evaluate the situation in Switzerland in a comprehensive manner. A fully referenced report is to appear elsewhere (Lutz & Schlatter, in press).

Materials and Methods

Average intake of dietary carcinogens in Switzerland was taken mainly from two sources (Aeschbacher, 1991; Staehelin et al.,1991) and was expressed in the units of ng/kg/day. Carcinogenic potency values TD_{50} were derived from animal bioassays (Gold et al.,1991). The TD_{50} values approximate the daily carcinogen dose per kg b.w. which halves the probability of remaining tumorless within a standard lifespan (2 years in the database). It is used in the units mg/kg/day. The cancer risk was calculated by multiplication of dose with potency (equivalent to dividing dose by the TD_{50}) and was expressed per 10^6 lives. Results were rounded off to one digit.

The same carcinogenic potency TD_{50} was used irrespective of the dose, i.e., a linear dose-response extrapolation was adopted. Evidence to support a nonlinearity in the dose-response curve (Lutz, 1990) was discussed in some cases of potential high-risk situations. It was based primarily on the putative mechanism of carcinogen action assigned to the listed carcinogens.

Humans and rodents were assumed to be of similar sensitivity. This assumption is supported in general by comparison of the TD_{50} values with epidemiological potency data (Crouch & Wilson, 1979). It does, however, not exclude specific situations, where the TD_{50} values for humans could be much lower, for instance when pharmacokinetic differences result in higher tissue levels for longer periods of time (e.g., Ochratoxin A; 2,3,7,8-TCDD).

All well known classes of genotoxic carcinogens were evaluated. In addition, high-potency or high-dose carcinogens were included independently of the putative mechanism of carcinogen action. For situations of trace level exposure or for low potency carcinogens, only one or two model representatives were investigated. When the risk turned out to be negligible, the situation was not investigated any further.

Results

In Table 1, the carcinogens are listed in order of decreasing risk. The putative mechanism of carcinogenic action as indicated in the last column might be of value to discuss the probability of a

Table 1.

The relative importance of mutagens and carcinogens in the diet.

Compound or Class	Average Human Intake Estimate for Switzerland [ng/kg bw/d]	Tumorigenic Dose in Animals: TD_{50} [mg/kg bw/d]	Estimated Cancer Cases per 10^6 Lives	Putative Mechanism(s) of Action[a]
Ethyl alcohol (ethanol)			<8,000[b]	DI/CT
Caffeic acid	10^6	>400	<1,000	?
Arsenic basal intake	150[c]	>0.2[d]	<400	DI
+ fish	500[c]	>0.2[d]	<1,000	DI
Cadmium (chloride)	200	>1.3	<80	DI
Heterocyclic aromatic amines	1,500	15	50	DA
Polycyclic aromatic hydrocarbons (Benzo[a]pyrene-equivalents)	200	3	30	DA
Nitroso compounds, volatile	14	1	8	DA
2,3,7,8-TCDD (TCDD-equivalents)	0.002	0.00007	10	CD
Estragole	1,000	50	10	DA
Aflatoxin B_1	0.25	0.02	6	DA
Ochratoxin A	2	11	0.09	CT(?)
Ethyl carbamate basal intake	20	30	0.3	DA
+ wine drinking	100	30	2	DA
+ spirit drinking	2,000	30	30	DA
Benzene	100	70	0.7	DA/DI
Trichloroethylene	50	1,000	0.03	DA/CT
1,1,1-Trichloroethane	50	500	0.05	DA/CT
Tetrachloroethylene	50	110	0.2	CT
Vinyl chloride	3	60	0.03	DA
Styrene	10	600	0.008	DA/CT
Di(2-ethylhexyl)phthalate	2,000	1,000	1	CD
Zearalenone	100	30	2	CD
Estradiol	2[e]	1	1	CD
DDT (including isomers)	30	30	0.5	CD
α + β-Hexachlorocyclohexane	30	20	0.8	CD
Captan	20	1,100	0.009	CD

a) DA: DNA damage / adducts
DI: DNA damage / indirect
CD: Cell division / differentiation
CT: Cell division / toxicity

b) Substantially less in non-smokers

c) Includes organic As (carcinogenicity proven for inorganic As only)

d) From epidemiological data

e) From meat (endogenous production / physiological concentration)

nonlinear dose-response extrapolation. A linear dose-response curve might be expected for the DNA adduct-forming (DA) carcinogens (Lutz, 1991). For indirect DNA damage (DI; for instance by oxygen radical formation linked to the metabolism of the carcinogen), or for nongenotoxic mechanisms associated with cell division (CD or CT), low dose levels are expected to be of lower carcinogenic potency. The four top-ranking carcinogens in our list, ethanol, caffeic acid, arsenic, and cadmium are not known to form DNA adducts. Therefore, the cancer risks most probably represent upper limit values.

DNA adduct-forming dietary carcinogens. Exposures to aromatic amines (mostly heterocyclic pyrolysis products), to polycyclic aromatic hydrocarbons (as benzo[a]pyrene equivalents), and to volatile nitroso compounds, average 1,500, 200, and 14 ng/kg/d. Together with the respective group estimates for the TD_{50}, the numbers of cancer cases expected per 10^6 lives are 50, 30, and 8.

Estragole, the most from fennel, appears in the same category. Caution must be expressed here, however, not to take this risks at face value. Many natural carcinogens are ingested with vegetables and at doses much below the levels required for a positive result in a bioassay. We therefore believe that the protective effects of antioxidants, vitamins, and fibres in vegetables outweigh the theoretical cancer risk from specific constituents.

Exposure to aflatoxins, ethyl carbamate (urethane), and benzene is expected to result in lower risks, except for the regular consumer of stone fruit brandies. For this group, the ethyl carbamate-derived cancer risk can increase to up to 30 per 10^6. Other genotoxic carcinogens in the diet, such as halogenated alkanes and alkenes or plastic monomers all rank far below 1 case per 10^6.

To summarize the DNA-reactive group of dietary carcinogens, not much more than one hundred cancer cases can be accounted for. In view of the extensive mutagenicity testing of all kinds of foods, we consider it unlikely that important genotoxic carcinogens have been missed. The question therefore is whether indirectly genotoxic (DI) or nongenotoxic carcinogens (CD; CT) are more important.

Non DNA adduct-forming carcinogens. When looking at this class of carcinogens, alcohol with an estimated 8,000 cancer cases per 10^6 is the most important single factor. Natural food constituents (Ames et al.,1990), sometimes present in high concentrations (e.g., caffeic acid), and carcinogenic metal ions (arsenic and cadmium) rank next (80-1,000). These figures are probably too high, however, because linear extrapolation to low dose might be too conservative and because the metal compounds present in the diet are less toxic than the ones for which the TD_{50} has been determined.

Fungal metabolites such as ochratoxin A or zearalenone, natural hormone residues (estradiol), residues of plasticizers or contaminations with persistent pesticides all are near or below a "virtually safe" dose (1 case per 10^6). For saccharin, a theoretical risk value of 100 per 10^6 would have been derived, based on an average intake of 0.5 mg/kg/d and a carcinogenic potency of the sodium salt TD_{50} = 2,000 mg/kg/d. However, saccharin is not listed in Table 1 because carcinogenesis by sodium saccharin in the rat bladder is based on factors which do not appear to be operating in humans (Cohen & Ellwein, 1990).

Combining the data obtained with specific dietary carcinogens of all possible mechanisms of action, it appears not to be possible to explain, on the basis of exposure and carcinogenic potency, the cancer cases attributed by epidemiologists to the diet. What are the missing carcinogens?

Discussion

It is interesting to note that the top-ranking carcinogen ethanol is of very low potency but is ingested in gram amounts. This could lead to the idea that those substances which are taken up in gram amounts should be more thoroughly investigated. This situation is met with the macronutrients (carbohydrate, fat, protein), and the following discussion is a speculative approach to assigning a carcinogenic potency to regular food in excess.

"Carcinogenic potency" of overnutrition. It has been known for more than 50 years that dietary restriction in mice dramatically reduces spontaneous and chemically induced tumour formation (Tannenbaum & Silverstone, 1953). Recently, a study with 1,200 rats has been completed (BIOSURE study). Again, it was clearly shown that the age-standardized risk of spontaneous malignant tumour formation was significantly correlated with the amount of food consumed (Roe, 1991).

We have analyzed the data in an unconventional manner. The low cancer incidence in the restricted animals was taken as a control rate and the high cancer incidence of the group fed *ad libitum* was considered to be the result of the additional food consumed. In the BIOSURE study, for instance, male rats restricted to 80% food showed a 13% tumour incidence within 30 months. The *ad libitum* group, which consumed an additional 3.2 g food per day, showed a 36% tumour incidence. On the basis of an average body weight of 541 g, a TD_{50} value of 11 g/kg/d can be calculated for standard rat maintenance diet in excess (3.2:0.541:(36-13)x(100-13):2=11.2; no correction to standard lifespan). A similar analysis with the female rats resulted in a TD_{50} of 20 g/kg/d.

Mechanism of carcinogenic action of overnutrition. Caloric restriction has been shown to be more protective in the promotion phase than in the initiation phase. It therefore appears to reduce clonal expansion of initiated cells, perhaps by reducing the rate of cell division to a minimum necessary. Cell division is a risk factor in carcinogenesis because it accelerates both the fixation of primary DNA lesions as mutations and the loss of heterozygosity for tumour suppressor genes by mitotic recombination.

Overnutrition in Switzerland and cancer risk. Caloric intake in Switzerland in the years 1985-87 was 2,315 kcal/person/d (Staehelin et al.,1991). With an estimated average minimum caloric requirement of 1963 kcal/person/d, overnutrition of 5.5 kcal/kg/d can be calculated. On the basis of the caloric content of the rat maintenance diet, this level of caloric overnutrition is equivalent to an excess of 1.9 g feed/kg/d. Using a carcinogenic potency TD_{50} of 16 g/kg/d for excess feed (average for male and female rats), 60,000 cancer cases per 10^6 lives could be explained. This is provocatively close to the 80,000 cancer cases attributed by epidemiologists to dietary factors.

We are fully aware of the speculative nature of our approach. A number of points will have to be investigated to test this working hypothesis, (i), the relative importance of the various types of macronutrients, (ii), differences between rodents and humans for the biological effects of various levels of overnutrition, (iii), mechanistic investigations, such as on the formation of oxygen radical formation (indirect genotoxicity) or on the stimulation of cell division (as a tumour-promoting factor).

In conclusion, the known carcinogens in the diet (other than alcohol) can only explain about one percent of the cancer cases attributed by epidemiologists to dietary factors. On the other hand, overnutrition alone could almost fully explain the situation. Dietary recommendations for cancer prevention should give this aspect high priority.

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