COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

Preface

The COT has again discussed a wide range of toxicological problems over the past year. Many of these have related to chemicals that may be present in food, including additives (intense sweeteners), processing aids (enzymes), supplements (French Maritime Pine Bark Extracts), food contact materials (terephthalic and isophthalic acids), natural constituents (fluorine, bromine and iodine) and contaminants (dioxins and dioxin-like polychlorinated biphenyls). Dioxins and dioxin-like polychlorinated biphenyls have formed three separate discussion items, with consideration of results of general dietary exposure, of a specific survey of free-range eggs as an indicator of environmental exposure, and the start of a major review of the tolerable daily intake of these contaminants.

The COT has also been asked to advise on the safety of breast implants, on an environmental pollutant, on aspects of research commissioned by the Food Standards Agency and the Department of Health and on papers dealing with the workings of scientific advisory committees. We are pleased to note that the Committee already follows most of the procedures considered to constitute best practice for advisory committees.

2000 was also a busy year for COT Working Groups. An open meeting was held in February to consult on the draft report of the Working Group on Food Intolerance. The final report from this Working Group was published in July 2000, under the title “Adverse Reactions to Food and Food Ingredients”. Two new Working Groups commenced work during the year, on Phytoestrogens in April, and on Risk Assessment for Mixtures of Pesticides/Veterinary Medicines in December, and expect to report in 2001 and 2002, respectively.

The predominance of food-related issues in the COT agendas led to the decision that the lead responsibility for the Secretariat should be moved to the Food Standards Agency, on its formation in April 2000.

As in previous years, we have been well served by the Secretariat who have continued to ensure the smooth-running of the Committee proceedings and have provided working documents of the highest quality.

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Adverse Reactions to Food and Food Ingredients

1.1 The COT Working Group on Food Intolerance completed its review of adverse reactions to food. A draft report was the subject of consultation at an open meeting of the COT in February 2000 and the final report was published in July 2000. The report, entitled "Adverse Reactions to Food and Food Ingredients" may be obtained from the COT secretariat at: The Food Standards Agency, Room 511C, Aviation House, Kingsway, London WC2B 6NH or by contacting Food Standards Agency Publications, PO Box 369, Hayes, Middlesex UB3 1UT (tel: 0845 606 0667; fax: 020 8867 3225).

Alitame

1.2 Alitame is an intense sweetener that was initially considered by the COT in 1989. Additional data were submitted during the period 1990-1994 and in 1998, both in response to requests made by the COT and as a result of requests made to the company by other regulatory bodies.

1.3 In 1998, the COT established an Acceptable Daily Intake of 0.3 mg/kg bw per day. This was subsequently confirmed in 1999, following submission of additional information by the company. The basis for determining the Acceptable Daily Intake was a significant elevation in liver weight in dogs treated with alitame for 18 months. There was a significant increase in liver weight at 500 mg/kg bw per day and a non-significant increase in male dogs receiving the next lowest dose (100 mg/kg bw per day). The COT considered that this finding was unusual and that it would be prudent to regard the dose of 100 mg/kg bw per day as a LOAEL. Consequently, the NOAEL derived for alitame was 30 mg/kg bw per day, the lowest dose tested. Uncertainty factors of 10 for inter-species and 10 for intra-individual variability were then applied, resulting in the Acceptable Daily Intake of 0.3 mg/kg bw per day.

1.4 The COT had also previously noted other observations of potential concern. Enzyme induction was reported in the dog study, with a NOAEL of 100 mg/kg bw per day. A study in diabetics given alitame at 10 mg/kg bw for 90 days, had reported a number of cardiovascular complications in some patients of both the alitame and placebo groups during the follow-up period.

1.5 In 2000, the company submitted the results of a new, more comprehensive study in which diabetics were administered alitame at 10 mg/kg bw per day. Particular emphasis was given to cardiovascular effects, the results indicating that alitame was well-tolerated and therefore the company asked for the Acceptable Daily Intake to be increased.

1.6 The COT noted that the diabetic studies had not included an assessment of enzyme induction, and the results of statistical analysis of the new study were questioned. The COT agreed that the new data were not adequate to justify decreasing the uncertainty factor and therefore did not warrant review of the Acceptable Daily Intake for alitame.

Breast implants

1.7 In 1999 the COT provided an emergency consideration for the Department of Health and the Medical Devices Agency (MDA) on the safety of breast implants containing soya bean oil. This contributed to the voluntary withdrawal of the Trilucent‘ breast implant due to a lack of adequate safety data. The MDA subsequently initiated a review on the safety and performance of all recently introduced breast implant fillers.

1.8 MDA reviewed the technical information provided by one manufacturer, Poly Implant Prosthesis, on their hydroxylpropyl cellulose hydrogel pre-filled breast implant. MDA asked the COT to consider the report of a study in which rats received subcutaneous injections of the filler material and were then observed for periods of up to 12 weeks.

1.9 The COT considered the rat study to be very limited in nature. There were serious deficiencies in the design, performance and reporting of the study. COT concluded that the findings of the rat study could not be discounted and suggested that a study employing a considerably longer period of observation should be conducted on the filler material. A statement outlining the conclusions reached by the COT is included at the end of this report.

1.10 On receipt of these conclusions MDA initiated regulatory activity which led to the voluntary withdrawal of these implants by the manufacturer. This was a precautionary measure until sufficient information to address MDA’s concerns over the manufacturer’s biological safety assessment of the device is available. The withdrawal was made public by an MDA Device Alert (MDA DA2000(07)) on 11 December 2000.

1.11 On 5 December MDA requested an emergency consideration of data on a second hydrogel filling material used in NovaGold‘ breast implants. This filling material was a polyvinylpyrrolidone and guar gum gel. As described in the 1999 Annual Report, emergency consideration can be undertaken with the agreement of the COT Chairman and provides the collated opinions of a limited number of individual members with particularly relevant expertise. The information was circulated to a number of members on 5 December. Their opinions were received by 8 December and were passed to MDA. MDA released an MDA Device Alert (MDA DA2000(08)) on 11 December,

which identified inadequacies in the manufacturer's biological safety assessment and concluded that as a precautionary measure these implants should not be implanted until the concerns have been addressed.

Code of Practice for Scientific Advisory Committees

1.12 In July 2000, the Office of Science and Technology published a consultation paper, inviting comments on a proposed code of practice for Scientific Advisory Committees. The paper outlined proposed guidelines for Scientific Advisory Committees and complemented a second document on "Review Of Risk Procedures Used By The Government's Advisory Committees Dealing With Food Safety", which was published in September 2000 and also discussed by the COT (see paragraphs 1.72 – 1.78). The consultation paper described the duties, rights and responsibilities of committee members and their independence from the committee's secretariat, stressing the need for inclusivity, transparency and proportionality and raising the issue of the manner in which confidential information is handled. It stressed the need for clear explanation of levels and types of uncertainty, and how this information is incorporated into advice, and called for training of committee members in communication skills.

1.13 The Secretariat noted that producing a set of uniform guidelines would enable interested parties, the public and the media to judge and comment on the standards required of such committees.

1.14 Members agreed that the COT already follows the procedures defined as far as is practicable. COT noted that considerable steps have been made to increase transparency. However there was concern that publication of some material or attribution of comments made during a meeting could compromise personal security.

1.15 Members also discussed the issue of confidential papers and noted that steps have been taken to reduce or eliminate use of material classified as confidential. Where commercial confidentiality precluded full publication, it was suggested that at least part of the paper and the Committee's deliberations should be published. The Secretariat informed Members that where material was "commercial in confidence", it is normal procedure to approach companies to determine whether they would be willing for part, if not all, of the papers concerning their product to be made publicly available. (Procedures for openness are outlined in Annex 3).

1.16 Members noted the suggestion that Chairs and Secretariats should review board members interests, taking into account: ”the proportion of the total equity value which is held” (where share holdings are under consideration). It was stressed that it is well-established COT procedure to tabulate Members’ interests in the annual report, but that it would be difficult to quantify interests.

1.17 With regard to Secretariat duties, Members noted that the COT would continue to encourage submission of Secretariat reviews to journals for publication in peer-reviewed journals.

Dioxins and dioxin-like PCBs - Dietary exposure

1.18 COT was asked to consider estimates of dietary exposure to dioxins and dioxin-like PCBs derived from the 1997 Total Diet Study. Dietary exposures to dioxins and dioxin-like PCBs had previously been estimated from the 1982 and 1992 Total Diet Studies. Since these earlier data were published, the WHO had recommended /revised Toxic Equivalency Factors (TEFs) for dioxins and dioxin-like PCBs, which were endorsed by the COT in 1998. Therefore, the 1982 and 1992 exposure estimates had been recalculated using these latest WHO-TEFs in order to be directly comparable with the new data.

1.19 In comparison with earlier similar surveys, dietary exposures to dioxin-like compounds, on a total toxic equivalent (TEQ) basis, for all three age groups, showed a continuing downward trend.

1.20 COT agreed the data indicated that changes in analytical sensitivity, or in the number of food groups analysed, had not contributed significantly to the decline in exposure. COT therefore agreed it should be stressed that the decline in exposure to these compounds was real and not an experimental artefact.

1.21 The COT agreed a statement (included at the end of this report) on dietary exposure to dioxins and dioxin-like PCBs, concluding that the current concentrations of dioxins and dioxin-like PCBs in food are unlikely to pose a risk to health.

Dioxins and dioxin-like PCBs in free range eggs

1.22 COT was informed of a Food Standards Agency survey of dioxins and dioxin-like PCBs in free-range hen and duck eggs. The aim of the survey was to examine the use of eggs as indicators of environmental contamination and the results were not considered as being representative of free-range eggs on sale throughout the UK.

1.23 Dietary exposure had been estimated using the concentrations of these compounds in free-range eggs together with age-specific food consumption data, and used different scenarios based upon average or maximum concentrations in the eggs.

1.24 Advice was sought from the COT on the public health significance of the estimated dietary exposures to dioxins and dioxin-like PCBs based on data from this survey of free-range eggs. Members were also asked to consider whether the survey was sufficiently robust to draw conclusions applicable to consumers of free-range eggs and whether the different exposure scenarios were realistic with respect to anticipated consumption patterns of free-range eggs.

1.25 COT agreed that the survey should be considered as a hypothesis generating study, indicating that analysis of free-range eggs is a potentially useful technique for investigating environmental contamination. However, because of the sampling methodology and the limited number of samples taken, the data from this survey should not be used to estimate dietary exposures to these compounds for consumers of free-range eggs. There was also a paucity of data on concentrations of these compounds in other types of eggs, such as battery hen eggs, against which meaningful comparisons could be made.

1.26 The COT statement on the survey is included at the end of this report.

Di-isopropylnaphthalenes

1.27 Di-isopropylnaphthalenes (DIPN) are used as solvents for the colour former in carbonless copy-paper, which may be included in recycled paper used in making board for food-packaging. Treatment of the recycled fibres may fail to remove all of the DIPN and thus some may be present in the finished board and could migrate into food. The Committee gave consideration to a survey on DIPN during 1998, and agreed that the toxicological information was inadequate and that additional studies should be submitted within 3 years. (See paragraphs 1.5 – 1.6 of 1998 Annual Report).

1.28 COM reviewed new mutagenicity data on DIPN in February 2000. It concluded that DIPN could be regarded as non-mutagenic and that no further mutagenicity testing was required (see paragraphs 2.11 - 2.12 of this report). COT was asked whether, in light of the new mutagenicity data and the advice from the COM, it wished to revise its previous position on DIPN and its earlier requirement for a long-term study.

1.29 The COT considered that, even though DIPN could be regarded as non-mutagenic, there was still a need for further safety studies. In view of the fact that there were no longer concerns that DIPN may be a genotoxic carcinogen, and that intakes of DIPN were low, a carcinogenicity study was no longer required. Instead the COT agreed that a 28-day sighting study for dose selection, followed by a 90-day study would be acceptable. Because the data on human exposure levels are limited, the Committee stressed the importance of ensuring that appropriate dose levels were used in the proposed studies, achieving some toxicity at the highest dose.

1.30 COT re-iterated its previous advice that it would be prudent to ensure that the levels of DIPN in food packaging made from recycled paper and board should be kept as low as reasonably practicable.

Enzyme submission - Amano 90

1.31 COT considered the Amano 90 submission by postal consultation in 1999. At that time COT required further evidence to support the company's claim that no residual enzyme activity would be expected in bread after baking, further validation of the enzyme assays and an increase in the frequency of testing for mycotoxins and antibacterial activity. COT agreed to recommend a twelve month temporary clearance of Amano 90 for use in bread making, while awaiting the additional data from the company.

1.32 In response the company had submitted the results of a study aiming to demonstrate that Amano 90 is inactivated during the baking process, together with data on the repeatability of the assay used to determine enzyme activity. The company also provided written assurance that one in every four batches of Amano 90 would be tested for mycotoxins and antibacterial activity.

1.33 In the study submitted, Amano 90 was added to flour, at the recommended concentration and also at a 40-fold higher concentration, either prior to or subsequent to baking. Enzyme activity was only detected in the bread sample in which the higher concentration of Amano 90 was added after baking, being below the limit of detection in all the other samples. However, COT considered that the method routinely used to assay enzyme activity in production batches of Amano 90 was not sufficiently sensitive to demonstrate

enzyme inactivation during baking of bread containing the recommended concentration of enzyme. COT recommended that a more sensitive method should be developed, and a limit of detection in bread defined. The improved assay should then be used in a repeat study, with duplicate analyses.

1.34 COT considered that the data submitted were not adequate to demonstrate the validity of the enzyme assay. COT agreed that a better description of the data would be helpful and this should include data on the linearity of the enzyme assay.

1.35 COT welcomed the statement of intent to increase routine testing of mycotoxins and antibacterial activity in at least one in four batches but was unable to recommend full clearance of the enzyme preparation, Amano 90.

Enzyme submission - Chymosin

1.36 Chymosin had previously been evaluated by COT and had been granted clearance. The manufacturer had now developed a modified recovery and purification procedure for this enzyme preparation.

1.37 COT considered that additional information was required to confirm the similarity between the product of the modified purification process and the original product. In addition several technical issues relating to the modified process required further clarification, as did the current specification for the enzyme preparation. The Committee agreed to one year's temporary clearance whilst this further information was provided.

Enzyme submission - Lipase D

1.38 COT conducted a postal consultation of a submission seeking approval of an immobilised enzyme preparation, Lipase D, to be used in manufacture of yellow fat spreads. The responses were discussed and agreed by the full Committee. COT agreed that the level of detail submitted on the manufacturing processes was appropriate and recommended that:

- the production strain of *Rhizopus oryzae* should be deposited with a recognised culture collection;
- the specification for the immobilised enzyme should include limits for heavy metals;

- testing for moulds and yeasts should be conducted on every batch and mycotoxins and antibacterial activity should be analysed in at least one in four batches;

- in the absence of toxicological data on a polymer used in the process, evidence that this polymer is not found in the final inter-esterified product or products should be provided.

1.39 COT agreed to recommend a two-year temporary clearance for the use of immobilised Lipase D in production of yellow fat spreads, pending submission of the requested analytical data.

Enzyme submission - Newlase

1.40 Newlase was granted temporary clearance pending the submission of further data in 1994. Additional data were submitted in 1998 and COT recommended further temporary clearance, pending the submission of a satisfactory method for the detection of the mycotoxin rhizoxin. Data on the detection of rhizoxin, submitted to the COT in 1999, were considered inadequate. The company subsequently submitted a revised methodology.

1.41 COT considered the new methodology would be sufficiently robust to demonstrate the absence of rhizoxin, subject to some additional requirements. These modifications involved the analysis of an appropriate Newlase sample spiked with rhizoxin with each batch and specification of the percentage recoveries of spiked samples compared to the equivalent concentration analysed by direct injection as part of the same analytical run.

1.42 COT agreed to extend the temporary clearance for an additional two years, provided that the recommended amendments to the protocol were adhered to and that batches of Newlase in which rhizoxin was detected should not be marketed. COT requested that during this period, the company collate analytical data on routine rhizoxin analyses of at least one in every four Newlase batches. These data should be submitted so that the COT could be assured that the methodology was adequate for routine assay of production batches of Newlase.

Fluorine, bromine and iodine

1.43 COT was informed of the results of analyses of fluorine, bromine, and iodine on samples collected for the 1997 Total Diet Study. COT was also provided with estimates of mean population, and mean and high-level adult consumer dietary intakes of fluorine, bromine, and iodine. Dietary intakes for age groups other than adults had not been estimated.

1.44 It was noted that there are no guidelines for fluorine against which to assess estimated dietary intakes. COT will await the findings of a review of fluorine by the Expert Group on Vitamins and Minerals (EVM) before considering any potential effects associated with intake of this element.

1.45 COT noted that since the essentiality of bromide is unclear, the FAO/WHO ADI of 0-1 mg bromide/kg body weight should be considered as a Tolerable Daily Intake (TDI) of 1mg bromide/kg body weight. It was agreed that the estimated intakes of bromide were not a cause for concern.

1.46 With regards to dietary intakes of iodine, COT confirmed that its 1999 advice (See paragraph 1.17 of 1999 Annual Report) still applied ie these intakes of iodine are unlikely to pose a risk to health. However, it reiterated its previous recommendation on the need for investigation of the bioavailability of iodine in milk and indicated that it may wish to reconsider its advice in light of the forthcoming findings of the EVM review of iodine. A statement on this study is included at the end of this report.

Food Standards Agency funded research and surveys

1.47 COT was informed that most of the current research portfolio within the Food Standard Agency (FSA) is based on research programmes inherited from MAFF. At the request of the FSA Board, a Research Review Group had been established to review research within the FSA and ensure that the overall research strategy and priorities reflect the FSA future requirements. The Group is expected to hold three meetings and is due to report in the spring of 2001.

1.48 The Review Group had set up a Working Party, comprising senior Agency officials and outside independent experts including academics, other research funders, consumer groups and industry, to be responsible for the detailed review. COT was informed that the Working Party is conducting a consultation exercise and was invited to contribute. COT requested and received clarification relating to:

- funds for research on risk management/risk communication;
- funds for research on animal feedstuffs;
- the basis for collaboration with MAFF and DH.
- openness and responsiveness to researchers with suggestions for new areas to be included on research agendas

1.49 COT was not in favour of making long term commitments to specific "centres of excellence", which could deter other potential applicants and inhibit development of new areas of research. However, it was agreed that longer term funding is needed to attract and retain good research staff. The Committee were informed that most research contracts cover a three-year period.

1.50 The issue of quality assurance for research was raised: COT was informed that there is a need to develop quality assurance criteria for aspects such as ensuring management protocols within laboratories and independent appraisal of the quality of the work.

1.51 COT agreed that the design of surveys should take into account the need to interpret human health implications of the data.

French Maritime Pine Bark Extracts

1.52 COT had reviewed French Maritime Pine Bark Extract on previous occasions (see paragraph 1.7 of 1998 and paragraph 1.11 of 1999 Annual Reports) and noted the possibility that the product might contain allergenic proteins. The manufacturers had submitted new information addressing this issue.

1.53 COT considered that elemental analysis for nitrogen was not sufficiently sensitive and could not be used to exclude the possibility that the extract contained allergenic proteins. The SDS-PAGE analysis was considered to be more reliable but more information on the method used was needed, particularly in view of the fact that pine bark extract was a complex material. In addition, each analysis should include a concurrent control.

Health effects in populations living close to landfill sites

1.54 In 1998, COT commented on a SAHSU (Small Area Health Statistics Unit) proposal for a study on health effects in populations living close to landfill sites (see paragraphs 1.9 - 1.15 of 1998 Annual Report). The protocol had been revised following identification of all relevant sites, and the Committee was asked to consider the amended protocol and comment on whether it was appropriate to proceed with the study.

1.55 The Committee noted that the primary objective of the study was to test the hypothesis that living near a landfill site is associated with an excess risk of giving birth to a child with a congenital anomaly or of low birth weight, or with an excess risk of stillbirth. The secondary objective was to test the

hypothesis that living near a landfill site is associated with an excess risk of certain cancers.

1.56 After discussion of aspects of the study design and possible confounding factors, the Committee considered that it was appropriate to proceed with the study but urged caution in interpretation of the results.

Hexachlorobutadiene

1.57 Hexachlorobutadiene (HCBD) is formed as a by-product during the manufacture of chlorinated solvents. COT was informed of public health concerns related to possible prolonged exposure to HCBD in the vicinity of a disused waste dump in a quarry in Cheshire, and was asked to provide advice on the toxicity of HCDB.

1.58 COT noted that advice had been sought from some members of the COM, who had reviewed the mutagenicity data on HCBD. They had advised that it was prudent to assume that HCBD is an *in vivo* somatic cell mutagen. COT therefore agreed that it was not possible to establish a safe level in relation to cancer or to identify a TDI. Thus, it would be more appropriate to determine margins of exposure, by comparing the measured air levels with the doses producing effects in the toxicology studies.

1.59 On the basis of some conservative approximations, the NOAEL for non-cancer effects of 0.2mg/kg bw/day in animal studies was estimated to be equivalent to continuous inhalation of an air level of 60ppb HCBD. The effect level for non-cancer effects of 2mg/kg bw/day was estimated to be equivalent to 600ppb HCBD in air and the effect level for tumours of 20mg/kg bw/day was equivalent to 6,000ppb HCBD in air.

1.60 COT noted that there are qualitative similarities between humans and animals in the way that HCBD is distributed and metabolised in the body, and therefore continuous exposure to a concentration of less than 0.6 ppb HCBD in air (which allows for a 100-fold Margin of Exposure compared to the NOAEL equivalent of 60ppb) could be regarded as being without appreciable adverse health effects in respect of non-carcinogenic and reproductive effects.

1.61 This level was approximately 10,000 times lower than the dose that caused cancer in animals following lifetime dietary exposure and therefore COT considered that the carcinogenic risk at these low exposure levels was minimal and was not of appreciable health concern. However, given the uncertainties in the data, the Committee considered that exposure should be reduced to as low a level as reasonably practicable.

1.62 The Committee was informed that health studies are being undertaken of exposed individuals. There is also a proposal to develop a physiologically-based pharmacokinetic model for HCBD exposure. In addition, the Committee was informed that a technique is being developed to allow analysis for HCBD at parts per trillion concentrations in air. The Committee welcomed this information and considered that the results of these studies should inform a further review by the Committee, in due course, of its conclusions on the health significance of low-level exposures to HCBD.

1.63 The COT statement is included at the end of this report.

Multiple Chemical Sensitivity

1.64 COT last considered this item in 1999 when it agreed that there was a need to continue monitoring developments in the field so that the issues could be reconsidered when more information became available (see paragraphs 1.25 – 1.27, 1999 Annual Report). However, it noted that there were no consistent patterns of symptoms or exposure data to define the condition, and concluded that on the basis of knowledge current at the time, there was insufficient evidence to make comments on potential mechanisms or to recommend further research in this area.

1.65 COT was asked to consider a recent report published by the British Society for Allergy, Environmental and Nutritional Medicine (BSAENM) (Eaton *et al., J. Nutr. Environ. Med.* **10**, 39-84, 2000). This reviewed prevalence, possible mechanisms, clinical signs, diagnosis and patient management of Multiple Chemical Sensitivity (MCS). The review had generated considerable public interest and referred to links between MCS and allergy (including food allergy). However it contained little peer-reviewed data. One new paper (Kreutzer *et al*., *Am. J. Epidemiology* **150**, 1-12, 1999) which had not previously been considered by the COT, claimed a high prevalence (6%) of MCS, based on a telephone interview. COT was asked whether the BSAENM report warranted any change in its 1999 view.

1.66 COT remarked on the limited number of peer reviewed studies cited in the BSAENM report. There was discussion in the report of the need for tests to be developed to aid diagnosis but there was a major problem regarding the absence of any clear definition of MCS which was a condition based on patient-defined criteria with no consistent pattern of symptoms. The term is associated with a wide range of chemicals and symptoms so diverse that it is not possible to define mechanisms or formulate studies to consider possible mechanisms.

1.67 COT questioned the discussion in the BSAENM report of high dose effects of chemicals, such as depletion of nutrients, in considering low dose effects. The report also referred to TILT (Toxicant Induced Loss of Tolerance), and type B allergy, with reference to a collection of unexplained symptoms. COT noted that there is no scientific basis for these concepts, and that they are not accepted by the immunology community.

1.68 The new study of Kreutzer *et al* (1999) was based on telephone interviews with physician-assisted diagnoses. There was an indication that the participants may have been asked leading questions and the approach was considered to lack objectivity and accuracy. Another limitation was an almost complete lack of exposure data.

1.69 COT considered the case-files in the BSAENM paper. It was pointed out that when individual cases of MCS are investigated they often led to diagnosis of chemical allergy to a single specific chemical agent. People with allergy to one chemical may be more sensitive to effects of other chemicals. COT therefore agreed that problems with sensitivity to chemicals can occur but that these are not necessarily Multiple Chemical Sensitivity. The term "multiple" may be applied simply because a specific causal agent has not been identified.

1.70 COT also considered the suggestion that funds should be allocated on a ring-fenced basis for research on MCS. However, it considered that the lack of evidence for any mechanism of action prevented formulation of a sound research programme.

1.71 After careful consideration of the BSAEMN report COT concluded that there was no basis for modifying the view expressed in 1999.

Risk procedures used by the Government's Advisory Committees dealing with food safety

1.72 COT was informed that, at the Prime Minister's request, Sir Robert May (then Chief Scientific Advisor to the Government) together with the Chief Medical Officer, Professor Liam Donaldson, and the Chairman of the Food Standards Agency, Sir John Krebs, had carried out a review of risk procedures in scientific committees that deal with food safety. The review group also included representatives of the devolved administrations and Dr Jim McQuaid, former Health and Safety Executive (HSE) Chief Scientist and Chairman of the Interdepartmental Liaison Group on Risk Assessment (ILGRA). The completed review outlined how the committees approached risk analysis and provided recommendations for best practice.

1.73 Chairmen of the relevant committees (including the COT) were interviewed and asked to provide information on the committee approaches to risk assessment, information about risk communication, and its role in risk management.

1.74 COT considered that it is rigorous in its risk assessment and that the actual approach taken needs to be determined by the specific situation and not dictated by a formal systematic structure. However, a more structured framework for information gathering (for instance, details of literature searches) might help to increase transparency and confidence in the database.

1.75 There was considerable discussion over the issue of providing advice on risk management. It was agreed that, although the COT's primary aim is to provide advice on risk assessment, occasions can arise when it is necessary to review the toxicological implications of alternatives for risk management procedures. However, a clear distinction was made between technical assessments of policy options and making judgements on possible political trade-offs. It was noted that, in providing risk assessment advice to policy makers, committees need to clarify the assumptions made and the uncertainties involved in their assessments. Where the COT did provide views on possible risk management options these should be carefully delineated and not weighted by areas outside of Members' expertise.

1.76 COT considered that recent measures had greatly increased openness and that very significant moves had been made towards making the findings more accessible and transparent. It was agreed that minutes should remain anonymous because of personal security issues. It was stressed that COT reaches a collective decision and therefore unanimity is not an issue.

1.77 It was acknowledged that a degree of communication between expert committees arose mainly from cross membership of advisory committees. Members welcomed a suggestion that, at least on an occasional basis, they should meet with their counterparts on other committees.

1.78 Although Members were not usually called upon to discuss Committee conclusions with the media, it was agreed that training in risk communication would be helpful.

Sucralose

1.79 COT last discussed sucralose in 1999, when a new teratogenicity study in rabbits was presented. COT concluded that the "study was adequate and demonstrated that sucralose is not a specific developmental toxicant" and that the No-Observed Adverse Effect Level (NOAEL) for the study was

350mg/kg bw/day. COT was content to leave the determination of an Acceptable Daily Intake (ADI) to the Scientific Committee on Food (SCF).

1.80 COT was informed that the SCF had completed its review and concluded that the effects on the gastrointestinal tract of the dams in the teratogenicity study were most likely to be attributable to high doses of poorly digestible substances, to which the rabbit is particularly sensitivity. The NOAEL identified by the study was therefore not considered to be relevant to setting the ADI. A NOAEL of 1500 mg/kg bw per day was identified from a number of dietary and gavage studies. Application of a 100-fold safety factor resulted in an ADI of 0-15 mg/kg bw per day.

1.81 COT noted and endorsed the SCF opinion and ADI of 0-15 mg/kg bw per day.

Terephthalic and isophthalic acids in food

1.82 Terephthalic acid (TA) and isophthalic acid (IA) are starting materials in the manufacture of polyester resins, which are used in coatings on the internal surface of some metal cans designed to come into contact with food.

1.83 The views of the COT were sought on the health implications of the results of a survey of TA and IA migration from can coatings into food. In particular the COT was asked to give its views on the possibility that these compounds might have endocrine disrupting activity.

1.84 COT was provided with estimates of intake of IA and TA by infants, toddlers and adults, based upon levels found in canned foods in this survey.

1.85 The toxicology of both TA and IA had been reviewed by the European Commission's (EC) Scientific Committee for Food (SCF). The SCF had set a restriction (for migration) of 5mg/kg food for IA and a TDI for TA of 0.125 mg/kg bw per day.

1.86 COT considered that the available toxicology data were old and not carried out to modern standards. In particular the Committee noted the presence of urinary bladder stones and associated tumours that developed in a long-term rat study carried out with a concentration of 5% TPA in the diet and requested that the views of the COM should be sought on the available *in vivo* genotoxicity data.

1.87 COT concluded that the concentrations of TA and IA that had been determined in foods analysed in the survey were not of concern for public health on the basis of available information. However, it was considered that

the available toxicity studies were not adequate to exclude the possibility of endocrine disruptor activity, and therefore appropriate studies should be conducted.

1.88 The COT statement on the survey is included at the end of this report.

Working Group on Risk Assessment of Mixtures of Pesticides

1.89 Risk assessment of pesticides has been carried out by measuring residue levels of individual pesticides in food and calculating whether intakes were likely to exceed the ADI for that pesticide. Usually this has not taken into account concurrent exposure to a number of pesticides via the same route (termed "cumulative exposure") or concurrent exposure to one or more pesticides via a different route (termed "aggregate exposure"). This has been a source of concern to a number of groups including consumers. Interest in an aggregate approach has been fuelled by the US Food Quality Protection Act, which mandates that intakes from all sources including food, drinking water and other sources should be considered. It also mandates that toxicological effects of exposure to more than one pesticide functioning by the same mechanism of action (eg cholinesterase inhibitors) should be considered. In addition, a considerable body of work has been carried out on the toxicology of mixtures in the US and the assumption is made that compounds with the same toxicological action will act in an additive fashion whereas those with different actions will act independently.

1.90 COT was informed that the Food Standards Agency considers that "combined" risk assessment of pesticides is a priority area. In order to consider cumulative and aggregate exposures, consideration needs to be given to the relative toxicity of the compounds, the magnitude of residues and the amounts of foods consumed. It may also be necessary to consider other sources of these chemicals such as drinking water and veterinary residues with similar action to the pesticide under consideration, and other means of exposure, such as occupational and domestic exposure. COT was asked to consider establishing a Working Group to review these issues.

1.91 COT agreed to the establishment of the Working Group and approved the terms of reference and membership. The Working Group expects to report within 18 months.

Ongoing work

Dioxins and dioxin-like PCBs - Consideration of the TDI

1.92 COT has commenced a review of the recent risk assessments of dioxins carried out by the World Health Organisation (WHO), the EU Scientific Committee on Food (SCF), and the United States Environmental Protection Agency (US-EPA). As part of this review COT will be reconsidering the tolerable daily intake (TDI). The Committee aims to complete its review of dioxins as soon as possible but accepted that it would not be complete before mid-2001 at the earliest. Without reviewing of the available data independently, COT was not content to accept that the studies selected by the WHO and SCF to inform their tolerable intakes were the most appropriate for this purpose.

1.93 COT proposed to review the evidence of effects other than cancer, taking into account the information provided by EPA, WHO and SCF. The Committee on Carcinogenicity (COC) was asked to review the evidence of carcinogenicity and the risk assessment procedure adopted by the US-EPA. COT agreed that it would be valuable to consult additional experts in other specialised areas.

Background on the three major assessments being considered by COT.

1.94 In 1998, a consultation of the WHO European Centre for Environment and Health (WHO-ECEH) and the International Programme on Chemical Safety (IPCS) recommended a TDI for dioxins and dioxin-like PCBs in the range of 1-4 pg WHO-TEQ/kg. The WHO assessment was published in 2000 (van Leeuwen and Younes, *Food Additives and Contaminants* 17(4) 223-369). The WHO TDI was derived using the NOAEL/LOAELs of what were considered to be the most sensitive effects in experimental animals, and body burdens associated with these NOAEL/LOAELs (as opposed to daily intakes) were used to extrapolate between species. These body burdens were used in turn to calculate the estimated daily intake (EDI) considered to result in comparable steady state body burdens in humans. The use of body burdens was assumed to obviate the need for an uncertainty factor to account for species differences in toxicokinetics. TEFs were used to account for differences in toxicokinetics and potency between dioxin-like compounds. The consultation decided on an uncertainty factor of 10 to account both for interspecies and interindividual differences and the use of LOAELs instead of NOAELs. COT did not regard the information presented to be sufficient to make a judgement on whether the endpoints used by the WHO consultation to derive its TDI were the critical adverse effects.

1.95 A task force of the SCF reported its review of the TDI for dioxins in November 2000. It concluded that dioxins and dioxin-like PCBs should be allocated a temporary Tolerable Weekly Intake (t-TWI) of 7 pg WHO-TEQ/kg bw. The opinion is available on the SCF website at: http://europa.eu.int/comm/food/fs/sc/scf/outcome_en.html#opinions

1.96 The second draft of the US-EPA reassessment of dioxins was released during 2000. As in its previous (1995) assessment, the US-EPA considered that cancer is the critical endpoint and used low dose linear extrapolation to estimate the risk to humans. The validity of the US-EPA approach to the risks to health from exposure to of dioxins will be considered in addition to the TDI approach. The US-EPA draft reassessment is available on the EPA website at http://www.epa.gov/nceawww1/pdfs/dioxin/cd_index.html.

Hyperactivity and Food Additives

1.97 COT was asked to consider the results of a research project entitled "Do food additives cause hyperactivity and behaviour problems in a geographically defined population of three-year-olds?" A short statement was drafted, its release to coincide with release of the study results.

Polycyclic aromatic hydrocarbons (PAHs) - Pragmatic guideline limits in food for use in emergencies.

1.98 COT was asked to consider the appropriateness of setting pragmatic guideline limits for PAHs in food. Guideline limits would be helpful in formulating advice on dealing with incidents, such as fires or oil spills, which resulted in PAH contamination of food. In such situations, it may be necessary to make decisions on possible restriction of harvesting or marketing the affected foodstuffs.

1.99 COT noted that some of the PAHs are generally accepted to be experimental carcinogens and occupational exposure to mixtures of PAHs have been shown to be associated with human cancer. The COC had identified three compounds as being of greatest concern in respect of carcinogenic hazard on the basis of *in vivo* mutagenicity and/or multi-site carcinogenicity. These are benzo(a)pyrene, benz(a)anthracene and dibenz(a,h)anthracene.

1.100 The COT was informed by published data on reported concentrations of individual PAHs that have been detected in various foods, and noted that smoking of food and some cooking processes, such as grilling and barbequing, may result in higher concentrations being detected.

1.101 COT is considering a statement on pragmatic guidelines for PAHs in food for approval and release in 2001.

Statements of the COT

Statement on a Toxicity Study in the Rat of a Hydrogel Filler for Breast Implants

Statement on Dietary Exposure to Dioxins and Dioxin-Like PCBs

Statement on Dioxins and Dioxin-Like PCBs in Free-Range Eggs

Statement on the 1997 Total Diet Study – Fluorine, Bromine and Iodine

Statement on Hexachlorobutadiene

Statement on Terephthalic Acid and Isophthalic Acids from Can Coatings

Statement on a Toxicity Study in the Rat of a Hydrogel Filler for Breast Implants

Introduction

1. The Committee was informed that, because of concerns raised by clinicians about the safety of the fillers used in breast implants, the Medical Devices Agency (MDA) had decided to review the safety data on a hydrogel pre-filled breast implant manufactured for Poly Implant Prostheses. The MDA had asked the Committee to consider the report of a study in the rat in which the animals had received subcutaneous injections of the filler material and had then been observed for periods of up to 12 weeks.[1]

The implant

2. The filler comprises 92% of physiological saline gelled with 8% of a polysaccharide. It is understood that the polysaccharide is based on a cellulose derivative and forms long, linear chains linked by bridges. This gel is contained within a silicone elastomer shell.

The rat toxicity study

3. The Committee was advised that the only toxicity study of any duration was one in which groups of five rats were injected once subcutaneously on either flank with the gel filler material or with saline as a control. Groups of dosed and control rats were killed after 3 days, 4 weeks and 12 weeks. Limited observations were made during life and at necropsy. In the groups of rats that were killed at 4 and 12 weeks no abnormal clinical signs or differences in body weight were reported for either treated or control animals. However, in the treated animals residues of the gel and poorly characterised tissue damage were observed at the injection site. At these times there were histopathological changes in lymph nodes, livers and, to a lesser extent, the kidneys of the treated animals.

4. The Committee considered that, despite having been carried out in 1996, the study was unsatisfactory in its design, execution and reporting. It was the view of the Committee that the changes in the lymph nodes represented a real effect and were consistent with a chronic inflammatory response. These changes require further study, including investigation of lymph nodes close to and distant from the site of injection. In addition, there should be investigation of the lesions reported in the liver and kidney and of the reversibility of any changes observed.

Conclusions

i) The Committee considered that the conclusion of the study, namely that there were no pathological findings in the organs examined, was not supported by the limited experimental results provided, which were considered to be imprecise and inadequate.

ii) The Committee agreed that the findings from the study could not be discounted. The Committee was not able to exclude the possibility that the reported lesions were indicative of a toxic or immunologically-mediated response.

iii) The Committee considered that further testing should be undertaken involving the administration of single doses of the filler gel with longer-term follow-up and with more detailed reporting compatible with current guidelines for chronic toxicity tests.

September 2000
COT Statement 2000/09

Reference

1. Picard F C & Therin M (1996). Subacute toxicity in the rat on a gel (Hydrogel AQT 10-15) used in the filling of mammary prosthesis. Unpublished study No. 121E4041 carried out by BIOMATECH, Chasse sur Rhone, France. Submitted to the Medical Devices Agency by Poly Implant Prosthesis, ZAC les Playes Jean Monnet, 83500 La Seyne sur Mer, France.

Statement on Dietary Exposure to Dioxins and Dioxin-Like PCBs

Introduction

1. We have been informed of the results of a study conducted by the former Joint Food Safety and Standards Group of the Ministry of Agriculture, Fisheries and Food and the Department of Health in which Total Diet Study (TDS) samples collected in 1997 were analysed for the presence of polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), collectively referred to as dioxins, and polychlorinated biphenyls (PCBs).[1]

Tolerable Daily Intake

2. In 1992 we endorsed a Tolerable Daily Intake (TDI) for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) of 10 picograms/kilogram body weight (10 pg/kg bw) that had been recommended by the World Health Organization (WHO) Regional Office for Europe. We also recommended that when considering mixtures of dioxins the TDI could be regarded as being expressed in Toxic Equivalents of TCDD (TEQs), calculated using internationally agreed Toxic Equivalency Factors (TEFs) for dioxin congeners, ie 10 pg TEQ/kg bw.[2]

3. In our 1997 review of the health hazards of PCBs, we were unable to set a TDI for total PCBs. However, we considered that the use of TEFs for certain dioxin-like PCB congeners offered a pragmatic approach to assess the potential toxicity of these dioxin-like PCBs and that they should be considered in combination with dioxins.[3]

4. Recently, we have endorsed the TEFs recommended by a WHO European Centre for Environment and Health (ECEH) consultation for the seventeen 2,3,7,8-substituted dioxin congeners and twelve dioxin-like PCB congeners.[4, 5]

5. We are aware that a recent WHO International Program for Chemical Safety (IPCS)/ECEH consultation has recommended a TDI range for dioxins and dioxin-like PCBs of 1-4 pg TEQ/kg bw.[6] We have not yet had the opportunity to review the data used by the consultation to derive the recently recommended WHO-TDI. We will undertake such a review when a full report of the consultation is available. In the interim we have considered the results of the 1997 TDS survey using both the current UK-TDI and the recently recommended WHO-TDI.

Estimated dietary exposure to dioxins and dioxin-like PCBs

6. We have been provided with estimates of dietary exposure to dioxins and dioxin-like PCBs of adults, schoolchildren and toddlers ie children aged $1\,^1/_2$ to $4\,^1/_2$. The same methodology has been used to estimate dietary exposures from the 1997 TDS as was used to estimate exposures for these age groups from the 1982 and 1992 TDS.[1] We note that where concentrations of these compounds in food were below the limit of detection, the concentration has been assumed to be at the limit of detection. It is considered that this approach overestimates dietary exposures to dioxins and dioxin-like PCBs. We have been informed that dietary exposure of adults and schoolchildren has been estimated using food consumption data for these specific groups.[7, 8]

7. While food consumption data for toddlers do exist,[9] due to a current limitation in the methodology used to estimate exposures, the consumption of 'toddler-specific' foods cannot yet be determined. As a result, toddler food consumption data were not used directly to estimate toddler dietary exposures from previous Total Diet Studies.[10] Toddler dietary exposure has been estimated previously by scaling the estimated dietary exposure of adults by the relative energy contents of adult and toddler diet. The energy content of the latter was calculated from the toddler food consumption data.[9] For comparative purposes, this approach has also been used to estimate dietary exposure of toddlers from the 1997 TDS.[1] However, toddler exposures have now also been estimated from the 1997 TDS (and retrospectively from the 1982 and 1992 TDS for comparative purposes) directly using toddler food consumption data. We note that this approach does not take into account exposures resulting from the consumption of 'toddler-specific' foods but we consider that it provides a more robust estimate of toddlers' dietary exposure than the earlier approach. However, we recommend that the methodology is revised as soon as possible so as to take account of consumption of 'toddler-specific' foods and we ask to see these revised exposure estimates at the earliest opportunity.

8. Dietary exposure to dioxins and dioxin-like PCBs, estimated from the 1982, 1992, and 1997 Total Diet Studies, for average and high-level (97.5th percentile) adult, schoolchild, and toddler consumers (using both approaches) are presented in the Table. The Table presents toddler dietary exposures estimated from toddler food consumption data and also presents exposures estimated by scaling adult consumption patterns by the energy content of the toddler diet. Dietary exposures estimated using toddler food consumption data are higher than when estimated by scaling adult consumption patterns by the energy content of the toddler diet. Exposures estimated from the 1982 and 1992 TDS have been recalculated using the new WHO-TEFs so that the data are comparable to dietary exposures estimated from the 1997 TDS.

Table: Estimated dietary exposures to dioxins and dioxin-like PCB from TDS samples
(pg TEQ/kg bw per day)

Year	1982		1992		1997	
Consumer type	**Average**	**High-level**	**Average**	**High-level**	**Average**	**High-level**
Age-group						
Adults	7.2	13	2.5	4.3	1.8	3.1
Schoolchildren	8.6	15	3.0	4.7	2.2	3.5
Toddlers (estimated using toddler food consumption data)						
$1^1/_2$ to $2^1/_2$	23	49	7.5	14 5.	1 1	0
$2^1/_2$ to $3^1/_2$	19	41	6.3	11	4.4	8.4
$3^1/_2$ to $4^1/_2$ (boys)	17	33	5.6	9.2	4.0	6.9
$3^1/_2$ to $4^1/_2$ (girls)	17	34	5.6	9.6	4.0	7.2
Toddlers (estimated by scaling adult consumption patterns by the energy content of the toddler diet)						
$1^1/_2$ to $2^1/_2$	18	28	6.3	9.8	4.6	7.2
$2^1/_2$ to $3^1/_2$	17	25	5.8	8.6	4.2	6.3
$3^1/_2$ to $4^1/_2$ (boys)	16	23	5.7	8.0	4.1	5.8
$3^1/_2$ to $4^1/_2$ (girls)	15	23	5.3	8.0	3.9	5.8

9. The estimated dietary exposures to dioxins and dioxin-like PCBs for both average and high-level consumers from the three age groups are at or within the current UK-TDI of 10 pg TEQ/kg bw. Furthermore, the estimated average and high level dietary exposures for adult and schoolchild consumers are also below the upper value of the recently recommended WHO-TDI of 1-4 pg TEQ/kg bw. However, the estimated dietary exposures for toddlers who are average consumers are at or slightly above the upper value of this TDI. The upper value of this TDI is exceeded approximately two-fold by all toddlers who are high-level consumers.

10. The estimated dietary exposures to dioxin-like compounds, on a total TEQ basis, for all three age groups show a continuing downward trend, albeit less steeply compared with the decline between 1982 and 1992. However, the dietary exposures to dioxin-like PCBs estimated from the 1997 TDS are very similar to those estimated from the 1992 TDS.

11. We have seen data which indicate that the decline in dietary exposure is real and not attributable to changes in analytical sensitivity or number of food groups analysed in different Total Diet Studies. This decline in dietary exposure is primarily due to either a reduction in emissions to the environment or a change in food consumption patterns, or both.

Environmental controls

12. Abatement measures have been taken to control the emission of dioxins to the environment and hence foods. In particular the imposition of strict emission limits on municipal waste incinerators have reduced emissions from this sector by an estimated 90%. The UK is introducing Regulations to give effect to EC Directive 96/59, which requires the phasing out and disposal of remaining identifiable PCBs. The Regulations follow on from consultation last year, and the publication of the UK action plan in 1997.[11] It is anticipated that as a result of these measures dietary exposure to dioxins and dioxin-like PCBs will continue to decline gradually. We understand that the Government is in the process of producing an UK position paper on dioxins and dioxin-like PCBs, which will assess the effectiveness of current and future abatement measures.

Recommendations

13. We are *reassured* by the evidence of a continuing decline in dietary exposure to dioxin-like compounds. We welcome the evidence that average and high-level adult and schoolchild consumers do not exceed the current UK-TDI or the upper value of the recently recommended WHO-TDI.

14. We *note* that estimated dietary exposures of toddlers do not exceed the current UK-TDI but that approximately 50% of toddlers will exceed the upper value of the newly recommended WHO-TDI. However, we *note* that there are limitations in the methodology used to derive these estimated exposures for toddlers, which means that such estimates should be viewed with caution. We *recommend* that robust characterisation and estimates of toddler exposure, taking into account consumption of 'toddler-specific' foods, are carried out and we request that we see such information at the earliest opportunity.

15. We *note* that the WHO-IPCS/ECEH consultation recommended that continued efforts should be made to reduce exposure towards the lower end of the newly recommended WHO-TDI range. We will undertake a review of the WHO-TDI when a full report of the consultation is available and we will pay particular attention to the relevance of the WHO-TDI to toddlers.

16. We *recommend* that dietary exposure to dioxin-like compounds should continue to be monitored at regular intervals to confirm that the overall downward trend in exposure continues as a result of current and future abatement measures.

17. The available data indicate that some 50% of toddlers in the UK will exceed the upper value of the WHO-TDI but not the current UK-TDI. However, we do not consider that this exceedence necessarily poses a health risk and, in advance of a detailed review of the WHO-TDI, we do not recommend any intervention with respect to the diets of toddlers. This interim position is based upon the following considerations:

    i) it is not yet clear to what extent the WHO-TDI is particularly relevant for toddlers;

    ii) evidence that some toddlers may exceed the WHO-TDI is based upon estimations of dietary exposure that need to be treated with some caution; and

    iii) there is a continuing decline in the overall exposure to dioxin-like compounds.

Conclusions

18. Estimated exposures to dioxins and dioxin-like PCBs for adults, schoolchildren, and toddlers are all at or below the current UK-TDI. Estimated exposures for adults and schoolchildren are also below the upper value of the newly recommended WHO-TDI, although toddlers may exceed this value. However, estimated exposures for all age groups have substantially declined since 1982 and we anticipate that exposures will continue to decline in the future due to the environmental controls already in place and those planned. We conclude that the current concentrations of dioxins and dioxin-like PCBs in food are unlikely to pose a risk to health.

August 2000
COT Statement 2000/03

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11. Department of Environment (1997). United Kingdom action plan for the phasing out and destruction of polychlorinated biphenyls (PCBs) and dangerous PCB substitutes. London, Department of the Environment.

Statement on Dioxins and Dioxin-Like PCBs in Free-Range Eggs

Introduction

1. We have been informed of the results of a study conducted by the Food Standards Agency (FSA) in which free-range hen and duck eggs were analysed for the presence of polychlorinated dibenzo-p-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs), collectively referred to as dioxins, and polychlorinated biphenyls (PCBs).[1]

Survey design

2. A total of 45 free-range hen and duck egg samples, each sample consisting of six individual eggs, were collected from farms or private houses in Kent, Essex, Norfolk, and Buckinghamshire between November 1994 and April 1996. We have been informed that the purpose of this exercise was to examine the use of free-range eggs as indicators of environmental contamination, rather than to estimate dietary exposure to these compounds through the consumption of free-range eggs. The sampling sites were selected for practical convenience rather than on the basis of concerns about local contamination. We note that these free-range egg samples may not be representative of those on sale throughout the United Kingdom.

Concentrations of dioxins and dioxin-like PCBs

3. Concentrations of dioxins and dioxin-like PCBs in the combined yolk and white of hen eggs were in the range of 1.1-22 (mean 6.3, median 3.5) ng Toxic Equivalents (TEQ)/kg fat. In the combined yolk and white of duck eggs concentrations were in the range of 1.9-49 (mean 12, median 5.2) ng TEQ/kg fat. We note that in both cases the distribution of values appeared to be skewed. We have been informed that there were no obvious major point sources of contamination in the immediate vicinity of these sampling sites to account for the higher values. We have been told that the most likely source of contamination of free-range eggs by these compounds is via the ingestion of soil and sediment by hens and ducks as they forage for food. However, environmental sampling at the sites of egg collection was not undertaken.

Estimated dietary exposures

4. We have been provided with estimated dietary exposures for toddlers, schoolchildren, and adults to dioxins and dioxin-like PCBs based on the concentrations of these compounds in free-range eggs in this survey. However, we consider that, because these free-range eggs may not be representative of those on sale throughout the UK, the data from this survey cannot be used to estimate dietary exposures to dioxins and dioxin-like PCBs with any confidence from these sources. Nor can the data from this survey be used to draw any comparisons between free-range eggs and other hen and duck eggs, for which there are few data available.

Conclusions

5. We consider that this survey of dioxins and dioxin-like PCB in free-range hen and duck eggs cannot be used to estimate the risk to health of consumers of such eggs in the UK.

6. The concentrations of dioxins and dioxin-like PCBs in free-range hen and duck eggs might be used as an indicator of environmental contamination. A larger, more rigorously designed study would be needed to investigate this.

July 2000
COT statement 2000/06

References

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Statement on the 1997 Total Diet Study – Fluorine, Bromine, and Iodine

Introduction

1. We have been informed of the results of a study conducted by the Food Standards Agency in which Total Diet Study (TDS) samples collected in 1997 were analysed for the presence of three halogen elements, namely fluorine, bromine, and iodine.[1]

Estimated dietary intakes

2. We have been provided with estimates of mean population, and mean and high-level (97.5th percentile) adult consumer dietary intakes of fluorine, bromine, and iodine. Mean population intakes are based on household, rather than individual, consumption data that are updated yearly and thus can be used to follow trends in dietary intakes. Mean and high-level consumer intakes are based on adult consumption data from the 1986/87 National Diet and Nutrition Survey of British Adults.[2] We note that dietary intakes for age groups other than adults have not been estimated.

3. We note that the analytical techniques used to determine the concentrations of fluorine, bromine, and iodine in the TDS samples did not distinguish between the different chemical forms in which these elements may exist in food.

Fluorine

4. The mean population dietary intake of fluorine estimated from the 1997 TDS is 1.2 mg/person per day. Estimated dietary intakes for mean and high-level adult consumers are 0.94 and 2.0 mg/person per day respectively. Dietary intakes for fluorine were last estimated in 1984 when the mean population intake, calculated from concentrations of fluorine determined in selected food samples from the 1978, 1979, and 1980 total diet studies, was estimated as 1.8 mg/person per day.[3] However, due to changes in the TDS design since 1981 and the limited number of samples that were used to estimate this intake in 1984, a direct comparison between the 1997 TDS mean population intake estimate and this earlier estimate cannot be made. There are no guidelines for fluorine against which to assess these estimated dietary intakes. However, we have been informed that the Expert Group on Vitamins and Minerals (EVM) will be considering fluorine in due course and we will await the findings of that body before considering any potential effects associated with these intakes.

Bromine

5. We have not previously considered dietary intakes of bromine. The mean population dietary intake of bromine estimated from the 1997 TDS is 3.6 mg/person per day. Estimated dietary intakes for mean and high-level adult consumers are 3.8 and 6.2 mg/person per day. We have had the opportunity to review an evaluation of bromine by the Joint Food and Agriculture Organization (FAO) and the World Health Organization (WHO) Meeting on Pesticide Residues (JMPR), which established an Acceptable Daily Intake (ADI) range of 0-1 mg/kg body weight.[4] It is not certain whether bromine is essential[5] so we consider it inappropriate to recommend a range for intakes of bromine that includes zero. However, we consider that the upper value of this range represents a bromine intake below which intakes are unlikely to pose a risk to health. In this respect the upper value of 1 mg bromine/kg body weight per day, equivalent to 60 mg/day for a 60 kg individual, can be considered to be a Tolerable Daily Intake (TDI). Estimated mean and high-level adult consumer dietary intakes of bromine are within this guideline and are therefore not a cause for concern.

Iodine

6. We have considered dietary intakes of iodine on a number of previous occasions, most recently earlier this year when we considered a survey of iodine in cows' milk.[6] We concluded that the concentrations of iodine in cows' milk were unlikely to pose a risk to health,[7] despite calculations that suggested that dietary intakes of iodine by some toddlers may exceed the Provisional Maximum Tolerable Daily Intake (PMTDI) for iodine of 0.017 milligrams per kilogram body weight (17 (g/kg body weight) as recommended by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).[8] Dietary intakes for mean and high-level adult consumers estimated from the 1997 TDS of 240 and 420 (g/person per day are within the JECFA PMTDI, which is equivalent to 1000 (g/day for a 60 kg individual, and are therefore not a cause for concern. While dietary intakes for children aged $1^1/_2$ to $4^1/_2$ have not been calculated from the 1997 TDS, we have been informed that intakes for this age group are likely to be comparable to the intakes we considered in relation to the survey of iodine in cows' milk. There is no new information that would lead us to alter our previous advice[7] that estimated dietary intakes of iodine by toddlers are unlikely to pose a risk to health. However, we have been informed that the EVM are in the process of considering iodine and thus we may wish to reconsider these results in the light of the findings of that body.

Conclusion

7. We conclude that the estimated total dietary intakes of bromine and iodine based on data from the 1997 Total Diet Study are unlikely to pose a risk to health. However, further information on the different chemical forms of these elements in the diet would assist in risk assessment. We will await the findings of a review of fluorine by the Expert Group on Vitamin and Minerals before considering any potential effects associated with the intakes of this element.

July 2000
COT statement 2000/05

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Statement on Hexachlorobutadiene

Introduction

1. The fully chlorinated hydrocarbon hexachlorobutadiene (HCBD, C_4C_{l6}) is formed as a by-product during the manufacture of chlorinated solvents.

2. Environmental contamination with HCBD has recently been detected around a disused waste dump in a quarry at Weston in Runcorn, Cheshire. This was used by ICI for about 50 years until the early 1970s. The release of HCBD into the underlying strata and groundwater came to light as a result of a project carried out by ICI to investigate the environmental impact of its previous industrial and waste disposal activities. HCBD has been detected in the indoor air of properties close to the site.

3. We have been informed that there are 128 houses built close to the former dump which have been investigated and HCBD has been detected recently in the indoor air of 21 of these, at concentrations of under 10 parts per billion (ppb) in all houses apart from one, where a concentration of 1000 ppb was detected. The current limit of detection is 2 ppb in air. People living in most of the houses where HCBD has been detected have been moved to other accommodation. North Cheshire Health Authority has offered health checks to those residents who were, at the time, living in houses where HCBD was detected.

4. In view of public health concerns, the Committee has been asked by the Department of Health to provide advice on the toxicity of HCBD. This is given below.

Toxicology of HCBD

5. There is very little information on the toxicological effects of HCBD derived from studies on humans. Consequently, an assessment of the possible risks to human health has to be based on laboratory and animal data. However, most animal toxicity studies on HCBD have been conducted using oral exposure and there are few studies of exposure by inhalation, the prime route of exposure for residents at Weston.

6. The results of studies of repeated oral administration indicate that HCBD can cause damage to the kidneys at doses of 0.5 milligrams/kilogram body weight per day (mg/kg bw per day) and above in female mice[1] and at doses of 2 mg/kg bw per day and above in both sexes of rats.[2] Damage to other tissues (liver, nervous system) has been reported at a higher dose of 20 mg/kg bw per

day in rats.[2] In reproduction studies at this dose foetal toxicity, predominantly manifested as retardation of foetal growth, was also recorded in rats.[3] However, these effects were attributed to maternal toxicity because adverse developmental effects were not induced at doses that were not toxic to the dam. Limited information from the animal studies indicates that exposure by inhalation results in the same toxic effects, with the kidney being the prime target organ.

7. Thresholds for each of these adverse effects have been demonstrated in several studies. The Committee considered that the response in the kidneys of mice is the most sensitive indicator of the toxicity of HCBD but that the response of one female mouse dosed with 0.2 mg/kg bw per day for 13 weeks[1] was not sufficient evidence to warrant the use of a lower figure for a No Observed Adverse Effect Level (NOAEL). Therefore, the Committee considered that, for non-carcinogenic effects, the NOAEL is 0.2 mg/kg bw per day.[4,5]

8. Members of our sister committee, the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) have reviewed the mutagenicity of HCBD. There are *in vitro* data, mainly from studies using Salmonella TA100, that indicate that HCBD has mutagenic potential.[6,7] Negative results have been reported from *in vivo* assays in bone marrow [8,9] but these were inadequate to draw definite conclusions. COM members considered that further *in vivo* studies were needed, particularly in the kidney, before any definite conclusions could be drawn. On the data currently available it would be prudent to assume that HCBD is an *in vivo* somatic cell mutagen.

9. A carcinogenic response has been seen in the kidneys of rats in a study in which HCBD was administered continually in the diet for two years at a dose of 20 mg/kg bw per day (the highest dose tested). No tumours were observed in the kidneys of male or female rats administered doses of 2 mg/kg bw per day or lower.[2]

10. In view of the advice from the COM that HCBD should be regarded as an *in vivo* mutagen the COT were unable to establish a safe level in relation to cancer or to identify a tolerable daily intake (TDI) for HCBD.

Conclusions

11. From animal studies, the Committee agreed that a NOAEL of 0.2 mg/kg bw per day had been established for the **non-carcinogenic** effects of HCBD.

12. The Committee considered that, in order to estimate the concentration in air that would result in humans inhaling a dose of 0.2 mg/kg bw per day, it was necessary to make the following assumptions:

- the toxicity of HCBD following inhalation exposure is essentially the same, both qualitatively and quantitatively, as the toxicity of HCBD following oral exposure;

- there are no significant differences in the extent of absorption of HCBD by either route; and

- a 60 kg adult would inhale 20 cubic metres (m^3) of air per day.

On this basis the Committee considered that, as an approximation, a dose of 0.2 mg/kg bw per day would correspond to the continuous inhalation of air containing 0.6 mg/m^3 of HCBD, equivalent to an air concentration of about 60 ppb.

13. In view of the evidence that there are qualitative similarities between humans and animals in the way that HCBD is distributed and metabolised in the body, the Committee considered that continuous exposure to a concentration of HCBD in air of less than 0.6 ppb (ie the Margin of Exposure below 60 ppb is at least 100) can be regarded as being without appreciable adverse health effects in respect of non-carcinogenic and reproductive effects.

14. In respect of concerns about a potential **carcinogenic** effect, the Committee noted that exposures to less than 0.6 ppb HCBD were 10,000 times lower than the equivalent dose of HCBD which, when fed daily throughout a lifetime to rats, had resulted in kidney tumours. The Committee considered therefore that the carcinogenic risk at these low exposure levels was minimal and was not of appreciable health concern. However, given the uncertainties in the data, the Committee considered that exposure should be reduced to as low a level as reasonably practicable (ALARP).

15. The Committee was informed that health studies are being undertaken of exposed residents of Weston[10] and members of the ICI workforce.[11] There is also a proposal to develop a physiologically-based pharmacokinetic model for HCBD exposure.[11] In addition, the Committee was informed that a technique is being developed to allow analysis for HCBD at parts per trillion concentrations in air. The Committee welcomed this information and considered that the results of these studies should inform a further review by the Committee, in due course, of its conclusions on the health significance of low-level exposures to HCBD.

June 2000
COT Statement 2000/04

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Statement on Terephthalic and Isophthalic Acids from Can Coatings

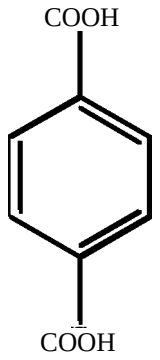
Introduction

1. The views of the Committee were sought on the health implications of the results of a survey[1] of terephthalic acid (TA) and isophthalic acid (IA) migration from can coatings into food. In particular the Committee was asked to give its views on the possibility that these compounds might have endocrine disruptor activity.

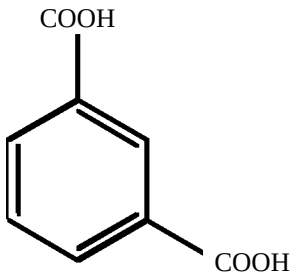
Background

2. TA and IA (see Figure) are starting materials in the manufacture of polyester resins, which are used in coatings on the internal surface of some metal cans designed to come into contact with food.

Figure 1 Terephthalic acid (TA) Isophthalic acid (IA)



Terephthalic acid (TA)



Isophthalic acid (IA)

3. As part of the Food Standards Agency's continuing programme of surveillance on the migration of chemicals from food contact materials a two-part survey for TA and IA was carried out. In the first phase of the survey various canned foods were purchased and the cans were tested for the presence of coatings made from polyester resins. In the second phase, further samples of the products in those cans which had polyester coatings were analysed to determine whether migration of TA and IA into the can contents had occurred.[1]

Survey results

4. Twenty-eight products were identified as being in cans coated with polyester resin on all, or part, of their internal surfaces. In samples of the contents of these cans, TA was found in 3 of 28 samples at or just above the limit of quantification* and in 7 samples at levels between the limit of detection† and limit of quantification. IA was detected in 4 of 28 samples at levels between the limit of detection and limit of quantification.

5. Estimates were made of the potential intakes of TA and IA from canned foods studied in the second phase of the survey. Intakes were estimated for different age groups according to the types of foods in which these substances were found. The estimates used the analytical results for samples in which TA and/or IA were found. Intakes were calculated by summing the intakes of 97.5th percentile consumers‡ for each food in which the given substance was detected, giving greatest weight in this summation to the two highest estimates of intake. The intake estimate was divided by bodyweight to derive contaminant exposure in milligrams per kilogram of bodyweight (mg/kg bw) per day, bodyweights used were: 8.8 kg for infants, 14.5 kg for toddlers ($1^1/_2$-$4^1/_2$ years old) and 60 kg for adults.

6. The potential intake of TA by infants between 6 and 12 months old who were 97.5th percentile consumers was estimated as 0.0074 mg/kg bw per day. For toddlers who were 97.5th percentile consumers the potential intake of TA was estimated as 0.083 mg/kg bw per day. For adults who were 97.5th percentile consumers the potential intake of TA was estimated as 0.0025 mg/kg bw per day.

7. The intake of IA by adult 97.5th percentile consumers was estimated as 0.0013 mg/kg bw per day. There are no estimates of intake by infants as no IA was detected in baby foods.

* Limit of quantification: the lowest level at which the amount of a substance can be stated with confidence.
† Limit of detection: the lowest level at which a substance can be detected with confidence.

‡ 97.5th percentile consumers are those whose consumption of a specific food or group of foodstuffs corresponds to the 97.5th percentile point on a distribution curve for consumption of the given food or foods.

Toxicology of TA and IA

8. The European Commission's Scientific Committee for Food (SCF) reviewed studies of the toxicity and migration of both TA and IA.

9. In view of the availability of data from long-term studies the SCF was able, pending submission of full reports, to set a temporary Tolerable Daily Intake (TDI) for TA of 0.125 mg/kg bw, which was based on 3-month and 2-year dietary studies in rats.[2] The major finding in the long-term study with TA was the occurrence of malignant and benign tumours of the urinary tract at high doses.[3,4] These were documented as being associated with the formation of stones in the urinary bladder which represents a potential non-genotoxic mechanism for the formation of such tumours.

10. On the basis of the available data from migration and toxicity studies submitted by industry the SCF has also set a restriction (for migration from plastics) of 5 mg/kg food for IA.[2] This limit was based on negative genotoxicity data and a 90-day dietary study in rats, from which a No Observed Effect Level of 250 mg/kg bw per day was established.

11. The manufacturers of TA and IA submitted a commentary on the available reproductive and developmental toxicity data for both compounds. In this it was proposed that the weight of the evidence from these studies does not support a role for these acids in modulating the endocrine system.[5]

12. The Committee noted that the toxicity studies on TA and IA were not carried out to modern standards. It was recognised that the limited nature of the published work would not allow them to address fully the questions that they had been asked.

13. It was requested that, in the light of the urinary tumours occurring in rats fed the highest dietary concentration of TA, the view of the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment be sought on the potential *in vivo* genotoxicity of this compound.

14. It was noted that the estimated intakes of TA by infants, toddlers and adults who were 97.5th percentile consumers were below the temporary TDI established by the SCF. In addition, it was noted that the concentrations of IA found in samples of canned food in the survey were below the migration limit set by that committee.

Conclusions

i) The Committee *concluded* that the concentrations of TA and IA that had been determined in foods analysed in the survey were not of concern for public health on the basis of available information.

ii) The Committee *noted* the commentary of the manufacturers on possible endocrine disruptor activity of TA or IA. However, it was considered that the toxicity studies were inadequate to exclude this possibility. It was therefore *recommended* that appropriate studies should be carried out to determine whether TA or IA possess endocrine disruptor activity.

September 2000
COT Statement 2000/08

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2000 Membership of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

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B Maycock BSc MSc

Declaration of interests during the period of this report

Member	Personal Interest		Non-Personal Interest	
	Company	Interest	Company	Interest
Professor H F Woods (Chairman)	Halifax Bank HSBC	Shares Shares	University of Sheffield, Faculty of Medicine Wide range of national & international food & chemical companies.	University of Sheffield, Faculty of Medicine. Has extensive activity in teaching and research in nutrition and toxicology and in topics related to and supported by many companies in the food and chemical industry. Trustee of Hallamshire Therapeutic Research Trust Ltd, Harry Bottom Charitable Trust and Special Trustee for the former United Sheffield Hospitals.
Professor P J Aggett	Nestec, Wyeth, Borax	) Ad hoc Consultancy,) Lecture and Chairing) Meetings	Nestec, FDF Abbot Unilever Meat and Livestock Commission	Departmental commissioned research and student placements
Professor N A Brown	Merck Glaxo Wellcome Searle Styrene Information Research Centre Du Pont	Consultancy Consultancy Consultancy Consultancy Consultancy	EC (DGXI and DGXII) Glaxo Wellcome US EPA	Research Support Research Support Research Support
Dr P Carthew	Provalis Unilever Cambridge Antibody Technology	Share Holder Share Holder Consultancy	NONE	NONE
Professor J K Chipman	Boots Healthcare International Quintiles	Consultancy Consultancy	Astra-Zeneca Glaxo- Wellcome Water Research Centre SmithKline & Beecham ICI	Research Support Research Support Research Support Research Support Research Support
Dr M Joffe	Ilzro	Research grant	NONE	NONE
Profesor I Kimber	British Airways British Petroleum-Amoco ICI Halifax AstraZeneca	Share Holder Share Holder Share Holder Share Holder Share Holder Employee	Unilever plc	Grant for Research

Member	Personal Interest		Non-Personal Interest	
	Company	Interest	Company	Interest
Professor A G Renwick	International Sweeteners Association	Consultant	Hoffmann-La Roche Unilever SmithKline Beecham Pfizer Flavor and Extract Manufacturers Association (FEMA)	Research Support Research Support Research Support Research Support Research Support
Professor P A Routledge	Health Care Services Edinburgh	Fee	Paracetamol Information Centre	Member of Advisory Group
Professor I R Rowland	Colloids Naturels International (CNI) Rouen, France Danisco	Consultancy Consultancy	Various	Departmental teaching & research funded by various food companies
Dr L Rushton	Institute of Petroleum Transport and General workers union	Consultancy, contracts and grants – completed Consultancy – completed	Concawe EU	Contract to Institute for Environment and Health – Now completed Contract to Institute for Environment and Health
Ms J Salfield	Alliance & Leicester Halifax Woolwich Northern Rock	Shares Shares Shares Shares	NONE	NONE
Dr A Smith	Abbey National British Telecom Halifax Bank	Share Holder Share Holder Share Holder	Rhône Poulenc Glaxo-Wellcome	Research Support Research Support
Professor S Strobel	NONE	NONE	NONE	NONE
Dr A Thomas	NONE	NONE	NONE	NONE
Professor J A Timbrell	Shook, Hardy & Bacon (Law firm) Sorex Ltd	Occasional Fee Occasional Fee	Glaxo Wellcome Taisho Pharmaceutical Co	Research Support Research Support
Dr M Tucker	Zeneca	Pension	NONE	NONE