Fd Cosmet. Toxicol. Vol. 9, pp. 65–80. Pergamon Press 1971. Printed in Great Britain

Review Section

Trace Chemical Contaminants in Food: Potential for Harm*†

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(*Received 20 August 1970*)

Introduction

The organizers of this Symposium are to be congratulated on its timeliness. No one can deny that we are going through a stressful period in the history of food safety evaluation. During three decades of steady progress, immense benefits were conferred on the public through advances in agriculture and food technology, developments that had involved the introduction into food of a variety of chemical additives and contaminants. Considering the state of knowledge at the time when decisions were made on the acceptability of these materials, the record of safety of these chemicals is truly remarkable and stands as a tribute to those on whom the burden fell to make the critical judgements. Despite the fact that some of these men are now being vilified, we honour them and recognize, as History will, the magnitude of their achievements.

The reaction we are witnessing is a well-known social phenomenon, in which established standards in general are in process of demolition. Not only is there a movement in many countries to ban food additives as unnecessary and dangerous, but the harmlessness of trace contaminants is particularly called in question. It is appropriate that we undertake a critical reappraisal. My task, as I see it, is to explore the wider implications of food contaminants in order to assess, in practical terms, the problems and degrees of hazard associated with some of the major categories of these chemical agents.

Scope of the issues considered

When the Food Protection Committee (1959) defined safety as "practical certainty that injury will not result from use of a substance in a proposed quantity or manner" they had in mind a degree of certainty which, while not the theoretically desirable state of perfect assurance, is yet an attainable measure in practice. In the present climate of opinion, questions are raised: Is practical certainty acceptable when the potential hazard, however remote, is one that may be shared unwittingly by vast numbers of people of various ages and in various states of health? Not only is this degree of safety deemed insufficient, but

*Research reported here was supported by Research Grant P-01-ES-276-02 from the National Institute of Environmental Health Sciences, NIH, USPHS, by the National Institutes of Health Training Grant 5T01-ES 000103-03, and by the P.M.A. Foundation.

†Presented at a Symposium on "Chemical Contaminants in Food—Hazard or Not?", sponsored by the Food and Drug Directorate, Department of National Health and Welfare, Ottawa, Ontario, and held in Ottawa on 18–19 June 1970.

equally inadequate is much of the traditional supporting evidence of safety—as, for instance, a long history of safe use of a chemical agent that contributes a trace residue to food.

Bolstering the insistence on 'absolute' safety is the introduction of what one might call 'tenets of uncertainty', many of which would not have been regarded as insurmountable in the recent past. As a reflection of this uncertainty, much of my presentation will be concerned with categories of potential hazard regarding which, in the opinion of some authorities and many would-be experts, no generally-acceptable assessment can be made to-day. The process began with the concept of 'zero tolerance' for chemical carcinogens, and the Delaney Amendment has enshrined this dogma beyond the reach of scientific criticism or the exercise of informed judgement. The underlying reasoning has been set out by Weisburger & Weisburger (1968) and in the Report of the Secretary's Commission on Pesticides and Their Relationship to Environmental Health, the so-called Mrak Report (Commission on Pesticides, 1969, p. 492).

Almost imperceptibly, the same reasoning has been extended to teratogenic effects of food contaminants: even though, in my view, the scientific basis of zero tolerance for carcinogens is inapplicable to teratogens. The strong emotional reaction stirred up by fears of genetic hazard to future generations has sufficed to stretch the zero tolerance concept yet further, to the area of mutagenic effects. To my knowledge, not a single case exists in which a food contaminant of any sort, even a mycotoxin, is known to have produced mutagenic effects in man. As the crowning pediment of the entire structure of largely hypothetical hazards, we have the thesis that the phenomena of mutagenesis, carcinogenesis and teratogenesis are so closely linked that a positive result in any one of these areas automatically renders the compound suspect on all three counts. On the other hand, should it happen that a chemical agent turns out negative in all the tests applied, it remains under suspicion until such time as someone can discover an organism, devise a route of administration or achieve a sufficiently heroic dose to produce some positive biological result, however bizarre. Thus there is an obvious premium on ingenuity and persistence!

Carried to their logical conclusion, these considerations of carcinogenesis, teratogenesis and mutagenesis strike at the very roots of technological advance in food production, processing and distribution. Hence the practical reality of the potential hazards in these categories merits special discussion in the context of food contaminants.

Carcinogenesis

Numerous factors are known to influence an animal's response to a dietary carcinogen, so that any extrapolation to man of a no-effect level in animals is fraught with great uncertainty. The statisticians have embellished this plain biological fact with mathematical adornments (Commission on Pesticides, 1969, p. 493), but what they have failed to stress are the uncertainties attending the demonstration of weak carcinogenic activity. Even with a compound as extensively studied as DDT, the conclusions based on the Bionetics study (Innes, Ulland, Valerio, Petrucelli, Fishbein, Hart, Pallotta, Bates, Falk, Gart, Klein, Mitchell & Peters, 1969) are subject to dispute both on statistical grounds (Weil, 1969, 1970) and on such questions as the interpretation of liver nodules without antecedent study of their pathogenesis, without looking for possible regression on discontinuing administration of the test compound, without adequate attempts to transplant the hepatic nodules without trying to grow the cells making up the nodules in tissue culture (Slifkin, Merkow, Pardo, Epstein, Leighton & Farber, 1970) and without detailed attention to pulmonary metastases, both in controls and test animals.

The insistence on administration of a 'maximum tolerated dose' may also be misleading if this is the only dose tested, as in the Bionetics study (Innes *et al.* 1969). No justification is forthcoming for abrogating the need to establish a dose-response relationship, which is fundamental to all toxicological endeavour. Furthermore, the route of administration is all-important in tests for carcinogenesis or teratogenesis. We are told that "parenteral administration is an appropriate test route for pesticides to which humans are exposed by inhalation, or for pesticides which are systemically absorbed, following ingestion" (Commission on Pesticides, 1969, p. 660). Alas, the lessons of yesteryear are so readily forgotten! The production of subcutaneous malignant tumours by water, salt, glucose and a host of other common nutrients (Grasso & Golberg, 1966a) seems not to act as a deterrent to undiscriminating experimentation by this route, despite the demonstration that physical properties of a compound, such as the surface activity, lipid solubility, amphipathic character or hyperosmolarity of the solution injected determine the neoplastic outcome in many instances (Grasso & Golberg, 1966b; Giangolli, Grasso & Golberg, 1967). It is safe to predict that, by appropriate choice of dose, concentration of solution and frequency of administration by the subcutaneous route, any chemical agent can be shown to be a carcinogen in the rat and probably also in other species of laboratory rodent.

Teratogenesis

In checking on the potential teratogenicity of trace chemical contaminants in food, the height of absurdity is achieved by the combination of a maximum tolerated dose, a parenteral route of administration and the application of zero tolerance on the basis of the results. In this area we know full well that any one of a host of adverse influences on the mother is reflected in foetal deaths, resorptions and/or abnormalities. Teratogenic effects are elicited by: transport of mice by air on days 12 and 13 of pregnancy (Brown, Johnston & Niswander, 1970); fasting for 24 hr or less at a critical stage of gestation (Kalter & Warkany, 1959), a situation which may be brought about inadvertently or unsuspectingly by inducing somnolence, lethargy, muscle weakness or ataxia; a diet of raisins for 1 day (Peters & Strassburg, 1969); severe limitation of movement or avoidance behaviour (Rosenzweig & Blaustein, 1970); and many other non-specific factors probably acting through a stress mechanism, as well as hyper- or hypothermia and endocrine influences (Kalter & Warkany, 1959). Even subcutaneous sodium chloride is teratogenic in mice (Nishimuta & Miyamoto, 1969).

Here above all is a situation that demands the utmost care in selecting doses that do not render the mother sufficiently ill to produce even transient inappetance. The use of a maximum tolerated dose overlooks the possibility of non-specific toxic stress. Apart from artefacts that arise by this means, attention should be directed to the mechanism by which particular teratogenic effects are elicited. The production of even transient deficiency of one of many vitamins or minerals suffices to induce reproductive failure or malformations. An example is the case of EDTA, which is teratogenic in mice (Tuchmann-Duplessis & Mercier-Parot, 1956). The production of congenital malformations by an excess of vitamin A is well known. A tenfold excess of nicotinamide is embryotoxic in the pantothenate-deficient rat (Lefebvres-Boisselot, 1951). Maximum tolerated doses of other B vitamins or of most amino acids have not been studied. A single injection of 2 mg leucine elicited abnormalities in 41% of chick embryos in an experiment in which 4 mg thalidomide brought about abnormalities in 22%, against an incidence of 2% in the control group (Bergström, Lilja & Pirskanen, 1967).

These considerations are provided as a background to recent developments that led to the withdrawal of a petition to establish negligible residue tolerances for 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). The petition would have set tolerances of 0·2 ppm for 2,4,5-T from the application of the acid form or certain salts or esters in or on a variety of foodstuffs. Subsequently it was announced that the use of 2,4,5-T on food crops would be *cancelled*.

This interesting case study began with the observation that 2,4,5-T was teratogenic and foetocidal in two strains of mice when administered either subcutaneously or orally and in one strain of rats when administered orally (Courtney, Gaylor, Hogan, Falk, Bates & Mitchell, 1970). Analyses of the specimen of 2,4,5-T that had been tested revealed the presence of approximately 30 ppm 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (referred to henceforth as dioxin). Subsequent study of standard 2,4,5-T containing less than 1 ppm dioxin, given to rats by gavage in doses up to 24 mg/kg daily, failed to reveal evidence of teratogenic or embryotoxic effects (Emerson, Thompson, Gerbig & Robinson, 1970). Under similar conditions, the dioxin produced no discernible effect at a dose of 0·03 μg/kg/daily, while doses of 0·125 μg/kg/day or greater manifested toxicity to the foetus and, at 8·0 μg/kg/day, to the mother also (Sparschu, Dunn & Rowe, 1970).

Finally in evidence presented before Senator Hart's subcommittee, samples of 2,4,5-T containing less than 1 ppm dioxin were reported to have been tested by the oral route in rats at levels up to 150 mg/kg, with negative results. In three strains of mice, levels of 100–150 mg/kg/day, given subcutaneously in dimethyl sulphoxide, proved teratogenic; so did the dioxin in both species tested (*Food Chemical News*, 1970).

Even assuming that doses of 100 mg/kg daily did not serve to introduce sufficient dioxin to account for the observed effects, it should be realized that such quantities of 2,4,5-T are ill-tolerated by mice. They lie within the range of doses studied by Sos & Kertai (1958) and, later, by Florsheim & Veleoff (1962) and Florsheim, Veleoff & Williams (1963) in the case of 2,4-dichlorophenoxyacetic acid (2,4-D). In experiments on rats, 2,4-D was shown to produce a striking reduction in the serum level of protein-bound iodine, as a consequence of the displacement of thyroxine from serum proteins into the liver and to a lesser extent into the kidney. In this way a characteristic 'hyperthyroid' state is created in these organs. Ethyl chlorophenoxyisobutyrate acts in a manner similar to 2,4-D, though some differences in detail may be observed (Ruegamer, Ryan, Richert & Westerfeld, 1969).

The profound effect exercised by 2,4-D, and presumably also by 2,4,5-T, may not be related in any way to the observed teratogenic action of 2,4,5-T in mice. Nevertheless the metabolic and other actions exercised by massive doses on the mother, the foetus, or both, should be taken into consideration in extrapolating from 100 mg/kg/day in mice to residue levels below 0·2 ppm associated with a limited number of foods in the human diet—a ratio possibly exceeding 5000. The possibility of introducing dioxins into the environment has been put forward as a further reason for taking action against 2,4,5-T. This aspect of polychlorinated compounds is dealt with below.

Quite apart from concern with mechanisms of action, or the avoidance of artefacts due to non-specific stress, the metabolism of a test compound is a highly relevant consideration in teratogenesis brought about by drugs or food contaminants. If the metabolic pathway in the test animal differs radically from that in man, the results are unlikely to be useful for the assessment of hazard arising from trace contaminants. The finding of embryotoxicity only has meaning in an appropriate animal model.

There is a further aspect that has been insufficiently stressed in the past: the fact that the

use of a maximum tolerated dose involves risks of artefacts, among them those arising from abnormal metabolism—either qualitatively or quantitatively, or both. There is no metabolic pathway that cannot be overloaded, with consequent diversion into other metabolic routes and/or abnormally prolonged retention or excretion of the unchanged compound. Such situations may be totally unrepresentative of the body's handling of the test compound at levels of exposure approaching more realistically the practical conditions of intended use. While the object of the toxicologist is to seek out target-organ effects elicited by high doses, his purpose in doing so is to provide guidance to informed searching for effects at lower doses. Grossly aberrant pathways and rates of metabolism that may exist at exaggerated doses make it imperative not to assume that effects observed at these doses are necessarily characteristic of the changes occurring at lower levels of exposure.

Mutagenesis

The risk of mutagenic effects to future generations of mankind is now thought to be so great and imminent that no chemical agent may be regarded as acceptable for use in the diet without being subjected to a battery of tests for mutagenicity. We are assured that these tests are "entirely practical and feasible . . . precise, efficient and relatively inexpensive . . . practical, sensitive and relevant" (Commission on Pesticides, 1969, p. 572). Why then the reluctance to apply tests of this sort to all food contaminants? Presumably any positive result in any one test at any dose makes it necessary to consider the compound as dangerous until proved safe—though how such proof of safety can ever be achieved in these circumstances is not clear. On this basis, for example, it becomes necessary to dispose of chelating agents, since all those tested so far are mutagenic (Kihlman, 1966). The problem is that chelators are plentifully present in food and throughout the body. Adenine, a common constituent of food, breaks chromosomes; that is it acts as a 'clastogen' (Shaw, 1970) by chelating certain bivalent metal ions.

It is not my intention to convey the impression that as a toxicologist I am less concerned than the geneticists over the possibility of mutagenic effects of food contaminants. Where we differ is on priorities for testing and possibly on the degree of satisfaction with the tests available at present. The range of compounds tested so far for mutagenic and clastogenic potential is so limited (Table 1) that in effect we know virtually nothing about the response of the test systems to the multitude of common chemicals found in 'natural' food or in the body. I fail to see how, lacking such background experience, we can assess the potential for harm of trace contaminants in food by equating them with carcinogens and with powerful alkylating agents used in cancer chemotherapy.

In the months that have elapsed since the publication of the Mrak Report (Commission on Pesticides, 1969) the view has gained wider acceptance that non-mammalian systems are too far removed from the areas of concern to be adequate test systems for assessing potential mutagenic hazard to man. Unfortunately, for the detection of point mutations, the host-mediated assay still employs micro-organisms; but this situation will no doubt be remedied through the use of mammalian cells maintained in tissue culture and implanted into the host animal treated with the test compound. A variety of interesting approaches are under development, based on *in vivo* cytogenetics, the dominant lethal test and *in vitro* cell-culture systems. All these tests call for careful evaluation and the acquisition of substantial experience and perspective before being applied indiscriminately for predictive purposes to new compounds.

Table 1. *Food clastogens (chromosome-breaking agents; C) and mutagens (M)*

I. C or M in non-mammalian organisms				
Acetate	Cyanide	K^+ (excess)	Ethylene bromohydrin	DDT
Amyl alcohol	Ethanol	Captan	Ethylene chlorohydrin	Nitrite
Acetophenone	Formate	Ethylene oxide	Ethylene dibromide	Pyrophosphates
II. C in mammalian organisms				
Hexamethylenetetramine				
III. C in human cells *in vitro* or *in vivo*				
Adenine	Bisulphite	Cyclohexylamine	Theobromine	
Aflatoxin	Caffeine	Lead (excess)	Theophylline	
Arsenates	Cyclamate	Methylmercury		
IV. Suspected of being M or C				
Acetone	Ethyl acetate	Methyl acetate	Monosodium glutamate	
Benzo[*a*]pyrene	Methanol	Propanol	Toluene	

Mainly from Shaw (1970).

Pollutants derived from environmental sources

Many and varied are the possibilities for the entry into food of chance contaminants whose existence in the environment was unrecognized or whose harmful potential was not fully realized. In recent years contamination of food with persistent chlorine-containing pesticides, principally DDT, aldrin and dieldrin, has commanded increasing attention. The environmental and other problems presented by these compounds have been discussed in numerous publications and reviewed most comprehensively in the report of the Commission on Pesticides (1969). On the basis of this report, action has been taken to eliminate the use of DDT and DDD and, progressively, the uses of aldrin, dieldrin and other compounds that "cause or can cause contamination of the environment and damage to various life forms within it". A price of unknown magnitude, possibly involving serious future repercussions, has thus been paid for the protection of wildlife and the environment. As far as trace contamination of human food is concerned, the report states clearly that no evidence has ever been produced of harm to man stemming from this source. The sole known consequence of human exposure to traces of DDT in food is the acquisition of measurable levels of DDT and DDE in blood, body fat and other tissues. No harmful effect has been found to follow such storage (Hayes, 1967). Essentially similar conclusions were reached in a British report on persistent organochlorine pesticides (Advisory Committee on Pesticides and Other Toxic Chemicals, 1969), and again the recommendations have been followed by restriction of the use of these materials.

By a remarkable coincidence the present age of ferment has witnessed the discovery of the presence of polychlorinated biphenyls in a wide range of organisms (Risebrough, Rieche, Peakall, Herman & Kirven, 1968) as well as further recognition of the evil potentialities of chlorinated naphthalenes and dioxins (Friedman & Shibko, 1969; Bauer, Schulz & Spiegelberg, 1961; Jones & Krizek, 1962; Higginbotham, Huang, Firestone, Verrett, Ress & Campbell, 1968). To eliminate such materials from the food supply or from the environment is a more complex undertaking than might appear at first glance. 2,4-Dichlorophenol, a potential precursor of chlorinated dioxins, is synthesized by a strain of Penicillium from soil (Ando, Kato & Suzuki, 1970). A diligent search will probably reveal a variety of

chlorinated compounds of this sort synthesized in Nature (Hylin, Spenger & Gunther, 1969). 2,4,5-Trichlorophenol, formed as a metabolite of the organophosphate pesticide Ronnel, is stored in body fat and other animal tissues (Menzie, 1969).

The distinction between polychlorinated biphenyls and polychlorinated dioxins is more apparent than real. Thus Vos, Koeman, van der Maas, ten Noever de Brauw & de Vos (1970) have demonstrated that the striking toxicity of commercial polychlorinated biphenyls is associated with the presence of tetrachloro- and pentachlorodibenzofurans. These furans closely mimic the toxic properties of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin but at tenfold dosage. Attention should also be directed to the question of photo-oxidation products, several of which, in the case of pentachlorophenol, are potentially capable of undergoing further cyclization to tricyclic and pentacyclic polychlorinated dioxin derivatives (Munakata & Kuwahara, 1969).

In an era of increasing concern about lead as an atmospheric pollutant as well as a food pollutant, there comes, as a final blow, the recognition that hazards of mercury contamination are not confined to fish from remote Swedish lakes, but, as forecast so accurately by Berglund (1969), are here on the American continent. Each of these problems has its own individual characteristics, yet there is a common thread running through them all: the fact that past ignorance or disregard of ecological implications is only now being overcome as present-day methods of analysis, in all their tremendous sensitivity, specificity and accuracy, are brought to bear on the complex questions at issue.

The mercury problem is typical in this respect. An excellent account of its various facets has been presented by several authors in a volume edited by Miller & Berg (1969). An already difficult environmental situation, stemming from treatment of seed grain with organic mercury compounds, has been confounded by the discovery that inorganic mercury can be methylated by anaerobic micro-organisms (Jensen & Jernelöv, 1969), specifically by methanogenic bacteria (Wood, Scott, Kennedy & Rosen, 1968). The existence of mechanisms by which methylcobalamin can readily transfer its methyl group to mercuric ion introduces a new dimension into the problem, since we are now concerned exclusively, or almost exclusively, with methylmercury residues far more than with inorganic mercury in fish and other foods. Such a transfer of interest has far-reaching implications, in view of allegations of subliminal neuronal damage, potential for teratogenesis and observed mutagenic effects in lower organisms.

Emphasis on the accumulation of methylmercury in the central nervous system, with preferential injury to certain groups of neurones, such as the cerebellar granule cells (Kurland, Faro & Siedler, 1960; Miyakawa & Deshimaru, 1969), has been extended to the peripheral nerves, where the initial impact of methylmercury was found to elicit specific selective damage to sensory fibres (Miyakawa, Deshimaru, Sumiyoshi, Teraoka, Udo, Hattori & Tatetsu, 1970). Accounts of human poisoning with methylmercury also refer to initial peripheral sensory disturbances, ataxia and polyneuritis (Kurland *et al.* 1960; Miyakawa & Deshimaru, 1969; Tsubaki, 1968). The suggestion that accumulated methylmercury has the capacity to "pick off" individual neurones raises three questions that are the core of the issue concerning methylmercury:

> 1. Is the nature of local binding sites for methylmercury in certain individual neurones such that selective accumulation occurs within these cells, more or less independently of the rate of intake of methylmercury, the resulting total body burden and the nature and extent of redistribution of the methylmercury that occurs

within the body with the passage of time, and, finally, irrespective of the rate of excretion of the methylmercury and the resulting decrease in total body burden?
2. Does localized selective damage to individual neurones or groups of neurones represent a permanent and irreplaceable loss which may not necessarily become apparent, at least initially, as a functional deficit?
3. If such loss does indeed occur, what is the extent of the damage that must be sustained before clinical signs and symptoms are manifest? In other words, how useful is clinical evidence as a means of establishing a threshold or 'no ill-effect' dose for methylmercury in food?

Consideration of the accumulation of methylmercury must also take into account excretion from the brain and from the body (Berglund & Berlin, 1969). The body burden, expressed as the concentration of methylmercury per gram of brain, does bear a direct relationship to intake and to the appearance of neurological signs. The brain content of methylmercury, however, may not reflect adequately the extent of irreversible damage to susceptible neurones or other structures. Despite the elegant studies of distribution of organic mercury in mice (Ostlund, 1969) and men (Aberg, Ekman, Falk, Greitz, Persson & Snihs (1969), we have as yet no means of knowing the amount of methylmercury needed to cause a critical degree of long-term irreversible damage to the foetal nervous system, which is said to be more susceptible than that of an adult (Berglund & Berlin, 1969). Equally, possibilities of effects on germ cells cannot as yet be gauged by measuring body burdens.

The generally-accepted value for the biological half-life of methylmercury is about 70 days. According to Aberg *et al.* (1969), a weekly intake of unit amount of methylmercuric nitrate will result in a total body burden of 15·2 units of mercury at infinite time. The long-term consequences of such storage remain to be determined, particularly in man. The opportunity for epidemiological study of exposed populations must not be missed.

Preoccupation with those problems that are currently the most pressing must not cause us to lose sight of traditional, yet increasingly serious contaminants like lead, or environmental contaminant hazards of uncertain magnitude like cadmium or asbestos. The dimensions of the lead problem in food and drink are still not accurately comprehended. A recent series of analyses of basic foodstuffs in Germany (Lehnert, Stadelmann, Schaller & Szadkowski, 1969) revealed an average intake of lead through food of 0·518 mg/day, with green vegetables contributing a major proportion. Undoubtedly some of this lead originates as an air pollutant (Everett, Day & Reynolds, 1967; Danielson, 1970). Also, unsuspected lead hazards abound, particularly for children, as exemplified by the consequences of intrauterine and neonatal exposure of the offspring of mothers consuming untaxed whiskey in the southeastern United States (Palmisano, Sneed & Cassady, 1969).

The complexities of biological interrelationships of trace minerals, both commonplace and rare, in food and water are attracting increasing attention on the part of those interested in hypertension and cardiovascular disease (Masironi, 1969), cancer (Rose, 1968; Kanisawa & Schroeder, 1969) and dental caries (Losee & Adkins, 1968; Jenkins, 1969). With each passing day it becomes more difficult to disentangle potentially-harmful from potentially-beneficial effects of many trace metal contaminants of food.

Interactions between contaminants

Concern has often been expressed that, among the thousands of chemical contaminants present in food, some subtle forms of interaction with one another or with food components

will be manifested as unexpected toxic effects. Instances of this sort that have arisen in the past (Golberg, 1967; Friedman & Shibko, 1969) indicate that there is no room for complacency. On the other hand, one must be rational in assessing the extent of real hazard that exists in practice.

Thus, in the case of pesticides, a masterly analysis of possible interactions and their significance has been presented in the Mrak report (Commission on Pesticides, 1969). Among many topics covered, this account places in proper perspective the rather minuscule dangers, under current conditions of use, that are presented by interactions between pesticides on the one hand and methylenedioxyphenyl synergists and methylenedioxyphenyl food components on the other. Several attempts to unearth other forms of hazard arising from mixtures of pesticide residues have yielded so little evidence of biological interaction as to discourage further exploration of such possibilities. Suggestive indications of cocarcinogenicity with aflatoxin can be obtained when cyclopropenoid fatty acids are tested (Sinnhuber, Wales & Lee, 1966). The results, however, probably have little relevance to the conditions that obtain in human or animal diets.

Radioisotopes

The issue of "Fallout, Food and Man" was thoroughly aired in a Symposium held in 1963 (Menzel, 1963; Comar, 1963; Eisenbud, 1963). Among more recent developments, the strenuous efforts that have been made to achieve acceptability of irradiated foods will be discussed later in this Symposium in connexion with contaminants arising from food processing. A new controversy has recently arisen over the suggestion put forward by Sternglass (1969a) who states in effect that nuclear fission products and other forms of radiation in food, particularly ^{90}Sr in milk, are the primary cause for the interruption in the decline of foetal and infant mortality at the present time. The possibility exists that gonad-dose calculations made in the past and based largely on ^{137}Cs were grossly in error, by not taking into account ^{90}Sr and its yttrium daughter product as well as radioisotopes such as ^{14}C and ^{3}H that "seek out specific critical sites in the mammalian cell" (Sternglass, 1969b, c). Attempts to refute the allegations concerning foetal and infant mortality (Tamplin, 1969; Sagan, 1969; Lindop & Rotblat, 1969) have only partially succeeded in restoring confidence that both the total level of radioactivity in food, as well as that portion of it that most directly affects the gonads, are well within acceptable limits.

An attack from a different quarter has been launched by Gofman & Tamplin (1969) on the question of tritium levels in water issuing from nuclear-fuelled power stations (Weaver, Harward & Peterson, 1969). Here the substance of the charge is that the existing allowable dose of whole-body ionizing radiation laid down by the Federal Radiation Council (0·17 rads/year), is too high by a factor of 10. The practical implications, in terms of public health and of the design of power stations to conform with these higher safety standards, are of such magnitude as to demand critical consideration of the Gofman & Tamplin proposals (Holcomb, 1970).

Fundamentally the problems that arise over the assessment of hazard from prolonged exposure to low levels of radioactivity in food and water are exactly analogous to those that confront us in the case of carcinogens. They involve extrapolation from known effects at high levels of exposure to presumed potential effects at very low levels, levels that are often below the natural background of radiation or of carcinogens from other sources. The effects on the body are in both instances regarded as strictly additive, despite evidence that natural food stock ration contains one or more factors that protect against X-irradiation

carcinogenesis in mice (Ershoff, Bajwa, Field & Bavetta, 1969) and that anticarcinogenic factors and mechanisms abound (Shamberger, 1970).

Among the few voices to dispute the rigid orthodoxy of the majority, Budinger (1970) has pointed to dose rate, rather than total dose, as the determining factor which, at low values, may permit recovery and repair mechanisms to operate with exquisite sensitivity. From all we know of the systems involved, the likelihood that effective thresholds do exist at low dose rates seems greater than the prophets of doom will admit. This statement applies to cancer, genetic effects and chromosomal aberrations induced by exposure to radiation.

Residues of drugs and feed additives

Trace contaminants present as residues in foods of animal origin constitute another critical area. In an era of increasingly intensive production of animal foods, the use of chemical agents as feed additives serves to improve efficiency of feed utilization directly, or indirectly by preventing disease. Residues derived from these additives are augmented by trace contaminants resulting from the use of chemotherapeutic agents and pesticides applied directly to the animal, as well as the pesticide residues forthcoming indirectly from consumption of feed of plant origin.

Detailed consideration of the implications of the use of drugs in animal feeds has been presented in a Symposium (National Academy of Sciences, 1969). Munro & Morrison (1970) have also dealt with this topic. The most crucial issue at present is that of antibiotic residues, a subject dealt with at length in the report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine (1969). This UK committee (the 'Swann Committee') has arrived at far-reaching conclusions. Despite the fact that present antibiotic residues in food were not considered by the Committee to constitute a toxic or allergic hazard to the consumer, evidence of potential risks resulting from administration of antibiotics to farm livestock was deemed sufficiently great to justify prompt legislative action. This evidence related to a marked increase in the number of strains of enteric bacteria of animal origin that showed resistance to one or more antibiotics and were able to transmit this resistance to other bacteria; to the observation of human infection with enteric bacteria derived from animals as a result of consumption of foods of animal origin; and to the possibility that antibiotic resistance could thereby be introduced into organisms that are highly pathogenic to man.

The sweeping recommendations of the Committee, and the resulting legislative measures applied in the UK have given authorities in other countries much food for thought. Without entering here into the detailed data supporting these actions, one can decide that there are grounds for reasonable suspicion of hazard but as yet little conclusive epidemiological information. In this situation, as in so many others involving food contaminants, one is left with the alternatives of drastic action on a slender basis of fact or the introduction of limited precautions during the period of grace needed to try to establish the reality or otherwise of the presumed hazards. The crucial issue seems to be our increasing doubts as to the usefulness, if any, of antibiotic growth supplements in well-conducted animal husbandry. This, more than any other factor, militates against continued acceptance of the hazards of what has been termed a "potentially explosive situation".

Migrants from food-contact materials

Here we have a vast heterogeneous group of some 5000 chemical agents which for the most part are present in food in small numbers and in minute amounts at any one time.

Determination of the precise nature and quantities of compounds migrating into various foods from any single packaging material often presents formidable obstacles. Nevertheless, such information is necessary if the components of the package extractable into food are regarded in essence as food additives (McCollister, 1964).

Faced with these difficulties, the extent of migration has been assessed by means of food-simulating solvents and various schemes have been devised for broad flexible approval (British Plastics Federation; Golberg, 1963), recipe-type approval (West German Federal Health Office) or approval by end use (US Food and Drug Administration.) A recent report by the UK Food Additives and Contaminants Committee (1970) recommends that a total migration limit should be laid down, based on the use of specified food-simulating solvents. Statutory control would be exercised by drawing up permitted lists of ingredients, presumably similar to the German lists.

In an effort to rationalize various approaches on the basis of likely hazard to the consumer, Frawley (1967) elaborated a general plan, based on experience of no-effect levels of chemicals (other than pesticides and heavy metals) deduced from lifespan studies in animals. The basic conclusion drawn from this experience was that any material suitable for use as a functional component in food packaging at a level of 0·2% or less could not attain an unsafe level in food contained in such packaging material.

A further step in the process of bringing common sense to bear on these problems was taken by the National Academy of Sciences- National Research Council's Food Protection Committee (1969) in a report entitled *Guidelines for Estimating Toxicologically Insignificant Levels of Chemicals in Food.* There was every reason to believe that some logical implementation of these approaches by the US Food and Drug Administration would at long last culminate in a rational method of regulating food-contact materials (Oser, 1969).

At this point, unfortunately, progress has been halted and in the prevailing climate of doubt it is hard to foresee whether any fresh solution will emerge. The need for action is greater than ever, for the development of entirely new forms of food packaging needs to be encouraged if mankind is to solve its problems of waste disposal.

In the meantime, we have to recognize frankly some of the difficulties inherent in this area of food contaminants. Considering the five major classes of food-packaging materials, namely glass, coated metal, paper, regenerated cellulose and plastics, one has to take account of the amounts of the same compound contributed to the diet from several of these sources (Ingle, 1968), or the addition to food-grade oils of what is, in effect, a food additive (BHT, 4,4'-thiobis-6-*tert*-butyl *m*-cresol or other antioxidant) derived from low-pressure or, more particularly, high-pressure polyethylene (Woggon, Uhde & Zydek, 1968).

Another problem often arises: how to dispel notions of hazard based upon the results of administering huge doses to animals, when the amounts migrating from food packaging are minute. Probably nothing can better exemplify this absurdity than the case of ethylene glycol (EG) which, if permitted for use in food packaging at extremely low levels, would serve several important technical purposes. EG suffers from two stigmata. In man, rats and other species given large doses it produces renal calculi, calcification and tubular damage (Rowe, 1963). Diethylene glycol, which is probably metabolized along lines similar to EG, gives rise to bladder stones and bladder tumours. The attendant controversy over this form of 'carcinogenesis' has been resolved by evidence that implantation even of glass beads into the rat bladder produces bladder tumours (Weil, Carpenter & Smyth, 1965). In the monkey, Blood, Elliott & Wright (1962) showed that dietary levels of 0·2 and 0·5% EG could be tolerated for up to 3 years without apparent effect. Recently we have demonstrated the

capacity of rats and monkeys to excrete and metabolize small amounts of EG with great dispatch (McChesney, Golberg, Parekh, Russell & Min, 1971). This facility is shared by man (F. Coulston, J. H. Wills, L. Golberg & J. C. Russell, in preparation, 1970). Finally, it now transpires that the normal mammalian organism has EG among the 'diol lipid' components of its tissues (for references see Bachmann & Golberg, 1971).

The consumer's organoleptic threshold for taint acts as a limiting factor to volatiles transferred from plastics and other packaging to food. With increasing complexity of packaging materials, for instance polyvinylidene chloride-cellophane-polypropylene laminates, traces of residual solvents may be transferred to food. Toluene, a typical example, is probably innocuous at levels well above those that cause rejection of the food because of taint (Wilks & Gilbert, 1969). Similarly, in the case of polyvinyl chloride, the extent of migration of monomers and oligomers is so small as not to influence consumer acceptability. Nevertheless, now that vinyl chloride has been reported to be "highly cancerogenic"—admittedly by inhalation—in rats (Viola, 1970), other considerations enter into the picture. It will be interesting to see how 'zero tolerance' is applied in this instance.

In an age when problems of waste disposal loom large, the toxicity of pyrolysis products of materials like vinyl plastics assumes importance. Studies of polyvinyl chloride homopolymer and vinyl chloride–vinyl acetate copolymer have established the presence of HCl, CO, methyl and ethyl chlorides, benzene, toluene and a variety of short-chain alkanes among the products formed (Le Moan & Chaigneau, 1969; Cornish & Abar, 1969).

A rapidly-increasing and advantageous use of plastics is in the transport of potable water. The five major types of thermoplastics in water pipes all contribute minute amounts of contaminants. In some countries the use of stabilizers containing lead or cadmium is accepted practice; it is doubtful whether the amounts of these elements entering the water supply from this source appreciably increase the total intake into the body from the environment as a whole (Lefaux, 1968).

Conclusion

I could cite many more groups of food contaminants that furnish examples of uncertainty as to what constitutes a safe level in food. Sufficient has been said, however, to establish that the potential for harm is not confined to any one class of compounds or to any one source of contaminants. In the presence of this multitude of trace chemicals entering into our food, what should the regulatory approach be? Should we strive to return food to its 'natural' pristine state? Chemically-uncontaminated food has never existed. In fact, if one includes all forms of contamination, our present diet is the least contaminated in human history.

There are, as I have indicated, many disturbing features in the present situation. The accumulation of complex issues and scientific imponderables makes it necessary to grapple with urgent practical necessities by adopting more limited objectives than the establishment of levels or other conditions of use that ensure practical certainty of freedom from hazard. In many instances the most we can hope to do is to try to define as clearly as possible the likely hazard associated with particular conditions of exposure; in other words the price, in terms of potential harm, that the consumer may be expected to incur for a certain increment of contaminant level in his diet. We should cease trying to assure the public that all food is safe and nutritious when we recognize that, in clinical terms, the capacity for harm of 'natural' food is virtually unknown. All that the toxicologist can claim to accomplish, or hope to do at present, is to assess the degree to which particular levels of food

contaminants, in designated foods consumed in defined amounts at defined intervals, add to the pre-existing potential for various sorts of harm that the diet already possesses.

Given an indication that the increment in potential harm attributable to the presence of a food contaminant is unacceptably great, how much information is needed before preventive measures are taken? Here we are on a delicate tightrope, balanced between rushing in with *ill-considered action before results have been adequately established and, on the contrary,* awaiting detailed confirmation of every aspect of an experimental or epidemiological finding, in spite of mounting evidence that calls urgently for decisive intervention. Too many facile solutions to this problem have been proposed. Least heed of all should be given to the demand that every straw in the scientific wind should prompt immediate withdrawal of the product thus impugned—with the rather naïve idea *that the material can readily* be restored on the market once its safety has been successfully re-established.

We have had ample experience recently of the chaos, public alarm and confusion, waste of food and economic loss that can result when precipitate restrictions are introduced too late and without adequate warning, in place of measured and timely precautions instituted as the data develop. Neither neglect nor panic is the answer. Somewhere between these two extremes lies the course of reasonable action appropriate to each chemical-contaminant contingency. Given good science, good judgement and, above all, freedom from extraneous pressures, the right course can be found.

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