POLICY FORUM: PUBLIC HEALTH

Reducing Liver Cancer—Global Control of Aflatoxin

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Liver cancer is an important public health problem, ranking fifth in frequency of cancers worldwide with 427,000 deaths in 1990 (*1*). Incidence rates in developing countries are estimated to be approximately 2 to 10 times those in developed countries; 76% of cases are found in Asia (Fig. 1) (*2*). There are many risk factors for liver cancer, including exposure to hepatitis B or C (HBV or HCV) and to aflatoxins (*1, 3–6*). Recently, a United Nations organization, the Codex Alimentarius, requested a quantitative risk assessment to evaluate the health risk posed by aflatoxin-contaminated foods moving in world trade (*4*). This represented the first time such an approach was used at an international level. This assessment also addressed how different worldwide population incidences of hepatitis B affect these risks and the international regulatory and public health implications of the assessment. Analysis of the conclusions of the report and its impact on policies affecting world trade indicate the challenges of using science to implement public policy.

The Codex Alimentarius was formed after World War II to facilitate world trade and to protect international public health. Codex is funded by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations, and includes up to 165 member nations. Codex sets standards for food additives, residues of veterinary drugs and pesticides, naturally occurring toxicants, and human-derived contaminants. Codex has designated as one of its advisory groups the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

Until 1996, Codex had recommended that aflatoxins in foods be kept to an "irreducible level" on the basis of a qualitative concern for risk. However, with increasing sensitivity of analytical methods, this approach was creating a nontariff barrier to trade, as well as wasting valuable food sources. A further complication has been the wide variation in national aflatoxin standards. For example, Canada and the United States have set aflatoxin standards of 15 to 20 parts per billion (ppb) in finished food products; France and the Netherlands have standards of 4 ppb, and India has set 30 ppb (*7*). Exposure varies greatly; for example, an average individual consuming a typical "European" diet could consume 19 ng per day, whereas an individual consuming a typical "Far Eastern" diet, could consume 103 ng per day (*4*). At the same time, this approach has not provided insights into public health benefits achieved, particularly from a risk-reduction perspective.

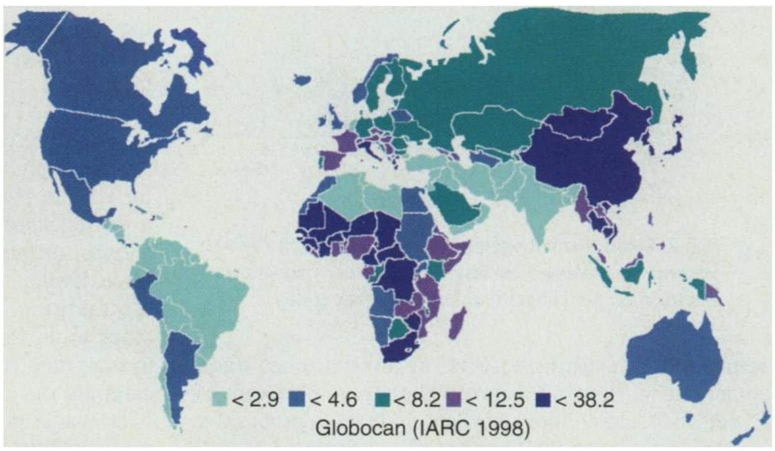

Fig. 1. International prevalence of liver cancer in males. [From (*2*) with permission]

Why Aflatoxin?

Aflatoxins, which are metabolites of some *Aspergillus* species, are among the most potent hepatocarcinogens known, as well as being mutagenic and hepatotoxic. The most toxic aflatoxin has since been designated aflatoxin B1 (AFB1); aflatoxin M1 (AFM1), the hydroxylated metabolite of AFB1, may be found in milk or milk products obtained from livestock consuming contaminated feed. Species sensitivity varies widely (*8*). Aflatoxins exert adverse effects on immunocompetence, growth, and disease resistance in livestock and laboratory animals. Unfortunately, research on effects of long-term exposure to low concentrations of AFB1, as would be encountered in environmental situations, and the effects of exposure to mixed mycotoxins has been neglected (*9*).

Aflatoxins are found as contaminants in human and animal food as a result of fungal contamination during growth and after harvest. Drought, insect damage, and suboptimal storage conditions affect aflatoxin occurrence. Aflatoxins are most commonly associated with peanuts, corn, rice, cottonseed, dried fruit, tree nuts, spices, figs, crude vegetable oils, cocoa beans, and copra, as well as milk and milk products if dairy cattle have consumed contaminated feed (*10*). Crop losses due to aflatoxin contamination can be considerable; in 1998, growers in Texas, Louisiana, and Mississippi sustained losses estimated at $85 to $100 million from corn that could not be utilized because of high aflatoxin concentrations (*11*).

In parts of Africa, China, and Southeast Asia, food-borne aflatoxin exposure is common. Several ecological studies have shown a correlation between liver cancer incidence and aflatoxin consumption at the population level, but findings are not entirely consistent, as quantification of lifetime individual exposure to aflatoxin is difficult. Case-control studies with dietary questionnaires or biomarkers of recent exposure to aflatoxin have also provided inconsistent results (*1, 5, 6*).

Public Health Risks of Aflatoxin

To make a risk-based recommendation to Codex, JECFA attempted to separate the risk of liver cancer attributable to aflatoxin and that from other factors. Adequate epidemiological data on the relative roles of HCV and aflatoxin were not available. Earlier epidemiology studies may have underestimated the prevalence of HBV because of different detection methods.

Dose-response curves as modeled from animal and human epidemiological studies showed a dramatic distribution of carcinogenic potencies for aflatoxin in animals and humans (Fig. 2). The risk of liver cancer from aflatoxin consumption was approximately 30 times as high in individuals who had been exposed to hepatitis B ($HBsAg^+$) as in $HBsAg^-$ persons (*4*).

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The JECFA then considered two hypothetical scenarios to estimate the effect of lowering current aflatoxin contamination; the first pertained to areas in which the amount of aflatoxin in food is low (average consumption <19 ng per day) and the proportion of $HBsAg^+$ persons in the population is about 1%. Reducing the regulatory standard for aflatoxin from 20 to 10 μg/kg [10 μg/kg is equivalent to 10 parts per billion (ppb)] would yield a reduction in the estimated population risk of approximately two liver cancers per year per billion persons—a concentration undetectable by epidemiological methods. The second example pertained to areas with higher concentrations of aflatoxin contamination (125 ng per person per day) and 25% of the population $HBsAg^+$. Here, reducing the hypothetical regulatory standard from 20 to 10 μg/kg, yields an estimated reduction in liver cancer cases of 300 cases per year per billion persons (*4*).

Populations such as those in Western Europe and the United States with a low prevalence of $HBsAg^+$ individuals (or populations with a low mean intake of aflatoxin) are unlikely to achieve a decrease in liver cancer cases from more stringent aflatoxin standards. Populations with a high prevalence of $HBsAg^+$ persons and a high intake of aflatoxins may benefit from reductions of aflatoxin intake, assuming (i) that such a reduction could be accomplished without loss of valuable food sources and risk of malnutrition or starvation and (ii) that such a reduction could be measured by epidemiological methods.

As was stated in the report of the Third Joint FAO/WHO/UNEP International Conference on Mycotoxins (*12*) "Especially in the developing countries, where food supplies are already limited, drastic legal measures may lead to lack of food and to excessive prices. It must be remembered that people living in these countries cannot exercise the option of starving to death today in order to live a better life tomorrow." Although some reduction in aflatoxin exposure could be accomplished by improving farming methods and storage practices, adopting modern agricultural practices, including uses of pesticides, would be prohibitively expensive in many developing countries.

Unduly strict regulative standards will lead countries to ban or limit the import of commodities, such as certain food grains and animal feedstuffs, which can cause difficulties for exporters in finding markets for their products (*12*). This market distortion may mean that the least contaminated foods and feeds are exported. This leaves the more highly contaminated products at home for consumption by populations who have the greatest risk from aflatoxin exposure, because they also have the highest rates of HBV infection in addition to marginal nutritional status and possibly other diseases.

As a result of the JECFA report, Codex has adopted the 15 ppb limit for aflatoxin B1 in raw peanuts; the regulation went into effect in the European Union on 1 January 1999. This is a higher value than previously accepted in many Western European countries; data are not yet available on the resulting effects on international trade. However, concern about possible exposure of children to aflatoxin led to a proposal to lower the limit for AFM1 from 0.5 to 0.05 ppb in milk and milk products (*13*). This was despite the fact that the JECFA risk assessment for aflatoxin stated that AFM1 is about one-tenth as toxic as AFB1 and further suggested that no measurable reduction in liver cancer risk will result from lowering the standard in milk. In addition, a critically important food product will be wasted as contaminated milk cannot be reconditioned. This issue will be revisited in the Spring of 2000.

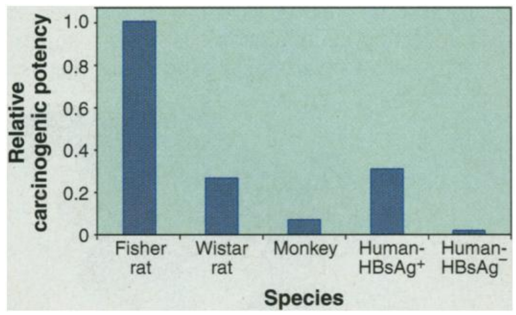

Fig. 2. Relative carcinogenic potency in different species. Potency is expressed as cases per year per nanogram of aflatoxin B1 per kilogram of body weight per day.

A Better Approach to Reducing Liver Cancer?

Given a limited public health budget, the JECFA report concluded that a more substantial reduction in liver cancer would be obtained by vaccination against HBV and reduction of prevalence of carriers than by drastically lowering aflatoxin standards (*4*). In two countries with high risks for liver cancer and relatively high concentrations of aflatoxin contamination, the efficacy of universal HBV vaccination programs has already been demonstrated. A significant decline in the incidence of liver cancer has been shown among cohorts of vaccinated newborns and children in Taiwan and in vaccinated adults in Korea without a concurrent reduction in aflatoxin standards (*14, 15*). Although the United States and most Western European countries have national HBV vaccination programs, many high-risk areas, such as most African countries, do not. An effective vaccine has been available since 1980, and the WHO recommends universal vaccination; yet political and economic factors have prevented the implementation of vaccination programs in many countries where the need is greatest (*1*). At present there is no vaccine against HCV; screening blood products and educating potentially high-risk populations should be emphasized.

In conclusion, international food standards can be developed to ensure consumer health protection and to facilitate fair trade. Given the existing state of scientific knowledge about aflatoxins in a world of competing health risks and scarce public health resources, especially in the developing countries, it is a sensible use of scientific knowledge, as well as an ethical approach (i) to use scarce resources where they will do the most good; in other words, give vaccination for HBV a higher priority than lower aflatoxin regulatory standards; (ii) to enact no national or international measures that will force developing countries to keep at home the marginally aflatoxin-contaminated crops in the absence of anticipated benefit to importing countries; and (iii) to examine carefully the estimated reduction in risk of liver cancer potentially achieved by lowering aflatoxin standards in the context of other public health interventions.

References and Notes

1. X. Bosch, J. Ribes, J. Borras, *Semin. Liver Dis.* **19**(3), 271 (1999).
2. J. Ferlay, D. M. Parkin, P. Pisani, Globocan 1: Cancer Incidence and Mortality Worldwide (CD-ROM, International Agency for Research on Cancer, Lyon, France, 1998).
3. C. Brechot *et al.*, *J. Hepatol.* **29**, 173 (1998).
4. S. Henry *et al.*, in *Safety Evaluation of Certain Food Additives and Contaminants* (WHO Food Additives Ser. 40, Geneva, Switzerland, 1998), pp. 359–468.
5. D. Eaton and J. Groopman, Eds., *The Toxicology of Aflatoxins: Human Health, Veterinary, and Agricultural Significance* (Academic Press, San Diego, 1994).
6. A. J. Hall and C. P. Wild, in (*5*).
7. *Worldwide Regulations for Mycotoxins: A Compendium* (FAO Food and Nutrition Paper no. 64, FAO, Rome, Italy, 1995), ISBN 92-5-103960-7.
8. J. M. Cullen and P. M. Newberne, in (*5*), pp. 3–21.; B. D. Roebuck and Y. Y. Maxuitenko, in (*5*), pp. 27–41; M. McLean and M. F. Dutton, *Pharmacol. Ther.* **65**, 163 (1995); N. J. Gorelick, *Risk Anal.* **10**, 539 (1990); F. P. Guengerich, *et al.*, *Environ. Health Perspect.* **104**, 557 (1996); T. E. Massey, R. K. Stewart, J. M. Daniels, L. Liu, *Proc. Soc. Exp. Biol. Med.* **208**, 213 (1995).
9. D. M. Miller and D. M. Wilson, in (*5*), pp. 347–367.
10. D. M. Wilson, G. A. Payne, J. Groopman, in (*5*), pp. 309–322 (1994).
11. Anonymous, *Agric. Res.* **47**(6), (1999).
12. H. P. Van Egmond, Third Joint FAO/WHO/UNEP (U.N. Environment Program) International Conference on Mycotoxins, Tunis, Tunisia, March 1999.
13. Codex Alimentarius Commission, 23rd session, June 1999.
14. M. H. Chang *et al.*, *N. Engl. J. Med.* **336**, 1855 (1997).
15. M. S. Lee *et al.*, *Intl. J. Epidemiol.* **27**, 316 (1998).

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