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APPLICATION OF PROBABILISTIC MODELLING TO FOOD CHEMICAL EXPOSURE ASSESSMENTS

By

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DECLARATION

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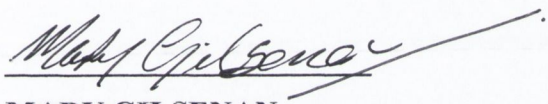

MARY GILSENAN

To: Mam & Dad

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PUBLICATIONS

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Scientific papers

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Gilsenan, M.B., Thompson, R.L., Lambe, J., and Gibney, M.J., 2003, Validation analysis of probabilistic models of dietary exposure to food additives. *Food Additives and Contaminants*, **60**, S61-S72.

Gilsenan, M.B., Lambe, J., and Gibney, M.J., 2003, Assessment of food intake input distributions for use in probabilistic exposure assessments of food additives. *Food Additives and Contaminants*, **20**, 1023-1033.

Gilsenan, M.B., and Gibney, M.J., 2004, Assessment of the influence of energy under-reporting on intake estimates of four food additives. *Food Additives and Contaminants*, *in press*.

Abstracts

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ABBREVIATIONS

ADI	Acceptable daily intake
AD	Anderson-Darling
ARfD	Acute reference dose
ALBA	Dutch Food Intolerance databank
ALSPAC	Avon Longitudinal Study of Parents and Children
AR	Acceptable reporter
BMR	Basal metabolic rate
BMR_{est}	Estimated basal metabolic rate
BS	Bootstrapped sample
CI	Confidence interval
EDF	Empirical distribution function
EDI	Estimated daily intake
EI	Energy intake
EI_{rep}	Reported energy intake
EPA	Environmental Protection Agency
EU	European Union
FAO	Food and Agricultural Organisation of the United Nations
FFQ	Food frequency questionnaire
GPI	Grootverbuik Product Informatie
IBEC	Irish Business and Employers Confederation
IEFS	Institute of European Food Studies
ILSI	International Life Sciences Institute
INFID	Irish National Food Ingredient Database
INNS	Irish National Nutrition Survey
INRAN	National Institute for Food and Nutrition Research
KS	Kolmogorov-Smirnov
LOD	Limit of detection
MAFF	Ministry of Agriculture Fisheries and Food
MLE	Maximum likelihood estimation
MPL	Maximum permitted level
NDNS	National Diet and Nutrition Survey
NESTI	National estimate for short term intake
NOEL	No observed effect level

NSIFCS	North South Ireland Food Consumption Survey
Obs	Observed
PDF	Parametric Distribution Function
ppm	Parts per million
PTWI	Provisional Tolerable Weekly intake
RAC	Raw agricultural commodity
SCF	Scientific Committee on Food
SCOOP	Scientific Cooperation
SD	Standard deviation
TAMDI	Theoretical added maximum daily intake
TMDI	Theoretical maximum daily intake
UK	United Kingdom
UR	Under-reporter
US EPA	United States Environmental Protection Agency
USDA	United States Department of Agriculture
WHO	World Health Organisation

SUMMARY

Risk assessment of food chemical intake is at the core of food safety policy within the EU and the assessment of food chemical exposure is an integral part of the risk assessment process. There is an increasing demand to improve current methods to assess food chemical exposure. The research presented in this thesis demonstrates the usefulness of a National Food Ingredient Database within the exposure assessment process and focuses thereafter on the application of probabilistic modelling to food chemical exposure assessments.

An existing National Food Ingredient Database was expanded, updated and used to provide qualitative information on patterns of additive usage in the Irish food supply and changes in patterns of additive usage between the periods 1995-1997 and 1998-1999. Of the 300 additives permitted for use according to the EU food additive Directives, some 54% were recorded in INFID. Colours, emulsifiers and acids were the most frequently used additive categories, representing 18, 13 and 12% of the total additives used, respectively. All diet soft drinks (n=37), low fat spreads (n=25) and liver pâtés (n=10) recorded the use of at least one additive. Colours were most commonly recorded in sauces (n=182 brands, 26% of sauces), emulsifiers were most commonly recorded in biscuits (n=181 brands, 47% of biscuits) and acids were most commonly recorded in sauces (n=304 brands, 43% of sauces). Carotenes (E160a), mono- and di-glycerides of fatty acids (E471) and citric acid (E330) were the most commonly recorded colour, emulsifier and acid, respectively. When expressed in terms of the number of brands that contain additives, sauces (n=522, 73% of sauces), biscuits (n=323, 84% of biscuits) and preserves (n=321, 85% of preserves) were ranked highest. For most food additive categories, there appeared to be a minimal change in qualitative additive usage between the two time periods. However there was a significant increase in the frequency of use of emulsifiers ($P<0.001$), acids ($P<0.01$), sweeteners ($P<0.05$) and acidity regulators ($P<0.05$), and a significant decrease in the frequency of use of antioxidants ($P<0.05$) during the two time periods. It appeared that changes in the types of brands on sale between the two time periods were more apparent than actual changes in qualitative ingredient formulations across brands, as some 17% of brands that were on sale during the period 1995-1997 were no longer on sale during the period 1998-1999.

The fit of a range of parametric distributions in the BestFit® distribution fitting software program with the distribution of observed food consumption data for 22 food

groups was examined to ascertain the type of parametric distribution that could be used to model variability in food consumption model inputs in probabilistic food additive exposure assessments. This analysis indicated that the lognormal distribution was most commonly accepted as a plausible distribution to model food consumption data expressed as g/day (16 of 22 foods) and as (g/kg bw/day) (18 of 22 foods). This finding was supported by graphical inspection of the fits for a number of food categories. In a further analysis, the influence of using a lognormal distribution to model food consumption input data on probabilistic estimates of food additive intake was explored by comparing modelled intake estimates with observed intakes. Results from this analysis indicated that some level of caution regarding the use of a lognormal distribution as a mode of input for food consumption data in probabilistic food additive exposure assessments is warranted. The need for further research in this area was highlighted.

A simple conceptual model for the estimation of food additive intakes using probabilistic analysis, which combined food consumption data, the probability of an additive being present in a food group and additive concentration data was developed. Each of the three model components assumed two possible modes of input. Therefore, the validity of eight (2^3) model combinations was assessed. Modelled intake estimates that fell below conservative deterministic estimates of intake and above 'true' intakes (calculated from a brand level food consumption database) were considered to be in a valid region. Whilst the distribution of modelled intake estimates from fell below conservative deterministic estimates, modelled intake estimates were not consistently above 'true' intakes. These results indicated the need for less simplistic models for the estimation of food additive intakes using probabilistic analysis. Such models should incorporate information on market share and/or brand loyalty.

The influence of energy under-reporting in dietary survey data on food additive intake estimates was explored. Deterministic intake estimates of four food additives based on the total sample of reporters (*i.e.* acceptable and under-reporters), acceptable reporters only and under-reporters only and were calculated and compared. Food additive intake estimates amongst acceptable reporters were higher than corresponding intake estimates amongst the total sample of reporters and amongst under-reporters. With the exception of one food additive (erythrosine), ratios of upper percentile additive intakes amongst acceptable reporters to corresponding intake estimates amongst the total sample of reporters did not exceed 1.06 when results were expressed as total population or consumer only intakes. The findings from this study, based on the food

additives that were studied, illustrated that energy under-reporting did not materially influence estimates of food additive exposure. However, a number of situations were under-reporting may exert a more significant impact on exposure estimates.

Chapter 1

Introduction

1.1 Food chemical exposure assessments

A wide range of chemicals is present in the food supply today. These include naturally occurring, intentionally added and unintentionally added substances, which may be desirable (*e.g.* nutrients, additives, flavouring substances, dietary fibre, novel food ingredients) or undesirable (*e.g.* environmental contaminants, natural toxins, pesticide residues, mycotoxins, packaging material migrants). Risk assessment of chemical hazards in foods is at the core of food safety policy within the EU, and the assessment of dietary exposure is an essential component of the risk assessment process. There is an increasing demand for the assessment of exposure to food chemicals together with demands for improvements in the methods used to carry out these assessments. These demands are fuelled by the growing need to maximize the safety of the food supply for the purpose of consumer protection and the need to facilitate international trade.

The research presented in this thesis focuses specifically on food chemical exposure assessments with particular emphasis on the application of probabilistic modelling to the exposure assessment process. Whilst the analyses presented focus specifically on food additives, many of the areas covered are applicable to exposure assessments of other food-borne chemical hazards.

1.1.1 Exposure assessments within the context of risk assessments

Exposure assessments constitute an integral part of a risk assessment process (figure 1.1). The underlying objective of a food chemical risk assessment is to provide a scientific basis for the control and management of potential adverse health effects, which may result from human exposure to the food chemical. Risk assessments are characterized by four stages, which include hazard identification, hazard characterization, exposure assessment and risk characterization (EU Scientific Steering Committee 2000). Hazard identification, the first step in a risk assessment process, involves the identification of potential hazards entering the food supply. A hazard is defined as a biological, chemical or physical agent with the potential to cause an adverse health effect (FAO/WHO 1995). Examples of food chemical hazards include chemical contaminants, pesticide residues, food contact migratory compounds, veterinary drug residues and mycotoxins. Potential hazards may also be drawn into the risk assessment system through applications for product approvals and licences (Benford and Tennant 1997). Hazard characterization quantifies potential adverse effects (*e.g.* reduced weight gain, organ enlargement), which may result

from human exposure to a chemical using dose-response studies, which are usually conducted in laboratory animals. Results from hazard characterization are used to derive acceptable or tolerable levels of intake of a food chemical. Hazard characterization is closely linked to hazard identification, since it is often based on evaluation of the same toxicological studies. Exposure assessment is defined as the qualitative and/or quantitative evaluation of the likely intake of biological, chemical or physical agents via food as well as exposure from other sources if relevant (FAO/WHO 1995). All dietary exposure assessments of food chemicals revolve around the provision of information on whether a chemical is present in a food and if present, the level at which the chemical is present and the amount of food consumed. Finally, risk characterization combines results from exposure assessments and hazard characterization to estimate the likelihood that a chemical may cause harm and how severe the effect may be. Risk characterization provides the primary basis for risk managers to make decisions about how to manage the risk in different situations (*e.g.* whether it is necessary or feasible to reduce exposure or to provide advice to susceptible subgroups *etc.*).

1.1.2 Principles of exposure assessments

The primary purpose of exposure assessments is to assess whether exposure to a chemical is below acceptable or tolerable levels for the ultimate protection of the consumer. Exposure assessments may also be carried out to assess compliance with legislation of intentionally added food chemicals and to monitor trends in food chemical intakes. Several methods exist to estimate the intake of a chemical from food. The choice of method is dependent on the purpose of the assessment, the nature of the chemical and the availability of resources to conduct the assessment (Petersen and Barraj 1996, Kroes *et al.* 2002). For example, an assessment conducted for the purpose of monitoring trends in additive intakes in the total population would require fewer resources than a more detailed additive intake assessment in a population considered at risk due to specific dietary practices (*e.g.* sweetener intakes in diabetics). Whether a chemical is authorized for use in a restricted number of food products (*e.g.* food additives) or whether it may have entered the food supply unintentionally and sporadically (*e.g.* chemical contaminant) will also influence the type of method used.

Available methods range from crude 'screens' based on theoretical concentration and consumption data to more sophisticated methods employing food consumption data at

individual level and analytical chemical concentration data pertaining to representative samples from target populations (*e.g.* total diet studies) or estimates of internal exposure using biomarkers. Since most food chemicals are considered to be consumed at acceptable levels, employing a sophisticated analysis to begin an exposure assessment may not be cost effective (Douglass and Tennant 1997). The general approach used is a step-wise approach, which begins with crude screening methods based on worst case assumptions and then proceeds to more refined methods, if results from crude methods dictate the need to do so (Nutriscan 1994, Gibney and Lambe 1996, European Commission 1998, Kroes *et al.* 2002). Such a prioritization system has won general acceptance internationally (Douglass and Tennant 1997). The primary objective of screening is to prevent unwarranted data collection and to ensure that resources for the collection of data are put to best use (Gibney and Lambe 1996). Refining crude data can be achieved by means of more precise intake data or more precise concentration data.

When comparing results from food chemical exposure assessments with acceptable or tolerable levels, high level intakes (*e.g.* upper percentiles of exposure) are usually required (Nutriscan 1992, European Commission 1998, Lambe 2002). This ensures that the majority of consumers are protected from potential adverse effects associated with a particular chemical. Consideration should also be given to 'at risk' groups (European Commission 1998, Leclercq *et al.* 1999, Verger *et al.* 1999). Such groups might include individuals who might have higher intakes of a particular chemical compared to the general population on the basis of their dietary habits or their specific geographical location (*e.g.* diabetics and weight reducers may have a higher intake of intense sweeteners compared to the general population or individuals residing in a particular geographic region who might have a high intakes of a particular contaminant where the contaminant is localized).

1.1.3 Toxicological end points

As mentioned in the previous section, the primary purpose of exposure assessments is to assess whether exposure to a chemical is below acceptable or tolerable levels for the ultimate protection of the consumer. In the case of food additives, the acceptable daily intake (ADI) is widely used to describe 'safe' levels of intake (Herrman and Younes 1999). The ADI, as defined by WHO (1987), is an estimate of the amount of a food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk. Therefore, by definition, intakes at or below the ADI are

not a health concern (Renwick 1996). Although originally developed in relation to food additives, the ADI is also applied to pesticide residues and veterinary drug residues (Walker 1998), since these chemicals are intentionally added to confer benefits in safe food production. In contrast, chemical contaminants are unwanted but may be unavoidable and may accumulate in the body with continued ingestion. Therefore, levels of contaminants that are not expected to produce harmful effects are designated as tolerable (permissible) rather than acceptable and a longer reference period is applied. Hence, the term provisional tolerable weekly intake (PTWI) is typically applied for contaminants.

Derivation of the ADI is based upon a series of toxicological tests to establish which type(s) of effect (*e.g.* reduced weight gain, organ enlargement) a particular substance may cause, and the relation between the dose (intake) of the substance and the occurrence of that effect. In most cases, these tests are based on lifetime feeding studies in experimental animals. In the case of food additives, the highest dose (expressed as mg/kg bw/day) at which no effect is observed is defined as the no observed effect level (NOEL). This NOEL is then divided by a safety (uncertainty) factor to establish an ADI. A safety factor of 100 has generally been used, which is based on the assumption that humans are 10 times more sensitive to the substance than experimental animals and that there is a 10-fold range in sensitivity within the human population (Herrman and Younes 1999). Renwick (1993) developed an approach for the utilization of data-derived safety factors for inter-species and inter-individual variability, in place of default values. This approach subdivides each of the 10-fold inter-species and inter-individual safety factors into two separate sub-factors to allow for differences in toxicokinetics (fate) and toxicodynamics (effect) of the chemical in each case. If actual data are available for any sub-factor for given compound, they may be used. Thus, the overall approach for the establishment of the ADI contains a number of safety margins. The WHO (1987) states that 'because in most cases, data are extrapolated from lifetime animal studies, the ADI relates to lifetime use and provides a margin of safety large enough for toxicologists not to be particularly concerned about short term use at exposure levels exceeding the ADI, providing the average intake over longer periods does not exceed it'. Therefore, short term excursions above the ADI are not considered to pose a health risk. With regard to prolonged excursions above the ADI, it is not possible to determine a general frequency or degree of excursion that may pose harm, since the NOEL does not indicate the dose level (threshold) at which an effect is observed. Therefore, the significance of prolonged excursions above the ADI needs to be considered

on a case by case basis, which requires reference to the toxicological study that lead to the derivation of the safety statement (Renwick 1996). However, Douglass and Tennant (1997) note that the consumption of most food chemicals is at acceptable levels. Within the EU, three food additives Directives (European Commission 1994a,b, 1995) include an obligation on member states to introduce systems to monitor the consumption of food additives. The objective of this requirement is to ensure that food additive intakes do not exceed ADIs set by the Scientific Committee on Food (SCF). To this end, a Scientific Cooperation (SCOOP) task (task 4.2) was set up on 'methodologies for monitoring food additive intakes' (European Commission 1998). Member states proposed a tiered approach to meet the monitoring requirements set out in the Directives (European Commission 1994a,b, 1995). Results from this monitoring process, which employed conservative assumptions regarding the presence and concentration of food additives, indicated that for the majority of additives, the dietary intake was below ADIs (European Commission 2001). However, not all member states followed the agreed methodology proposed for monitoring. Therefore, the monitoring process will be repeated and a new report on the overall situation on food additive intake in the EU will be compiled in three years from the publication of the preliminary report.

For some additives, evaluation of the available toxicological data may lead to the conclusion that the total potential intake from all sources does not represent a hazard to health. In this situation, it may be considered unnecessary to specify a numerical value for the ADI, and the term ADI *not specified* is used (*e.g.* Pectin (E440)). In this case, the additive must be used in accordance with good manufacturing practice. That is, it should be used at the lowest level required to produce a technological effect. Where the approval of use of an additive is being sought, a temporary ADI may be allocated for a defined period whilst the approval process for that additive is in place. In this instance, a larger safety factor (*e.g.* two fold higher than otherwise) may be applied as a precautionary measure until the proposed food additive is fully evaluated.

1.2 Sources of variability and uncertainty in food chemical exposure assessments

All food chemical exposure assessments contain inherent sources of both variability and uncertainty. Variability represents diversity or heterogeneity in a population that is irreducible by additional measurements whereas uncertainty represents partial

ignorance or lack of knowledge on the part of the analyst and may be reduced by further measurement (Anderson and Hattis 1999). Examples of variability in food chemical exposure assessments include natural variability in food intakes, both within and between individuals, variability between individual body weights or variability in chemical concentrations between foods. Examples of uncertainty include measurement errors in the dietary survey methodology on behalf of the interviewer and/or the respondent, lack of knowledge about the presence of a chemical in a given food or lack of knowledge about the effects of cooking and processing on the chemical concentration. Ignoring the presence of variability and/or uncertainty in food chemical exposure assessments may generate exposure estimates that do not adequately reflect true chemical intakes. Benford and Tennant (1997) and Kroes *et al.* (2002) describe uncertainties relating to dietary exposure assessments of food chemicals. Sources of variability and uncertainty inherent in food chemical exposure assessments are discussed below.

1.2.1 Food consumption

Variability in food consumption databases occurs as a result of natural variation in food intakes between individuals (inter-individual variability) and as a result of variability in food intakes within individuals (intra-individual variability). Inter-individual variability may occur as a result of differences in taste preferences, geographical location, product availability, cost, or as a result of religious, cultural or health reasons. Intra-individual variability occurs as a result of natural variability in food choice for a given individual. Sources of uncertainty in food consumption data include under-reporting, coding errors, data entry errors, incorrect estimation of weights of food consumed *etc*. These have been reviewed by Bingham (1987). Under-reporting is identified as one of the major biases in exposure assessments based on dietary surveys (Kroes *et al.* 2002). Under-reporting of foods has been observed consistently in food consumption surveys and across a range of population subgroups (Black *et al.* 1991). It is likely that under-reporting exists due to a failure of the respondent to record the consumption of a given food, a failure to correctly estimate the amount of food consumed (portion size), and/or a tendency to under-estimate the frequency of consumption of a given food (Becker *et al.* 1999, Krebs-Smith *et al.* 2000). Levels of under-reporting are routinely calculated in dietary surveys by dividing the reported energy intake (EI) of the subjects by their estimated basal metabolic rate (BMR_{est}) based on age, gender and body weight, in order to assess the quality of the food

consumption data. Goldberg *et al.* (1991) have formulated study-dependent cut-off points, based on the ratio of EI to BMR_{est}, to assess the occurrence of under-reporting in dietary surveys. These cut-off values, known as the 'Goldberg cut-offs' have since been evaluated and revised by Black (2000a). If the foods in which a chemical may be present are under-reported, then it is likely that food chemical intakes may also be under-reported. With regard to food chemical exposure assessments, quantification of the potential distortion of an assessment attributed to under-reporting as well as improved data and correction procedures have been identified as a future challenge and research need (Kroes *et al.* 2002).

Most food consumption surveys have been conducted primarily for assessing nutrient intakes of the population. This means that foods consumed by survey respondents are allocated food codes on the basis of the nutrient composition of the foods. In most cases, food intake information at brand level is not retained in the electronic food consumption database. Since the occurrence of food additives may vary between brands within the same food category (Leclercq *et al.* 2003a), there is uncertainty regarding the presence of an additive in any given food consumed. For the assessment of dietary intakes of food additives, food categories in which additives are permitted according to the EU additive Directives (European Commission 1994a,b, 1995) need to be matched with food descriptions in food consumption databases. However, the food categories in the additive Directives are described in terms of their state at manufacture (*e.g.* 'liquid egg (white, yolk or whole egg)'), whereas the foods described in the food consumption databases reflect the foods as consumed (*e.g.* chocolate gateaux). This introduces some difficulty when food descriptions, which are required for an exposure assessment are matched with the food descriptions in the food consumption database (Gibney and Lambe 1996, Langlais 1996, European Commission 1997). There may also be ambiguity when interpreting the food categories in the EU additive Directives. For example, when estimating the intake of the food colour annatto (E160b) as part of the SCOOP (task 4.1) project (European Commission 1997), the food category 'edible ices' had to be considered. Under this term some member states included ice cream whereas others only included sorbets and other water based ices. In recognition of this source of uncertainty, the UK Food Standards Agency has developed guidance notes on food additive legislation, which include guidance on interpretations of Directive food categories (Food Standards Agency 2002). Similarly, pesticides are mainly applied to raw agricultural commodities (RACs), which do not always reflect the food as eaten (*e.g.* wheat is not eaten as wheat, but as bread, breakfast cereals

etc.). Leclercq *et al.* (2003a) note that not all food consumption databases have recipe databases attached, which convert foods back to ingredients or raw agricultural commodities.

Although many large nutritional surveys are of very high quality and provide a great deal of solid information, they may fail to capture adequate information relating to specific foods (Petersen 2000). This may be because these foods are rarely consumed or are not of significant nutritional value. Examples include luxury foods such as caviar and seasonal foods such as Christmas cake and Christmas pudding.

1.2.2 Chemical occurrence

If a chemical is permitted for use in a given foodstuff, it does not necessarily follow that the chemical will be present in that foodstuff (Löwik 1996), since different recipe formulations of a food product may not necessarily include the same additive to perform a particular technological function. One way to deal with uncertainty regarding the occurrence of an additive in a given food is to assume that the additive is always used in every food in which it is permitted. However, this assumption will almost always lead to a considerable overestimate of true additive intakes (Nutriscan 1994). Since legislation governing the labelling of foods (European Commission 2000) requires a declaration of the qualitative use of additives in a given brand, a food ingredient or food additive database, constructed from food labels, can be a useful means of ascertaining the occurrence of an additive in a food. Because this information is in the public domain, there are no issues regarding commercial sensitivity. Food ingredient databases were proposed as useful tools in the overall scheme of routine monitoring of food additives in the EU (Nutriscan 1994). Löwik (1996) suggested the use of ingredient or food additive databases as a starting point for more accurate estimation of food additive exposure in the EU and inspection of food labels was proposed as one means of obtaining more detailed information on qualitative additive usage for monitoring food additive usage across the EU (European Commission 1998). A number of food ingredient or food additive databases are currently in existence in the EU, though not all have been developed specifically for the purpose of monitoring additive intakes. In an assessment of the intake of ten food additives, Löwik *et al.* (1998) employed the use of two food ingredient databases, the Dutch food intolerance databank and the Grootverbuik product informatie (GPI) to obtain information on the proportion of brands within food groups that contained the selected food additives. This information was

used in conjunction with intake estimates of the food additives to determine the likelihood of exceeding their respective ADIs. In an exposure assessment of antioxidants, Leclercq *et al.* (2000a) used an Italian food labels databank to identify brands of processed foods that contained ingredients that were likely to contain the antioxidants in question. In a study, which compared deterministic and probabilistic estimates of exposure to flavouring substances, Lambe *et al.* (2002) used an Irish food ingredient database to determine the proportion of brands that were flavoured. One limitation associated with the use of food ingredient databases relates to the fact that foods that are not packaged (*e.g.* certain breads and cakes sold in store) or foods that do not require an ingredient declaration (*e.g.* beverages that contain more than 1.2% alcohol by volume) are not accounted for. In such cases, information on food additive occurrence should be sought from other sources.

Use of food chemical analytical data can provide useful information on the occurrence of a chemical in a food. Residue data for pesticides and certain additives (*e.g.* benzoates, sorbates) in foods are routinely monitored throughout the EU to ensure compliance with legislation. However, there are a number of issues to consider when interpreting results from analytical studies. Firstly, the samples which are analysed may represent target samples which are not likely to be representative of the total population of samples. If the limits of the analytical method do not detect the presence of a chemical, one has to consider whether these values represent real zeros or whether the chemical is present but is below the limit of detection (LOD) of the analytical method.

Expert opinion from industry can reveal useful information about the foods in which particular additives are likely to be present. Discussion with trade associations or other industry experts was suggested as an alternative option for obtaining more detailed information on qualitative additive usage for monitoring additive usage across the EU (European Commission 1998). In a study designed to compare methods for estimating exposure to intentionally added flavouring substances (Hall and Forde 1999), a group of experts was convened to provide information on the likelihood that a particular flavouring substance would be used in specific foods. Lambe *et al.* (2002) also used expert opinion from industry to obtain information on flavouring usage in 31 food categories.

1.2.3 Chemical concentration

Levels of chemicals in food products vary significantly (Kroes *et al.* 2002, Leclercq *et al.* 2003a). In the case of food additives, natural variability in food additive

concentration may occur as a result of differences in recipe formulations between manufacturers, the presence of the natural occurring form of an additive (*e.g.* ascorbic acid may be present naturally or intentionally added), effects of processing and degradation of the level of an additive over time. For example, Armentia-Alvarez *et al.* (1993) have shown that the concentration of sulphites is reduced with frying and cooking and is often far lower than the maximum legal limit. Additional sources of variability relating to other food chemicals such as pesticide residues and nutrients include seasonal and geographical variation, whilst sources of variability specific to pesticide residues include differences in agricultural practices, year-to-year variation in the application of pesticide residues and unit-to-unit variability in composite samples. In the case of the assessment of dietary exposure to food additives, MPLs are typically employed, thereby ignoring the variability in additive concentrations that may occur in foods. According to Langlais (1996), MPLs in the eyes of the EU food industry do not lend themselves to reliable additive intake estimates. This statement is supported by results from studies where concentration information was either sought from industry or by analytical determinations. In a survey of artificial sweetener intakes in Italian teenagers, Leclercq *et al.* (1999) obtained concentrations of artificial sweeteners from manufacturers, where such information was not already reported on the wrapper labels. In all of the foods examined, mean sweetener concentrations were lower than MPLs and maximum concentrations did not exceed MPLs for any food. In a survey on colour usage in foods, MAFF (1987) obtained information from manufacturers on amounts of coloured ingredients used in foods. When the authors examined the distribution of colour concentrations for each colouring matter, most of the distributions exhibited a peak at low concentrations. Analytical studies that have determined levels of artificial food colours (Cecilia *et al.* 1992), preservatives (Ishiwata *et al.* 1997a,b), sulphites (Leclercq *et al.* 2000b) and antioxidants (Maziero *et al.* 2001) have, in most part, indicated low concentration levels of additives relative to MPLs. In the case of flavouring substances, Lambe *et al.* (2002) reported wide variations on likely concentrations of flavouring concentrations in 31 food categories using information from flavour manufacturers. Likely concentrations ranged from <0.0001 to >1000 ppm.

Ascertaining levels of additive concentrations in foods has been identified as a difficult task as analytical determinations are expensive and obtaining such information from the food industry is considered commercially sensitive (Nutriscan 1992, 1994, Langlais 1996). Technological levels of use may provide more refined estimates than MPLs

(Nutriscan 1994). However, these, along with actual concentrations from manufacturers may not reflect the true concentration in the food as eaten, since 'overages' are necessary at the manufacturing stage to compensate for the loss of the additive that may occur over time due to oxidation (Nutriscan 1994). When attempting to determine levels of additive usage from manufacturers, an additional source of uncertainty occurs if the manufacturer does not buy the food additive in isolation but buys ingredients which already have the additives added to them (European Commission 1998). This situation arose in the MAFF colour survey (MAFF 1987) where ingredient suppliers had to be contacted to ascertain levels of additives used in coloured ingredients, which added complexity to the task of monitoring and made the whole process more time consuming. For some food additives such as sulphites and nitrites, it is known that the amount added by a manufacturer does not represent the amount present in the food when it is consumed. In these situations, it may be necessary to determine the amount of the additive actually consumed using chemical analyses of representative samples of the relevant foods to obtain a more accurate estimate of intake. Concentrations for certain food additives may be obtained from monitoring programmes for assessing compliance with legislation. However, use of these data requires consideration of their relevance for the exposure assessment in question, since there may be uncertainties regarding the analytical method used, treatment of values below the LOD, laboratory-to-laboratory variation in analytical results and the time frame to which the analyses pertain.

1.3 Approaches for the estimation of food chemical intakes

As mentioned in section 1.1.2, the general approach for the estimation of food chemical intakes is to begin the process using crude screening methods and only proceed to more refined methods if results from crude screening methods dictate the need to do so. Examples of crude screening methods are described elsewhere (Rees and Tennant 1993, Nutriscan 1994, European Commission 1997). The approaches described hereon, are located higher up on the prioritization scheme for the estimation of food chemical intakes and would only be employed if results from less refined methods dictated the need to do so.

Ideally, the food consumption data required for an exposure assessment should mirror the foods on which the food chemical concentration data are based (Leclercq *et al.* 2003a). However, with the exception of duplicate diet studies, exposure assessments do not have consumption, occurrence and concentration data related to the same individuals in the

population. Therefore, some degree of modelling is usually required in assessments of exposure to food chemicals to attempt to create a representation of the real-life situation (Kroes *et al.* 2002, Lambe 2002). Exposure estimates can then be compared with toxicological end points (*e.g.* ADIs) to assess the relevance of exposure to human health. Petersen *et al.* (1994), Petersen and Barraj (1996), Parmar *et al.* (1997), Kroes *et al.* (2002) and Lambe (2002) describe approaches to combine food consumption with chemical concentration data. These can be summarized as (i) point estimates (ii) simple distributions and (iii) probabilistic analysis. These are described below, together with examples of exposure methods relating to each.

1.3.1 Point estimates

The point estimate approach is a single 'best guess' estimate of each variable within a model to determine the model's outcome(s) (Vose 2000). Typically, a fixed value for food consumption (*e.g.* mean population value) is multiplied by a fixed value for chemical concentration relevant to that food (*e.g.* mean concentration or maximum permitted level (MPL)). The chemical intake from all foods is then summed to estimate total dietary exposure (Kroes *et al.* 2002, Lambe 2002). A common assumption inherent in the point estimate approach, is that all individuals consume the specified food(s) at the same level, that the food chemical is always present in the food(s) and that it is always present at an average or high level (Kroes *et al.* 2002, Lambe 2002). The approach ignores the existence of variability in food consumption and chemical concentration levels and therefore, does not provide an insight into the range of possible exposures that may occur within a population. Examples of food additive exposure methods, which come under the heading of the point estimate approach, include the theoretical maximum daily intake (TMDI) and the estimated daily intake (EDI) (FAO/WHO 1989). Examples of equivalent exposure methods for pesticides and flavouring substances include the national estimate for short-term intake (NESTI) (PSD 2001, López *et al.* 2003) and the theoretical added maximum daily intake (TAMDI) (Cadby 1996), respectively. Both the theoretical maximum daily intake (TMDI) and estimated daily intake (EDI) for food additives (FAO/WHO 1989) involve the utilization of information from food consumption databases. In the TMDI method, average per capita daily food consumption is multiplied by the MPL for the additive in question for a given food group, assuming a 100% probability of presence of the additive in the food group. Intakes are then summed to calculate overall

additive intakes. The TMDI is considered a hypothetical figure based upon an extreme theoretical case, which can ensure safety if the intake falls below the ADI (FAO/WHO 1989). Leclercq *et al.* (2000a) and Garnier-Sagne *et al.* (2001) have used the TMDI method as part of a stepwise approach to estimate the intake of antioxidants and sweeteners, respectively. The EDI method is a refinement of the TMDI and can be used in situations where estimates based on the TMDI do not fall below ADIs. Estimated daily intakes represent the amount of an additive ingested by an average consumer based on actual use levels, as opposed to MPLs. Actual use levels can be sought from the industry (FAO/WHO 1989). Jung Yoon *et al.* (2003) conducted a study in which the intake of benzoates was estimated using the EDI method. Whilst the TMDI and EDI methods, which employ the use of food consumption databases provide a more realistic picture of additive intakes compared to the other methods described thus far, neither variability in food consumption nor variability in additive concentrations is taken into account. Furthermore, when high percentile values are used to represent food consumption and/or chemical concentration, summing the intakes from multiple sources may lead to very conservative and often implausible estimates of intake. This feature is often referred to as 'creeping conservatism' in literature pertaining to probabilistic analyses.

1.3.2 Simple distributions

In the context of exposure assessments, the term 'simple distribution' is used to describe a method that employs distributions of food intake but uses a fixed value for the concentration variable (Kroes *et al.* 2002). The Step 2 method for food additives (European Commission 1997) comes under the umbrella of the simple distribution approach. When using this method, each individual's intake of each of the foods in which an additive is permitted is multiplied by the MPL of the additive in those foods. Additive intakes from each food group are summed to estimate each individual's total intake of the additive. A distribution of additive intakes from all individuals in the database is generated, from which additive intakes at any given percentile can be obtained. This method requires a computerised food consumption database and is usually performed when results from exposure estimates based on less refined methods suggest that additive intakes may exceed ADIs and therefore, do not rule out the possibility of potential concern. The method generates a more accurate and realistic estimate of additive intakes compared to the TMDI and EDI approaches since it takes account of inter-individual variability in food intakes.

Arcella *et al.* (2003) used the Step 2 method in a study that aimed to assess the validity of a probabilistic model of intense sweeteners in Italian teenagers. Whilst the simple distribution approach takes account of variability in food consumption patterns, it still assumes 100% occurrence of an additive in every food included in the exposure assessment and that the additive is present in every food at its MPL (fixed value). Typically, a point estimate of exposure is presented (*e.g.* mean or upper percentile) for comparison with safety statements (*e.g.* ADI). Therefore, the approach can still be considered deterministic.

1.3.3 Probabilistic approach

Whilst the deterministic approach is relatively simple, inexpensive and has served exposure assessors well in the past and has gained widespread acceptance in the regulatory community, it has a number of associated shortcomings. Burmaster and von Stackelberg (1991), Thompson *et al.* (1992), Finley and Paustenbach (1994), Thompson and Graham (1996), ILSI (1998), Cullen and Frey (1999), Petersen (2000), Kroes *et al.* (2002) and Lambe (2002) discuss these. By employing conservative assumptions to generate 'worst case' estimates of exposure, deterministic modelling swamps the uncertainty and variability associated with the exposure variables. Therefore, no information is available to exposure assessors and risk managers on the range of possible intakes within a population, on the proportion of the population likely to exceed a given intake level, and on the main factors that influence the results of an assessment. This obscures the ability of regulators to determine which scenarios present a risk that is likely to occur and needs to be addressed. Furthermore, the definition of high-level consumers varies between different regulatory authorities but is normally either the 90^{th}, 95^{th} or 97.5^{th} percentile of the distribution of individual intake values (Benford and Tennant 1997). This makes comparisons of results across assessments more difficult.

A demand for more realistic estimates of exposure together with an increasing need amongst risk managers to obtain a full distribution of risk has focused attention in recent years on the use of probabilistic techniques for the estimation of dietary exposure to food chemicals. Probabilistic techniques are also referred to in the literature as Monte Carlo analysis, quantitative uncertainty or distributional analysis. Probabilistic analysis of dietary exposure to food chemicals uses distributions for both food consumption and chemical concentration data to characterize their variability (*i.e.* natural variation in a model input that is irreducible) and/or uncertainty (*i.e.* lack of knowledge about the true values of a

given model input, which may be reduced by further measurement). Use of the probabilistic approach for the estimation of dietary exposure to food chemicals addresses the weaknesses of traditional deterministic methods (Burmaster and von Stackelberg 1991, Thompson and Graham 1996). A probabilistic analysis makes results from exposure assessments more informative to risk managers by giving some perspective of the uncertainty behind point estimates (Thompson *et al.* 1992). The benefits of a probabilistic analysis are summarized by Finley and Paustenbach (1994), ILSI (1998), US EPA (2001) and Ferrier *et al.* (2002). Table 1.1 illustrates the benefits of a probabilistic analysis for the estimation of food chemical exposure. Two primary advantages of the probabilistic approach for exposure assessments as discussed by Kroes *et al.* (2002) and Lambe (2002) are (i) it permits the exposure assessor to consider the whole distribution of exposure, from minimum to maximum, with all modes and percentiles, and (ii) it includes a comprehensive analysis of the sensitivities of the resulting exposures with respect to uncertainties in parameters. Results from sensitivity analyses permit risk managers to consider the relative merits of different strategies for reducing exposure in cases where levels of exposure are deemed unacceptably high. Confidence intervals related to uncertainty in the measurements can be calculated for the parameters of all frequency distributions, allowing an estimate of uncertainty in probabilistic estimates of food chemical intakes to be quantified.

The technique requires the use of software modelling programs. Use of generic software programs such as @RISK® (Palisade Corporation, Newfield NY) and Crystal Ball (Decisioneering, Inc., Denver, Colo.) are commonly cited in the literature regarding probabilistic assessments. The structure of a probabilistic model may be similar to a deterministic model (*e.g.* food chemical intake = {food consumption x chemical concentration}/body weight), except that each input variable is represented by a distribution instead of a point estimate. Model input distributions are inputted to the software modelling program using distribution parameters (*e.g.* a mean and standard deviation can be used to represent a lognormal distribution). Let us consider the simple model of exposure mentioned above. In a process called iteration, a value is drawn at random from a food consumption distribution, with a probability of being selected governed by the shape of the underlying distribution. A value is then drawn from a discrete distribution representing the likelihood of a chemical being present in that food. If a value drawn from the discrete distribution denotes that the chemical is absent from that food (*e.g.* zero), then the chemical intake for that particular iteration is zero. If the value drawn from the discrete distribution

indicates that the chemical is present (*e.g.* one), then the computer randomly selects a value from a chemical concentration distribution pertaining to that food, with a probability of being selected governed by the shape of the underlying distribution. The consumption and concentration values are multiplied together and then divided by a randomly selected body weight, to produce one intake estimate of the chemical. The process is repeated many (*e.g.* 1000) times, in a process called simulation, where each time, a different random set of values are selected from each input distribution to produce a new possible outcome value. The result is a distribution representing the full range of exposure of the chemical intake for the given sample. From this output distribution, the assessor can select any level of exposure and read the probability of its occurrence and determine the proportion of the population above any selected level of exposure (*e.g.* ADI). Figure 1.2 depicts a graphical illustration of the process. A convenient way to understand the probabilistic approach for quantifying variability is to visualize each iteration as a hypothetical subject and the collection of all iterations (*i.e.* simulation) as representing the population of interest. The illustration in figure 1.2 serves as a simplified example to illustrate the application of probabilistic modelling to food chemical exposure assessments. In reality, additional model inputs would be employed, such as information on the percent consumers of a food, body weights of individuals, the presence of correlations between input distributions and effects of processing, storage *etc*. These are simulated in a similar manner consistent with the mathematical model (equation) used to describe the exposure process. From a practical point of view, once a model and input data have been selected and entered into an appropriate software program, the required number of iterations and simulations are set and the model is analysed to determine the range and probabilities of all possible outcomes (Palisade Corporation 1997a).

Most commercial software modelling programs such as @RISK® offer two types of sampling. These are Monte Carlo sampling and Latin Hypercube sampling (Palisade Corporation 1997a). Monte Carlo sampling is entirely random. That is, a value is randomly drawn from any point on the input distribution, with values more likely to be drawn in areas of the distribution, which have a higher probability of occurrence. This technique, according to Vose (2000) is the oldest and best known. Its limitation, however, is that values will less likely be drawn from areas of an input distribution which have a low probability (*i.e.* distribution tails) compared with areas of the distribution which have higher probability outcomes. This limitation led to the development of stratified sampling

techniques such as Latin Hypercube sampling (Palisade Corporation 1997a). Using this sampling technique, the input distribution is divided into intervals (stratified) and sampling is forced to select values from each interval. This ensures that values from the entire range of the input distribution will be sampled in proportion to their probabilities of occurrence. Because the distributions are sampled over the entire range of probable values, the number of iterations required to adequately represent an input distribution is less for Latin Hypercube sampling compared to random Monte Carlo sampling.

Probabilistic models which employ distributions that reflect variability in model inputs are known as one-dimensional probabilistic analyses, whereas models which employ variability and uncertainty distributions are known as two-dimensional probabilistic analyses. In a two-dimensional probabilistic analysis, the variability in a population is described by a probability distribution and uncertainty is modelled by placing a distribution on the parameters of the variability distribution (*i.e.* the uncertainty distribution). Therefore, variability and uncertainty distributions are simulated in tandem during the modelling process. One-dimensional and two-dimensional probabilistic techniques are also referred to as one-stage and two-stage Monte Carlo modelling. Although recommendations regarding the separation of variability and uncertainty (*i.e.* two-dimensional modelling) were incorporated into the *Guiding Principles for a Monte Carlo Analysis* developed by the US EPA (1997), one-dimensional probabilistic techniques are currently more common than two-dimensional probabilistic techniques. The latter require more data (*i.e.* specifying uncertainty distributions in addition to variability distributions) and are more computationally intensive than the former. Nevertheless, Cullen and Frey (1999) note that two-dimensional probabilistic concepts are gaining increasing attention in the context of human exposure and risk assessment. Within the context of this thesis, however, work conducted with regard to probabilistic analyses, relates solely to one-dimensional probabilistic techniques.

Whilst the probabilistic technique has been used in many disciplines of science as well as engineering, finance and insurance over the past 50 years, its application to human health risk assessments was rarely used prior to 1989 (Finley and Paustenbach 1994). Advances in computer technology have facilitated more recent use in this area. However, generic risk analysis software modelling programs such as @RISK® and Crystal Ball have not been designed for the estimation of food chemical exposure. Probabilistic analysis is also beginning to benefit from advances in parallel processing technology to dramatically

speed up simulations (Kroes *et al.* 2002). Whilst environmental (Carrington *et al.* 1996, Hoover 1999) and microbiological (Hope *et al.* 2002) exposure assessments employing probabilistic techniques have been carried out, application of probabilistic techniques to food chemical exposure assessments is less common. Examples of studies carried out to date include an assessment of acute dietary exposure to pesticide residues in fruit and vegetables (Hamey and Harris 1999, Hamey 2000) and the assessment of dietary exposure to intentionally added flavouring substances (Lambe *et al.* 2002).

1.4 Application of probabilistic modelling to food chemical exposure assessments

Whilst probabilistic methods confer many advantages over deterministic methods, not every exposure assessment warrants the application of this technique for the estimation of food chemical intakes. For example, it may be unnecessary to perform a Monte Carlo analysis when screening calculations show exposures or risks below levels of concern. Since the use of a probabilistic analysis is more complex, more time consuming and more resource intensive than traditional deterministic methods, often a tiered approach can be helpful to decide whether a probabilistic analysis can add value to an assessment (US EPA 1997). That is, starting with a crude and simple analysis (*i.e.* deterministic methods) and only proceeding to a more sophisticated analysis (*i.e.* a probabilistic analysis), if results from crude methods dictate the need to do so.

The US EPA (1997) describes the following steps, which should be considered in a probabilistic analysis:

- Defining the assessment question.
- Selection and development of the conceptual and mathematical models.
- Selection and evaluation of available data.
- Selecting input data and distributions for use in the analysis.
- Evaluating variability and uncertainty.

Cullen (1999) describes a similar sequence of steps. With regard to the first step, consideration should be given to the purpose of the assessment, the population group for which the exposure assessment is required and whether the assessment aims to assess acute

exposure (*e.g.* intakes per meal or per day) or chronic exposure (*e.g.* average daily intakes). The remaining steps are described in more detail throughout the following sections.

1.4.1 Development of conceptual models

After defining the purpose of an exposure assessment, the next important step in a modelling process is the development of a conceptual model. A model may be viewed as a mathematical representation about how a system works. The purpose of a model is to represent as accurately as necessary a system of interest (Cullen and Frey 1999). Within the context of food chemical risk assessment, conceptual models should strike a balance between embracing as many factors as possible and not being excessively elaborate (Gibney and van der Voet 2003). The degree of accuracy required will depend on the purpose of the assessment. For example, a model designed for screening purposes may not need to be accurate, but it may need to be conservative whereas a model designed to estimate an accurate intake of a pesticide in a population may need to employ various model components such as unit to unit variability, treatment of analytical residue values below LODs, effects of processing *etc*. Conceptual models are usually illustrated in terms of flow charts or diagrams to represent the assessment of interest. An illustration of a conceptual model for a food additive is depicted in figure 1.3. Extensive potential exists for the use of probabilistic approaches to many different types of food chemicals, but this potential can only be realized if there is sufficient knowledge of the pathways of exposure, the effects on concentration at various stages in the food chain, food consumption patterns and other pertinent exposure factors, to create reliable models and provide reliable input distributions (Kroes *et al.* 2002). Models are usually developed in a transparent and iterative process and involve liaisons between a team of specialists from several different disciplines. Such experts can contribute knowledge and identify important factors that should be included in the model, provide advice on the likelihood of obtaining relevant data for model components and provide insight into the relevance of existing data and/or surrogate data that may be used. In the case of food chemical exposure assessments, such specialists comprise food consumption experts, chemical sampling experts, analytical chemists, food technologists, nutritionists, statisticians and computer specialists. Whereas conceptual models describe the inter-relationship of datasets, which best determine exposure, in reality not all relevant data will be available. For example, whilst the influence of processing is included in a conceptual model for dietary pesticide exposure, such data

may not be easily attainable for every pesticide commodity combination (Boon *et al.* 2003). Until such data become available, a default value of one could be employed (*e.g.* a default of one would imply no effect of processing). Once a model has been developed, peer review by other experts in the field is important prior to commencing data collection or simulations. Furthermore, making a model accessible and encouraging other practitioners to use it and provide feedback may lead to further improvement and development of the model within the risk assessment community (ILSI 1998).

1.4.2 Model Validation

Whilst probabilistic modelling confers many advantages over deterministic estimates, the reliability of results from a probabilistic analysis is dependent on the validity of the model and the quality of the model inputs. Model validation, as described by Cullen and Frey (1999), is the comparison of modelled results to observations from the system being modelled. Ideally, all models should be validated to ensure that modelled estimates represent as closely as possible the reality that is being modelled. However, it is acknowledged that this can be a difficult and costly task (Kaplan and Burmaster 1999). Whilst peer review of models will likely be an essential component of the model validation process, it is recognized that it can only offer partial validation of a model (ILSI 1998). These authors note that in certain situations, consultants may consider their model proprietary and are reluctant to release them to potential competitors. Validation of individual model components (*e.g.* food consumption input data or chemical concentration input data) with observed measurements is a useful tool to ensure that all sub-parts of the model are valid. This process is particularly useful to identify any flaws in the model's components, which may not be detected if the overall results from the full model are considered acceptable. However, such an approach can only be considered as a partial validation (Cullen and Frey 1999). In certain situations, it may not be possible to use measured data to validate a model. For example, it is not possible to validate habitual or lifetime exposure to a food chemical since the duration of most food surveys ranges from 24 hours to seven days. Comparing results from different modelling approaches using the same datasets represents a possible option to use during model validation. If different approaches lead to similar conclusions, confidence is increased in both the models and the results. However, unless the model which is to be used as a benchmark has itself been validated, the comparison of models can be highly misleading as different approaches could

lead to similar but inaccurate results, or similar results but for different reasons (ILSI 1998, Cullen and Frey 1999). Therefore, this approach is only recommended to form part of a validation process (ILSI 1998). Comparison of modelled outputs with actual exposure measurements constitutes a central component of any validation process (Kroes *et al.* 2002). Owing to a current lack of validated probabilistic models for food chemical exposure assessments coupled with a critical need to test and validate distribution models against actual exposure/dose data (ILSI 1998, Petersen 2000, 2003), an EU funded Fifth Framework research project entitled *Development, validation and application of stochastic modelling of human exposure to food chemicals and nutrients*, commonly referred to as the 'Monte Carlo' project, was commissioned (Gibney and van der Voet 2003). One of the objectives of this project was to develop conceptual models for a range of food chemicals (food additives, pesticide residues and nutrients) and to validate these models using actual exposure measurements from brand level food consumption and concentration databases (additives), duplicate diets (pesticide residues) and biomarkers (nutrients). From a risk assessment perspective, one of the most important considerations is that a model should not under-estimate exposure. Therefore, validation studies should consider not only the predictive accuracy of the model, but also its overall usefulness as a tool for assessing exposure (Kroes *et al.* 2002). Furthermore, validation of modelled estimates should take into account the entire distribution of exposure, or at least the portion of the distribution that is of interest for the exposure assessment.

1.4.3 Data quality

The quality of results derived from a probabilistic analysis depends, to a large extent, on the quality of the data used in the assessment (Petersen and Barraj 1996, Petersen 2000, Binkowitz and Wartenberg 2001, Ferrier *et al.* 2002, Kroes *et al.* 2002). According to Kaplan and Burmaster (1999), the main sources of uncertainty in risk analysis are the lack of complete data and how the available data are interpreted for use in risk analysis. Therefore, a probabilistic food chemical exposure assessment should include an evaluation of the quality and completeness of the data used in the assessment. The quality of the data may be evaluated in terms of temporal relevance and relevance in terms of population and food groups (Kroes *et al.* 2002, Lambe 2002). It is also worth noting that many of the issues relating to the quality and quantity of the data are also relevant to deterministic exposure assessments.

Ideally, an exposure assessment for a food chemical, and thus the food consumption data underpinning it, should reflect the time frame of the toxicological end point (*e.g.* ADI) for that chemical (Löwik 1996, Löwik *et al.* 1998, 1999). Since the toxicological end points upon which intakes of food chemicals are based reflect lifetime exposure (WHO 1987), ideally consumption data would be monitored over prolonged periods. However, practicality dictates that detailed food consumption studies are conducted over periods of a few days (typically 24 hours to seven days). Therefore, it is important to be aware of this source of uncertainty and to make allowances for the limitations of the methods used. Whilst longer-term survey durations (*e.g.* 7-day records) provide a good estimate of habitual food intakes, short-term survey durations (*e.g.* 24 hour recalls) will over-estimate the prevalence of low and high intakes (Löwik *et al.* 1996). Renwick (1999) notes that a 7-day survey duration is a good compromise between reliability and relevance. Lambe *et al.* (2000a) explored the influence of survey duration on estimates of food chemical intakes. The results from this study revealed that an increase in survey duration (from one day to 14 days) was associated with an increase in the percent consumers of foods and a corresponding decrease in mean intakes amongst consumers. Another study conducted by Lambe *et al.* (2000b) explored whether food intakes derived from a short term survey duration (*i.e.* 3-day diary) combined with a qualitative food frequency questionnaire (FFQ) could be used to predict mean consumer only food intakes derived from a longer term survey duration (*i.e.* 14-day diary). Although based on a specific population group (*i.e.* teenagers), this baseline study indicated that a combination of a 3-day food diary plus a food frequency questionnaire gives similar data to those obtained by the more intensive and expensive method of a 14-day diary. Therefore, in situations where it is not possible to conduct lengthy food diary surveys, the addition of a qualitative FFQ to a shorter diary could be considered as a possible alternative. Advanced statistical methods (*e.g.* the Nusser method) are available for extrapolating from short term to long term intakes. However, Löwik (1996) suggests that before applying advanced statistical techniques to obtain distributions of usual intakes, it may be wise to consider whether this is necessary from a risk management perspective. Since estimates based on short term survey durations will lead to over-estimation at distribution tails, and therefore err on the side of conservatism, exposure estimates based on lifetime intakes will be lower (Löwik *et al.* 1998). For certain chemicals (*e.g.* pesticides), acute toxicological end points (*e.g.* acute reference dose (ARfDs)) form the basis of safety statements (Hamey and Harris

1999, Hamey 2000). In this case, acute rather than chronic toxicological end points must be considered in an exposure assessment. In surveys covering more than one day, consumption per episode may be higher than intake values (expressed per day) calculated over the survey duration (Löwik *et al.* 1999). Therefore, acute exposure assessments should ideally employ consumption data based on a single eating occasion or consumption over a single day (Rees and Day 2000).

Since chemical concentration levels may vary depending on when they were measured and when the chemical was applied (Petersen 2000), the time frame to which chemical concentration data pertain should, to the extent possible, aim to encompass the time frame relevant for the consumption data used in the assessment.

Whilst national nutritional surveys are of very high quality and provide a great deal of information, they may not capture information about the specific parameters required in a given analysis (Petersen 2003). Specific population groups considered 'at risk' on the basis of previous knowledge of dietary habits serve as an example to illustrate this. Examples of such populations include diabetics or weight reducers, in the case of artificial sweeteners, or children, who consume more food and fluids than adults on a body weight basis. In many cases, separate ad hoc surveys may be required to obtain more realistic exposure estimates for these population subgroups. Examples of exposure assessments which have been undertaken for specific population subgroups include a study which estimated artificial sweetener intakes amongst Italian teenagers (Leclercq *et al.* 1999) and an assessment of intakes of artificial food colours by Brazilian children (Cecilia *et al.* 1992). An issue that has been the subject of discussion in the past is whether exposure estimates should be expressed as total population (*i.e.* consumers and non consumers) or consumers only. In general, the intake of a food chemical amongst consumers will be higher than the intake amongst the total population (except in a situation where there are 100% consumers of the food). Therefore, to err on the side of caution, it is generally considered that intake estimates generated for risk assessment purposes be based on intakes amongst consumers only (Gibney 1995, European Commission 1998). However, Löwik *et al.* (1998, 1999) advocate the use of total population intakes so that quantification of the prevalence of risk will have the same basis for the various chemicals.

As mentioned in section 1.3, the food consumption data included in an exposure assessment should ideally mirror the foods in which the chemical concentration data are based. However, this ideal is often difficult to achieve (Lambe 2002, Leclercq *et al.* 2003a),

especially if the food consumption data has been collected primarily for the purpose of estimating nutrient intake (Gibney and Lambe 1996, Langlais 1996). This issue of relevance in relation to food groups has been discussed in detail in section 1.2.1. Energy under-reporting is an important consideration with regard to data quality of food groups. Whilst the implications of this issue with regard to food chemical exposure assessments has been raised Gibney (1999), it not yet possible to determine which foods may be under-reported more than others (Gibney 1999).

Food chemical exposure assessments are usually required to reflect exposure at the upper tail of a distribution (Lambe 2002). Unless the sample size is very large, there will be few data points at the tails of the distribution, and this will lead to large uncertainties associated with estimates based on distribution tails (Lambe 2002). Therefore, regardless of the percentile of intake chosen for comparison with ADIs, accurate estimates of high percentile values can only be obtained if the sample size is sufficiently large (European Commission 1998, Kroes *et al.* 2002). In this regard, guidance on minimum sample size requirements for high percentile values (>P75 percentile) is presented by Kroes *et al.* (2002). These authors suggest that for a simple random sample, the sample size (n) satisfies the rule $n(1-P) \geq 8$ for high (>P75) percentile values.

Bootstrapping is a statistical technique that can be used to measure the uncertainty associated with parameters of a distribution due to sample size (Cullen and Frey 1999). This technique involves random sampling with replacement from an original sample of values to generate an estimate of uncertainty surrounding a selected statistic from that sample. For example, given a sample of size *n*, a bootstrap sample of size *n* is created by sampling with replacement from the original sample. The process is repeated *y* times (*e.g.* 1,000) to generate *y* bootstrap samples of size *n*. A required statistic (*e.g.* median or 97.5^{th} percentile) for each bootstrapped sample is calculated. The distribution of 97.5^{th} percentile estimates generated from the 1,000 bootstrapped samples represents the bootstrapped estimate of uncertainty about the 97.5^{th} percentile calculated from the original sample. An illustration of the bootstrap technique to assess sample uncertainty is depicted in table 1.2. This technique has been applied to assess sample uncertainty by Boon *et al.* (2003) and by López *et al.* (2003), as part of validation of a probabilistic model of dietary exposure to pesticide residues in infants.

1.4.4 Selecting modes of model inputs

Having selected a conceptual model and evaluated the data to incorporate into the model, the next step in the process is to consider the mode of model input data. Model inputs representing continuous random variables can be entered as raw data or as distributions. One prerequisite for the use of raw food consumption data is the availability of an electronic food consumption database. This may be at the level of individual eating occasions or at average daily intake level. The advantages of using raw food consumption data, as described by Lambe (2002), is that data are maintained at the level of the individual and the need to build in correlations between intakes of multiple foods is negated. Moreover, there is greater flexibility for designing models to combine consumption data and concentration data. However, Lambe (2002) also highlights the potential disadvantage that the minimum and maximum of the observed food consumption data, which is entered into the model, may not reflect the population minimum and maximum.

Model input distributions may be empirical (*e.g.* histograms, cumulative distributions and discrete distributions) or parametric (*e.g.* normal, lognormal, gamma). Empirical distributions represent a mathematical description of their shape, whereas parametric distributions are based on a mathematical function whose shape and range is determined by one or more distribution parameters (Vose 2000). This section focuses specifically on the selection of distributions to characterize variability in model inputs (*e.g.* variability in food intake patterns). One reason that has been cited for the limited use of probabilistic techniques in exposure assessments is the lack of consensus on the most appropriate distributions to use for key exposure variables (Finley and Paustenbach 1994, Finley *et al.* 1994). The reliability of the results of a probabilistic analysis is dependent on the quality of the distribution of values used to represent the input variables in a model (Lipton *et al.* 1995, Seiler and Alvarez 1996, Petersen 2000, Binkowitz and Wartenberg 2001, US EPA 2001, Kroes *et al.* 2002). Poor selection criteria and/or inadequate justification for the choice of an input distribution contribute to skepticism regarding probabilistic techniques. Bukowski *et al.* (1995) have shown that distributional shape can have a substantial influence on estimates of risk. A critical review of input distributions for use in Monte Carlo simulation revealed that even where extensive data existed, investigators used a variety of different distributional shapes to approximate the same data (Binkowitz and Wartenberg 2001). The implication of this finding is that the choice investigators have made for input distributions may substantially affect the outputs of their

analyses. Two key components of a food chemical exposure assessment relate to food consumption and the concentration of a chemical in a food. Therefore, an inappropriate choice of distribution to represent these two model components may have an important influence on the distribution of chemical exposure, in particular if the choice of distribution leads to an under-estimation of exposure at upper tails. Whilst there are no firm rules governing whether one should choose an empirical or parametric distribution to represent model inputs, there are a number of considerations to bear in mind. These are discussed below.

1.4.4.1 Empirical distributions

Experts attending a workshop on *Selecting Input Distributions for Probabilistic Assessments* (US EPA 1999) expressed the general opinion that the choice of empirical distribution function (EDF) versus a parametric distribution function (PDF) for use in probabilistic assessments is usually a matter of preference, and that there should be no rigid guidance requiring the use of a PDF or an EDF in any particular situation (US EPA 1999). Nevertheless, they suggested the following situations where they would prefer to use an EDF:

- Where there is a large number of data points (*e.g.* 12,000).
- Where there is access to high speed storage and retrieval systems.
- Where there is no theoretical basis for selecting a PDF and/or
- Where one has an 'ideal' sample.

The advantages of using EDFs to represent model inputs as described in a subsequent report by the US EPA are as follows (US EPA 2001):

- They provide a complete representation of the observed data with no loss of information.
- They do not depend on the assumptions associated with estimating parameters for theoretical probability models.
- They are designed to provide direct information about the shape of the distribution, which reveals skewness, multi-modality and other features of the dataset.

One key criticism of the use of EDFs in probabilistic assessments is that they are limited to the range of observed data and therefore, may not adequately represent the tails of a distribution (Taylor 1993, US EPA 1999, 2001). For some chemicals, residue data are available in EDF format. For example, EU pesticide residue data are available in histogram format with 12 intervals and residue data from the Spanish pesticide residue monitoring programme are available in histogram format with three intervals (Carcamo and Ocio 2001). Whilst such data provide useful information on the distribution of pesticide residues, they do not provide much scope for flexibility in model input format for use in probabilistic models. Access to observed residue data allows an assessor to create EDFs where the number of intervals can be manipulated in accordance with the level of detail required for the assessment. Histograms of food consumption and food chemical concentrations have been created from observed data in a model used to estimate the intake of intentionally added flavouring substances (Lambe *et al.* 2002) and a model used to estimate dietary exposure to pesticide residues (Hamey and Harris 1999, Hamey 2000). However, access to observed data is not always easily attainable and in such cases, the assessor may have to consider alternative options. In an effort to encourage the use of probabilistic modelling coupled with a lack of consensus on the proper distributions to use for key exposure variables, Finley *et al.* (1994) have suggested standard empirical and parametric distributions for a range of exposure variables that are commonly used in exposure assessments. However, the exposure variables cited in this paper (*e.g.* skin surface area, inhalation rate, tap water and soil ingestion rates, time spent at one job *etc.*) are of little relevance to food chemical exposure assessments.

1.4.4.2 Parametric distributions

Whilst the range of values from an EDF are usually confined by the minimum and maximum of the observed data, one key advantage of a parametric distribution is that it can extend beyond the range of the observed data. A second advantage is that it can represent a large set of data values in a compact way (Cullen and Frey 1999, US EPA 1999, 2001). That is, instead of reporting the individual data values, one can report the distribution (*e.g.* lognormal) and the estimated parameter values of that distribution (*e.g.* arithmetic mean and standard deviation). One key source of uncertainty regarding the use of parametric distributions in probabilistic modelling is the selection of the most appropriate distribution

to represent key exposure variables. Given the range of parametric distributions, it is generally recommended to narrow the set of possible distributions to those that are considered plausible based on knowledge of the underlying data, and then apply goodness-of-fit tests to the candidate distributions to ascertain the fit (US EPA 1997, US EPA 1999, Vose 2000, US EPA 2001). Lipton *et al.* (1995), US EPA (1997, 1999) and Vose (2000) and provide guidance on the selection of input distributions to represent variability in model inputs. An initial step is to determine if the random variable is continuous (*e.g.* amount of fish consumed) or discrete (*e.g.* number of times fish was consumed in one week). Another important consideration is whether there are plausible bounds or limits to a variable (*e.g.* are values below zero likely to exist?). If a random variable is known to take on only positive values (*e.g* food intakes), then the range of plausible distributions may be refined to those that have a lower bound at zero. Graphical inspection of the data can reveal important characteristics of the distribution shape (*e.g.* whether the observed data are likely to be skewed or symmetric or whether the distribution is multi-modal). According to the US EPA (2001), graphical methods are invaluable for exploring a dataset to understand the characteristics of the underlying population. In addition to considering the characteristics of the variable, if a given distribution is found to be a close fit to a given input variable in the published literature, then this distribution may serve as a useful candidate to consider (Ruffle *et al.* 1994).

1.4.5 Goodness-of-fit tests

Having identified a distribution or class of parametric distributions (*e.g.* right skewed distributions), which may be used to represent a given model input (*e.g.* food consumption), the next step in the process is to assess the quality of fit of the distribution to the observed dataset. Goodness-of-fit tests are one tool that can be used to assess the quality of fit. A goodness-of-fit statistic tells one how probable it is that a given distribution function produced a given dataset (Palisade Corporation 1997b). Lipton *et al.* (1995), US EPA (1997, 1999, 2001), Cullen and Frey (1999) and Vose (2000) discuss these. Three commonly used goodness-of-fit tests are the Chi-square, the Kolmogorov-Smirnov (KS) and the Anderson-Darling (AD). The Chi-Square test can be used with discrete or continuous data whereas the KS and AD tests can only be used with continuous data (Palisade Corporation 1997b). The AD test is generally recommended when the interest is on distribution tails (Palisade Corporation 1997b, US EPA 2001). Goodness-of-fit tests

allow an assessor to decide whether a particular theoretical probability distribution (*e.g.* lognormal) is a close enough approximation to claim that it represents a sample frequency distribution (Lipton *et al.* 1995). These tests involve a comparison of the actual data and the theoretical distribution under consideration. If one can conclude that the sample represents a known theoretical probability distribution, this distribution can be used in a probabilistic analysis. In goodness-of-fit tests, the null hypothesis states that the sample data were obtained from a population described by the specified distribution. The alternative hypothesis is that the sample data were obtained from a population described by a different distribution. Therefore, the objective of goodness-of-fit tests is to *fail* to reject the null hypothesis (US EPA 2001). Commercial software programs such as BestFit® (Palisade Corporation, Newfield, NY) run goodness-of-fit tests against a long list of candidate distributions. Observed data are inputted to the program, the program then makes a first guess at the parameters of candidate distributions and then assesses how well the candidate distributions match with the distribution of observed (sample) data using goodness-of-fit tests. When comparing a sample distribution to a theoretical distribution, a test statistic is calculated. This represents the maximum difference between the theoretical distribution and the distribution of sample values. The value of this test statistic is then compared to a distribution of that test statistic. If the value of the test statistic falls within the range of likely values of the test statistic, then the null hypothesis that the data were obtained from the hypothesized distribution cannot be rejected (Cullen and Frey 1999). If, on the other hand, the value of the statistic exceeds reasonable values of the distribution of the test statistic, then the null hypothesis is rejected, and therefore, the hypothesized distribution is rejected. A significance level is used to evaluate the fit of a theoretical distribution to the observed data. For example, a significance level (P) of 0.05 implies that a value of the test statistic below the 95^{th} percentile of the distribution for the statistic is acceptable and leads to an inability to reject the null hypothesis. If the value of the test statistic falls above the 95^{th} percentile of the distribution for the statistic, this would lead to a rejection of the null hypothesis. Cullen and Frey (1999) note that the selection of a significance level is one of the subjective aspects of goodness-of-fit tests. Whilst no recommendations on arbitrary significance levels for use in goodness-of-fit tests are provided by Lipton *et al.* (1995), US EPA (1997,1999, 2001) and Vose (2000), Cullen and Frey (1999) do note that a significance level of 0.05 is typically used. Moreover, it is generally recommended that the

(P) values of fitted distributions be documented so that the quality of the fit can be assessed (US EPA 1999, 2001).

Lipton *et al.* (1995) list the following general steps which are involved in a goodness-of-fit test:

- Formulate null and alternative hypotheses about the distribution of the variable, and select a significance level.
- Draw a random set of observations from the sample data.
- Derive a set of theoretical frequencies from a known distribution.
- Compare the observed frequencies from the sample data to the expected ones generated from the known distribution.
- If the overall discrepancy between the observed and theoretical frequencies is too great to attribute to chance at the selected significance level, reject the null hypothesis.

From a practical point of view, once an exposure assessor formulates null and alternative hypotheses and selects a significance level, the remainder of the above-mentioned steps can be carried out using commercially available software. However, the US EPA (2001) caution against the use of commercially available software programs to make the choice of a distribution based on a test statistic. The US EPA (2001) also note that goodness-of-fit tests have low statistical power and often provide acceptable fits to multiple distributions. In general, the larger the sample size (n), the greater one's confidence in the choice of probability distribution and the corresponding parameter estimates. Conversely, for small sample sizes, goodness-of-fit tests will often fail to reject many of the hypothesized distributions. These authors also state that although goodness-of-fit testing is a necessary part of distribution fitting, and tests are readily available with commercial software, it is less important than mechanistic considerations or graphical data exploration for choosing a candidate distribution (US EPA 2001). Therefore, the general recommendation is that results from goodness-of-fit tests be accompanied by graphical inspection of the fits (Burmaster and Anderson 1994, US EPA 1999, 2001, Vose 2000).

1.4.6 Truncation

An additional consideration regarding the use of parametric distributions in probabilistic food chemical exposure assessments relates to truncation. Truncation refers to imposing a minimum and/or maximum value on a probability distribution to prevent implausible or nonsensical values being generated (US EPA 2001). Truncation is typically considered when using unbounded probability distributions (*e.g.* normal, lognormal, gamma, Weibull). The decision of when to truncate should take into account whether the data are bounded (Matalas and Bier 1999). Identifying appropriate truncation limits that reflect 'plausible bounds' for an exposure variable will often require judgement. Therefore, choices should be made with caution and should be justified (Seiler and Alvarez 1996, Matalas and Bier 1999, US EPA 2001). There may be physiological or physical factors that can aid in setting plausible truncations limits. For example, a distribution of food intake might have a lower truncation limit of zero (since negative food intakes do not exist) and an upper truncation limit of (50g/kg bw/day), based on a physiological upper limit to the amount of energy that could be consumed on a daily basis (Hansen 1979). The advantage of truncating unbounded probability distributions is that the central tendency and high percentile risk estimates will not be biased by unrealistic values (US EPA 2001). However, a disadvantage is that the original parameter estimates (*e.g.* mean and SD) of the non-truncated distribution are potentially altered (US EPA 1999, 2001). Examples of truncation of unbounded distributions are described in studies conducted by Carrington *et al.* (1996) and Hoover (1999). The former study relates to a probabilistic analysis of dietary lead exposure where lognormal consumption and concentration model inputs were truncated with empirically selected values to avoid selection of unrealistic values (Carrington *et al.* 1996). The latter study refers to a probabilistic assessment of organochlorines in breast milk where a normal distribution used to represent the fat content of breast milk was truncated with a lower limit of zero, to prevent the generation of negative values in the simulation (Hoover 1999). At a *Workshop on Selecting Input Distributions for Probabilistic Assessments* (US EPA 1999), the issue of truncation of the tails of a parametric distribution was discussed, and received mixed opinions. Most of the experts seemed to view truncation as often unnecessary and should be used as a last resort. It was felt that the need for truncation may be a result of an inappropriate selection of a parametric distribution and that use of alternative PDFs should be considered. Even if an unrealistic value is sampled for

one input, it may not produce an extreme event in the model output. If truncation bounds are inappropriately selected, some relevant data may be rejected. Finally, one expert at the workshop expressed the opinion that truncation is only warranted if one is concerned about getting a zero or negative value, or an extremely implausible value. The US EPA suggests the use of a sensitivity analysis to determine whether truncation limits are an important source of uncertainty in risk estimates (US EPA 2001). This would involve running a model with and without truncation limits to ascertain the influence of truncation on intake estimates.

1.4.7 Modelling dependencies

An important issue closely related to the assignment of model input distributions for use in a probabilistic exposure assessment relates to the assessment of interdependence between two or more input variables. For example, a high consumption of food A may be associated with a high consumption of food B. Correlation is a measure of association between two quantitative random variables, which can be positive or negative, and a correlation coefficient (r) is a numerical measure of the strength and direction of the relationship between two variables (US EPA 2001). Ignoring the presence of correlations between distributions of foods in probabilistic exposure assessments of food chemicals may lead to an under-estimation of food chemical intakes, in particular if strong correlations exist between foods that make a large contribution to the intake of the food chemical. Burmaster and Anderson (1994) classify correlations ≥ 0.6 as strong correlations. Although the issue of dependencies between input variables in probabilistic exposure assessments is widely recognized (Smith *et al.* 1992, Thompson *et al.* 1992, Taylor 1993, Burmaster and Anderson 1994, Finley e*t al.* 1994, Bukowski *et al.* 1995, US EPA 1997, 2001, ILSI 1998, Cullen 1999, Cullen and Frey 1999, Petersen 2000, Vose 2000, Kroes *et al.* 2002, Hart *et al.* 2003), Lambe *et al.* (2002) report that there is little information on the extent of correlations between intakes of foods. A sensitivity analysis can be a useful first step to ascertain whether correlations are important in an exposure assessment (Burmaster and Anderson 1994, US EPA 2001). If the impact of including correlations is significant, then they should be identified and accounted for in a model. Such an approach has been taken by Hamey and Harris (1999) and Hamey (2000) using Spearman correlation coefficients ranging from 0.1 to 0.6 between distributions of intakes of fruit and vegetables. The authors reported only a marginal effect on results when simulations were run with and without

correlations. Therefore the use of correlations was omitted from the exposure analyses. An alternative way to account for correlations between model inputs is to create groups of parameters that co-vary, and treat each group as a new parameter (Cullen and Frey 1999). (*e.g.* creating an input variable for intake rate per unit body weight, as opposed to two separate input variables, representing input rate and body weight). The degree to which correlations affect the distribution of exposure is dependent on the strength of the correlation between the two variables and the contribution of the correlated variables to overall variance in the output (Cullen and Frey 1999). According to these authors, weak correlations and correlations between input variables that do not contribute significantly to the variance in the output, can be safely ignored without compromising the analytical results. In a probabilistic food chemical exposure assessment, correlations may exist between foods regarding (i) the percent consumers (ii) the amount consumed (iii) the likelihood of a chemical being present (iv) the amount of chemical present (v) the amount consumed and the level of residue present. As the Spearman rank correlation coefficient is a distribution-free method (*i.e.* can be applied to any type of distribution) of assessing correlation levels, this type of correlation is suitable for assessing the relationship between model inputs relating to distributions of food consumption and chemical concentration. Commercial software modelling programs such as @RISK® (Palisade Corporation, Newfield, NY) and Crystal Ball (Decisionnering, Inc., Denver, Colo.) use Spearman rank correlation coefficients (Rho) during simulation. The Phi coefficient can be used to assess the relationship between the percent consumers of two foods and to assess the relationship between the likelihood of a chemical being present in two foods.

1.4.7.1 Brand loyalty and market share

Brand loyalty, which is referred to as consumers' tendency to repeat the purchase of the same brand of a product (Arcella *et al.* 2003, Leclercq *et al.* 2003b) could theoretically be one of the most important anticipated dependencies in a model (Leclercq *et al.* 2003b). As mentioned in previous sections (1.2.2 and 1.2.3), the presence and concentration of a given food chemical may vary between different brands of the same product. For example, if an additive is permitted for use in sugar-free soft drinks, it does not necessarily follow that all brands of sugar-free soft drinks will contain that additive. Moreover, the additive will not necessarily be present at the same concentration in all brands. If an individual or group of individuals is loyal to a particular brand, which contains

the highest concentration of a food chemical, then failure to account for brand loyalty within a model may under-estimate exposure amongst high consumers. Indicators of brand loyalty at individual level may be estimated by the number of purchases of a single brand in proportion to the number of purchases of the food category of interest. Different cut-off points for this proportion can be used to categorize subjects as loyal or not loyal. Indicators of brand loyalty at population level may be the percentage of consumers of a specific brand that did not consume another brand of the same product within the time period of interest. Long term brand loyalty data can be obtained from repeated household purchase data whereas short term brand loyalty may be estimated from nutritional surveys, which typically last from 24 hours to 14 days (Leclercq *et al.* 2003b). Where no information on brand loyalty is available, hypothetical scenarios may be included in a model (*e.g.* assuming no brand loyalty or assuming 100% brand loyalty).

Closely related to the issue of brand loyalty is that of market share. The market share of brand A is the ratio between the level of consumption of brand A and that of all brands of the same products (Arcella *et al.* 2003, Leclercq *et al.* 2003b). The market share of a brand is a function of advertising, distribution and price (Leclercq *et al.* 2003b) and may be equally distributed between brands or a few brands with a large market share may dominate the market. Information on market share can be purchased from commercial market research companies. Numeric experiments carried out by Leclercq *et al.* (2003b), in which different hypotheses regarding market share and brand loyalty were included in a model of exposure to intense sweeteners, indicated that the distribution of sweetener intake varied in accordance with the hypothesis formed in relation to the extent of data on market share and brand loyalty. The authors concluded that information on market share should be included in a model, especially if the market is not equally distributed between brands. Where no data on market share are available, default conservative factors may be included in a model. Whilst the importance of including indicators of brand loyalty and market share in a model of dietary exposure to a food chemical has been clearly illustrated, Leclercq *et al.* (2003b) note that such information is only necessary where the presence/absence and concentration of a chemical is shown to have a wide variation between brands.

1.4.8 Number of iterations

Improvements in the speed and capabilities of modern computer processors have facilitated an increase in the application of probabilistic techniques for exposure

assessments. However, a question that consistently emerges relates to the number of iterations required to undertake a probabilistic analysis. Since the output distribution will depend on the nature of the input data and the algorithms used, suggesting a fixed number of iterations for all situations would not be meaningful (Monte Carlo project team 2003). The number of iterations reported in probabilistic food chemical exposure assessments ranged from 10,000 (Hamey 2000, Lambe *et al.* 2002) to 100,000 (Hamey and Harris 1999). Numerical stability refers to the stochastic variability associated with random sampling. It can be calculated by running multiple simulations with the same set of input assumptions and calculating the average percent change (*e.g.* ±1%) in a specified percentile of the output distribution. As a rule of thumb, the stability of the output distribution improves with increasing numbers of iterations (US EPA 2001) and the stability of the central region of an output distribution is generally better than the stability at the tails (Burmaster and Anderson 1994). Therefore, more iterations may be required when the risk management decision is associated with the distribution tails. Burmaster and Anderson (1994) suggest ≥10,000 iterations as a general guide to demonstrate the numerical stability of the tails of the output distribution, whereas the US EPA (2001) suggest that a sufficient number of iterations should be run to obtain numerical stability in percentiles of the output distribution that are important for decision making. They encourage exposure assessors to run multiple simulations with the same inputs using different numbers of iterations each time in order to evaluate the stability of the risk estimate of concern. The latter approach was adopted by Lambe *et al.* (2002) using a model to estimate the intake of flavouring substances. The authors compared output distributions of two flavouring substances based on a model run with 5,000, 10,000 and 15,000 iterations and reported very little difference between the three output distributions. Therefore, subsequent models were run for 10,000 iterations. Some commercial software programs such as @RISK® have a built in convergence monitoring feature which can help monitor the stability of an output distribution created during a simulation and can auto-stop if desired, once all outputs have converged.

1.4.9 Presenting the results of a probabilistic analysis

Compared with traditional deterministic estimates of exposure, a probabilistic exposure analysis can provide risk managers with information on the full distribution of exposure for a given population incorporating variability and/or uncertainty in exposure

estimates. To interpret the results of an exposure assessment, it is extremely important to provide adequate detail about the datasets, models, software and statistics used during the assessment. Vose (2000) states that a risk analysis model, however carefully designed, is of no value unless its results are understandable, useful and tailored to the problem at hand. The US EPA (1997) suggested the following guidance for presenting the results of a probabilistic analysis:

- Provide a complete and thorough description of the exposure model and its equations.
- Provide detailed information on the input distributions selected. This information should identify whether the input represents largely variability, largely uncertainty or a combination of both. Furthermore, information on goodness-of-fit statistics should be discussed.
- Provide detailed information and graphs for each output distribution. Graphs should be accompanied by a summary table of the relevant data.
- Discuss the presence or absence of dependencies and correlations.
- Calculate and present point estimates.

With regard to a food additive exposure assessment, a complete and thorough description of the conceptual model upon which the modelling is based should be illustrated. This should specify how food consumption and chemical concentration model inputs are combined, whether and how market share and/or brand loyalty are accounted for and whether the model accounts for the effects of processing, storage, cooking *etc*. The model algorithm should be documented, or at least reference made to where the algorithm is documented. For each of the model inputs, there should be a clear description of the datasets that have been used. For food consumption data, this should include a description of the population sample, the food consumption method used (*e.g.* food records), the survey duration and the level of energy under-reporting in the survey. Furthermore, reference should be made to the foods that were used to define the food categories used in the assessment. For example, was ice-cream assumed to be an 'edible ice' or a 'dessert'? Additive concentration data should also be accompanied by a description of the source of the data (*e.g.* laboratory data or manufacturers' information). Where concentration data derive from a laboratory, it is

important to consider whether the laboratory is accredited for the analytical method used, the number of samples analysed and whether the sampling was targeted or random. For each of the input variables in the model, there should be a clear description of the mode of data entry (*e.g.* empirical distribution, parametric distribution, raw data), a justification for that choice of format and a description of the units of measurement (*e.g.* g/day or g/kg bw/day for food consumption). Where a parametric (*e.g.* lognormal) distribution is employed, the sample size and results from the goodness-of-fit test used should be documented to allow a reader to objectively assess the quality of the fit. Results from goodness-of fit tests should be accompanied by a graphical inspection of the fit. Where food consumption model inputs are expressed as raw data, the assessor should indicate whether these data are expressed as average daily intakes or in a less aggregated form such as at the level of each eating occasion. Where available, information used to develop distributions representing uncertainty in food chemical model inputs (*e.g.* distributions reflecting measurement error) should be clearly documented. The results of a probabilistic model can be presented graphically or in tabular format. It would be prudent to firstly examine the full distribution of exposure and then perhaps concentrate on areas of the distribution that are of particular interest for the assessment in question. Cumulative distributions are particularly informative as a reader can view the proportion of the population that has intakes above or below a given intake level (*e.g.* ADI). Histograms provide useful information on the shape of the output distribution and box plots are useful for viewing the range of exposures and for identifying specific output ranges (*e.g.* the 95% confidence interval around the mean). An accompanying table of results allows the exact intakes at specific percentiles of exposure to be ascertained. Furthermore, the population group (*i.e.* consumers only versus the total population) to which the results refer should be clearly documented. Where correlations between food consumption and/or additive concentration model inputs (*e.g.* Spearman) or between the percent consumers of two foods (*e.g.* Phi coefficient) are used, the type and strength of the correlation should be documented. Corresponding exposure estimates using a deterministic approach (*e.g.* the Step 2 approach, section 1.3.2) should be calculated and presented with corresponding probabilistic exposure estimates. In addition to these, the name of the software modelling program and the settings used for running the model (*e.g.* number of iterations) should be documented. All of these measures will serve to ensure transparency and reproducibility of

a probabilistic analysis, which in turn will contribute to the widespread use and acceptance of this technique.

1.5 Background and objectives of thesis

Food chemical exposure is an integral part of the work carried out at the Institute of European Food Studies (IEFS) at Trinity College, Dublin. In the past, much of the research carried out in this area focused on improving methodologies for the estimation of food chemical intakes, with a particular emphasis on food additive exposure. Within this realm, the use of a National Food Ingredient Database was proposed as a useful screening tool to identify the pattern of additive usage in the food supply and to prioritize additives for more refined exposure assessments. Such methodologies were deterministic in nature. In February 2000, IEFS received funding from an EU 5th Framework programme for a project entitled 'Development, validation and application of stochastic modelling of human exposure to food chemicals and nutrients' (acronym Monte Carlo, Project No. QLKI-CT-1999-00155). This provided an opportunity to embrace the application of probabilistic methods to food chemical exposure assessments and to develop knowledge in this area. This was a multi-centre project, which involved seven research partners located in Ireland, the UK, the Netherlands, the Basque country and Italy. Much of the research described in this thesis (objectives ii, iii and iv below) emanates from the work plan of IEFS during this three year Monte Carlo project. The specific objectives of this thesis were as follows:

i) To illustrate patterns of food additive usage in the Irish food supply using a National Food Ingredient Database.

ii) To assess the types of food intake input distributions for use in probabilistic exposure assessments of food additives.

iii) To validate a probabilistic model for the estimation of dietary exposure to food additives.

iv) To assess the influence of energy under-reporting on estimates of food additive intake.

For objective (i), *to illustrate patterns of food additive usage in the Irish food supply using a National Food Ingredient Database*, I was solely responsible for contacting manufacturers to seek information on the list of ingredients used in their food products.

Having received this information, I entered ingredient information relating to each product into the existing database and performed the analyses on patterns of additive usage in the food supply. I wrote a scientific paper on my results, which was published in the *Food Additives and Contaminants* scientific journal (2002).

For objective (ii), *to assess the types of food intake input distributions for use in probabilistic exposure assessments of food additives*, I created the food categories used in the analysis, I performed all the analysis and I wrote my results as a scientific paper, which was published in the *Food Additives and Contaminants* scientific journal (2003).

Objective (iii), *validation of a probabilistic model for the estimation of dietary exposure to food additives* was conducted in collaboration with the Institute of Human Nutrition, University of Southampton, UK as part of the Monte Carlo project. I selected the food additives for the Irish study and I created the corresponding food categories that were used in the analysis. I was also actively involved in the development of a brand level food consumption database that was used to validate the model and I carried out the analyses to validate the model. All of the above-mentioned tasks were conducted on Irish data only. I compiled the results from Ireland with those from the UK and I prepared the joint paper, which was published in a supplement to the *Food Additives and Contaminants* scientific journal (2003).

For objective (iv), *to assess the influence of energy under-reporting on estimates of food additive intake,* I selected the additives and created the food categories, and I was solely responsible for carrying out all of the analyses. I wrote a scientific paper based on my results, which was accepted for publication in the *Food Additives and Contaminants* and is due for publication in 2004.

Table 1.1 Benefits of a probabilistic analysis for the estimation of food chemical exposure

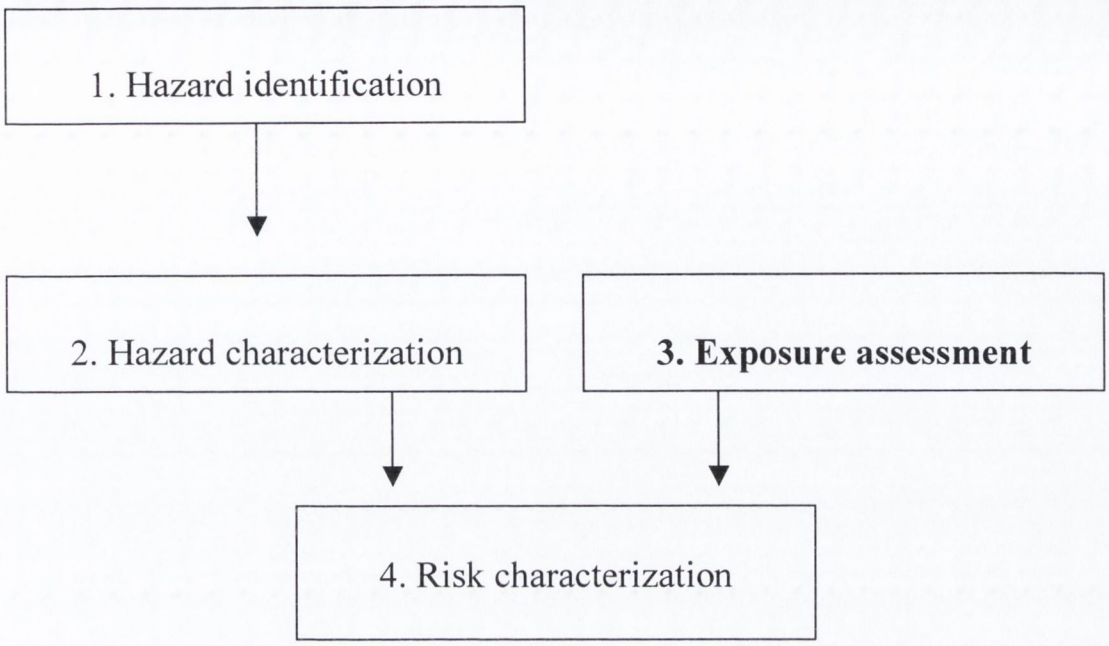
- Provides a more refined and more realistic estimate of exposure.
- Eliminates creeping conservatism associated with the deterministic approach. For example, when multiple conservative default values are combined in the deterministic approach, the resulting level of conservatism is compounded.
- Generates a distribution of exposure estimates from which the probability of exceeding any given value on the distribution can be ascertained.
- Can provide a quantitative evaluation of the degree of conservatism inherent in the deterministic approach.
- Can provide a more comprehensive characterization of variability *(i.e.* natural variation) in risk estimates, thereby providing more meaningful information on likely exposures that may occur within a population.
- Can provide a quantitative measure of uncertainty in estimates of exposure, which may support statements regarding confidence in exposure estimates.
- Can assess the sensitivity of exposure to input variables (*e.g.* to determine which model inputs have the most effect on the exposure).
- Allows one to make more complete use of available data when defining model inputs.
- Avoids disputes over the best point estimate to use (*e.g.* mean or upper percentile).

Table 1.2 Illustration of the bootstrap procedure to assess sample uncertainty

Original sample	BS_1	BS_2	BS_3	BS_4	BS_5
1	1	4	6	8	9
2	1	5	5	5	8
3	9	8	4	9	7
4	8	9	7	7	5
5	9	9	8	5	6
6	9	2	9	2	9
7	7	2	3	4	4
8	5	2	3	2	9
9	6	1	9	4	8
5	**7**	**4**	**6**	**5**	**8**

The original sample (n=9) is sampled with replacement five times to generate five bootstrapped samples (BS_1–BS_5), each with a sample size of (n=9). In this example, the median (50^{th} percentile) calculated from the original sample and for each bootstrapped sample is illustrated in bold typeface. The distribution of medians generated from BS_1 to BS_5 (*i.e.* 7,4,6,5,8) represents the bootstrapped estimate of uncertainty around the median (5) of the original sample.

Figure 1.1 Illustration of exposure assessment in the risk assessment process



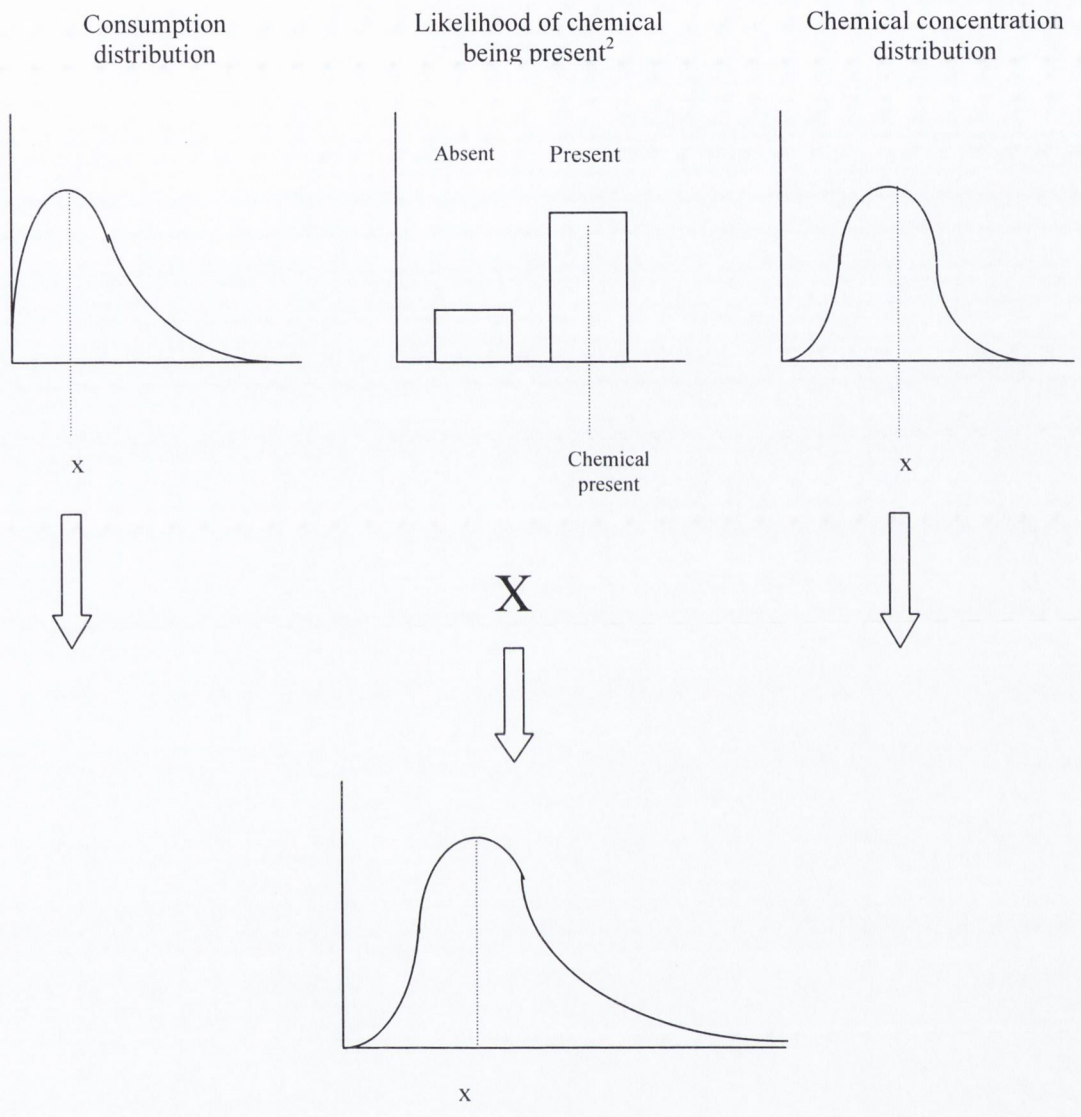
1. A battery of tests are carried out (usually on laboratory aminals) to define the potential to cause harm (irrespective of dose) at different stages of the life cycle.

2. The most important adverse effect(s) are identified and the dose-response level that is without an effect is identified. Inter-species differences and differences between humans and animals are taken into account (usually by applying a 100 fold safety factor to estimate the ADI).

3. The potential daily intake is estimated based on the foods in which the additive is permitted and potential use levels.

4. Comparison of potential daily intake with the ADI.

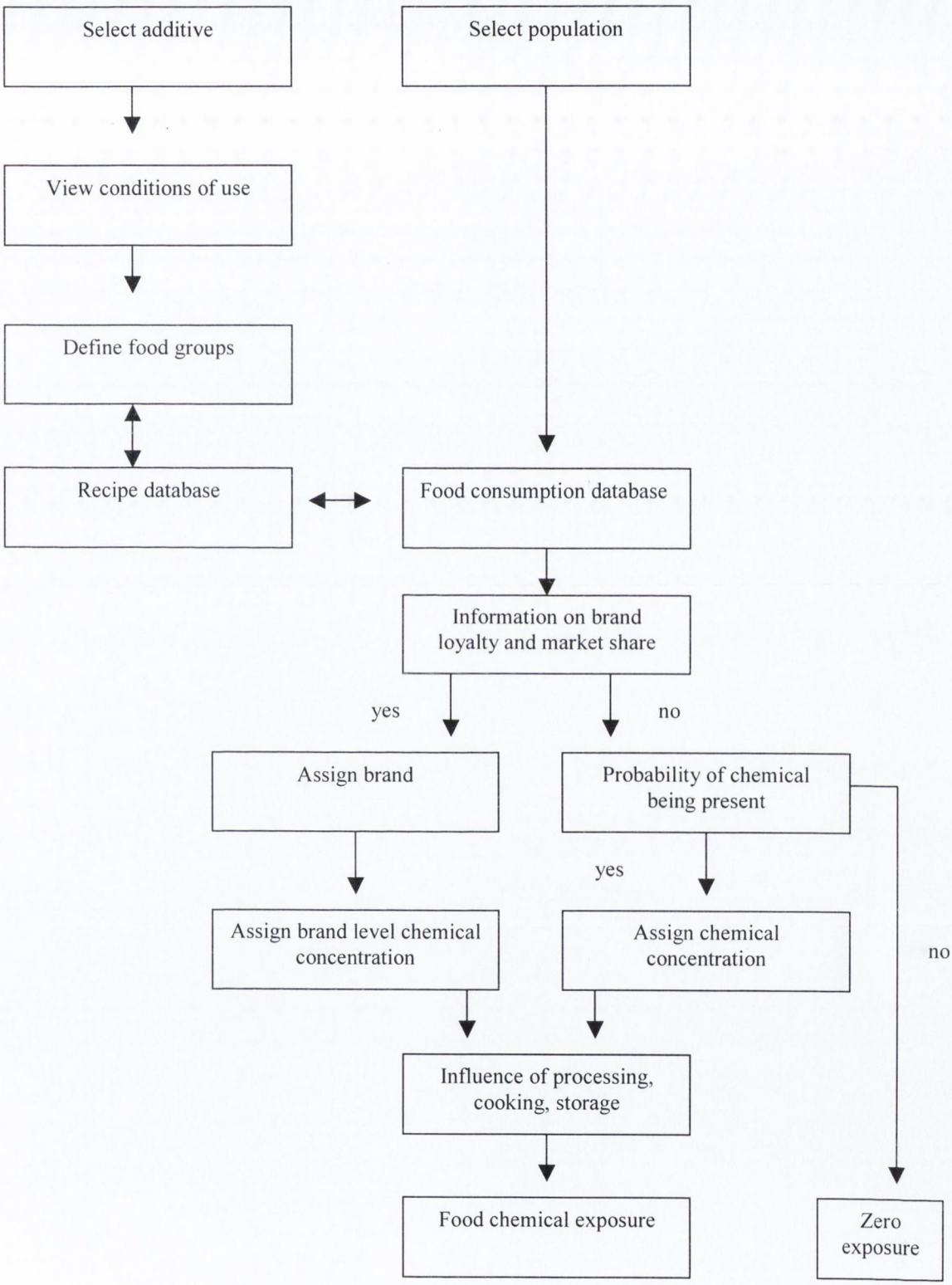
Figure 1.2 Illustration of one iteration in the estimation of food chemical intake using probabilistic modelling[1]



[1]The process is repeated *n* times (*e.g.* 1,000) during a simulation, where each time a different random variable is selected from each input distribution, to generate a distribution of chemical intake estimates.

[2] If the chemical is absent, then the random variable generated from the food consumption distribution is multiplied by zero to generate a chemical intake equal to zero.

Figure 1.3 Conceptual model for probabilistic modelling of food additive intake



Chapter 2

Irish National Food Ingredient Database, application for assessing patterns of additive usage in foods

Gilsenan, M.B., Lambe, J., and Gibney, M.J., 2002, Food Additives and Contaminants, 19, 1105-1115.

2.1 Introduction

This paper describes the use of a National Food Ingredient Database to assess additive usage in the food supply. The term *usage* refers to the pattern and frequency of use of additives in different types of foods and not the quantity of additives used in different foods. To date, few studies have generated comprehensive data on food additive usage. In the UK, a survey was carried out among manufacturers of foods in which colours are permitted, examining the amount and types of colours used in foods (MAFF 1987). Manufacturers were required to provide a full description of each product, including a list of colourable ingredients used, together with the level of addition of colours. Quantitative usage data about ingredient formulations were then sought from suppliers. Whilst this survey pertained only to colours, a major problem encountered was the maintenance of commercial confidentiality (MAFF 1987).

In various sweetener intake studies, information about the amount and type of sweeteners used in various foods has been established either from manufacturers' information (Hinson and Nicol 1992, Leclercq *et al.* 1999) or by chemical analyses (Toledo and Ioshi 1995). Sweeteners are suitable to these approaches as the major vehicles for their intakes (*e.g.* low calorie products) are easily identified and sweeteners are single chemicals that are easily determined analytically.

A food ingredient database has been proposed as a method to estimate food additive usage (Nutriscan 1994). Such a database contains qualitative information on the ingredient and additive content of a broad range of foods as they appear on the product label. Databases that contain information on food ingredients or food additives currently exist in a number of countries. In 1989, a food additive database was developed by the Ministry of Agriculture Fisheries and Food (MAFF) which listed the types of preservatives used in foods (MAFF 1993). The database was subsequently expanded to record the use of all additives in additive-containing foods. Whilst this type of database is a useful tool to illustrate patterns of additive usage in additive-containing foods, it does not provide information about the proportion of foods which contain additives and the proportion which are additive free.

The United States Department of Agriculture (USDA) nutrient data laboratory developed a food ingredient database to assist with its work on processed formulated foods (Cutrufelli and Blaufarb 1997). The label ingredient information is used to provide

information to calculate missing nutrient values for USDA's Nutrient Database for Standard Reference and the Primary Data Set, which supports USDA food surveys.

In France, food products are coded using a framework for food description called LANGUAL. This food coding system allows the user to describe and retrieve information about foods according to a combination of several characteristics, one of which includes an ingredient of a food. The database that stores this information is managed by CREDOC and contains information on more than 30,000 food products (Chambolle 1999).

In the Netherlands, a food intolerance databank (ALBA) was developed to store information on the composition of foods in terms of the presence or absence of certain components and make this information available to patients, medical specialists, dietitians and general practitioners. Emphasis was given to food components acknowledged as being responsible for food intolerance. ALBA contains information on 17,000 products provided by 125 companies on a voluntary basis (van Dusseldorp, M., 2002, Personal communication). All data are updated on a continuing basis. In 1995, the Grootverbuik Product Informatie (GPI) database on food information was established by a number of different wholesalers for the purpose of providing brand level information to catering establishments, restaurants and hospitals *etc*. The database contains packaging information on approximately 12,000 food products which are sold by wholesalers and can provide nutritional information, ingredient and additive information, information on the presence or absence of allergens, storage conditions, packaging material *etc*. (Boon, S., 2000, Personal communication).

An Italian food labels database for processed foods was developed as a pilot databank of approximately 400 brand foods by the National Institute for Food and Nutrition Research (INRAN 1999, Piccinelli *et al*. 2000). The database was developed to supplement existing information in nutritional databases. Each food is described using 24 variables, some of which include a list of ingredients, a list of additives and nutrient composition data (Turrini 1994, Piccinelli *et al*. 2000). Information on nutrient composition and ingredients can be directly exported to the Italian food composition databank to update existing information (Leclercq, C., 2002, Personal communication). The database has also been used to identify foods likely to contain particular additives when estimating intakes (Leclercq *et al*. 2000a). In the case of sweeteners, the food label databank has been integrated with quantitative information obtained from producers (Leclercq *et al*. 1999).

Whilst these databases provide useful information on the ingredient or additive content of foods, not all have been established for the purpose of monitoring additive usage. The present paper describes the construction and use of the Irish National Food Ingredient Database (INFID) to illustrate patterns of food additive usage in the Irish food supply and changes in patterns of food additive usage between the periods 1995-1997 to 1998-1999.

2.2 Materials and Methods

Irish National Food Ingredient Database (INFID)

In 1995, INFID was initiated to fulfil the requirements of the EU Directives (European Commission 1994b, 1995) to monitor the usage and consumption of food additives. The database is a relational database, established using Microsoft Access® for Windows Version 2.0 (Microsoft Corporation, Redmond, WA), which lists qualitative information about the ingredients, including additives of packaged brand foods available in the Irish food supply.

Data collection

The list of ingredients for inclusion in INFID was obtained from the wrappers of food products. During the period 1995-1997, 189 manufacturing and distribution food companies received a written request for ingredient labelling of their products on sale in the Republic of Ireland. A further 188 food companies were contacted during the period 1998-1999. Company names were obtained from a list of suppliers associated with two major supermarket retailers and from a directory listing companies in Ireland (Kompass Ireland 1998). Additional ingredient information was transcribed directly from product wrappers in two major supermarket retail outlets. Foods were not confined to those containing additives, but aimed to encompass a generally representative sample of packaged foods in the food supply as recorded in a list of food products stocked in a major retail outlet. Product information entered into INFID included the brand name, a brief description, the date on which product information was sought, product weight (g), manufacturer details, packaging details (*e.g.* box, jar, packet), a list of ingredients as they appeared on the wrapper and a list of additives including the function (*e.g.* colour), specific name (*e.g.* annatto) and E number (*e.g.* E160b). Additional information included an average portion size of the food (determined by packet details or a food portion sizes manual) (Crawley

1993), a food composition code (Chan *et al.* 1994, 1995, 1996, Holland *et al.* 1988, 1989, 1992, 1993) and a designated food category (Lee and Cunningham 1990).

Forty-five of the original 189 companies who supplied ingredient information during 1995-1997, were re-contacted in 1999 and asked again to forward their product wrappers. This allowed a direct comparison of the ingredient profiles of approximately 1,000 common foods collected during both periods. When all data entry was complete, the additive information of each product was rechecked. The number of brands in INFID was compared to the number of products stocked on the shelves of a major retail outlet.

Data analysis

The frequency of use of additive categories was calculated. The most commonly used additive categories are presented in table 2.1. The types of additives used to perform the most common additive functions were identified and their frequency of occurrence was calculated. The distribution of additive categories within food groups was also calculated. As the number of brands in food groups in INFID varied widely (*e.g.* sauces-711 brands, liver pâté-10 brands), the use of additive categories across food groups was expressed both as the number of brands containing the particular category of additive and the percentage of brands within each food group containing that additive category.

An assessment of changes in additive usage between 1995-1997 and 1998-1999 was carried out using a McNemar test. All statistical analyses were carried out in SPSS® for Windows Version 9.0 (SPSS Inc. Chicago, Illinois).

2.3 Results

The number of foods in INFID (n=5,684) represented approximately 65% of food products listed in a leading Irish supermarket. Fresh produce, catering produce, non pre-packaged food items, foods which are too small to include an ingredient listing on their wrappers and alcoholic beverages are excluded. Sixty-seven percent of foods in INFID recorded the use of at least one additive. The additives recorded represented 54% of permitted additives in the EU additive Directives (European Commission 1994a,b, 1995). These included 37 (86%) colours, five (46%) sweeteners and 120 (49%) miscellaneous additives. Sixteen additive categories represented 93% of the frequency of overall additive usage (table 2.1). The numbers in brackets corresponding to each E number in table 2.1 indicate the percentage of usage of each additive within the additive category to which it

belongs. A maximum of nine additives within an additive category are recorded. The nine colours listed represented 65% of colour usage. For the remaining 15 additive categories in this table, the additives listed within each category represented at least 80% of additive usage within a given category. Six additive categories (flour improvers, firming agents, humectants, modified starch, sequestrants and anti-foaming agents) represented less than 0.3% of the frequency of overall additive usage and five additive categories (carriers, propellants, packaging gases, bulking agents and foaming agents) were not recorded in any of the 5,684 brand foods in INFID. Approximately 7% of additives were labelled without a specified additive function. These additives were excluded from these analyses. Colours, emulsifiers and acids were the most commonly recorded additive categories. They represented 18, 13 and 12% of the frequency of overall additive usage, respectively (table 2.1). Carotenes (E160a) (15% of colour usage), mono-and diglycerides of fatty acids (E471) (39% of emulsifier usage) and citric acid (E330) (70% of acid usage) were the most commonly recorded additives in these three additive categories (table 2.1). Citric acid was the most common additive recorded in INFID (n=20% brands).

The percentage of brands within food groups that contained an additive and the distribution of the most commonly occurring additive categories across these food groups are presented in table 2.2. The seven additive categories given in table 2.2 represented 75% of overall additive usage. All (100%) diet soft drinks (n=37), low fat spreads (n=25) and liver pâtés (n=10) recorded in INFID contained at least one additive. The most commonly recorded additive categories in the diet soft drinks food group were acids (89%) and preservatives (86%). Colours (96%) and emulsifiers (88%) were the two most predominantly recorded additive categories in the low fat spreads food group, whilst preservatives (100%) were the most commonly used additive category in the liver pâté food group. When expressed in terms of the number of brands that contain additives, sauces (n=522 brands, 73% of sauces), biscuits (n=323 brands, 84% of biscuits) and preserves (n=321 brands, 85% of preserves) were ranked highest. For the three most commonly used additive categories, sauces contained the highest number of brands containing colours (n=182 brands, 26% of sauces) and acids (n=304 brands, 43% of sauces) and biscuits contained the highest number of brands containing emulsifiers (n=181 brands, 47% of biscuits). When expressed in terms of the proportion of brands within food groups that contain these additive categories, low fat spreads, margarines and other soft drinks (*i.e.* not

diet) contained the highest proportion of brands containing colours (96%, n=24), emulsifiers (89%, n=24) and acids (91%, n=180), respectively.

The ingredients of approximately 1,000 foods were updated between 1995-1997 and 1998-1999. The frequency of use of the most commonly used additive categories during these two periods is illustrated in table 2.3. Some 17% of foods which were recorded in INFID in 1995-1997 were no longer manufactured in the 1998-1999 period. Thus, these foods were deleted from INFID in 1998-1999. With the exception of colours, antioxidants and to a lesser extent flavour enhancers, there was a slight trend towards an increase in the frequency of use of additives in 1998-1999 compared to 1995-1997. There was a significant increase in the frequency of use of emulsifiers ($P<0.001$), acids ($P<0.01$), acidity regulators ($P<0.05$) and sweeteners ($P<0.05$) and a significant decrease in the frequency of use of antioxidants ($P<0.05$) in 1998-1999. Table 2.3 also compares the pattern of additive usage between both time periods in terms of the number of brands containing additives. A significant increase was observed for the number of brands containing emulsifiers ($P<0.05$), acids ($P<0.05$) and thickeners ($P<0.05$) and a significant decrease was observed for the number of brands containing antioxidants ($P<0.05$) in 1998-1999. Additional analyses revealed that citric acid (E330) and potassium phosphates (E340) represented the most common new occurrences of acids and acidity regulators (n=27 and n=15 new occasions of use, respectively). Lecithin (E322) and cyclamic acid & salts (E952) primarily accounted for the increase in the use of emulsifiers and sweeteners (n=19 and n=8 new occasions of use, respectively). Butylated hydroxyanisole (E320) represented the greatest decline in antioxidant usage in 1998-1999 (n=-19 occasions of use).

Incidences of new occurrences of acids in 1998-1999 were observed in 11 food groups, of which sauces recorded the highest number of new occasions of use (36%). Of the 12 food groups in which new occurrences of emulsifiers were recorded in 1998-1999, biscuits and chocolate confectionery recorded the highest number of new occurrences (22% and 22%, respectively). Seven food groups recorded new occurrences of acidity regulators in 1998-1999. The majority (57%) was recorded in soups. New cases of sweetener usage occurred across three food groups. Other soft drinks (*i.e.* not diet) represented the highest number of new occurrences (66%). The decline in antioxidant usage in 1998-1999 occurred across seven food groups. The greatest decline (30%) was recorded in soups.

The term new occurrence (usage) refers to the usage of an additive in a given brand in the period 1998-1999 that had not been used in that brand in the period 1995-1997.

In some cases, new occurrences of an additive in a given brand were used to replace a different additive within an additive category for that given brand (*e.g.* replacement of one colour for another in a given brand). Further analysis revealed that with the exception of thickeners, new occurrences were recorded both in brands not previously containing the additive category and within brands that already contained the additive category. Thickeners displayed an increase in usage only in brands that did not previously contain this additive category in 1995-1997. Furthermore, for acids, acidity regulators, raising agents, stabilisers, emulsifiers and sweeteners, some foods recorded more than one new occurrence of an additive in 1998-1999. The reduced number of uses of colours in 1998-1999 occurred in products containing a single colour and in products containing more than one colour. The decline in the use of antioxidants and in the use of flavour enhancers occurred in foods which contained only one of these additives.

2.4 Discussion

The food ingredient database proved to be a useful tool for providing qualitative information on food additive usage and changes in patterns of food additive usage in the food supply. In doing so, such a database enabled the requirement of EU additive Directives (European Commission 1994b, 1995) to monitor food additive usage, to be fulfilled for Ireland. When interpreting the results however, a number of limitations should be borne in mind.

The omission of catering produce, fresh produce, non-packaged food items and foods which do not require ingredient labelling, may account for the fact that certain permitted additives were not recorded in INFID. Therefore, for a comprehensive review on total additive usage, alternative methods must be considered for these food groups. Another limitation of the use of a food ingredient database for assessing qualitative additive usage is the issue of incorrect labelling. In *Options for the routine collection of data on usage levels of food additives in the European Union*, the prevalence of faults in labelling of additives was reported (Nutriscan 1994). The studies included in the report, which employed the use of chemical analyses, reported both cases where an additive was labelled but was not present and cases where an additive was present but not labelled. Such observations indicate that surveillance of food additives based solely on labelling should be used with caution.

Patterns of additive usage in INFID were compared with a report on food additive usage in the UK (MAFF 1993). The UK report included a preliminary analysis of additive usage pertaining to 5,286 products in a UK food additive database (MAFF 1993). Citric acid (E330), mono- and di-glycerides of fatty acids (E471) and mono-sodium glutamate (E621) were the most commonly occurring additives recorded in INFID, whilst citric acid (E330), sulphur dioxide (E220) and acetic acid (E300) were the most commonly occurring additives recorded in the UK database. Carotenes (E160a) and caramel (E150a) were the most common colours in INFID, whilst caramels (E150) and annatto (E160b) were the most common colours in the UK database. However, it must be noted that the analyses from the UK database represent foods which contain additives only, whilst the analyses from INFID include both foods which contain additives and foods which are additive free. Citric acid was recorded in 20% of foods in INFID. However, when only additive containing foods are taken into account, this figure increased to 30%. It must also be noted that the results from both studies do not cover the same period of data collection.

Although there was a significant increase in the overall frequency of use of acids, acidity regulators, emulsifiers and sweeteners in the period 1998-1999 compared to the period 1995-1997, such trends were not consistent. Indeed for all additives except emulsifying salts, which displayed an overall increase in their frequency of use in the period 1998-1999, there were also occurrences of additives from the same category, in foods in 1995-1997, which were no longer used in foods in the period 1998-1999. For example, whilst there were 36 new occasions of use of acids in 1998-1999, there were also 13 occasions of use in 1995-1997 which were no longer used in 1998-1999, yielding a net increase of 23 occasions of use (frequency of use) (table 2.3). A similar observation was made for antioxidants. Whilst there was a significant decrease in the use of antioxidants in the period 1998-1999, there were also a number of new occasions of use of antioxidants during the same period. Commercial reasons may play a role in determining why a manufacturer may substitute a given additive for another and in determining which additives within a particular additive category are more commonly used than others.

Despite these observations, the overall increase in the frequency of use of emulsifiers in the period 1998-1999 from 267 to 365 occasions of use is partially accounted for by the fact that emulsifiers were labelled as a carry-over additive in the margarine and vegetable oil ingredients of many brands of biscuits and chocolate confectionery in 1998-1999. These were not labelled in the corresponding products collected during the 1995-

1997 period. Such additives may not have been present in these foods in the period 1995-1997. Another possibility is that more specific labelling of the additive content of foods (including a declaration of carry-over ingredients) may have identified the use of emulsifiers in foods in the period 1998-1999 which were not labelled in the same foods in the period 1995-1997. A trend towards more specific labelling of additives in 1998-1999 was also observed for the colour caramel. In many foods, caramel was labelled as 'caramel' or 'E150' in the period 1995-1997. In the period 1998-1999, the colour was labelled with the more specific form of caramel *e.g.* plain caramel (E150a) or sulphite ammonia caramel (E150d).

For many categories of additives, although there was an increase in frequency of use in the period 1998-1999, this did not correspond with the number of brands that recorded an increase in use of a given additive category (table 2.3). For example, whilst there were 23 new occasions of use (frequency of use) of acids in 1998-1999, the number of brands containing acids only increased by 12. These observations suggest that new occurrences of additives (frequency of use) may also occur within foods that already contain that category of additive. For some additive categories, (*i.e.* preservatives), the number of new additive containing brands was in fact lower in 1998-1999 compared to 1995-1997, despite an increase in the frequency of use of the additive category during the same period.

In recent years, there has been a growing trend away from the use of synthetic additives towards the use of equivalent substances extracted from natural products (Tennant 1997). Whilst substitution of one additive within the same food for another between 1995-1997 and 1998-1999 was most common for colours, no consistent trend towards the use of natural colours in 1998-1999 was observed.

It must be noted, that the manufacture of a significant number of products (17%), which were collected during the initial period of data collection in 1995-1997, had subsequently ceased during the follow-up period in 1998-1999. Thus, it appears that changes in the types of brands between 1995-1997 and 1998-1999 were more apparent than actual changes in ingredient formulations within brands.

The application of an ingredient database for monitoring trends in additive usage can help focus resources monitoring the intake of a food additive which may have increased in usage consistently over time. Alternatively, it may also negate the need to expend

resources on repeated surveys of food additive consumption, if results from monitoring programmes do not indicate any consistent changes in usage over time.

It should be noted that an ingredient database is never going to be truly representative of an entire food supply. Changes in ingredient formulations, introduction of new products, deletion of old products and regional variation of certain products all contribute to a dynamic food market. The aim of this ingredient database therefore, was to provide a broad representation of foods available in the Irish food supply pertaining to the period of data collection. The need to update the database on a regular basis to correspond with changing ingredient formulations, new product launches and removal of old products is strongly recommended.

Table 2.1 The 16 most commonly used additive categories in order of their percentage overall additive usage in INFID and the most commonly used additives (defined by E number) within each additive category[a]

Colours (18%)		Emulsifiers (13%)		Acids (12%)		Stabilisers (9%)		Preservatives (9%)		Raising agents (8%)		Flavour enhancers (6%)		Acidity Regulators (4%)	
E160a	(15)	E471	(39)	E330	(70)	E412	(20)	E202	(32)	E500	(48)	E621	(83)	E331	(55)
E150a	(12)	E322	(29)	E260	(12)	E415	(18)	E211	(17)	E503	(24)	E635	(14)	E330	(15)
E160b	(10)	E472e	(7)	E270	(8)	E410	(12)	E250	(12)	E450	(19)	E631	(1)	E340	(9)
E100	(6)	E442	(4)	E296	(4)	E407	(8)	E223	(11)	E341	(4)	E627	(1)	E334	(4)
E163	(5)	E472b	(3)	E300	(3)	E450	(6)	E220	(10)	E575	(2)	E920	(<1)	E331c	(4)
E124	(5)	E475	(2)	E334	(1)	E452	(6)	E251	(5)	E334	(2)	E160b	(<1)	E262	(3)
E110	(4)	E476	(2)	E338	(<1)	E440	(5)	E200	(3)	E541	(1)	E620	(<1)	E270	(2)
E104	(4)	E481	(2)	E355	(<1)	E466	(4)	E221	(3)	E339	(<1)	E339	(<1)	E296	(1)
E162	(4)	E477	(2)	E200	(<1)	E401	(4)	E252	(2)	E529	(<1)	E331	(<1)	E332	(1)

Gelling Agents (4%)		Sweeteners[b] (4%)		Antioxidants (3%)		Thickeners (1%)		Emulsifying[b] salts (1%)		Anti-caking agents (<1%)		Glazing agents[b] (<1%)		Flour treatment agents[b] (<1%)	
E440	(77)	E951	(47)	E301	(28)	E412	(43)	E339	(36)	E504	(31)	E903	(41)	E300	(66)
E418	(10)	E954	(36)	E320	(27)	E415	(20)	E450	(26)	E554	(24)	E904	(26)	E920	(32)
E407	(3)	E950	(17)	E300	(20)	E407	(12)	E452	(16)	E551	(15)	E414	(15)	E223	(2)
E450	(2)	E952	(<1)	E321	(9)	E466	(9)	E331	(12)	E535	(13)	E901	(11)	-	
E406	(2)	E420	(<1)	E306	(3)	E410	(7)	E341	(6)	E552	(4)	E418	(2)	-	
E339	(2)	-		E331	(2)	E440	(5)	E331c	(3)	E341	(4)	E500	(2)	-	
E340	(1)	-		E304	(2)	E418	(2)	E621	(1)	E470b	(4)	E422	(2)	-	
E401	(1)	-		E310	(2)	E460	(1)	E251	(1)	E339	(3)	-		-	
E508	(1)	-		E316	(2)	E413	(1)	-		E170	(2)	-		-	

[a] The additive categories represented 93% of overall additive usage. The numbers in brackets corresponding to each E number indicate the percentage of usage of each additive within the additive category to which it belongs. A maximum of nine additives within an additive category are recorded. The nine colours listed represented 65% of colour usage. For the remaining 15 additive categories in this table, the additives listed within each category represented at least 80% of additive usage within a given category.

[b] Only five sweeteners, eight emulsifying salts, seven glazing agents and three flour treatment agents were recorded in the 5,684 brand foods in INFID.

Table 2.2 The number and percentage of brands within each food group recording the seven most commonly used additive categories in INFID[a]

Food group (no. of brand foods in INFID within food group)	% brands within food category containing any additive	Colours		Emulsifiers		Acids		Stabilisers		Preservatives		Raising agents		Flavour enhancers	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Diet soft drinks (37)	100	25	(68)	-	-	33	(89)	9	(24)	32	(86)	-	-	-	-
Low fat spreads (25)	100	24	(96)	22	(88)	8	(32)	3	(12)	13	(52)	-	-	-	-
Liver pâté (10)	100	-	-	4	(40)	-	-	-	-	10	(100)	-	-	3	(30)
Sausages (53)	98	35	(66)	8	(15)	4	(8)	6	(11)	41	(77)	2	(4)	21	(40)
Bacon and ham (61)	98	1	(2)	20	(33)	-	-	11	(18)	53	(87)	-	-	15	(25)
Chocolate confectionery (180)	96	32	(18)	141	(78)	22	(12)	9	(5)	1	(1)	36	(20)	-	-
Other soft drinks (198)	93	103	(52)	-	-	180	(91)	35	(18)	135	(68)	-	-	1	(1)
Desserts (251)	92	136	(54)	162	(65)	48	(19)	138	(55)	23	(9)	24	(10)	-	-
Sugar confectionery (174)	91	143	(82)	35	(20)	83	(48)	11	(6)	1	(1)	4	(2)	-	-
Margarines (27)	89	24	(89)	24	(89)	6	(22)	-	-	3	(11)	-	-	-	-
Meat pies & pastries (43)	88	21	(49)	29	(67)	4	(9)	5	(12)	5	(12)	1	(2)	16	(37)
Preserves (377)	85	78	(21)	-	-	261	(69)	13	(3)	82	(22)	-	-	-	-
Biscuits (384)	84	76	(20)	181	(47)	51	(13)	2	(1)	2	(1)	290	(76)	3	(1)
Yogurt (171)	83	53	(31)	8	(5)	29	(17)	71	(42)	86	(50)	4	(2)	-	-
Egg &/or cheese dishes (30)	83	7	(23)	9	(30)	8	(27)	13	(43)	16	(53)	2	(7)	3	(10)
Soups (267)	80	122	(46)	92	(34)	39	(15)	59	(22)	-	-	-	-	172	(64)
Other meat products (49)	80	10	(20)	12	(24)	5	(10)	6	(12)	33	(67)	3	(6)	19	(39)
Cheese (136)	79	58	(43)	1	(1)	5	(4)	12	(9)	53	(39)	-	-	1	(1)
Buns, cakes & pastries	78	72	(35)	117	(57)	36	(17)	25	(12)	58	(28)	92	(44)	-	-
Savoury snacks (167)	75	17	(10)	25	(15)	47	(28)	3	(2)	7	(4)	22	(13)	80	(48)
Sauces (711)	73	182	(26)	48	(7)	304	(43)	94	(13)	74	(10)	-	-	118	(17)
Butter etc. (26)	69	16	(62)	12	(46)	1	(4)	2	(8)	2	(8)	-	-	-	-
Burgers (55)	67	11	(20)	3	(5)	1	(2)	9	(16)	23	(42)	2	(4)	22	(40)
Beef, veal & dishes (61)	62	15	(25)	5	(8)	3	(5)	6	(10)	12	(20)	1	(2)	10	(16)

Table 2.2 contd. **The number and percentage of brands within each food group recording the seven most commonly used additive categories in INFID[a]**

Food group (no. of brand foods in INFID within food group)	% brands within food category containing any additive	Colours n (%)		Emulsifiers n (%)		Acids n (%)		Stabilisers n (%)		Preservatives n (%)		Raising agents n (%)		Flavour enhancers n (%)	
Other vegetables & dishes (122)	57	12	(10)	3	(2)	35	(29)	17	(14)	23	(19)	4	(3)	1	(1)
Potatoes, other than chips (41)	56	6	(15)	8	(20)	1	(2)	12	(29)	8	(20)	3	(7)	6	(15)
White bread (55)	55	-	-	27	(49)	5	(9)	-	-	9	(16)	-	-	-	-
Chicken & turkey (134)	54	16	(12)	21	(16)	11	(8)	31	(23)	13	(10)	4	(3)	13	(10)
Lamb & dishes (16)	50	-	-	2	(13)	3	(19)	3	(19)	1	(6)	-	-	3	(19)
Peas (17)	47	5	(29)	-	-	-	-	-	-	2	(12)	-	-	-	-
Low fat & other milks (39)	46	1	(3)	6	(15)	1	(3)	6	(15)	-	-	-	-	-	-
Baked beans (13)	46	1	(8)	1	(8)	-	-	-	-	-	-	-	-	-	-
Other breads (47)	45	-	-	7	(15)	4	(9)	8	(17)	12	(26)	12	(26)	-	-
Cream (11)	45	1	(9)	1	(9)	-	-	4	(36)	-	-	-	-	-	-
Pork & dishes (18)	44	3	(17)	1	(6)	4	(22)	3	(17)	5	(28)	-	-	2	(11)
Breakfast cereals (96)	43	9	(9)	10	(10)	1	(1)	-	-	4	(4)	6	(6)	-	-
Other cereals (229)	42	24	(10)	20	(9)	27	(12)	10	(4)	9	(4)	15	(7)	48	(21)
Canned fruit & other fruit (100)	42	19	(19)	-	-	6	(6)	2	(2)	24	(24)	-	-	-	-
Wholemeal bread (35)	40	1	(3)	14	(40)	1	(3)	-	-	5	(14)	-	-	-	-
Miscellaneous (608)	37	70	(12)	60	(10)	78	(13)	49	(8)	17	(3)	5	(1)	27	(4)
Tomatoes (16) (includes tinned tomatoes)	31	-	-	-	-	3	(19)	-	-	-	-	-	-	-	-
Seafood (147)	27	8	(5)	5	(3)	14	(10)	16	(11)	7	(5)	6	(4)	7	(5)
Leafy green vegetables (14) (includes jarred vegetables)	21	-	-	-	-	3	(21)	-	-	-	-	-	-	-	-
Chips and other fried / roast potatoes (16)	19	3	(19)	-	-	-	-	-	-	-	-	-	-	-	-

Table 2.2 contd. **The number and percentage of brands within each food group recording the seven most commonly used additive categories in INFID[a]**

Food group (no. of brand foods in INFID within food group)	% brands within food category containing any additive	Colours n (%)		Emulsifiers n (%)		Acids n (%)		Stabilisers n (%)		Preservatives n (%)		Raising agents n (%)		Flavour enhancers n (%)	
Other pulses (47)	15	-	-	-	-	2	(4)	-	-	1	(2)	-	-	-	-
Coffee (28) (includes instant coffee powder)	7	-	-	-	-	-	-	2	(7)	-	-	-	-	-	-
Nuts (51)	10	-	-	1	(2)	-	-	-	-	-	-	-	-	2	(4)
Fruit juice (26)	8	-	-	-	-	2	(8)	-	-	-	-	-	-	-	-

[a] Food groups are listed in descending order of the percentage of brands within each food group containing any additive. Only 48 of the 63 INNS food groups (Lee & Cunningham 1990) were included in the analyses. The remaining 15 pertained to types of fresh fruit, fresh vegetables and alcoholic beverages which were not included in INFID and to tea, whole milk and table sugar, which were included in INFID but which did not contain any additives.

Table 2.3 Comparison of additive category usage[a] in foods[b] in the Irish National Food Ingredient Database (INFID) between the periods 1995-1997 and 1998-1999

Food additive category[c]	Frequency of use of additive category in brand foods			Number of brand foods containing additive category		
	1995-1997	1998-1999	P	1995-1997	1998-1999	P
Acidity regulators	141	154	*	137	147	NS
Acids	347	370	**	306	318	*
Antioxidants	63	48	*	62	46	*
Colours	391	376	NS	284	269	NS
Emulsifiers	267	305	***	192	213	*
Emulsifying salts	8	12	NS	8	9	NS
Flavour enhancers	93	92	NS	81	81	NS
Gelling agents	163	168	NS	152	154	NS
Glazing agents	6	6	NS	6	6	NS
Preservatives	161	163	NS	140	136	NS
Raising agents	223	231	NS	115	117	NS
Stabilisers	130	141	NS	91	91	NS
Sweeteners	93	103	*	69	68	NS
Thickeners	28	33	NS	27	33	*

[a]The frequency of use of an additive category in brand foods refers to the number of times an additive within an additive category was recorded in INFID. The number of foods containing an additive category refers to the number of foods in INFID, which contained at least one additive from that additive category.

[b]Of the 1,000 foods for which ingredient information was updated, approximately 90% were represented by the following food categories listed in table 2.2: preserves, sauces, biscuits, soups, chocolate confectionery, desserts, seafood, other soft drinks, other cereals, breakfast cereals, cheese, canned fruit and other fruit, cakes and pastries, other vegetables and dishes, yogurt and diet soft drinks.

[c]Analysis excluded additive categories with an insufficient number of data points. These included: anti-caking agents, antifoaming agents, firming agents, flour improvers, flour treatment agents, humectants and sequestrants.

*P < 0.05, **P < 0.01, ***P < 0.001, NS - not significant

Chapter 3

Assessment of food intake input distributions for use in probabilistic exposure assessments of food additives

Gilsenan, M.B., Lambe, J., and Gibney, M.J., 2003, Food Additives and Contaminants, 20, 1023-1033.

3.1 Introduction

Exposure analysis is an integral part of any food chemical risk assessment (Kroes *et al.* 2002). Exposure assessments using probabilistic methods are essential to represent the complexity of real life situations and to improve the comprehension of the consumer in risk communication (EU Scientific Steering Committee 2000). Probabilistic analysis uses distributions in place of point estimates to represent key exposure variables. Thus, instead of presenting a single point estimate of exposure, probabilistic techniques characterize the full range of potential exposures and their likelihood of occurrence, allowing risk managers to make more informed decisions regarding risk. The reliability of results from a probabilistic analysis and subsequent risk management decisions based thereon is dependent on the quality of the model inputs. This includes the selection of the most appropriate distribution to represent exposure variables in an exposure model (Lipton *et al.* 1995, Seiler and Alvarez 1996, Binkowitz and Wartenberg 2001, Kroes *et al.* 2002).

Food consumption represents a key component of any food chemical exposure assessment. Options available to describe variability in food consumption data for use in probabilistic models include empirical distributions (*e.g.* histograms) or theoretical (parametric) distributions (*e.g.* gaussian, lognormal) (Lambe 2002). A limitation to the use of empirical distributions is that they are restricted to the range of observed data (Taylor 1993, US EPA 1999, 2001). Furthermore, they may require access to the raw food consumption data. A parametric distribution can be used to represent food consumption in a probabilistic analysis. A key advantage of the use of parametric distributions is that they can provide estimates of the tails of a distribution beyond the range of observed values (US EPA 1999, 2001). This is of particular importance for food chemical exposure assessments, which tend to focus on distribution tails.

Although food chemical exposure assessments have begun to employ the use of probabilistic analyses (Hamey and Harris 1999, Hamey 2000, Lambe *et al.* 2002), there remains little guidance on the selection of the most appropriate distribution to represent food consumption in probabilistic models. Whilst a few studies have begun to explore this issue (Murray and Burmaster 1994, Ruffle *et al.* 1994, Driver *et al.* 1996), the majority are confined to foods relevant to environmental exposure assessments (Murray and Burmaster 1994, Ruffle *et al.* 1994). The purpose of the present study was to investigate the type of parametric distribution, which could be used to model variability in food consumption data

for use in probabilistic exposure assessments of intentionally added food chemicals, such as food additives.

3.2 Methods

Selection of food additives

Three food additives, annatto (E160b), potassium sorbate (E202) and phosphoric acid (E338) were selected. Annatto (E160b) and potassium sorbate (E202) represented two of the most commonly recorded food additives in the Irish national food ingredient database (Gilsenan *et al.* 2002) and both were recorded in a wide range of food categories (n=9) and (n=15), respectively. Phosphoric acid (E338) was chosen to represent a food additive permitted in only one food category.

Creation of relevant food categories

Food categories (n=22) were created from the food composition codes (Chan *et al.* 1994, 1995, 1996, Holland *et al.* 1988, 1989, 1992, 1993) in the North-South Ireland Food Consumption Survey (NSIFCS) database. These corresponded with the food categories in the Food Additives Directives (European Commission 1994b, 1995), in which the presence of the target additives was confirmed by the national food ingredient database. The food consumption survey data comprised seven day estimated food intakes from a nationally representative sample of 958 adults (aged 18-64 years), recorded using a food diary (Harrington *et al.* 2001). In addition, subjects' body weights were measured. These analyses did not account for the intake of foods present as ingredients in recipes or composite dishes. Recipe fractions of foods (expressed as the total weight of the food consumed from recipes / the total weight of food consumed) ranged from 0.1% (non alcoholic flavoured drinks) to 53% (dried fruit).

Distribution fitting of foods

Since exclusion of non-consumers of foods (which may result in a large peak at zero) enhances the ability to fit a parametric distribution to food consumption data (Murray and Burmaster 1994, US EPA 2000), the present study explored food consumption parametric distributions relating to food intakes amongst consumers only (*i.e.* excluding non-consumers of a given food). Mean daily intakes of each food category for each

consumer, expressed as both grams per day (g/day) and as grams per kilogram body weight per day (g/kg bw/day) were inputted into the BestFit® distribution fitting program version 2.0d (Palisade Corporation, Newfield, NY). A range of continuous parametric distributions, with a lower bound at zero, was fitted to the raw (sample) data using BestFit.® This program identifies the distribution(s) that best describe a given dataset using goodness-of-fit tests. For a given distribution (*e.g.* lognormal) fit to a dataset, the program calculates a test (goodness-of-fit) statistic. A goodness-of-fit statistic tells one how probable it is that a given distribution function produced a given dataset (Palisade Corporation 1997b). This value is then compared to the theoretical distribution of the test statistic. If the value obtained from the data analysis falls within the range of likely values of the test statistic distribution, then the null hypothesis that the data were obtained from the hypothesized distribution cannot be rejected (Cullen and Frey 1999). In these analyses, the number of intervals for classifying food intake data was selected using BestFit® prior to distribution fitting. For each relevant distribution in BestFit,® the parameters (*e.g.* mean and standard deviation (SD) for a lognormal distribution, or minimum and maximum for a uniform distribution) were estimated using maximum likelihood estimation (MLE) (Palisade Corporation 1997b). In the case of a lognormal distribution, BestFit® returns two sets of parameters (i) the estimated mean and SD of the lognormal distribution that best fits the observed data and (ii) the estimated mean and SD of the natural logarithms of the observed data. The Anderson Darling (AD) goodness-of-fit test was selected, as this test places more emphasis on distribution tails (Palisade Corporation 1997b). A significance level of 0.05 was used, implying that a value of the test statistic below the 95th percentile of the distribution for the test statistic (critical value) is acceptable and leads to an inability to reject the null hypothesis. Given that sample size may have an influence on results from goodness of-fit tests (Morgan and Henrion 1990, Cullen and Frey 1999, US EPA 1999, 2001), results for a number of food groups were accompanied by visual inspection of the fits using lognormal probability plots. These plots were created in Microsoft Excel 97 (Microsoft Corporation, Redmond, WA) by plotting the natural logarithms of the observed values against the Z-score associated with each percentile of a normal distribution, as described in detail by Burmaster and Hull (1997).

Modelling food additive intakes

To investigate the influence on exposure estimates of using a lognormal distribution to represent food consumption model inputs, intakes of annatto (E160b), potassium sorbate (E202) and phosphoric acid (E338) were modelled using @RISK® version 3.5.2, (Palisade Corporation, Newfield, NY). This software program, which can run as an add-in to Microsoft Excel, calculates probabilistic exposure estimates (using distributions in place of fixed point estimates) using Monte Carlo simulation. Values are randomly selected from each input distribution (*e.g.* food consumption) to provide an estimate of exposure in an iterative process. Repeated iterations using a different set of randomly selected input values generate a distribution of exposure estimates.

In the present study, the parameters of the lognormal distributions (*i.e.* mean and SD) describing the intake of food categories (g/kg bw/day) were calculated in three different ways. Therefore, three spreadsheet models were written in @RISK®. In the first model (LognormData), the parameters of the lognormal distributions for each food were calculated from the observed data (g/kg bw/day). In the second model (LognormBestfit), the parameters were the estimated mean and SD of the lognormal distribution that best fit the observed data. In the third model (Lognorm1Bestfit), the parameters were the natural logarithms of the observed data. The parameters of the latter models (LognormBestfit and Lognorm1Bestfit) were estimated in BestFit®. Within each model, total population additive intakes were calculated using a two stage process in which the probability of being a consumer of a given food, based on the percent consumers of each food group (calculated from the observed data) was entered as a discrete distribution, and food intake amongst consumers only (g/kg bw/day) was entered as a lognormal (parametric) distribution. A 100% chance of encounter of an additive in each food category was assumed and the concentration of the additive in each food category was fixed at maximum permitted levels (MPLs) (European Commission 1994, 1995).

The extent of correlations between groups of foods was examined using scatter plots in conjunction with a Spearman rank correlation analysis. Results indicated correlations less than 0.4 for the majority of food groups assessed. In the case of one food group pair (*i.e.* edible ices and ripened cheese) a high significant correlation ($r=0.84$, $P=0.001$) was observed. However, when the model was run with and without this correlation, only a marginal difference was observed in the results of both models. Therefore, subsequent

analyses in the present study did not include the use of correlations between food input distributions.

The Latin hypercube sampling method was selected to run models. This stratified random sampling method is more efficient than simple random sampling (Barton 1989, Palisade Corporation 1997a, Vose 2000). Each model was run for 5,000 iterations. A preliminary comparison of output distributions from additive models had suggested little difference between using 1,000, 5,000 and 10,000 iterations. Observed food additive intakes were calculated in SPSS® for Windows version 10 (SPSS Inc. Chicago, Illinois) according to the following equation:

$$a = \frac{\sum_{i=1}^{N} \left\{ \frac{\sum_{j=1}^{d} \sum_{h=1}^{z} \sum_{k=1}^{p_{ijh}} \left[f_{ijhk} \times c_{ijhk} \right]}{d \times bw_i} \right\}}{N}$$

where a is the average daily intake for the total population (mg/kg bw/day), f_{ijhk} is the consumption by individual *i* of the food product *h* on day *j* during eating occasion *k* (g), c_{ijhk} is the MPL of the additive for food product *h* eaten on occasion *k* by individual *i* on day *j* (mg/g), bw_i is the body weight of individual *i* (kg), z is the number of food products included in the exposure assessment, p_{ijh} is the number of eating occasions of food product *h* by individual *i* on day *j*, N is the number of individuals in the survey database and d is the number of survey days.

Thus, the only difference between observed and modelled intakes was the use of raw food intake data when calculating observed additive intakes and the use of a discrete distribution indicating the proportion of consumers combined with a lognormal distribution describing food intake data amongst consumers, when calculating modelled intakes. Food additive intake estimates modelled in @RISK® were compared with observed intakes.

3.3 Results

Table 3.1 ranks distributions according to the number of foods in which the fit of each distribution was accepted according to BestFit.® For the 22 foods examined, the lognormal distribution was the most commonly accepted distribution when food intakes were expressed as g/day and as g/kg bw/day.

Table 3.2 illustrates the number of accepted distributions corresponding to each food category (expressed as g/kg bw/day). These ranged from 13 (edible ices) to one (fat emulsions (excluding butter) with a fat content of 60% or more, and margarines, minarines, other fat emulsions and fats essentially free from water). Food categories with a smaller sample size had a larger number of accepted distributions compared to food categories with a larger sample size. The parameters of the lognormal distribution corresponding to each food category, estimated in BestFit,® and the calculated AD statistic are also presented in table 3.2. The AD statistic exceeds the critical value (2.49, 95% confidence level) for four of the 22 food categories, indicating a rejection of fit of a lognormal distribution for these foods.

Figure 3.1 illustrates lognormal probability plots of three food categories where the fit of a lognormal distribution was accepted in BestFit® (a-c) and three food categories where the fit of a lognormal distribution was rejected in BestFit® (d-f). In figure 3.1(a-c), the empirical data points fall in an almost straight line on the lognormal probability plots indicating that a lognormal distribution likely produced the given datasets. Figure 3.1(d-f) shows a slight curvature of the data points on the probability plots and a deviation from the straight line, in particular at the tails, indicating a poorer fit of a lognormal distribution to these datasets.

A comparison of food additive intakes modelled using a lognormal distribution in @RISK® with observed food additive intakes is presented in table 3.3. For all three additives, exposure estimates generated using a lognormal distribution with parameters calculated from the data (LognormData), were lower than observed food additive intakes at upper percentiles (90^{th} to 99^{th} %ile). Use of a lognormal distribution with parameters estimated from BestFit® (LognormBestfit) and (Lognorm1Bestfit) provided estimates of exposure which were higher than observed intakes at upper percentiles. Larger over-estimations were observed for intakes of potassium sorbate (E202) and annatto (E160b), based on 15 and nine food categories, respectively, compared to phosphoric acid (E338), where intake estimates were based on one food category (table 3.3).

3.4 Discussion

In this study, the AD goodness-of-fit test in BestFit® indicated that the lognormal distribution was the most commonly accepted distribution among the 22 food categories when food consumption data were expressed as absolute average daily intakes and as

average daily intakes expressed per kilogram body weight (table 3.1). This finding is in accordance with results from the very few published studies, which have explored this area with regard to highly focussed areas of food consumption (*i.e.* fish consumption (Murray and Burmaster 1994, Ruffle *et al.* 1994) and wine consumption (Driver *et al.* 1996)).

Results from goodness-of-fit tests using BestFit® were accompanied by a visual inspection of the fits using lognormal probability plots for a number of food categories. As the hypothesized distribution (*i.e.* lognormal) yields a straight line, these plots are particularly useful for evaluating deviations at distribution tails (US EPA 2001). The plots presented in figure 3.1 (a-f) support the results of goodness-of-fit tests (table 3.2) for the food categories presented. Figure 3.1 (d-f) illustrates that a lognormal distribution may not be the most appropriate fit to these foods, irrespective of sample size. Using an illustration of grape juice consumption, a poor fit of a lognormal distribution was also reported by Driver *et al.* (1996). Thus, whilst an adequate fit of a lognormal distribution to much food consumption data was demonstrated, it appeared that this distribution may not provide an adequate fit to all food consumption data.

An assessment of the influence on food additive exposure, of using a lognormal distribution to model food consumption, was carried out using the @RISK® modelling program (table 3.3). Considerable differences between modelled and observed intakes were shown at upper percentiles, depending on whether the parameters of the lognormal distributions used in the assessments were calculated from the observed data (LognormData) or estimated from BestFit® (LognormBestfit or Lognorm1Bestfit). It is likely that these differences occur as a result of the differences between input parameters used. Based on the present analysis, it appears that modelling food consumption data as a lognormal distribution using parameters (*i.e.* mean and SD) calculated from the observed data may potentially under-estimate food additive intakes at upper percentiles. Since food chemical exposure assessments tend to err on the side of conservatism, use of parameters estimated from BestFit® (LognormBestfit, Lognorm1Bestfit), which generated food additive intakes higher than observed intakes, would be deemed more appropriate to model food consumption data. Burmaster and Hull (1997) recommend the use of transformed values (*e.g.* Lognorm1Bestfit in the present study) to parameterize lognormal distributions in probabilistic assessments. They note that this approach is more consistent and numerically stable than the use of untransformed parameters.

Additional analyses in which models for potassium sorbate (E202) and annatto (E160b) were created, which excluded the food categories in which the fit of a lognormal distribution was rejected, were compared with observed additive intakes calculated excluding these same foods. Results indicated (data not shown) a decline in the ratio of modelled to observed additive intakes at upper percentiles. In the case of annatto, ratios were less than one. More investigative analyses are required in this regard before speculating on the implications of these findings.

It is acknowledged that ignoring the presence of moderate to strong correlations between input distributions may influence the output distribution in probabilistic exposure assessments (Burmaster and Anderson 1994, US EPA 2001). In the present study, results from a preliminary investigation of the strength of correlations between foods together with a comparison of model outputs with and without correlations, negated the use of correlations in the present study. A similar approach was adopted by Hamey and Harris (1999) and Hamey (2000), in probabilistic exposure assessments of pesticide residues. Correlations were also excluded from these studies as the authors reported only a marginal effect on results when simulations were run with and without correlations. Cullen and Frey (1999) note that the presence of weak correlations can be safely ignored without compromising the analytical results.

Given that a lognormal distribution is characterized by an extended tail to the right, the opportunity exists for the generation of implausible intakes. In this study, a maximum value almost six times higher than the observed maximum was generated for one food additive (table 3.3). A possible option to prevent the generation of implausible intakes with the use of a lognormal distribution is to truncate the food consumption input distribution at an appropriate upper bound. Whilst the issue of truncation limits for unbounded distributions in probabilistic assessments has been the subject of discussion elsewhere (Matalas and Bier 1999, US EPA 2001), there remains little guidance on appropriate truncation limits for food consumption distributions. Physiological factors (*e.g.* physiological upper limit to the amount of energy that could be consumed on a daily basis) might be a useful way to set plausible truncation limits for food consumption distributions. This is an area of research that warrants exploratory work.

A critical factor for the use of food consumption data in quantitative risk assessments is the availability of a representative data set for the assessment in question (Petersen 2000, Binkowitz and Wartenberg 2001, Kroes *et al.* 2002). The present study

used data from a nationally representative food consumption survey to explore the type of parametric distribution, which could be used to model variability (inherent variation) in food consumption patterns for the general population. Specific subgroups (*e.g.* diabetics, weight reducers), typically not adequately represented in national food consumption surveys, may have a higher intake of certain food additives (*i.e.* intense sweeteners) due to their dietary habits. Such population subgroups may require a separate assessment of food consumption distributions based on specific food consumption information relating to them. Furthermore, a specific assessment may be required for food intakes of children who have higher intakes of food chemicals when expressed per kg body weight compared to adults (Kroes *et al.* 2002).

Results from the present study pertain to food consumption data expressed as average daily intakes across the survey duration. Application of these results to acute dietary exposure assessments where food consumption data are expressed as intakes per eating occasion or per day (Rees and Day 2000) should be used with caution. Food consumption input distributions for use in acute probabilistic exposure assessments should be based on subsets of survey data (*e.g.* distributions of total daily food consumption) to avoid under-estimating variability in individual intakes that may occur when food intakes are expressed as mean daily intakes. Moreover, food consumption data derived from food frequency questionnaires, where intakes of foods are recorded in terms of portion sizes and frequencies of consumption, may warrant a separate analysis.

One of the cautions regarding goodness of-fit tests is that their results are influenced by sample size, *i.e.* small sample sizes are less likely to reject a fit to a distribution compared with larger sample sizes (Cullen and Frey 1999, US EPA 1999, 2001). This is illustrated in table 3.2 where a trend towards a higher number of accepted distributions was observed amongst food categories with a smaller sample size. It is therefore recommended to narrow a set of distributions to those that are considered plausible, by firstly considering the underlying physical properties of the data (*e.g.* consider whether food intakes are likely to be continuous or discrete), and then by applying goodness-of-fit tests to the candidate distributions to ascertain the fit (Cullen and Frey 1999, US EPA 1997, 1999, 2001, Vose 2000). In addition, it is strongly advised that results from goodness-of-fit tests be accompanied by graphical representations of the fit (Burmaster and Anderson 1994, US EPA 1997, 1999, 2001, Cullen and Frey 1999). Given the design of the food consumption survey (*i.e.* 7 day food record) from which the data used in these analyses were derived,

and given that negative food intakes do not exist, only continuous distributions in BestFit® with a lower bound at zero, were included in the present analysis.

The focus of the present study was to examine parametric food consumption input distributions for use in probabilistic exposure assessments of food additives. An alternative to the use of indicative data to describe food consumption model inputs is to use raw (observed) data using electronic databases. Lambe (2002) discusses the advantages of this approach. Gilsenan *et al.* (2003a) describe the application of raw input data in probabilistic models. These authors also identified potential limitations with this mode of input.

Given the likely increase in the use of probabilistic food chemical exposure assessments, an appropriate choice of input distribution to describe food consumption input data is of key importance when interpreting output distributions. The observations emanating from this study serve to warrant some level of caution regarding the use of a lognormal distribution to model food consumption data in food chemical exposure assessments. Clearly, this is an important area that merits considerable further research.

Table 3.1 Number of food categories in which distributions in BestFit® were accepted according to the AD goodness-of-fit test

Distribution	Number of food categories in which distribution was accepted[1,2]	
	g/kg bw/day	g/day
Lognormal	18	16
Lognormal2	17	14
PearsonVI	17	15
Inverse Gaussian	15	14
Gamma	13	12
PearsonV	11	10
Erlang	9	7
Weibull	8	8
Beta	6	6
Exponential	3	3
Rayleigh	2	2
LogLogistic	1	1
Pareto	1	2
Chi square	0	2

[1] Total number of food categories=22.
[2] Fourteen of nineteen continuous parametric distributions in the BestFit® program were used in these analyses. The remaining five distributions had lower bounds which extended below zero.

Table 3.2 The number of accepted distributions corresponding to each food category (g/kg bw/day) and the parameters of the best fitting lognormal distribution and corresponding AD[1] statistic calculated in BestFit®

Food category	Additive permitted in food category	Number of consumers (n)	Mean (±SD)[2]	Number of accepted distributions	Lognormal[3] distribution parameters	Rank where accepted	AD[4] test statistic
Fat emulsions (excluding butter) with a fat content of 60% or more	E202	678	0.24(0.21)	1	LognormBestfit (0.28,0.38) Lognorm1Bestfit (-1.90,1.06)	Rej	7.87
Margarine, minarine, other fat emulsions and fats essentially free from water	E160b	806	0.28(0.21)	1	LognormBestfit (0.33,0.33) Lognorm1Bestfit (-1.45,0.90)	Rej	10.45
Fine bakery wares	E160b, E202	842	0.59(0.52)	2	LognormBestfit (0.72,0.94) Lognorm1Bestfit (-0.80,1.06)	Rej	9.04
Non alcoholic flavoured drinks	E202, E338	629	2.59(3.1)	2	LognormBestfit (2.76,4.29) Lognorm1Bestfit (0.40,1.11)	1 2	0.96
Desserts	E160b	484	0.38(0.33)	4	LognormBestfit (0.38, 0.34) Lognorm1Bestfit(-1.26, 0.77)	2 3	0.74
Non-heat-treated dairy-based desserts	E202	321	0.61(0.52)	4	LognormBestfit (0.62,0.56) Lognorm1Bestfit (-0.79,0.78)	2 3	1.08
Emulsified sauces with a fat content ≥ 60%	E202	242	0.07(0.07)	4	LognormBestfit (0.07,0.07) Lognorm1Bestfit (-3.02,0.83)	3 4	2.23
Ripened orange, yellow and broken white cheese	E160b	543	0.19(0.19)	4	LognormBestfit (0.19,0.20) Lognorm1Bestfit(-2.02, 0.86)	1 2	0.80
Extruded, puffed and/or fruit flavoured breakfast cereals	E160b	409	0.3(0.3)	4	LognormBestfit (0.31,0.37) Lognorm1Bestfit (-1.63,0.95)	2 3	2.76
Fat emulsions with a fat content less than 60%	E202	292	0.22(0.2)	5	LognormBestfit (0.24,0.30) Lognorm1Bestfit (-1.92,0.98)	4 5	2.27
Processed cheese	E202, E160b	254	0.15(0.18)	5	LognormBestfit (0.15,0.16) Lognorm1Bestfit (-2.30,0.87)	3 4	1.49
Non emulsified sauces	E202	378	0.06(0.07)	5	LognormBestfit (0.06,0.06) Lognorm1Bestfit (-3.21,0.96)	Rej	1.15
Extruded or expanded savoury snack products	E160b	128	0.1(0.11)	6	LognormBestfit (0.1, 0.1) Lognorm1Bestfit (-2.64,0.79)	2 3	0.83

Table 3.2 contd. The number of accepted distributions corresponding to each food category (g/kg bw/day) and the parameters of the best fitting lognormal distribution and corresponding AD[1] statistic calculated in BestFit®

Food category	Additive permitted in food category	Number of consumers (n)	Mean (±SD)[2]	Number of accepted distributions	Lognormal[3] distribution parameters	Rank where accepted	AD test statistic
Smoked fish	E160b	59	0.26(0.24)	7	LognormBestfit (0.27,0.25)	4	0.51
					Lognorm1Bestfit (-1.64,0.79)	5	
Semi-preserved fish products including fish roe products	E202	185	0.22(0.18)	7	LognormBestfit (0.22,0.18)	2	0.54
					Lognorm1Bestfit (-1.75,0.71)	5	
Emulsified sauces with a fat content <60% fat	E202	84	0.05(0.07)	8	LognormBestfit (0.05, 0.04)	2	0.84
					Lognorm1Bestfit (-3.27,0.74)	3	
Dried fruit	E202	42	0.23(0.26)	9	LognormBestfit (0.24,0.42)	1	0.26
					Lognorm1Bestfit (-2.13,1.18)	2	
Unripened cheese	E202	38	0.29(0.22)	10	LognormBestfit (0.30,0.30)	2	0.44
					Lognorm1Bestfit (-1.53,0.82)	3	
Low sugar jams	E202	36	0.16(0.11)	11	LognormBestfit (0.18,0.19)	5	0.93
					Lognorm1Bestfit (-2.13,0.89)	6	
Olives and olive based preparations	E202	13	0.07(0.08)	11	LognormBestfit (0.07,0.06)	3	0.47
					Lognorm1Bestfit (-3.02,0.80)	4	
Edible ices	E160b	20	0.16(0.09)	13	LognormBestfit (0.16,0.09)	4	0.23
					Lognorm1Bestfit (-1.97,0.50)	5	
Pâté	E202	26	0.18(0.15)	12	LognormBestfit (0.18,0.15)	4	0.23
					Lognorm1Bestfit (-1.96,0.71)	5	

[1] If the AD statistic > critical value, distribution is rejected. Critical value=2.49 (95% confidence level).
[2] Mean intakes and SD (g/kg bw/day) amongst consumers only, calculated from the observed data.
[3]LognormBestfit: Parameters= mean and SD of the lognormal distribution that best fit the observed data, estimated in BestFit®, Lognorm1Bestfit: Parameters= mean and SD of the natural logarithms of the observed data, estimated in BestFit®.
[4]For a given food category, the AD test statistic for Lognorm1Bestfit is the same as the AD test statistic for LognormBestfit

Table 3.3 Comparison of total population food additive intakes (mg/kg bw/day) modelled using a lognormal distribution[1] in @RISK® with observed (Obs) food additive intakes

	Observed (Obs)	Lognorm-Data	Lognorm-Data/Obs	Lognorm-Bestfit	Lognorm-Bestfit/Obs	Lognorm1-Bestfit	Lognorm1-Bestfit/Obs
			Annatto (E160b)				
Mean	0.016	0.016	0.99	0.017	1.10	0.018	1.15
SD	0.011	0.010	0.93	0.013	1.23	0.015	1.43
Median	0.013	0.013	1.00	0.014	1.06	0.014	1.07
P90	0.030	0.027	0.89	0.032	1.05	0.033	1.10
P95	0.036	0.033	0.92	0.041	1.13	0.042	1.18
P97.5	0.042	0.040	0.95	0.049	1.18	0.052	1.25
P99	0.051	0.049	0.96	0.066	1.30	0.070	1.38
Max	0.070	0.209	2.99	0.185	2.64	0.383	5.49
			Potassium sorbate (E202)				
Mean	2.20	2.17	0.99	2.33	1.06	2.60	1.18
SD	1.49	1.45	0.98	2.08	1.40	2.59	1.74
Median	1.86	1.85	1.00	1.80	0.97	1.93	1.04
P90	4.10	3.88	0.95	4.54	1.11	5.01	1.22
P95	5.05	4.77	0.94	5.94	1.18	6.89	1.36
P97.5	5.86	5.83	0.99	7.52	1.28	8.93	1.52
P99	7.16	7.15	1.0	10.40	1.45	12.30	1.72
Max	10.26	20.81	2.03	30.13	2.94	59.51	5.80
			Phosphoric acid (E338)				
Mean	1.20	1.18	0.98	1.27	1.05	1.27	1.05
SD	1.96	1.90	0.97	2.44	1.24	2.54	1.29
Median	0.48	0.60	1.26	0.48	1.00	0.47	0.99
P90	3.24	3.01	0.93	3.32	1.02	3.27	1.01
P95	4.75	4.35	0.92	5.10	1.07	5.10	1.07
P97.5	6.75	6.04	0.90	7.15	1.06	7.52	1.11
P99	10.22	8.99	0.88	11.23	1.10	11.94	1.17
Max	17.81	34.87	1.96	43.75	2.46	49.24	2.76

[1]LognormBestfit: Parameters=arithmetic mean and SD for the lognormal distribution which best fit the observed data, estimated in BestFit® - this corresponds to the 'Lognormal' distribution presented in table 3.1.
Lognorm1Bestfit: Parameters=arithmetic mean and SD for the natural logarithms of the observed data, estimated in BestFit® - this corresponds to the 'Lognormal2' distribution presented in table 3.1.
LognormData: Parameters=arithmetic mean and SD calculated from the observed data.

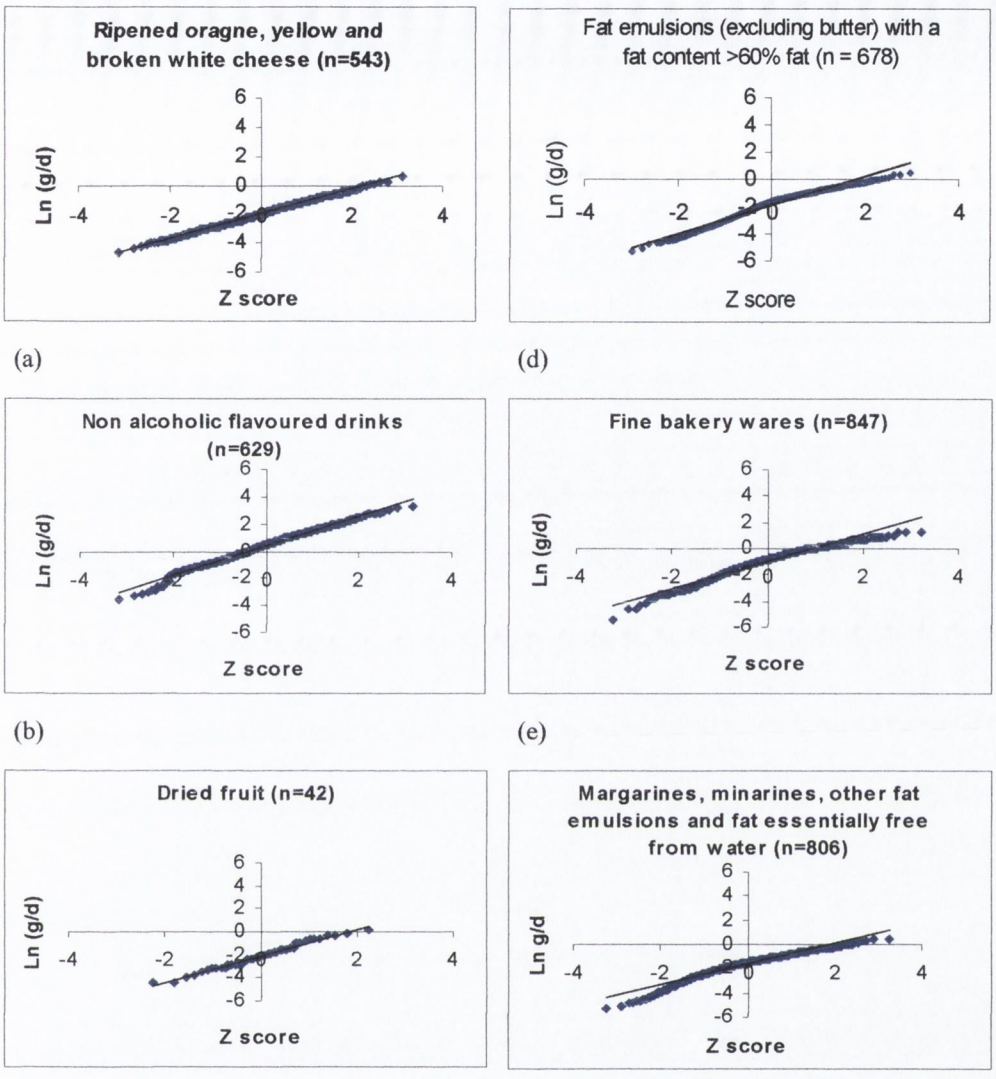


Figure 3.1 **Lognormal probability plots of three food categories in which the fit of a lognormal distribution was accepted and ranked first in BestFit® (a-c) and three food categories in which the fit of a lognormal distribution was rejected in BestFit® (d-f)**

Chapter 4

Validation analysis of probabilistic models of dietary exposure to food additives

Gilsenan, M.B., Thompson R.L., Lambe, J., and Gibney, M.J., 2003, Food Additives and Contaminants, 60, S61-S72.

4.1 Introduction

The estimation of food additive intakes follows a 'decision tree' in which the methodology employed proceeds from crude screening methods to more refined methods if results from screening methods dictate the need to do so (Nutriscan 1994, Gibney and Lambe 1996, European Commission 1998). Screening methods such as the Budget method (Douglass *et al.* 1997) and the theoretical maximum daily intake (TMDI) (FAO/WHO 1989) and more refined methods such as the Step 2 approach (European Commission 1997) that are currently used follow a deterministic approach. Deterministic approaches usually employ a single point estimate to represent exposure variables. An inherent assumption relating to both screening methods and to the more refined methods is that the food chemical is always present in the food(s) in which it is permitted. Furthermore, conservative assumptions relating to the concentration of a chemical in a food(s) are made (*e.g.* maximum permitted levels (MPLs) are commonly employed). Whilst the conservative assumptions inherent in the deterministic approach offer a margin of safety to protect the consumer, the potential exists to significantly over-estimate exposure. Furthermore, there is little flexibility to determine the probability of exceeding a proposed toxicologically safe range of intake (*e.g.* ADI) or to determine which model inputs most influence exposure.

In contrast to deterministic estimates of exposure, probabilistic analysis involves the use of distributions in place of single point estimates to represent exposure variables. A full distribution of exposure is then simulated by randomly selecting values from the input distributions according to a mathematical model which describes the exposure process (Vose 2000). Whilst probabilistic analysis is more resource intensive than the deterministic approach, this method of exposure analysis addresses many of the limitations of the deterministic approach. One of the key advantages relates to the provision of a full distribution of exposure, allowing exposure assessors to assess the influence of different scenarios on different sections of the distribution (Kroes *et al.* 2002). Nevertheless, the reliability of results generated from a probabilistic analysis is dependent on the validity of the model designed to examine exposure and the quality of the model inputs (Burmaster and Anderson 1994, Lipton *et al.* 1995, Binkowitz and Wartenberg 2001, Kroes *et al.* 2002). The aim of the present study was to assess the validity of a conceptual model designed specifically for the estimation of food additive intake using a detailed reference database of food additive intakes.

4.2 Methods and Results

The present study involved collaborative work between the Institute of European Food Studies (IEFS), Trinity College, Dublin and the Institute of Human Nutrition, University of Southampton, UK. Therefore, the data used to conduct this validation study derive from both Irish and British datasets.

Selection of food additives

A total of 10 additives were selected between both research centres. In the Irish study, two artificial colours, annatto (E160b) and erythrosine (E127), two preservatives, sorbates (E200-203) and benzoates (E210-213) and one emulsifier, polyglycerol polyricinoleate (E476) were selected. The selection process aimed to encompass food additives likely to be present in a wide range of foods (annatto and sorbates) and in a narrow range of foods (erythrosine and polyglycerol polyricinoleate). In addition, the likelihood of obtaining additive concentration data and the expected time frame required for the construction of brand level reference databases as described below, were taken into account during the selection process. In the case of benzoates, exposure from non-alcoholic flavoured drinks (soft drinks) only was estimated. This food group was selected based on results from previous research conducted at the IEFS, which indicated that non-alcoholic drinks made the largest contribution to the total intake of benzoates.

In the British study, three artificial sweeteners, acesulfame K (E950), aspartame (E951) and saccharin (E954) and two artificial colours, quinoline yellow (E104) and ponceau 4R (E124) were selected. These food additives were selected on the basis that they are permitted in foods likely to be commonly consumed by children.

Construction of reference databases

Within the context of the present study, a model was deemed valid if it generated exposure estimates that were lower than traditional deterministic estimates and higher than 'true' intake estimates. 'True' additive intakes were calculated using brand level reference databases (*i.e.* an Irish and a British brand level database) that were constructed specifically for the purpose of the present study. A summary of the construction of such brand level databases is documented by Leclercq *et al.* (2003a). A more detailed account of the steps involved is described below.

For the construction of the Irish brand level database, EU Directive food categories (European Commission 1994b, 1995) in which the presence of the five

selected food additives were recorded in a National Food Ingredient Database (INFID) (Gilsenan *et al.* 2002) were created using food composition codes from the North-South Ireland food consumption survey (NSIFCS) (Harrington *et al.* 2001). For the construction of the British brand level database, EU Directive food categories (European Commission 1994a,b) in which the five food additives selected for the British study are permitted, were created using food composition codes from the National Diet and Nutrition Survey of children aged 1.5 to 4.5 years (NDNS) (Gregory *et al.* 1995).

Whilst brand level information was recorded in the original food diaries of the NSIFCS and the NDNS, food consumption information was recorded at food code level in both electronic food consumption databases. Therefore, neither of the electronic food consumption databases retained information on the brands of food that were consumed. In the electronic NSIFCS, the subject number, the weekday, the time of day and the eating occasion were noted and the original food diaries were consulted to ascertain the brand consumed at a given eating occasion on a given day for a given subject. A new field entitled 'Brand code' was created in the electronic database. Once the brand name for a given eating occasion for a given subject was obtained, a specific brand code was allocated to that specific eating occasion in a new 'Brand code' field of the electronic food consumption database.

A request for the acquisition of the original food diaries of the NDNS was denied. Therefore, missing brand level information in the electronic British database was supplemented with brand level information from an additional British survey of toddlers, the Avon Longitudinal Study of Parents and Children (ALSPAC) (Emmett *et al.* 2002). Brand level dietary information recorded in the ALSPAC study was used to provide information on which brands associated with a particular food code or food group were most commonly consumed. This information was then used to populate the new 'Brand code' variable in the NDNS electronic database.

An additional new field was created in the NSIFCS and NDNS electronic food consumption databases entitled 'Presence' to indicate whether a given additive was present in a given brand consumed at a given eating occasion by a given subject. In the Irish study, the presence or absence on an additive in a given brand was ascertained using an existing food ingredient database constructed from ingredient labels of brand foods (Gilsenan *et al.* 2002). Where a given brand was not recorded in the food ingredient database, the presence or absence of the additive in that brand was determined by recording ingredient information from brand labels on the shelves of

Irish supermarkets. In the British study, the presence or absence of an additive in a given brand was determined using a purpose built food ingredient database. Information on the presence or absence of an additive in a brand was recorded in the new 'Presence' field of the Irish and British brand level databases, where a '1' indicated that an additive was present and a '0' indicated that an additive was absent from a given brand.

For brands that contained the given additives, concentration data were acquired in several ways. In Ireland, a task force of representatives of Irish food manufacturers was set up in conjunction with the Irish Business and Employers Confederation (IBEC). Options for supplying concentration data were explored and requests for concentration data for brands recorded in the food consumption survey were sent through IBEC to the relevant manufacturers. Brand level concentration information was sent to IEFS via IBEC. Concentration data for two food additives (benzoates and sorbates) were also obtained from Irish public analyst laboratories. Where concentration data from manufacturers and from public analyst laboratories were available, manufacturer data were used. Where concentration data from public analyst laboratories were below the limit of detection (LOD), a value corresponding to the limit of detection (LOD) or half the LOD was randomly assigned using the @RISK® modelling program[1] (Palisade Corporation, Newfield, NY). Where more than one concentration value was available for a given brand based on public analyst laboratory data, the average of the concentration values was used. The average of the values included the LOD or half the LOD that was randomly allocated using @RISK®, where applicable. Where concentration data for a given brand were available from more than one laboratory, the average value across laboratories was used. For some foods, concentration data from public analyst laboratories were only available at food type level *e.g.* 'Yoplait Yogurt' as opposed to *e.g.* 'Yoplait Raspberry Yogurt'. In this situation, concentration information at food type level was assigned to brands within that food type. In the British study, concentration data were collected at brand level from manufacturers and in some cases from ingredient labels (in the case of sweeteners). Table 4.1 depicts an illustrative example of the fields included in a brand level reference database used to calculate 'true' intakes in the present study.

[1] Using one iteration

Sources of uncertainty and assumptions used during the construction of brand level reference databases

During the construction of the above-mentioned brand level reference databases, a number of data gaps were identified. These included (i) incomplete records of the type of brand consumed in the original food diaries by the survey participants and (ii) incomprehensive food additive concentration data. The extent of missing brand level information recorded in food diaries varied across food groups. The food category with the lowest proportion of missing brands (20%) was non-alcoholic flavoured drinks. The extent of missing additive concentration data also varied across food groups. There were also a number of food categories for which no additive concentration data were available (*e.g.* emulsified sauces with a fat content of less than 60% fat, dried fruit, edible ices, savoury snacks, smoked fish, olives and olive based preparations). A scheme for assigning missing brand level data was developed and is summarized in figure 4.1. For each food group, a random sample of 10% of eating occasions was rechecked to ensure that the correct brand code had been assigned. All files were within a 3% error limit. Errors, where found, were corrected.

For brands for which no concentration data could be obtained in the Irish and British databases, a scheme for applying missing concentration data was developed and applied. Following this scheme, brands within a given food group that had missing concentration values were randomly assigned a concentration value using @RISK based on the distribution of existing concentrations for brands within that food group. For some food groups in the Irish database, there were insufficient concentration data available from which to assign concentration values to brands with missing values. In this situation, brands with missing concentration values were assigned a concentration value based the ratio of existing concentration values to MPLs for all other brands in all other food groups included in the assessment of exposure to a given additive. For example, no concentration data were available for any of the brands containing sorbates in the food group 'emulsified sauces with a fat content less than 60 fat'. In this situation, a distribution of ratios of concentrations to MPLs (conc:MPL) was created based on all brands in all other food groups used to estimate exposure to sorbates (zero concentrations were excluded). A value (*i.e.* ratio of conc:MPL) was randomly assigned to each brand in the 'emulsified sauces with a fat content less than 60 fat' that contained sorbates. Corresponding concentration values for each brand were then calculated by multiplying the ratio value assigned, by the MPL for sorbates in that food group. In the MPLs were assigned in a very small number of cases in the British study.

Given the range of uncertainties inherent in databases of food consumption and chemical concentration (Monte Carlo project team 2001, Kroes *et al.* 2002) coupled with the above-mentioned assumptions employed during the construction of brand level reference databases, the 'true' intake of a chemical within a population is unlikely to be known. Therefore, within the context of this paper, 'true' intakes should be understood as an approximate representation of a real life situation.

Development of conceptual model

A model for the estimation of food additive intake was developed. The model combined food intake data, the probability of an additive being present in a food group and additive concentration data. For each of the three model components, alternative modes of input were considered. Therefore, eight model combinations were developed (table 4.2). Raw food consumption data employed the use of food consumption information recorded at each eating occasion for each individual. Lognormal food consumption model inputs were expressed as average daily intakes amongst consumers of individual food groups, with the probability of being a consumer expressed as a binomial distribution. Whilst the use of moderate to strong correlations is recommended in probabilistic exposure assessments (Burmaster and Anderson 1994), no correlations were included in this study, since it was considered unlikely that correlations of this magnitude would be present between any of the foods. The probability of presence of an additive in a food group was expressed based on (i) the percentage of brands within a food group that contained an additive or (ii) the percentage of eating occasions within a food group that contained an additive[2]. Food additive concentration data within each food group were expressed as raw data using individual data points or as a lognormal distribution. Where lognormal distributions were employed, the parameters (*i.e.* arithmetic mean and standard deviation (SD)) were calculated from the reference datasets.

Validation criteria for conceptual models

Within this context, models were considered valid when they provided estimates that could not be shown to under-estimate 'true' exposure, but at the same

[2] *If a given food group within the reference database contained 10 brands, which were consumed over 20 eating occasions and a given food additive was present in five of these brands, then the probability of presence based on percentage brands would equal 50% (5/10). If each of the five brands in which the additive was present were only consumed once (during one eating occasion), then the probability of presence of this additive based on the percentage of eating occasions would equal 25% (5/20).*

time are more realistic than the currently used conservative estimates (Gibney and van der Voet 2003). Thus, probabilistic model estimates which were higher than 'true' intakes and lower than deterministic conservative intakes were considered to be in a valid region. For each additive, 'true' additive intakes were calculated in the Monte Carlo food chemical exposure analysis software program (McNamara *et al.* 2003) using the reference database according to the equation of Leclercq *et al.* (2003) where:

$$a_i = \frac{\sum_{j=1}^{d} \sum_{h=1}^{z} \sum_{k=1}^{p_{ijh}} f_{ijhk} \times c_{ijhk}}{d \times bw_i}$$

where a_i is the average daily intake by individual *i* over all survey days (mg/kg bw/day), f_{ijhk} is the consumption by individual *i* of the food product *h* on day *j* during eating occasion *k* (g), c_{ijhk} is the concentration of the additive for the brand of the food product *h* eaten on occasion *k* by individual *i* on day *j* (mg/kg), bw_i is the body weight of individual *i* (kg), z is the number of food products included in the exposure assessment, p_{ijh} is the number of eating occasions of food product *h* by individual *i* on day *j* and d is the number of days in the survey.

Conservative intake estimates were derived by applying MPLs from the EU Directives for the additives in question for the factor C_{ijhk}. Both 'true' and conservative intakes were calculated using one iteration and the ML_model 1 default modelling option[3] was used.

Validation of individual model components

Before embarking on running all eight model components, the validity of individual model components was assessed. As a first step, two simple chemical concentration models were developed for each food group and were run using the expression tester component of the Monte Carlo software. In the first model, the probability of presence of an additive based on the percentage of brands within a food group that contained the additive and the corresponding raw concentration data points for that additive ($P_{\%B}C_R$), were entered as a mathematical expression in the expression tester of the software. In the second model, the probability of presence of an additive and the corresponding raw concentration data points were entered as a mathematical

[3] *If brand level information is present in a food consumption database and corresponding brand level concentration data exists, then chemical concentration data will be directly assigned to food consumption data at brand level using this modelling option. Both brand level food consumption databases and brand level chemical concentration databases were employed for the calculation of 'true' and conservative intakes. Where no brand level information exists in a food consumption database, no brand information is assigned and chemical concentration data are randomly assigned to each individual eating occasion in the food consumption database.*

expression based on the percentage of eating occasions that contained the additive ($P_{\%E}C_R$). Each model was run for 50,000 iterations. Mean concentration values generated from the expression tester were compared with reference concentration values for each food category from the 'true' intake database using a Mann-Whitney non-parametric test. A value of $P < 0.001$ was used to define statistical significance, since with a large number of iterations (n=50,000) small numeric differences will often be statistically significant at $P<0.05$. An example of results using food groups relating to one food additive is presented in table 4.3. A summary of results from food categories relating to all 10 food additives is presented in table 4.4. Results from both tables indicate that a concentration model in which the probability of presence of an additive based on percent brands ($P_{\%B}C_R$), did not provide a good reflection of the concentrations in the reference dataset, whereas a concentration model with a probability of presence based on percent eating occasions, provided estimates of concentration that were not significantly different from the reference dataset for any single food group. These findings reduced the original number of plausible models from eight to four ($F_RP_{\%E}C_R$ (model 2), $F_RP_{\%E}C_L$ (model 4), $F_LP_{\%E}C_R$ (model 6) and $F_LP_{\%E}C_L$ (model 8)).

As a second step, the goodness-of-fit of a lognormal distribution to chemical concentration data based on percent eating occasions ($P_{\%E}C_R$) in each food group was assessed using the BestFit® distribution fitting program version 2.0d (Palisade Corporation, Newfield, NY). Results from these analyses indicated a rejection of the fit of a lognormal distribution for the majority of food groups assessed. Given these observations, the number of plausible models was reduced from four to two ($F_RP_{\%E}C_R$ (model 2) and $F_LP_{\%E}C_R$ (model 6)) *i.e.* in both models, the probability of presence of an additive in a given food category was based on the percent eating occasions that contained that additive and raw concentration data was employed. The only difference between both models was that food consumption data were entered as raw data (at individual eating occasion level) in the ($F_RP_{\%E}C_R$) model (model 2), and as a lognormal distribution of average daily intakes in the ($F_LP_{\%E}C_R$) model (model 6).

An assessment of the fit of a lognormal distribution to food consumption data expressed as average daily intakes (g/day), was undertaken using the BestFit® distribution fitting program, in addition to a graphical inspection of the fits using lognormal probability plots. The analyses using BestFit® indicated that a lognormal distribution was not universally accepted as a good fit for all of the food categories used in these analyses (table 4.5 a & b). However, graphical inspection of the fits revealed

that this was due to a poor fit of a lognormal distribution (over-estimation or under-estimation) at lower tails or an over-estimation at upper tails for a number of food groups (figure 4.2 a & b). Moreover, none of the food groups in which graphical inspection of the fits indicated under-estimation at upper tails made a large contribution (> 35%) to the intake of the food additive to which they pertained. Therefore, all 10 additives were included in the ($F_LP_{\%E}C_R$) model (model 6).

Validation of full conceptual models

The validity of models $F_RP_{\%E}C_R$ (model 2) and $F_LP_{\%E}C_R$ (model 6) was assessed using the Monte Carlo software program (McNamara *et al.* 2003). As will be discussed later in this section, the need for a further refinement of the $F_RP_{\%E}C_R$ (model 2) was revealed. The Monte Carlo program requires individual model components to be entered according to pre-defined database formats (McNamara *et al.* 2003). For the $F_RP_{\%E}C_R$ model (model 2), raw food consumption databases pertaining to each food group were uploaded at individual eating occasion level. These databases were coded at food code level. A subject characteristic table containing information on each individual's body weight was also uploaded. For the $F_LP_{\%E}C_R$ model (model 6), the probability of being a consumer of a food group was entered as a bernoulli distribution and food intakes amongst consumers were entered as a lognormal distribution. When food intake data is entered as a parametric distribution in the Monte Carlo software, the user is required to use the 'replicate subjects' simulation option to proceed with modelling. In this study, the number of subject replications was set to equal the number of subjects in the food consumption surveys relevant to the exposure assessment (n=958 Irish, n=1,591 British). All body weights in the subjects' characteristics table corresponding to this model were expressed as a lognormal distribution. For both models, the probability of presence of a chemical in a food group was entered in relevant fields in the additive concentration databases. Additive concentration data corresponding to each food group were entered as raw data points. Both models were run for 1,000 iterations, using the ML_model 1 default modelling option. An initial comparison of modelled results for all additives using 1,000 and 5,000 iterations revealed marginal differences in exposure estimates between both simulation options. Therefore, given that the former simulation option was less resource intensive than the latter, the former was used in subsequent analyses.

Exposure estimates from the $F_RP_{\%E}C_R$ and $F_LP_{\%E}C_R$ models (models 2 and 6, respectively) are compared with 'true' intakes in figure 4.3 (a-j). Given that

conservative intakes were considerably higher than 'true' and modelled intakes for all additives, these have been omitted from figure 4.3, to facilitate more informative comparisons. Corresponding model upper percentiles, together with 'true' and conservative intakes are tabulated in table 4.6. Within this table, considerable diversity between exposure estimates of additives selected in the Irish study (*i.e.* E160b, E210-213, E127, E476, E200-203) and those selected in the British study (*i.e.* E950, E951, E954, E104, E124) was observed. This is due to the fact that the results presented in this table pertain to two diverse populations. The 95% confidence intervals (CIs) associated with each percentile of exposure are also presented to demonstrate the variability in exposure estimates generated across 1,000 iterations. There was a tendency towards under-estimation of the $F_RP_{\%E}C_R$ model (model 2) at higher percentiles and a tendency towards over-estimation of exposure at lower percentiles (figure 4.3 a-j). Figure 4.4 presents a comparison of exposure estimates between modelled and true intakes at upper percentiles only (*i.e.* 90th, 95th, 97.5th 99th). Whilst exposure estimates from the $F_LP_{\%E}C_R$ model (model 6) at upper percentiles tended to be higher than 'true' intakes, for some additives (erythrosine (E127), benzoates (E210-E213), quinoline yellow (E104) and ponceau 4R (E124) and polyglycerol polyricinoleate (E476)), exposure estimates at the lower end of the upper percentiles were less than 'true' intakes (figure 4.3, table 4.6). At lower percentiles, the $F_LP_{\%E}C_R$ model showed a trend towards under-estimation of 'true' intakes (figure 4.3). In an attempt to understand why exposure estimates from the $F_RP_{\%E}C_R$ model (model 2) under-estimated 'true' intakes at upper percentiles, the percent consumers of the additive generated from the $F_RP_{\%E}C_R$ model was compared with the percent consumers of the additive from the 'true' intake database. This demonstrated that the $F_RP_{\%E}C_R$ model was over-estimating the number of consumers of the additive (table 4.7). Further exploratory work in this regard revealed that during the modelling process, each individual's eating occasion of a food in the raw food consumption database was treated as an independent event, thus ignoring the presence of any level of brand loyalty that may exist amongst individuals. Therefore, where individuals had multiple eating occasions of the relevant foods, there was a higher chance that the variable would receive the value 'present'. This resulted in a higher number of individuals being classified as consumers of the additive, which in turn resulted in lower additive intakes amongst consumers. As indicated earlier, these findings lead to an additional model being developed ($F_{R\text{-}Avedaily}P_{\%E}C_R$ (model 2b)). In

this model, food consumption data were also expressed as raw data, but at average daily intake level[4] rather than at eating occasion level, thus mimicking a situation where 100% brand loyalty existed amongst individuals. The probability of presence and chemical concentration model components were identical to the two corresponding models ($F_RP_{\%E}C_R$ (model 2) and $F_LP_{\%E}C_R$ (model 6)). Exposure estimates from this model ($F_{R\text{-}Avedaily}P_{\%E}C_R$) are also illustrated in figure 4.3 (a-j), table 4.6 and figure 4.4. This model showed less of a tendency to under-estimate 'true' intakes at upper percentiles compared to the $F_RP_{\%E}C_R$ model (model 2). However, for some additives, slight under-estimations were observed, in particular at the lower end of the upper percentiles (figure 4.3 (a-j), table 4.6 and figure 4.4). At lower percentiles, there was a trend towards under-estimation of 'true' intakes (figure 4.3). The percentage of consumers of the chemical from this model was similar to the percentage consumers from the $F_LP_{\%E}C_R$ model (model 6) (table 4.7). In both models, the percentage of consumers of the chemical was less than the percentage of consumers from the 'true' intake database (table 4.7).

4.3 Discussion

Estimates of additive intakes in the present paper must not be taken to represent actual intake, since comprehensive data on several parameters were not available. However, since the same data were used in 'true' and modelled estimates of exposure, this limitation does not apply to the validation process. As expected, the conservative intake estimates were very different from the values for 'true' and probabilistically modelled intake values. It is also evident that the models approximate 'true' values very closely. However, there is not sufficient conservative consistency to believe that these models and the related algorithms could yet be used in a real regulatory environment. Even taking the upper 95% CI of the simulated intakes for the 90^{th}, 95^{th}, 97.5^{th} and 99^{th} percentile (table 4.6), there was no consistency in that value exceeding the corresponding 'true' value. It would be unfair to say that these findings are surprising because the models used in this study were very simple, and probabilistic exposure modelling of food additives may require more complex models. Nevertheless, there are a number of issues that one needs to consider in terms of interpretation of these results.

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[4] *For a given consumer of a food group, the raw food consumption database contains one entry (average daily intakes) calculated over the survey duration.*

Consideration of how to incorporate food consumption data in models of exposure

In this study, two options were considered for inputting food consumption data in models of food additive exposure. These included the use of raw data or the use of a parametric (*i.e.* lognormal) distribution. A prerequisite for the use of raw food consumption model inputs (F_R) is the availability of a food consumption database in electronic format. In addition, this mode of input is largely dependent on the availability of sufficient computer resources. The advantages of raw food consumption model inputs are that food consumption data at the level of individual subjects is maintained, and the need to build correlations between intakes of multiple foods, if required, is negated. Furthermore, there is greater flexibility for designing models to combine food consumption data with additive concentration data (Lambe 2002). In this study, the raw food consumption data was firstly entered in its most disaggregated form (*i.e.* at individual eating occasion level for each subject). Results from full models indicated that models based on raw food consumption data underestimated 'true' additive intakes at higher percentiles. This was due to the fact that during the modelling process, each individual's eating occasion of a brand was treated as an independent event, thus ignoring the presence of any level of brand loyalty within subjects. As a result, more subjects were classified as additive consumers compared with the reference database, which in turn resulted in a lower additive intake amongst consumers. However, it must be stressed, that this limitation relates to the models and databases used in the present analyses. Where brand loyalty amongst individuals is unlikely to exist in a food consumption database, use of raw food consumption data in its most disaggregated form may represent a plausible model input. In an attempt to address this limitation, an additional model in which raw food consumption data was expressed as average daily intakes ($F_{R\text{-}Avedaily}P_{\%E}C_R$) (model 2b) was developed. In this model, all eating occasions of a food group for a given subject were aggregated to one value for each individual representing their average daily intake. This form of food consumption model input takes us from a situation where brand loyalty is not accounted for, to a situation where 100% brand loyalty is assumed. However, even with this model, the exposure estimates were not consistently within the valid region (*i.e.* above true and below conservative intakes) (Gibney and van der Voet 2003). This is discussed in more detail in the section below on the integration of food consumption and chemical concentration data. Use of a parametric (*e.g.* lognormal) distribution with parameters (mean and SD) may serve as an alternative mode of inputting food consumption (F_L) data where raw food consumption data are not available. A key advantage of the use of parametric distributions is that they

can provide estimates of the tails of a distribution beyond the range of observed data (US EPA 1999, 2001). They are also less resource intensive than raw model inputs. Previous research has suggested that a lognormal distribution may serve as a candidate distribution to model food consumption data amongst consumers (Murray and Burmaster 1994, Ruffle *et al.* 1994, Driver *et al.* 1996, Gilsenan *et al.* 2003b). However, examples of foods which indicated that the lognormal distribution was not universally acceptable, were also reported (Driver *et al.* 1996, Gilsenan *et al.* 2003b). In this study, the goodness of-fit of a lognormal distribution to all food categories used to estimate exposure to all 10 food additives was assessed using the BestFit® distribution fitting program. For the majority of additives, there were at least some food groups, for which the fit of a lognormal distribution was rejected. Following recommendations of Burmaster and Anderson (1994), US EPA (1997, 1999, 2001) and Cullen and Frey (1999), results from goodness-of-fit tests were accompanied by graphical inspection of the fits, which indicated a poor fit at the lower tails only for a number of food categories. This may be attributed to the fact that recipe fractions of foods were included in these analyses. Whilst slight under-estimations were observed for some food categories at upper tails, these did not contribute to a large extent to overall additive intakes. Therefore, all 10 additives were included in the $F_L P_{\%E} C_R$ model (model 6). Nevertheless, these findings do reveal the need for more exploratory work in this area. Results generated from these models, where food consumption data were entered as a lognormal distribution (F_L), were similar to results from models where food consumption data were entered as raw data expressed as average daily intakes ($F_{R\text{-}Avedaily}$) (table 4.6, figure 4.3 (a-j)) and figure 4.4.

Consideration of how to incorporate additive concentration data in models of exposure

Similar to food consumption model inputs, additive concentration data may be inputted into probabilistic models of food additive exposure expressed as raw data or as a parametric distribution. Whilst not easily attainable (Monte Carlo project team, 2003), the use of raw additive concentration data (C_R) can provide a more realistic picture of the distribution of additive concentrations within a food category. The need to include correlations between additive concentrations in multiple foods is also eliminated. Given the number of assumptions during the development of the reference 'true' databases, the fit of a lognormal distribution to additive concentration data in all food categories was rejected using the BestFit® distribution fitting program. Alternative parametric distributions were not considered due to the nature of the underlying additive

concentration data. Therefore, following good modelling practice, it was not deemed appropriate for this validation study to consider additive concentration data as a lognormal distribution. However, if better data were available, this could be considered as an appropriate mode of input.

Two options were considered for the probability of presence of an additive for a given eating occasion for a given subject. These were (i) information on the percentage of brands within a food group that contained an additive and (ii) information on the percentage of eating occasions within a food group that contained an additive. The former was considered a plausible model input given that this information is likely to be available from food ingredient databases. However, validation of this model component using the expression tester component of the Monte Carlo software indicated that the probability of presence based on percentage brands did not provide a good representation of additive concentrations in the 'true' intake database. This was due to the fact that this model input does not take the market share of individual brands into account during the modelling process. Within the context of this study, the market share of brand A of food product B, is equal to the number of eating occasions in which brand A has been consumed in proportion to the number of eating occasions of all brands of food product B which have been consumed. However, if all brands had an equal market share, this model input may be deemed appropriate. The probability of presence model input based on the percentage eating occasions was employed to mimic a situation where information on the probability of presence based on the percentage brands is accompanied with information on market share. Testing the validity of this model input using the expression tester indicated that this type of model input provides a good reflection of 'true' additive concentration data, both in terms of the number of eating occasions where an additive is present and the concentration values assigned. However, as mentioned below, the validity of this model input will depend on how it is integrated with the food consumption data during the modelling process.

Consideration of how to integrate food consumption and additive concentration data in models of exposure

Whilst testing individual model components indicated that a probability of presence model input based on percent eating occasions and raw additive concentration data provided a good representation of the observed food additive concentrations, when integrated with raw food consumption data in its most disaggregated form in the full model, exposure estimates at upper percentiles under-estimated 'true' intakes. As

mentioned previously, this was due to the fact that individuals' brand loyalty in the food consumption database was ignored when a presence variable was randomly assigned during the modelling process. Therefore, where brand loyalty is likely to exist in a food consumption database, this model has the potential to under-estimate food additive exposure and therefore would not be appropriate for risk assessment purposes. Use of models in which food consumption data was expressed as average daily intakes, either as raw data ($F_{R\text{-}Avedaily}$) or as a lognormal distribution (F_L), went someway towards improving this situation, giving results that more closely resembled 'true' intakes. Nevertheless, intakes at upper percentiles were not consistently higher than 'true' intakes, even when the upper 95% CI of the simulated intakes for each percentile was considered. Only at the 99th percentile did the average daily intake models exceed 'true' intakes for all 10 additives. As mentioned above, because models in which food consumption data expressed as average daily intakes ($F_{R\text{-}Avedaily}$), involve the assumption of 100% brand loyalty, these models lead to an under-estimation of the percent consumers of the additive, an under-estimation of additive intake at lower percentiles, and an over-estimation of additive intakes at upper percentiles. The exact percentile at which this over-estimation of upper percentiles occurred varied and appeared to be related to the number of consumers in the reference database.

4.4 Conclusion

Simple models of food additive exposure that do not take account of market share and/or brand loyalty may potentially under-estimate additive intakes at upper percentiles. Therefore, more sophisticated models of food additive exposure, which incorporate information on market share and/or brand loyalty into the modelling algorithms may be required. This approach was applied by Arcella *et al.* (2003), in the case of intense sweeteners. If lack of information on market share and/or brand loyalty dictates the need to use simpler models of food chemical exposure, exposure estimates from very high percentiles (*e.g.* 99th percentile or higher) should be used. These simple models will only be useful if attempts are made to incorporate information on brand loyalty (*e.g.* use of food consumption model inputs expressed as average daily intakes, either as raw data or as parametric data) and market share (*e.g.* incorporating market share information into the values used for probability of presence).

The present study highlights the need for a detailed evaluation of conceptual models, algorithms governing such models and the mode of input of data into associated probabilistic exposure software. The results presented in this paper represent the state of

knowledge at the end of the EU funded Monte Carlo programme and the models and software will be subject to continuing development and validation.

Table 4.1 Illustration of a brand level reference database used to calculate 'true' additive intakes[1]

Subject ID	Survey day	Time	Meal no.	Food code	Amount (g)	Brand code	Presence	Concentration (ppm)
1	1	11:00	2	11166 (*e.g.* chocolate biscuit full coated)	60	43 (*e.g.* McVitie's fully coated digestive biscuit)	0	0
1	1	14:00	3	11171	60	42	0	0
1	2	10:15	2	11177	13	41	1	5
1	2	14:00	3	11171	70	42	0	0
1	2	19:00	4	11171	60	42	0	0
1	3	10:00	2	11177	39	41	1	5
1	4	14:00	3	11182	50	44	1	6
1	4	18:00	4	11182	50	44	1	6
1	5	10:00	2	11166	40	43	0	0
1	6	18:00	4	11177	13	45	1	2
1	7	10:00	2	11177	13	49	1	8
2	1	14:30	3	11185	26	46	0	0
2	1	18:30	4	11185	26	47	0	0
2	2	14:00	3	11185	26	48	1	5
2	7	18:00	4	11185	26	46	0	0

[1]Note: Fields 1-6 in black font represent existing dietary information recorded in the electronic NSIFCS and NDNS databases. Fields 7-9 in red font represent new fields that were inserted and populated during the construction of the brand level reference database in the present study.

Table 4.2 Description of models of exposure to food additives included in the Monte Carlo validation study

Model input data formats				
Food consumption	Presence probability	Chemical concentration	Model name	Model number
Raw data	% brands	Raw data	$F_RP_{\%B}C_R$	1
Raw data	% eating occasions	Raw data	$F_RP_{\%E}C_R$	2
Raw data	% brands	Lognormal	$F_RP_{\%B}C_L$	3
Raw data	% eating occasions	Lognormal	$F_RP_{\%E}C_L$	4
Lognormal	% brands	Raw data	$F_LP_{\%B}C_R$	5
Lognormal	% eating occasions	Raw data	$F_LP_{\%E}C_R$	6
Lognormal	% brands	Lognormal	$F_LP_{\%B}C_L$	7
Lognormal	% eating occasions	Lognormal	$F_LP_{\%E}C_L$	8

Table 4.3 Comparison of 'true' mean (±SD) concentrations of annatto (E160b) mg/kg in food groups with mean concentrations generated from expression tester[1] based on $P_{\%B}C_R$ and $P_{\%E}C_R$ concentration models[2] using a Mann-Whitney test

Food group	True	$P_{\%B}C_R$	$P_{\%E}C_R$	True v $P_{\%B}C_R$ (P)	True v $P_{\%E}C_R$ (P)
Edible ices	0.127 (0.459) n=27	0.173 (0.518)	0.127 (0.459)	0.644	0.992
Desserts	1.054 (2.429) n=1029	1.332 (2.840)	1.029 (2.394)	<0.001	0.754
Fine bakery wares	0.201 (0.813) n=5353	0.176 (0.984)	0.204 (0.810)	<0.001	0.583
Flavoured & unflavoured processed cheese	1.090 (2.131) n=623	1.652 (3.948)	1.094 (2.144)	<0.001	0.974
Ripened orange, yellow and broken white cheese	2.474 (4.604) n=1585	4.335 (5.666)	2.494 (4.605)	<0.001	0.785
Margarine, minarine, other fat emulsions and fats essentially free from water	0.191 (0.852) n=9729	0.334 (1.177)	0.193 (0.852)	<0.001	0.714
Extruded, puffed and/or fruit flavoured breakfast cereals	0.179 (2.126) n=1498	0.787 (4.079)	0.179 (2.132)	<0.001	0.992
Extruded or expanded savoury snack products	0.763 (2.032) n=195	0.356 (1.336)	0.759 (2.020)	0.001	0.995

[1] n=50,000 iterations.

[2] $P_{\%B}C_r$ model denotes a concentration model component in which the probability of presence is based on the percentage of brands within a food group that contains an additive and raw concentration data is employed. $P_{\%E}C_R$ model denotes a concentration model component in which the probability of presence is based on the percentage of eating occasions within a food group that contains an additive and raw concentration data is employed.

Table 4.4 **The number of food categories corresponding to each food additive in which mean additive concentration (mg/kg) based on $P_{\%B}C_R$ and $P_{\%E}C_R$ concentration models[1] were significantly different[2] from 'true' mean additive concentrations in reference datasets**

Additive	E number	Number of food categories	Number of food categories in which estimated additive concentration (mg/kg) was significantly different from 'true' concentrations	
			$P_{\%B}C_R$	$P_{\%E}C_R$
Annatto	E160b	8	6	0
Benzoates	E210-213	1	1	0
Erythrosine	E127	1	0	0
Polyglycerol polyricinoleate	E476	2	1	0
Sorbates	E200-203	17	12	0
Acesulfame K	E950	6	4	0
Aspartame	E951	6	6	0
Saccharin	E954	5	4	0
Quinoline yellow	E104	5	4	0
Ponceau 4R	E124	5	4	0

[1] Mean chemical concentration generated using expression tester (n=50,000 iterations).
[2] $P < 0.001$; Mann-Whitney test.

Table 4.5a Assessment of the fit of a lognormal distribution to food consumption data expressed as average daily intakes (g/d) using the BestFit® distribution fitting program[1] – results from NSIFCS

Food group	Sample size	Whether fit was accepted/ rejected[2]	E number of additive present in food group
Candied, crystallised and glace fruit	178	Accepted	E200-203
Cocktail cherries and candied cherries	269	Accepted	E127
Cocoa based confectionery including chocolate	628	Accepted	E476
Desserts	494	Accepted	E160b
Dried fruit	204	Accepted	E200-203
Edible ices	23	Accepted	E160b
Emulsified sauces ≥ 60% fat	303	Accepted	E200-203
Emulsified sauces with a fat content < 60%	90	Accepted	E200-203
Extruded or expanded savoury snack products	128	Accepted	E160b
Extruded, puffed and/or fruit flavoured breakfast cereals	416	Rejected	E160b
Fat emulsions < 60% fat	298	Accepted	E200-203
Fat emulsions with a fat content ≥60%	782	Rejected	E200-203
Fillings of ravioli and similar products	3	Accepted	E200-203
Fine bakery wares	867	Rejected	E200-203 E160b
Low and very low fat spreads and dressings[3]	298	Accepted	E476
Low sugar jams, jellies, marmalades and similar low calorie and sugar free products and other fruit based spreads; mermelades	36	Accepted	E200-203
Margarines, minarines, other fat emulsions and fats essentially free from water	869	Rejected	E160b
Non alcoholic flavoured drinks	649	Rejected	E200-203 E210-213
Non emulsified sauces	468	Accepted	E200-203
Non-heat treated dairy based desserts	350	Rejected	E200-203
Olives and olive based preparations	13	Accepted	E200-203
Pâté	27	Accepted	E200-203
Processed cheese	263	Rejected	E200-203 E160b
Semi-preserved fish products including fish roe products	194	Accepted	E200-203
Smoked fish	59	Accepted	E160b
Unripened cheese	39	Accepted	E200-203

[1]BestFit® settings: The maximum likelihood estimation option was selected to estimate parameters of distributions. The number of intervals in the observed (sample) data was calculated automatically using BestFit®.

[2]Using the Anderson Darling goodness-of-fit test. A significance level of 0.05 was used to evaluate the fit.

[3] Analyses do not include *dressings* since no brand of dressings in Irish national food ingredient database contained E476.

Table 4.5b Assessment of the fit of a lognormal distribution to food consumption data expressed as average daily intakes (g/d) using the BestFit® distribution fitting program[1] – results from NDNS

Food group	Sample size	Whether fit was accepted/ rejected[2]	E number of additive present in food group
Cocoa confectionery	757	Accepted	E951
Confectionery	1217	Rejected	E104 E124
Edible ices	251	Accepted	E104 E124
Energy reduced soups	5	Accepted	E950
Fine bakery wares	1560	Rejected	E104
Fruit juice drinks	884	Accepted	E950 E951 E954
Milk based drinks	225	Accepted	E951 E954
Milk preparations	1326	Rejected	E950 E951 E954
No added sugar gum	9	Accepted	E951
Non alcoholic flavoured drinks	1507	Rejected	E104 E124
Preserves of red fruit	58	Accepted	E124
Sauces	1342	Rejected	E950 E954
Sauces[3]	795	Rejected	E104 E124
Water based desserts	188	Accepted	E950 E951
Water based drinks	1353	Rejected	E951 E950 E954

[1]BestFit® settings: The maximum likelihood estimation option was selected to estimate parameters of distributions. The number of intervals in the observed (sample) data was calculated automatically using BestFit®.
[2]Using the Anderson Darling goodness-of-fit test. A significance level of 0.05 was used to evaluate the fit.
[3]The sauces group corresponding to colours does not include tomato-based products, since colours are not permitted in tomato based products.

Table 4.6 Comparison of total population additive intakes (mg/kg bw/day) generated from $F_R P_{\%E} C_R$ (model 2), $F_{R\text{-}Avedaily} P_{\%E} C_R$ (model 2b) and $F_L P_{\%E} C_R$ (model 6) models[1] with true[2] and conservative[2] (cons) intakes

Additive[3]	P90					P95				
	Cons	True	$F_R P_{\%E} C_R$	$F_{L\%E} C_R$	$F_{RAvedaily} P_{\%E} C_R$	Cons	True	$F_R P_{\%E} C_R$	$F_L P_{\%E} C_R$	$F_{R\text{-}Avedaily} P_{\%E} C_R$
E160b	0.0310	0.0022	0.0019 (0.0018,0.0021)	0.0022 (0.0019,0.0026)	0.0023 (0.0019,0.0026)	0.0372	0.0030	0.0027 (0.0024, 0.0030)	0.0036 (0.0030,0.0043)	0.0037 (0.0031,0.0043)
E210-213	0.69	0.35	0.32 (0.29, 0.34)	0.34 (0.29, 0.40)	0.35 (0.30,0.41)	1.01	0.52	0.47 (0.43, 0.52)	0.58 (0.48, 0.68)	0.60 (0.52,0.70)
E127	0.0023	0.0005	0.0003 (0.0002, 0.0004)	0.00003 (0.0000, 0.0002)	0.00002 (0,0.00001)	0.0045	0.0011	0.0009 (0.0006, 0.0012)	0.0007 (0.0004, 0.0011)	0.0007 (0.0005,0.0010)
E476	3.05	0.04	0.05 (0.04, 0.06)	0.02 (0.01, 0.03)	0.02 (0.01,0.03)	4.09	0.08	0.09 (0.08, 0.11)	0.07 (0.05, 0.10)	0.08 (0.05,0.11)
E200-203	4.24	0.86	0.70 (0.66, 0.74)	0.82 (0.73, 0.92)	0.82 (0.75,0.91)	5.15	1.10	0.93 (0.87, 0.99)	1.20 (1.05, 1.36)	1.19 (1.06,1.34)
E950	21.47	1.93	1.73 (1.64,1.84)	2.23 (1.83,2.67)	2.17 (1.73,2.67)	25.57	2.97	2.29 (2.14,2.45)	4.31 (3.62, 4.99)	4.49 (3.80,5.21)
E951	39.11	10.32	9.17 (8.89, 9.44)	10.96 (10.19, 11.75)	10.71 (10.27, 11.18)	46.05	12.91	11.39 (10.96, 11.81)	14.74 (13.47, 16.12)	13.97 (13.13,14.84)
E954	5.31	3.31	2.88 (2.80, 2.96)	3.44 (3.22, 3.70)	3.45 (3.26, 3.59)	6.28	4.27	3.58 (3.47, 3.71)	4.59 (4.24, 4.97)	4.39 (4.21, 4.57)
E104	7.26	0.071	0.063 (0.058, 0.069)	0.048 (0.041, 0.058)	0.057 (0.048, 0.066)	8.65	0.114	0.089 (0.082, 0.098)	0.097 (0.080, 0.115)	0.106 (0.090, 0.124)
E124	3.39	0.035	0.038 (0.035, 0.041)	0.024 (0.021, 0.027)	0.031 (0.027, 0.036)	4.02	0.057	0.054 (0.049, 0.058)	0.043 (0.036, 0.051)	0.055 (0.047, 0.063)

[1]Modelled intakes refer to mean intakes of additive across 1,000 iterations for each statistic. Values in brackets represent 95% confidence intervals.

[2]True and conservative intakes were generated using one iteration.

[3] Exposure estimates of E160b - E200-203 are based on an Irish data, whereas exposure estimates of E950 - E124 are based on British data. Diversity in exposure estimates between these two groups of additives are attributed to differences in the underlying populations and databases employed.

Table 4.6 contd. **Comparison of total population additive intakes (mg/kg bw/day) generated from $F_RP_{\%E}C_R$ (model 2), $F_{R\text{-}Avedaily}P_{\%E}C_R$ (model 2b) and $F_LP_{\%E}C_R$ (model 6) models[1] with true[2] and conservative[2] (cons) intakes**

Additive[3]	P97.5					P99				
	Cons	True	$F_RP_{\%E}C_R$	$F_{L\%E}C_R$	$F_{RAvedaily}P_{\%E}C_R$	Cons	True	$F_RP_{\%E}C_R$	$F_LP_{\%E}C_R$	$F_{R\text{-}Avedaily}P_{\%E}C_R$
E160b	0.0433	0.0046	0.0035 (0.0031,0.0040)	0.0052 (0.0043,0.0064)	0.0053 (0.0045,0.0062)	0.0504	0.0059	0.0047 (0.0041,0.0055)	0.0078 (0.0060,0.0100)	0.0079 (0.0062,0.0099)
E210-213	1.43	0.08	0.66 (0.59,0.72)	0.85 (0.69,1.06)	0.89 (0.77,1.02)	2.07	1.17	0.93 (0.82,1.04)	1.30 (1.00,1.71)	1.38 (1.10,1.67)
E127	0.0065	0.0019	0.0017 (0.0013,0.0021)	0.0017 (0.0011,0.0024)	0.0017 (0.0011,0.0024)	0.0097	0.0024	0.0029 (0.0021,0.0042)	0.0035 (0.0023,0.0048)	0.0036 (0.0023,0.0054)
E476	5.03	0.15	0.14 (0.11,0.18)	0.16 (0.110,0.22)	0.16 (0.110,0.24)	7.04	0.25	0.23 (0.18,0.30)	0.35 (0.22,0.56)	0.36 (0.22,0.54)
E200-203	6.18	1.38	1.19 (1.10,1.28)	0.63 (1.39,1.89)	1.60 (1.41,1.82)	7.09	1.84	1.55 (1.41,1.71)	2.28 (1.85,2.81)	2.22 (1.82,2.66)
E950	30.50	3.93	2.87 (2.65,3.11)	6.62 (5.62,7.73)	6.87 (5.83,7,82)	35.92	5.39	3.67 (3.31,4.11)	10.10 (8.23,12.19)	10.10 (8.40,12.07)
E951	53.06	16.83	13.65 (13.05,14.33)	18.88 (17.05,20.87)	17.19 (16.14,18.15)	65.77	20.02	17.21 (16.15,18.45)	24.97 (21.74,28.74)	22.08 (19.59,24.49)
E954	7.35	5.21	4.29 (4.13, 4.50)	5.85 (5.31,6.42)	5.31 (55.0,5.66)	8.98	6.42	5.41 (5.05,5.78)	7.69 (6.75,8.83)	6.73 (6.33,7.12)
E104	9.83	0.155	0.115 (0.104,0.127)	0.161 (0.133,0.197)	0.167 (0.139,0.201)	11.82	0.21	0.150 (0.132,0.170)	0.282 (0.216,0.369)	0.278 (0.219,0.351)
E124	4.74	0.079	0.070 (0.064,0.077)	0.074 (0.059,0.100)	0.085 (0.071,0.103)	5.61	0.147	0.093 (0.082,0.106)	0.188 (0.115,0.289)	0.178 (0.109,0.304)

[1]Modelled intakes refer to mean intakes of additive across 1,000 iterations for each statistic. Values in brackets represent 95% confidence intervals.

[2]True and conservative intakes were generated using one iteration.

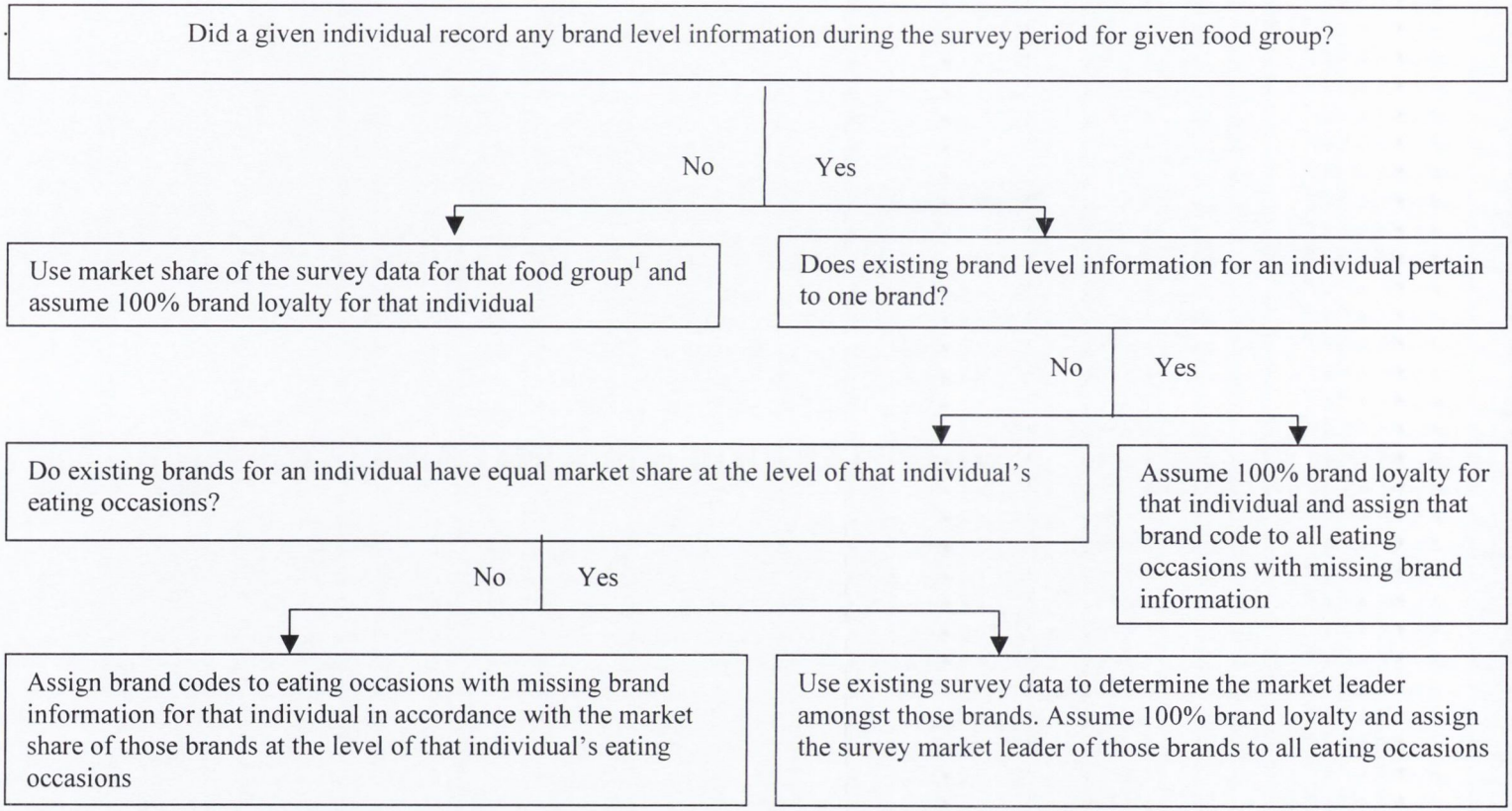
[3]Exposure estimates of E160b - E200-203 are based on an Irish data, whereas exposure estimates of E950 - E124 are based on British data. Diversity in exposure estimates between these two groups of additives are attributed to differences in the underlying populations and databases employed.

Table 4.7 **Comparison of percentage consumers of additives from $F_RP_{\%E}C_R$, $F_{R\text{-}Avedaily}P_{\%E}C_R$ and $F_LP_{\%E}C_R$ models with 'true' intakes from reference datasets**

Additive	True	$F_RP_{\%E}C_R$	$F_LP_{\%E}C_R$	$F_{R\text{-}Avedaily}P_{\%E}C_R$
E160b	65.08	82.85	50.82	50.56
E210-213	45.46	55.37	35.50	35.50
E127	13.61	14.67	9.63	9.70
E476	26.27	31.91	13.41	13.38
E200-203	85.34	95.90	80.66	78.59
E950	42.36	67.71	21.65	21.67
E951	87.18	93.30	80.66	80.89
E954	85.42	92.89	76.16	76.34
E104	48.15	54.25	30.25	30.21
E124	50.41	55.84	30.04	30.04

Figure 4.1 Scheme for assigning brand codes within a given food group where brand level information is missing

Note: This process is repeated for each subject.



[1] Assigning brand bodes at food group level was governed by the extent of missing brand information in the food diary for a given subject. For example, if a subject recorded the consumption of a 'biscuit', then a brand code would be randomly assigned from all types of biscuits. If, however, an individual recorded the consumption of a 'chocolate biscuit', then a brand code would be randomly assigned from existing brands if 'chocolate biscuits' as opposed to 'all biscuits'.

Note: Where all brand information was missing for all eating occasions of a given food group for all subjects, a brand was randomly selected from a food ingredient database for a given individual and 100% brand loyalty was assumed

Figure 4.2a Assessment of the fit of a lognormal distribution to food consumption data expressed as average daily intakes (g/d) using lognormal probability plots – results from NSIFCS

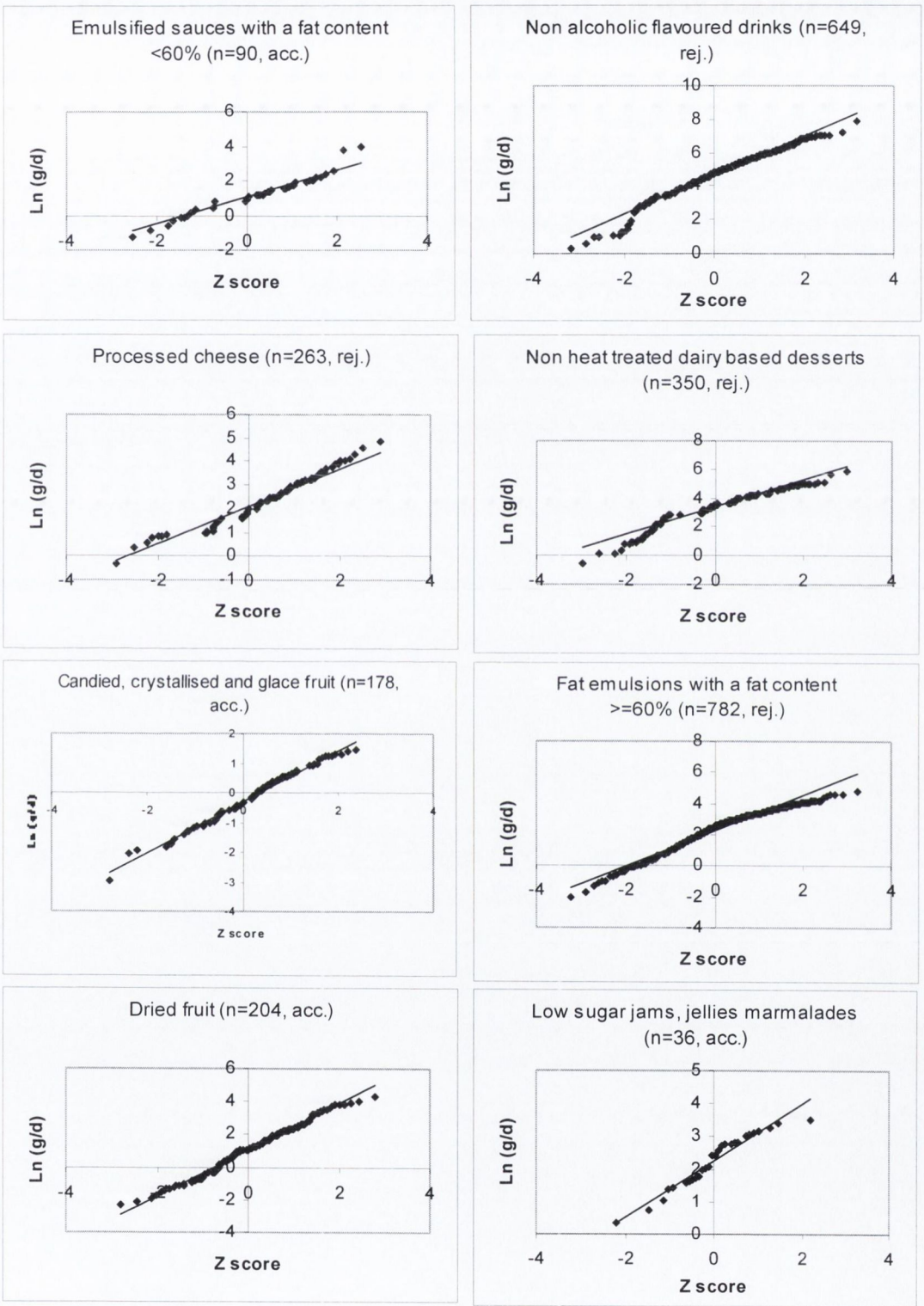
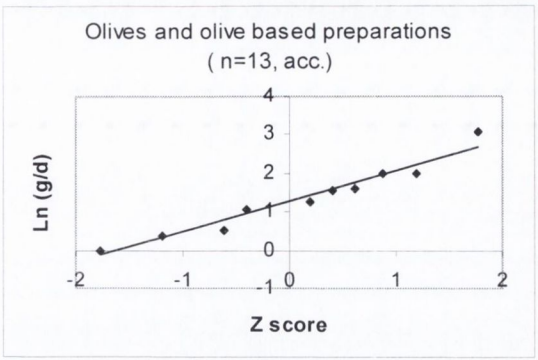
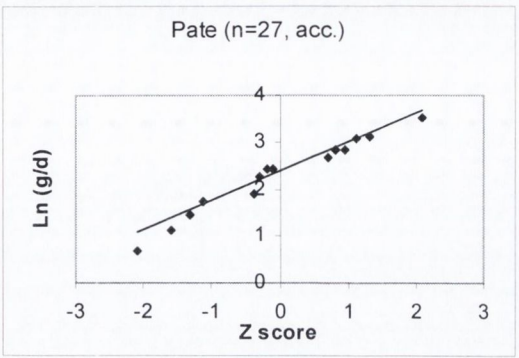
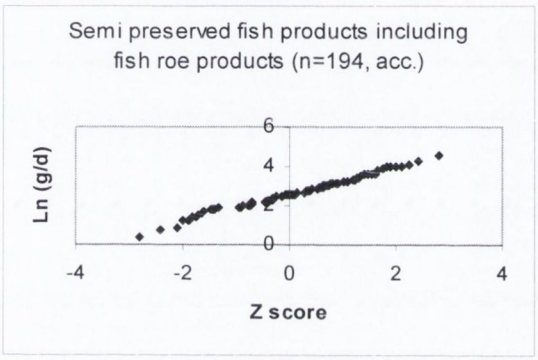
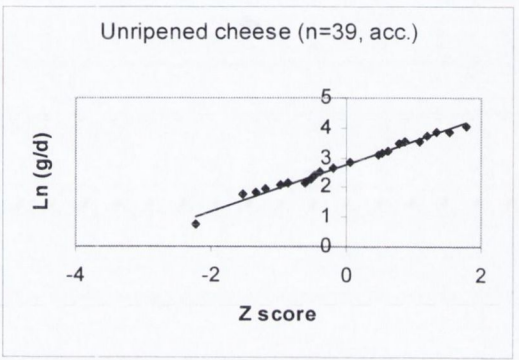


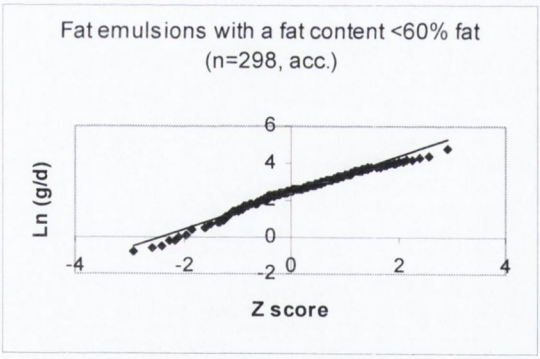
Figure 4.2a contd. **Assessment of the fit of a lognormal distribution to food consumption data expressed as average daily intakes (g/d) using lognormal probability plots – results from NSIFCS**

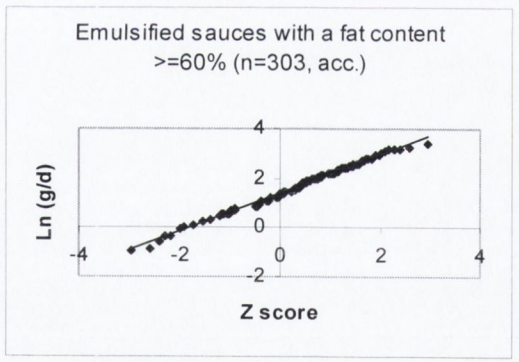


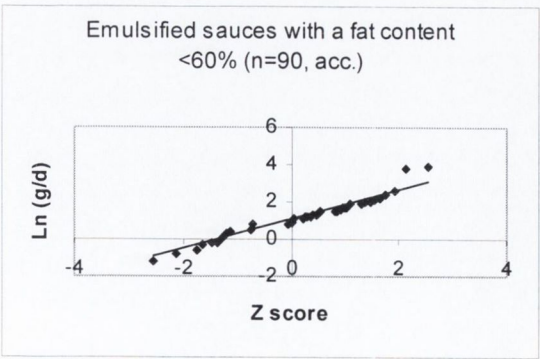












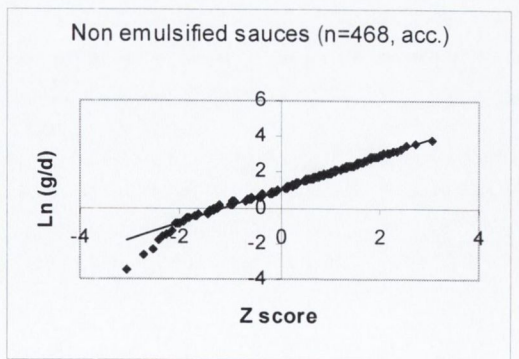


Figure 4.2a contd. **Assessment of the fit of a lognormal distribution to food consumption data expressed as average daily intakes (g/d) using lognormal probability plots – results from NSIFCS**

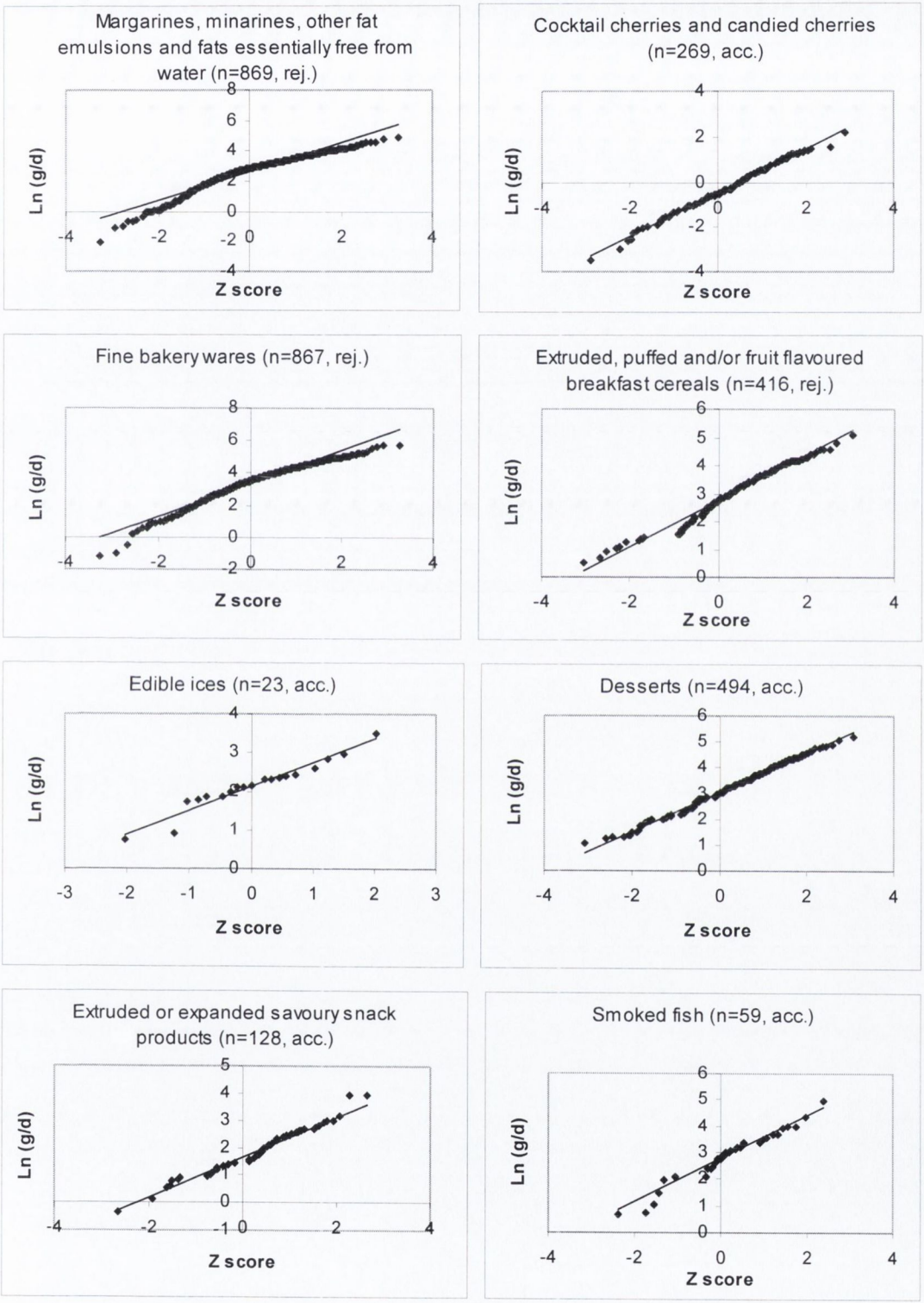
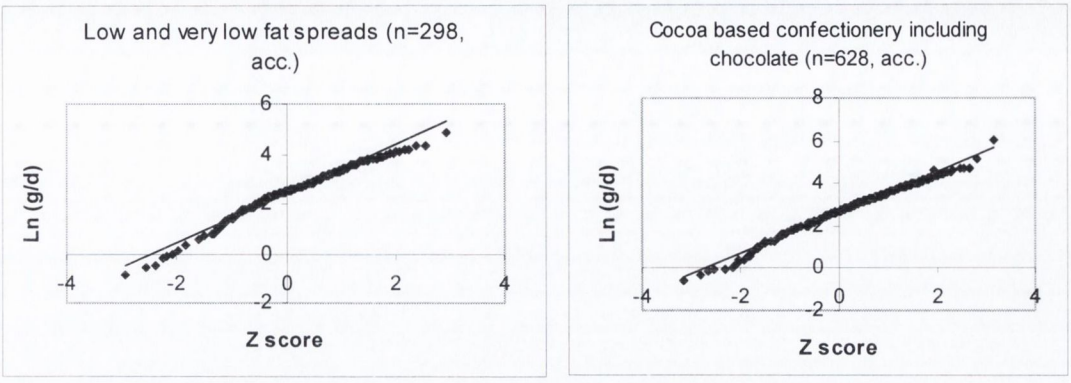


Figure 4.2a contd. **Assessment of the fit of a lognormal distribution to food consumption data expressed as average daily intakes (g/d) using lognormal probability plots – results from NSIFCS**



Note: *acc.* denotes that the fit of a lognormal distribution to observed food group intake data was accepted according to the BestFit® distribution fitting program; *rej.* denotes that the fit of a lognormal distribution to observed food group intake data was rejected according to the BestFit® distribution fitting program, as illustrated in table 4.5a.

Figure 4.2b **Assessment of the fit of a lognormal distribution to food consumption data expressed as average daily intakes (g/d) using lognormal probability plots – results from NDNS**

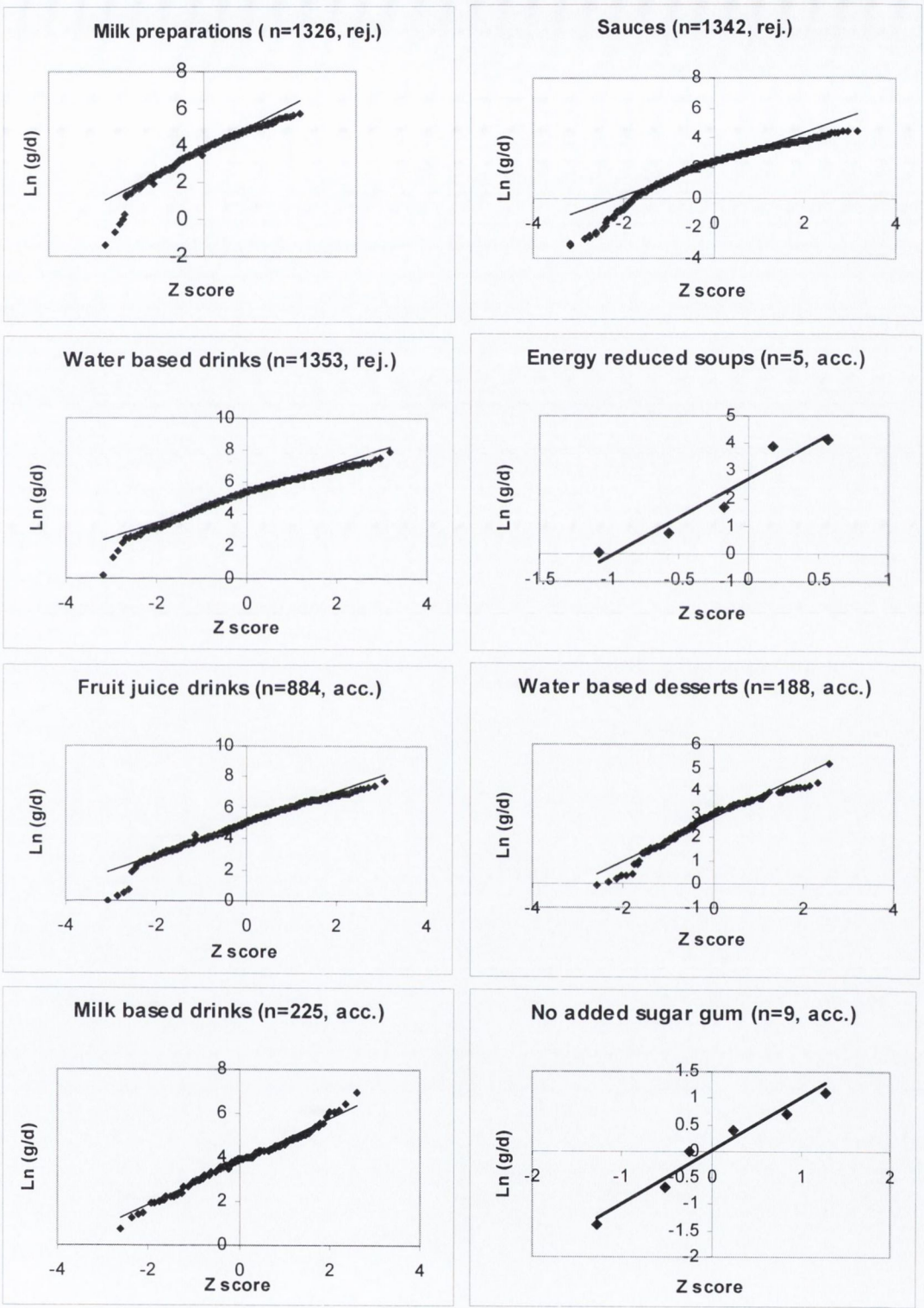
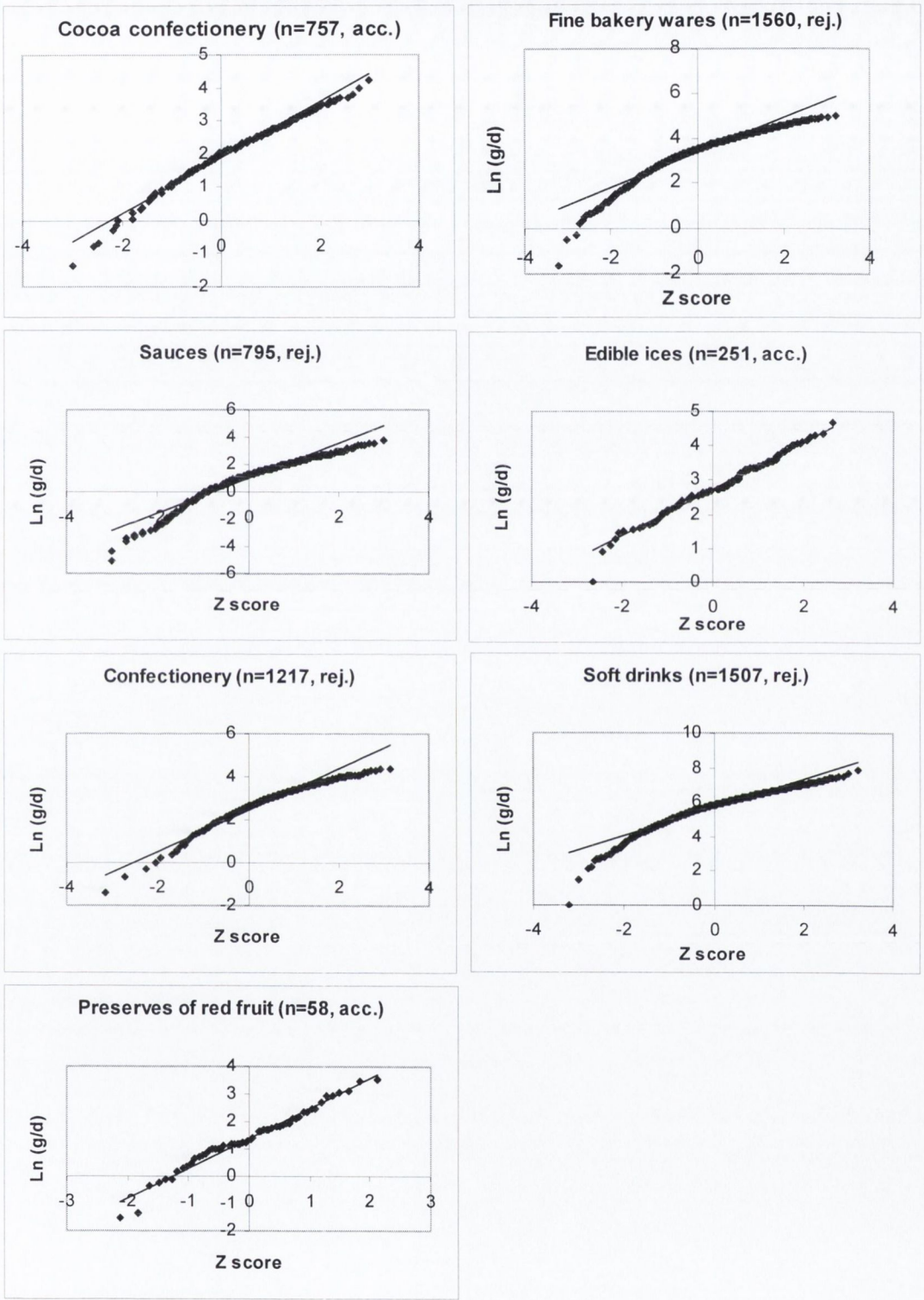
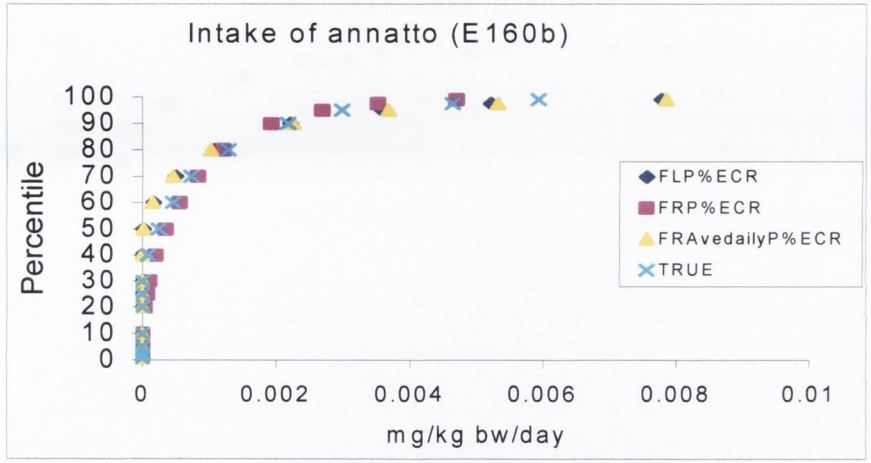
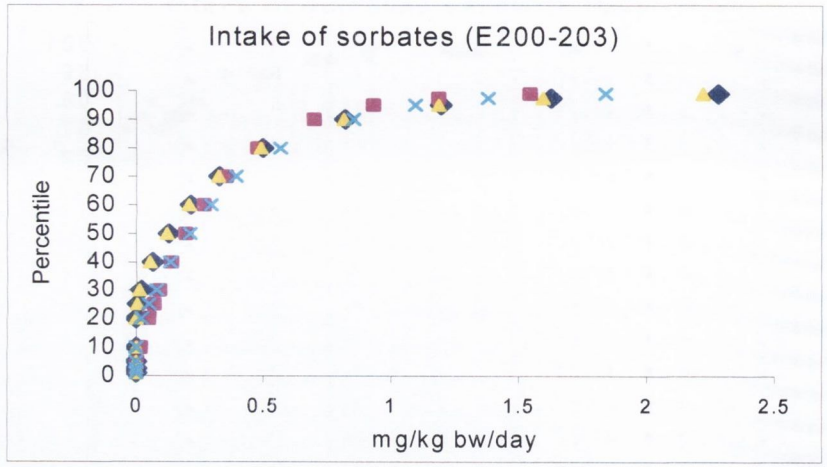


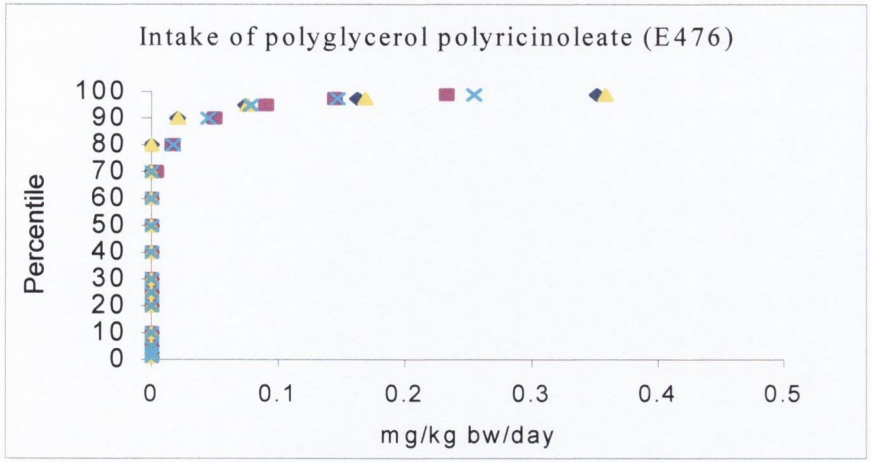
Figure 4.2b contd. **Assessment of the fit of a lognormal distribution to food consumption data expressed as average daily intakes (g/d) using lognormal probability plots – results from NDNS**



Note: *acc.* denotes that the fit of a lognormal distribution to observed food group intake data was accepted according to the BestFit® distribution fitting program; *rej.* denotes that the fit of a lognormal distribution to observed food group intake data was rejected according to the BestFit® distribution fitting program, as illustrated in table 4.5b.







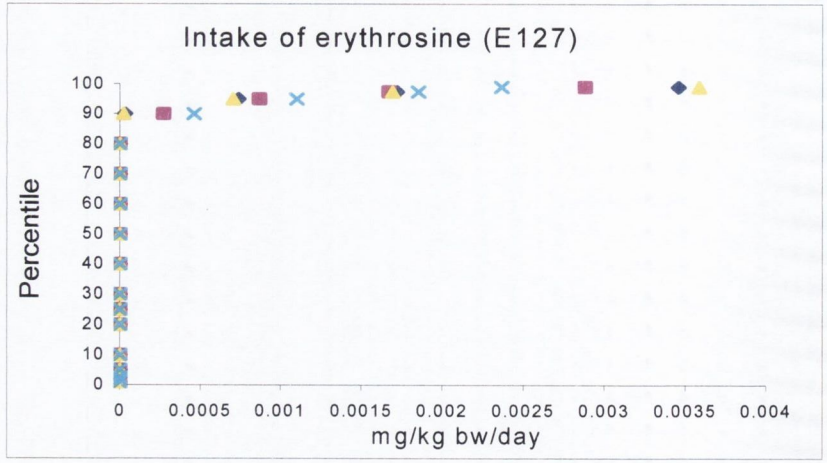
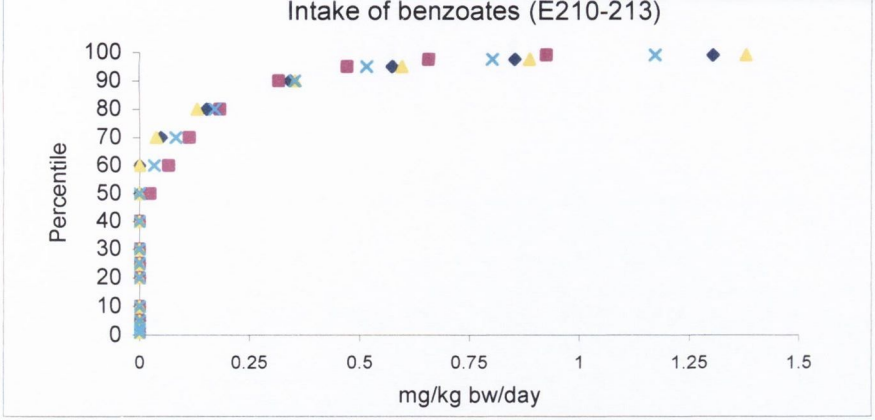
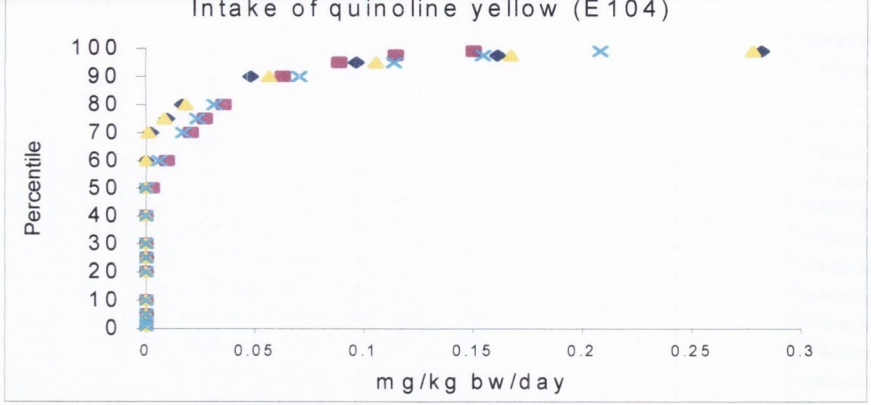
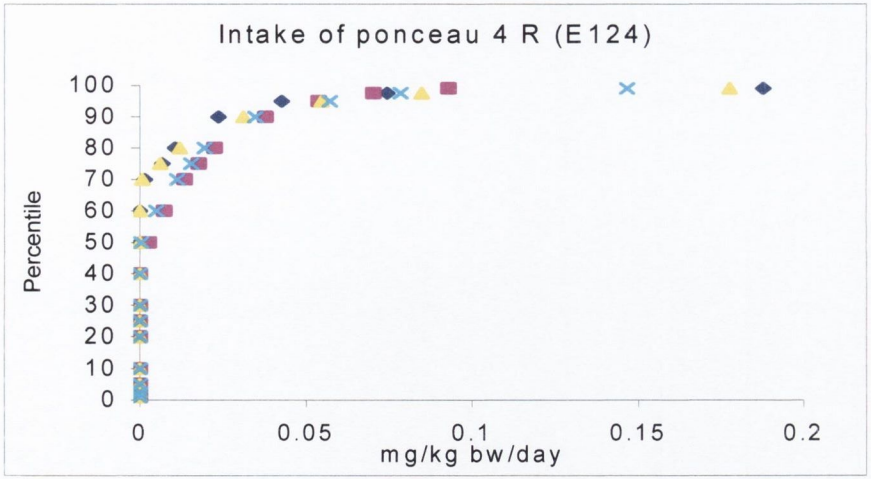


Figure 4.3 **Comparison of the full distribution of total population additive intakes (mg/kg bw/day) generated from $F_R P_{\%E} C_R$, $F_{R\text{-}Avedaily} P_{\%E} C_R$ and $F_L P_{\%E} C_R$ models with 'true' intakes**







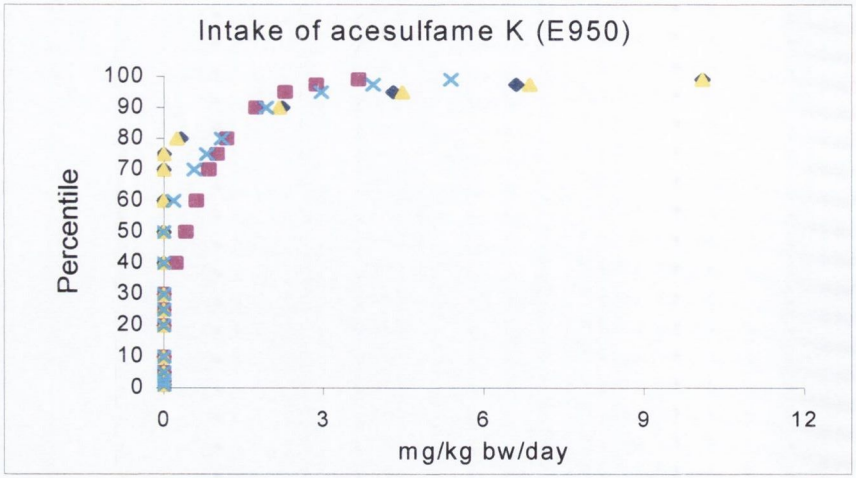
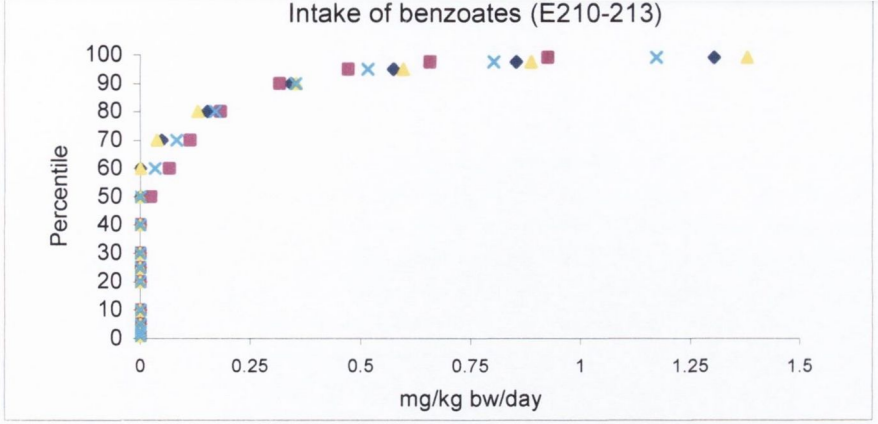
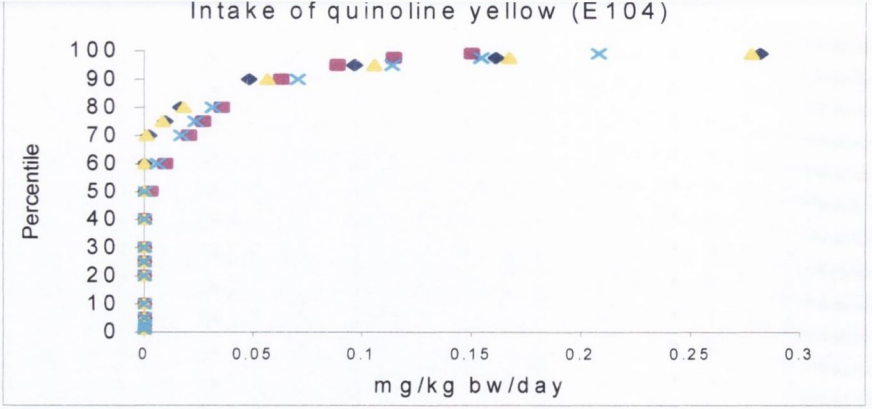
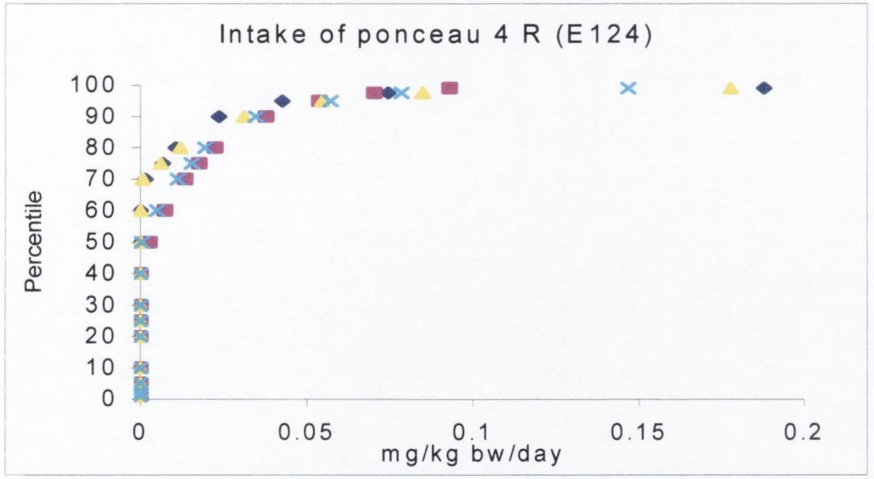


Figure 4.3 contd. **Comparison of the full distribution of total population additive intakes (mg/kg bw/day) generated from $F_R P_{\%E} C_R$, $F_{R\text{-}Avedaily} P_{\%E} C_R$ and $F_L P_{\%E} C_R$ models with 'true' intakes**







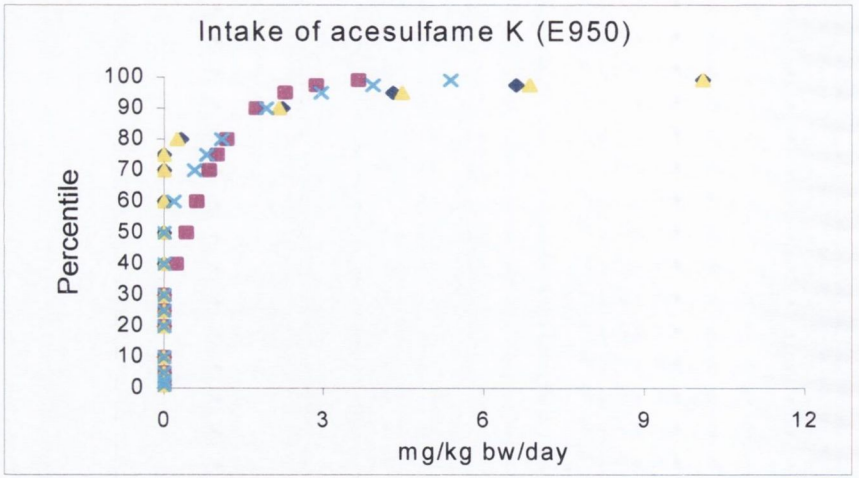
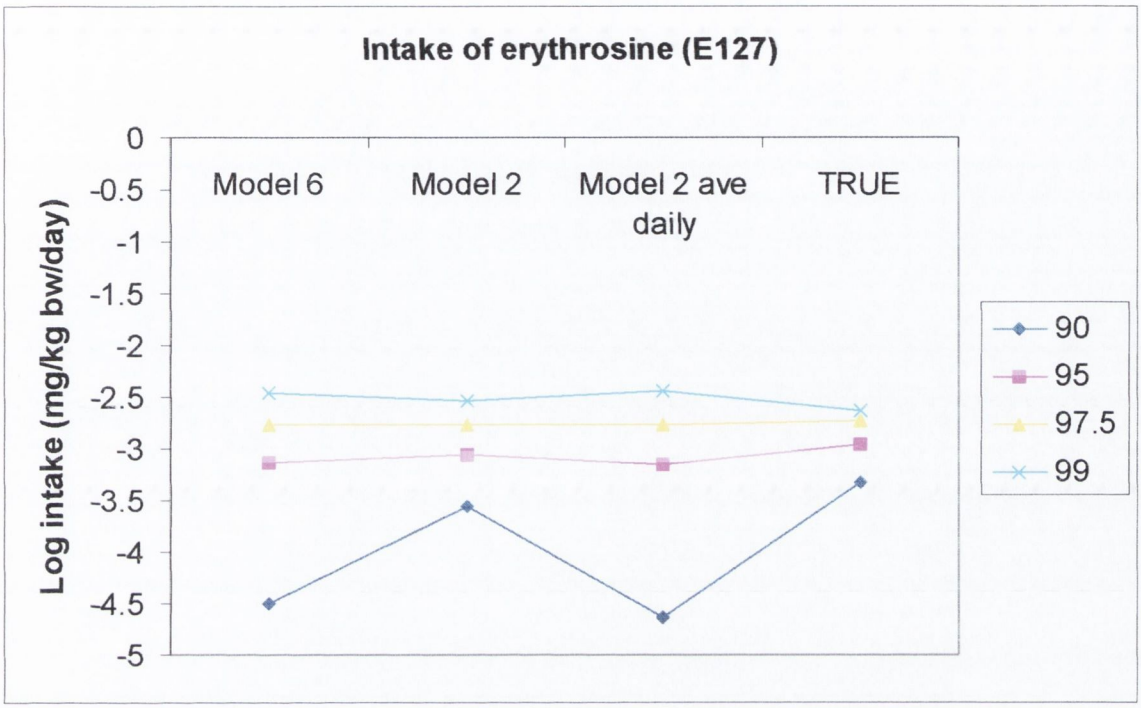
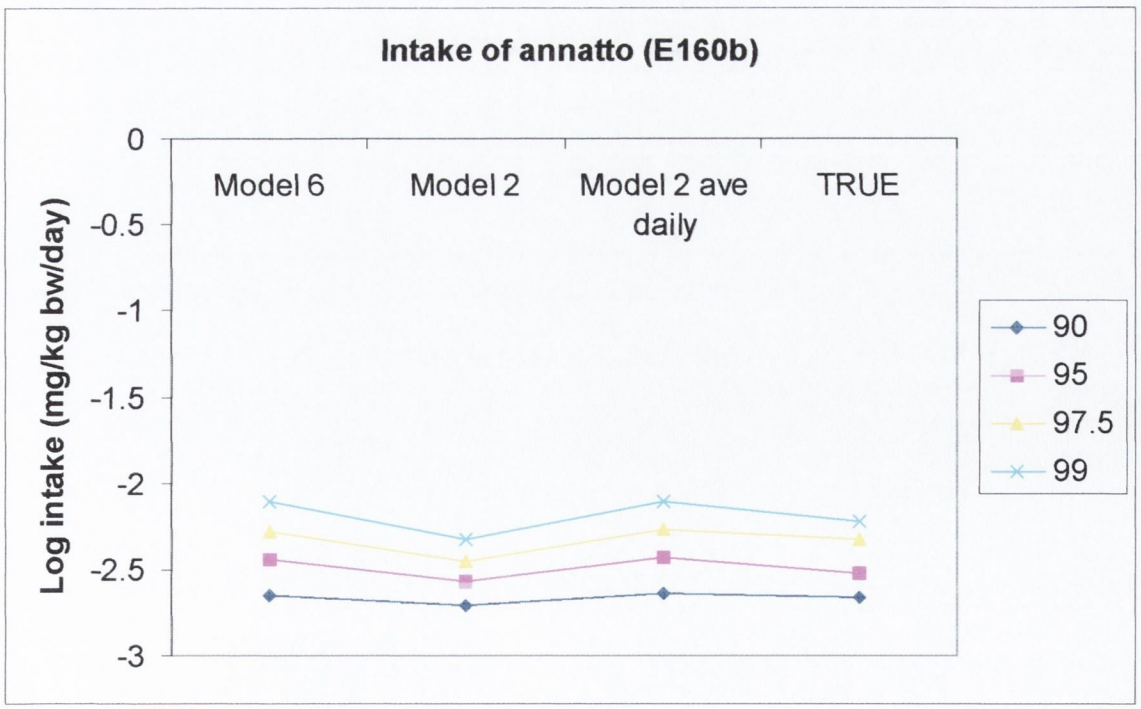


Figure 4.3 contd. **Comparison of the full distribution of total population additive intakes (mg/kg bw/day) generated from $F_RP_{\%E}C_R$, $F_{R\text{-}Avedaily}P_{\%E}C_R$ and $F_LP_{\%E}C_R$ models with 'true' intakes**

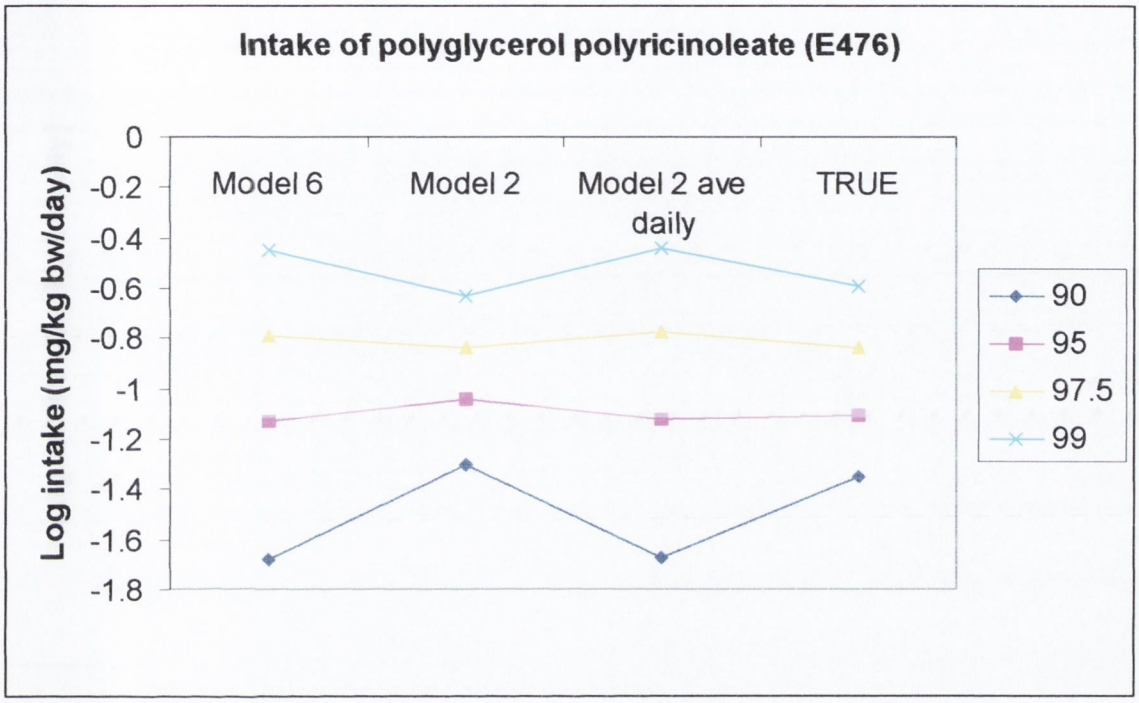
Figure 4.4 **Comparison of upper percentile[1] total population additive intakes (mg/kg bw/day) generated from $F_R P_{\%E} C_R$ (model 2), $F_{R\text{-}Avedaily} P_{\%E} C_R$ (model 2 ave daily) and $F_L P_{\%E} C_R$ (model 6) with 'true' intakes**

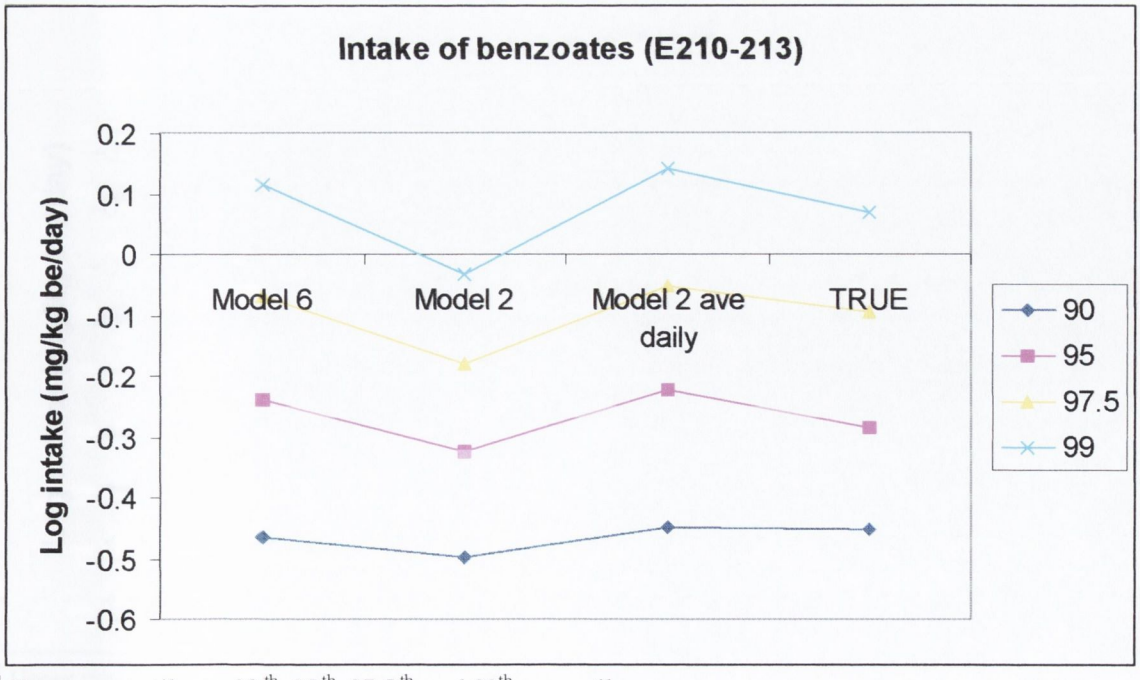




[1] Upper percentiles = 90th, 95th, 97.5th and 99th percentiles

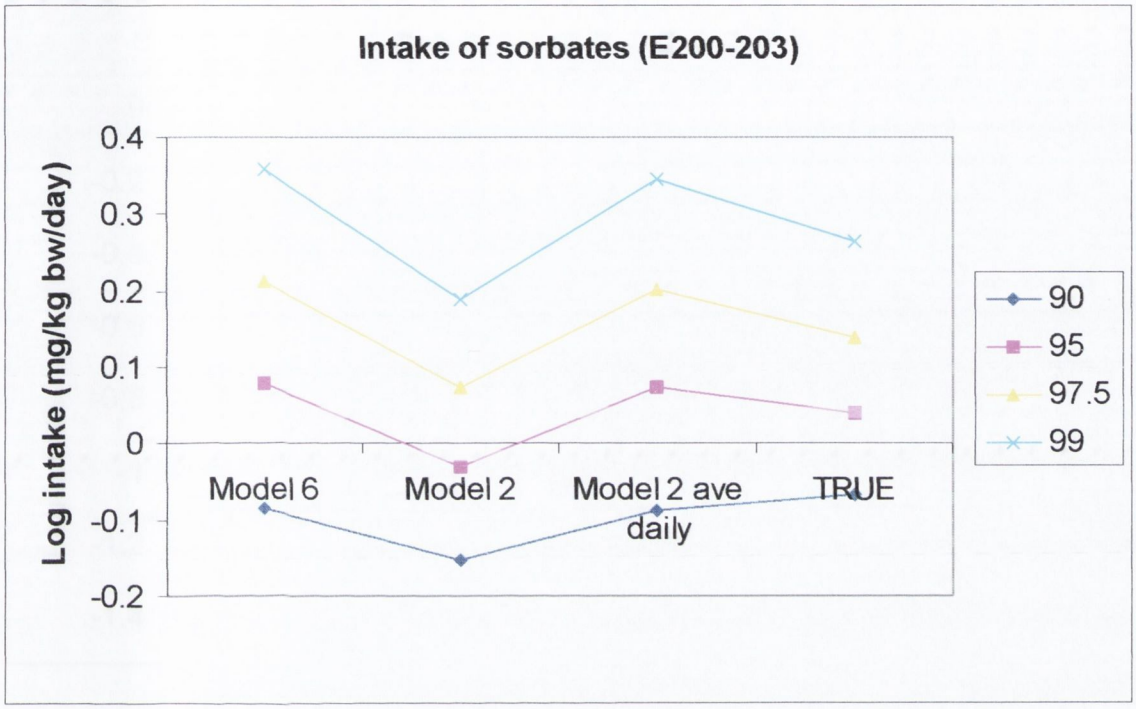
Figure 4.4 contd. **Comparison of upper percentile[1] total population additive intakes (mg/kg bw/day) generated from $F_R P_{\%E} C_R$ (model 2), $F_{R\text{-}Avedaily} P_{\%E} C_R$ (model 2 ave daily) and $F_L P_{\%E} C_R$ (model 6) with 'true' intakes**

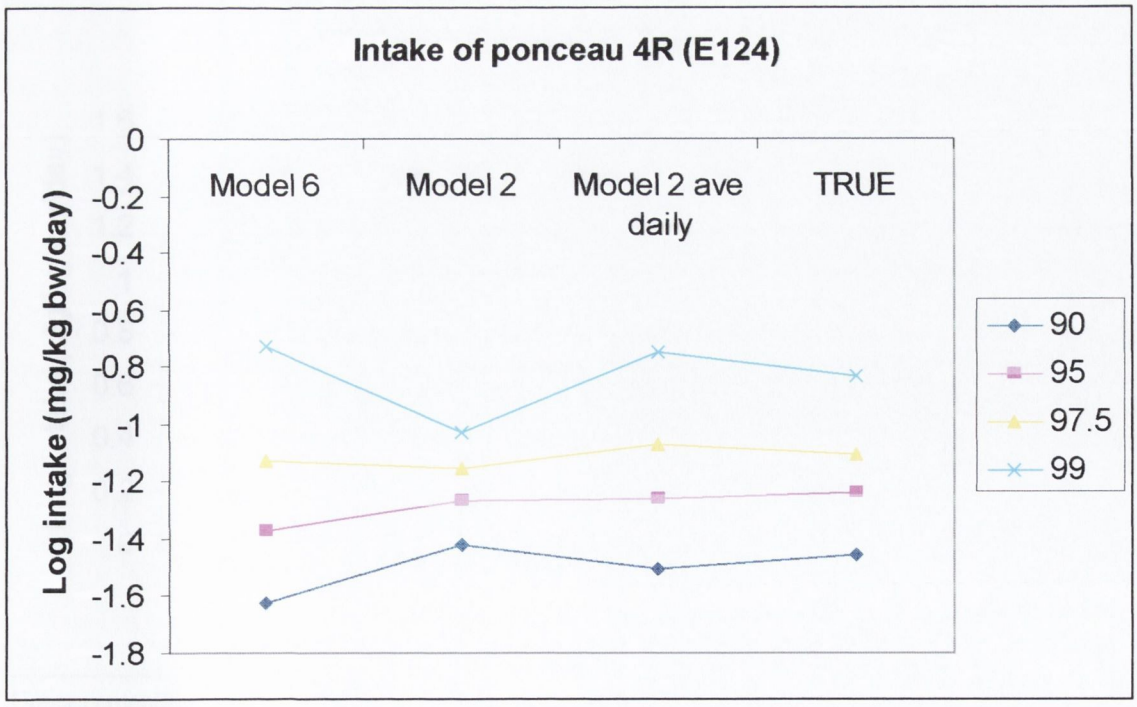




[1] Upper percentiles = 90 th, 95 th, 97.5 th and 99th percentiles

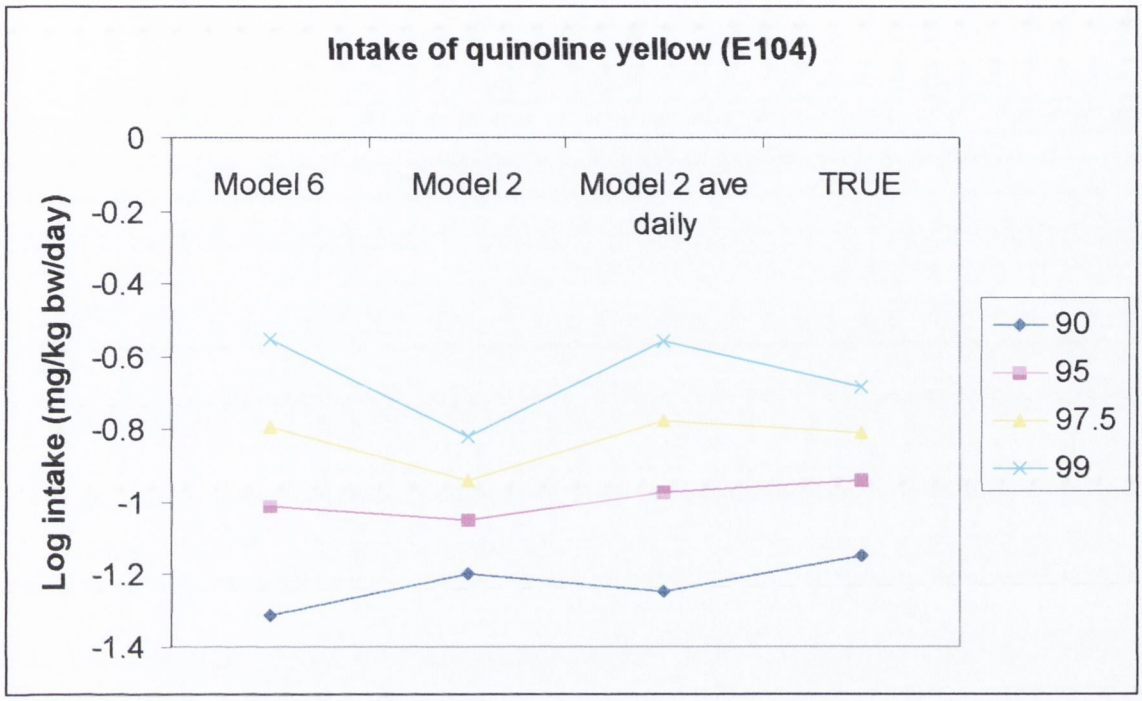
Figure 4.4 contd. **Comparison of upper percentile[1] total population additive intakes (mg/kg bw/day) generated from $F_R P_{\%E} C_R$ (model 2), $F_{R\text{-}Avedaily} P_{\%E} C_R$ (model 2 ave daily) and $F_L P_{\%E} C_R$ (model 6) with 'true' intakes**

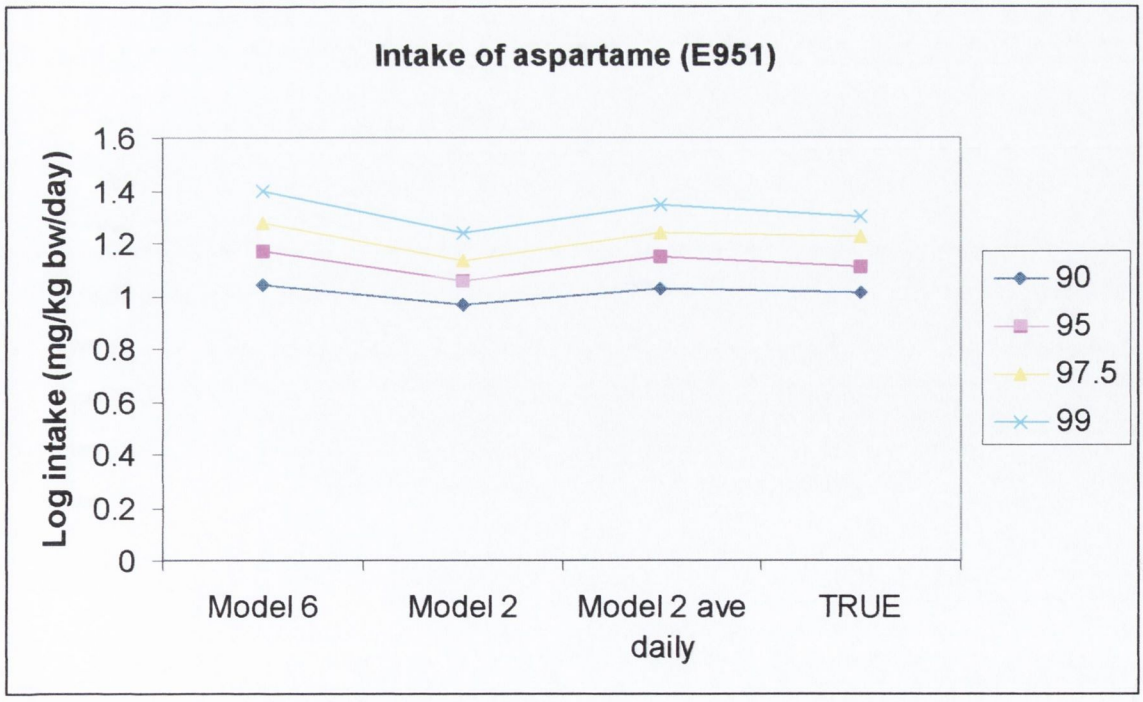




[1] Upper percentiles = 90th, 95th, 97.5th and 99th percentiles

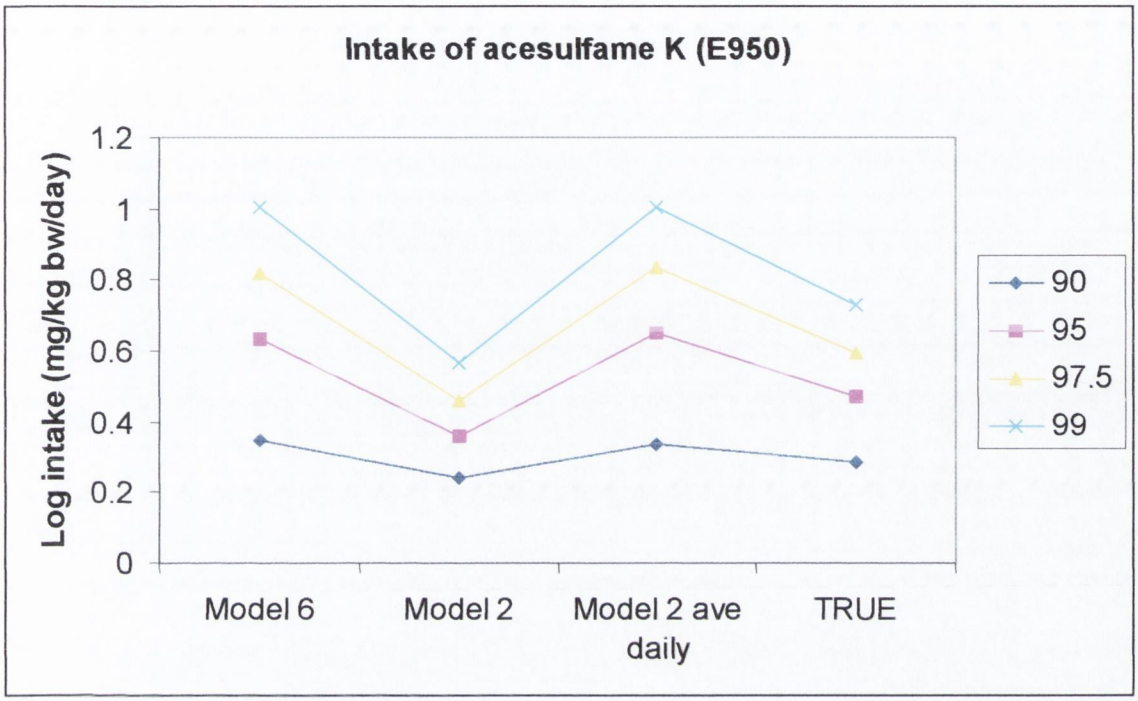
Figure 4.4 contd. **Comparison of upper percentile[1] total population additive intakes (mg/kg bw/day) generated from $F_R P_{\%E} C_R$ (model 2), $F_{R\text{-}Avedaily} P_{\%E} C_R$ (model 2 ave daily) and $F_L P_{\%E} C_R$ (model 6) with 'true' intakes**

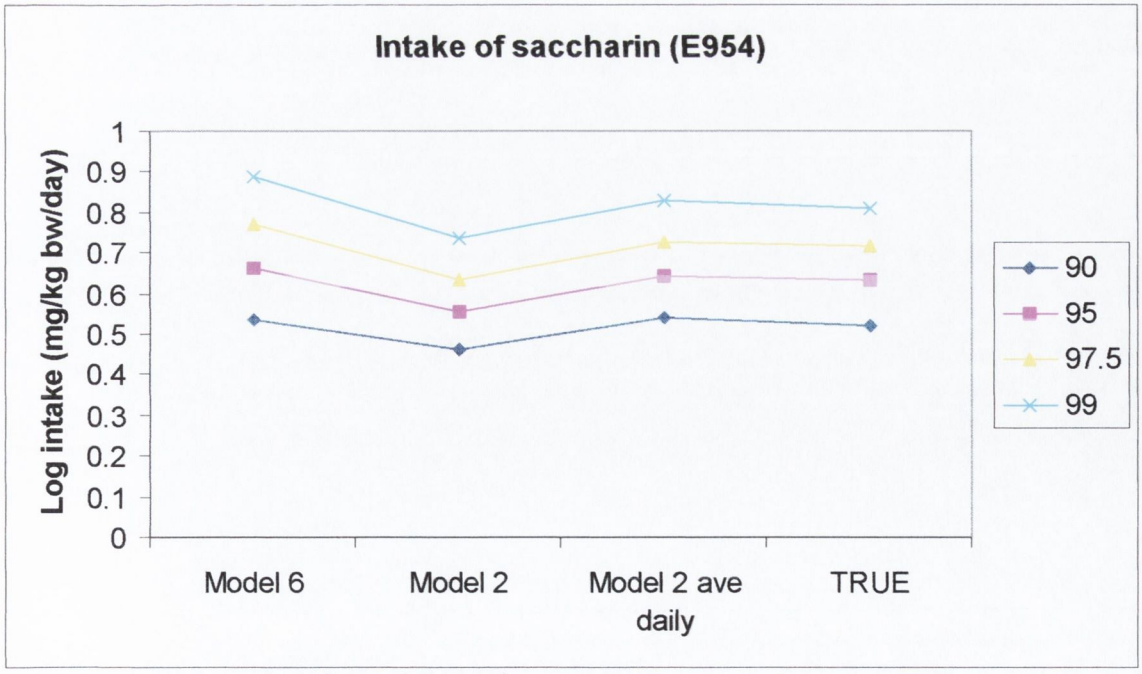




[1] Upper percentiles = 90 th, 95 th, 97.5 th and 99th percentiles

Figure 4.4 contd. **Comparison of upper percentile[1] total population additive intakes (mg/kg bw/day) generated from $F_R P_{\%E} C_R$ (model 2), $F_{R\text{-}Avedaily} P_{\%E} C_R$ (model 2 ave daily) and $F_L P_{\%E} C_R$ (model 6) with 'true' intakes**





[1] Upper percentiles = 90 th, 95 th, 97.5 th and 99th percentiles

Chapter 5

Assessment of the influence of energy under-reporting on food additive intake estimates

Gilsenan, M.B., and Gibney, M.J., 2004,
Food Additives and Contaminants, in press

5.1 Introduction

Food consumption represents a central component of any food chemical exposure assessment. Therefore, the quality of the results of a food chemical exposure assessment will depend to a large extent on the quality of the food consumption data used in the assessment. Under-reporting has been identified as an important source of uncertainty in food chemical exposure assessments based on dietary surveys (Kroes *et al.* 2002). This phenomenon, which is characterized by lower than expected energy intakes, has been observed with all types of dietary surveys of individuals and across a range of population subgroups (Black *et al.* 1991). In the field of nutritional research, the existence of energy under-reporting in dietary surveys is well recognized and has raised concerns that it may over-estimate the prevalence of low nutrient intakes and distort relationships between diet and disease. These concerns have fuelled numerous studies to attempt to identify and characterize individuals who under-report their energy intake (Hirvonen *et al.* 1997, Price *et al.* 1997, Pryer *et al.* 1997, Johansson *et al.* 1998), and to explore whether specific foods are more likely to be under-reported more than others (Bingham *et al.* 1995, Pryer *et al.* 1997, Johansson *et al.* 1998, Becker *et al.* 1999, Krebs-Smith *et al.* 2000, Lafay *et al.* 2000, Johansson *et al.* 2001). However, despite the wealth of attention which under-reporting has received in recent years, it continues to remain an inherent feature of all dietary surveys of individuals.

Levels of energy under-reporting are routinely calculated in dietary surveys using an approach conceived by Goldberg *et al.* (1991). Using this approach, reported energy intakes are compared with presumed energy requirements, where both energy intake and requirements are expressed as a multiple of basal metabolic rate (BMR) (Goldberg *et al.* 1991, Black 2000a). It is likely that energy under-reporting occurs as a result of under-recording the consumption of a food, under-reporting the frequency of consumption and under-reporting the amount consumed. If the foods employed in a food chemical exposure assessment are likely to be under-reported, then it is conceivable that food chemical intake estimates may also be under-estimated. The aim of the present study was to explore whether food categories in which food additives are permitted for use are likely to be under-reported and to examine the influence of energy under-reporting on food additive intake estimates.

5.2 Methods

Food categories

Four food additives sorbates (E200-203), annatto (E160b), erythrosine (E127) and polyglycerol polyricinoleate (E476) were selected and their usage in specific foods in the Irish food supply was established using an Irish National Food Ingredient Database (INFID) (Gilsenan *et al.* 2002). Food categories (n=26) were then created using food composition codes from the North-South Ireland food consumption survey (NSIFCS) (Harrington *et al.* 2001). The selection process aimed to encompass food additives that are permitted both in a wide range (annatto and sorbates) and a narrow range of foods (erythrosine and polyglycerol polyricinoleate).

Dietary data

Dietary data were derived from the North South Ireland Food Consumption Survey (NSIFCS) database (Harrington *et al.* 2001). In this survey, a nationally representative sample of 1,379 adults (aged 18-64 years) from the Republic of Ireland and Northern Ireland were asked to record the amount of all food and drink consumed over a one-week period using a 7-day dietary record. The present analysis pertains to data from the Republic of Ireland only (n=958). During the 7-day recording period, participants received three visits from a fieldworker to ensure completeness of diary records and were encouraged not to alter the their food and drink choices during the recording period (Harrington *et al.* 2001).

Evaluation of under-reporting

Under-reporting was assessed in the present study using an approach conceived by Goldberg *et al.* (1991). In brief, this approach uses the principles of energy physiology (*i.e.* energy intake (EI) = energy expenditure (EE)) to derive a study specific cut-off value, expressed as multiple of basal metabolic rate (BMR), to evaluate the validity of reported energy intakes against the expected level of energy expenditure. Goldberg *et al.* (1991) devised an equation that calculates these study specific cut-off values, often referred to as the 'Goldberg cut-offs'. The equation allows the comparison of an individual's reported energy intake (EI_{rep}) expressed as a multiple of their BMR (EI_{rep}:BMR) with their presumed EE, which is also expressed as a multiple of their basal metabolic rate (EE:BMR). The latter expression (*i.e.* EE:BMR) is also referred to as a

an individual's physical activity level (PAL). The Goldberg equation accounts for variability in reported energy intakes and variability in the estimation or prediction of BMR and PALs. In addition, it accounts for the survey duration and the number of individuals in the survey database. The cut-off value derived from the equation to identify the presence of under-reporting represents the lower confidence level of agreement between EI_{rep}, expressed as a multiple of BMR (EI:BMR) and a PAL of 1.55. This PAL value, which reflects a sedentary lifestyle, was chosen in the absence of other acceptable PAL values at the time of the original publication. Essentially, the calculated cut-off value tests whether reported energy intakes are a plausible measure of food consumed during the actual measurement period. Cut-off values based on sample size, survey duration and whether BMR was measured or predicted are presented in tabular format in the original publication of Goldberg *et al.* (1991). The original factors that were used in the Goldberg equation were later revised and updated by Black (2000a), who also presents examples of some updated cut-off values in tabular format in her scientific publication.

In the present study, a calculated cut-off value for each individual in the survey database, based on a sample size of (n=1) was calculated using the Goldberg equation with factors revised by Black (Goldberg *et al.* 1991, Black 2000a). The calculated cut-off value was 1.05. BMR values were previously estimated in the food consumption survey database using standard equations based on age, gender and measured body weight (McGowan *et al.* 2001). Each individual's reported energy intake was expressed as a multiple of their estimated basal metabolic rate (EI_{rep}:BMR_{est}). Given that 10 subjects had missing body weights, EI_{rep}:BMR_{est} values for 948 individuals were calculated. Each individual's reported EI_{rep}:BMR_{est} value was then compared with the study specific cut-off value (*i.e.* 1.05) derived using the Goldberg equation. Individuals with an EI_{rep}:BMR_{est} ratio <1.05 were deemed under-reporters (URs) and individuals with an EI_{rep}:BMR_{est} ≥ 1.05 were deemed acceptable reporters (ARs).

Assessment of the influence of energy under-reporting on food intakes

As a first step, the influence of energy under-reporting on reported food intakes was explored. For each of the 26 food categories, the proportion of consumers, the mean number of eating occasions reported over the 7-day survey duration (frequency of consumption) and the mean reported weight of food/drink consumed (g) per eating occasion (portion size), were calculated for acceptable reporters (*i.e.* individuals with an EI_{rep}:BMR_{est} ratio ≥ 1.05) and for under-reporters (*i.e.* individuals with an EI_{rep}:BMR_{est}

ratio <1.05). Values for acceptable reporters were expressed as a ratio of corresponding values for under-reporters. All analyses were carried out using SPSS version 11 (SPSS Inc., Chicago Ill).

Assessment of the influence of energy under-reporting on food additive intakes

As a second step, the influence of energy under-reporting on food additive intake estimates was investigated. Using a deterministic approach, average daily intakes of sorbates (E200-203), annatto (E160b), erythrosine (E127) and polyglycerol polyricinoleate (E476) (mg/kg bw/day) were calculated for the total population and for consumers only (*i.e.* excluding non consumers) according to the following equation:

$$a = \frac{\sum_{i=1}^{N} \left\{ \frac{\sum_{j=1}^{d} \sum_{h=1}^{z} \sum_{k=1}^{p_{ijh}} \left[f_{ijhk} \times c_{ijhk} \right]}{d \times bw_i} \right\}}{N}$$

where a is the average daily intake for the total population or for consumers only (mg/kg bw/day), f_{ijhk} is the consumption by individual *i* of the food product *h* on day *j* during eating occasion *k* (g), c_{ijhk} is the maximum permitted level (MPL) of the additive for food product *h* eaten on occasion *k* by individual *i* on day *j* (mg/g), bw_i is the body weight of individual *i* (kg), z is the number of food products included in the exposure assessment, p_{ijh} is the number of eating occasions of food product *h* by individual *i* on day *j*, N is the number of individuals in the survey database *(i.e.* 948) when *a* is expressed as total population intakes or N is the number of consumers of an additive, when *a* is expressed as consumer only intakes. Finally, d is the number of survey days.

Both consumer only and total population additive intakes amongst under-reporters, acceptable reporters and the total sample of reporters (*i.e.* acceptable reporters and under-reporters) were then compared.

5.3 Results

The percentage of energy derived from all food categories constituted 25% of the total energy from all foods in the overall survey database. Using a cut-off value of 1.05 to identify individual energy under-reporters (Goldberg *et al.* 1991, Black 2000a),

some 19% of the survey respondents were identified as - under-reporters. A comparison of patterns of food intakes between acceptable and under-reporters is presented in table 1. For 22 of the 26 food categories examined, the proportion of consumers amongst acceptable reporters was higher than the proportion of consumers amongst under-reporters. The proportion of consumers was lower amongst acceptable reporters compared with under-reporters for two of the 26 food categories. For 24 of the 26 food groups, reported frequencies of consumption were higher for acceptable reporters compared with under-reporters (table 1). For one food category (emulsified sauces with a fat content less than 60% fat), a similar frequency of consumption was observed between both groups.

Reported portion sizes for 17 of the 26 food categories were higher amongst acceptable reporters compared with under-reporters (table 1). Lower reported portion sizes were observed amongst acceptable reporters compared with under-reporters for eight food categories. Table 2 presents deterministic estimates of consumer only additive intakes amongst the total sample of reporters (*i.e.* acceptable and under-reporters), amongst acceptable reporters and amongst under-reporters. Intake estimates of all additives were lower than corresponding acceptable daily intakes (ADIs). For all additives, intake estimates amongst under-reporters were lower than corresponding estimates amongst acceptable reporters. Significant differences were observed between mean intakes for all additives when expressed as total population intakes and for all additives except erythrosine, when expressed as consumer only intakes. Additive intake estimates amongst acceptable reporters only (*i.e.* excluding under-reporters) were higher than corresponding intake estimates amongst the total sample of consumers at the 95th percentile for all additives. Intake estimates amongst acceptable reporters expressed as a ratio of corresponding estimates amongst the total sample of reporters did not exceed 1.05 for any additive. When expressed as a percentage of the ADI, intake estimates amongst acceptable reporters did not exceed corresponding estimates amongst the total sample of reporters by more than 3% (data not shown).

Corresponding deterministic additive intake estimates for the total population (*i.e.* consumers and non-consumers of an additive) are presented in table 3. Total population intake estimates were lower than corresponding intake estimates amongst consumers. Similar to results presented in table 2, additive intakes amongst under-reporters were significantly lower than corresponding intakes amongst acceptable reporters. Intake estimates amongst acceptable reporters were also higher than corresponding estimates based on all reporters. Ratios of intake of acceptable reporters

to all reporters at the 95th percentile did not exceed 1.06 for all additives except erythrosine, where a ratio of 1.20 was recorded.

5.4 Discussion

The present study set out to explore whether food categories employed in food additive exposure assessments are likely to be under-reported and to assess whether overall estimates of additive intakes are likely to be influenced by energy under-reporting. Although the implications of under-reporting have been acknowledged within the realm of food chemical exposure assessments (Löwik 1996, Gibney 1999, Kroes *et al.* 2002, Lambe 2002), the present study represents the first exploration of this issue.

Differential reporting of the majority of food categories between acceptable reporters and under-reporters was illustrated in these analyses. Under-reporters were less likely to report the consumption of a given food category and were more likely to under-report the number of times the food category was consumed compared with acceptable reporters. They also showed a tendency to under-estimate the portion size of the food consumed, although this trend was less consistent. Thus, under-reporting occurs across all three determinants of food intake (*i.e.* the likelihood of reporting the consumption of a given food, the frequency of consumption of a food and the reported portion size consumed). Differential reporting of food intakes between acceptable and under-reporters was also reported by Bingham *et al.* (1995), Pryer *et al.* (1997), Johansson *et al.* (1998), Becker *et al.* (1999), Krebs-Smith *et al.* (2000), Lafay *et al.* (2000) and Johansson *et al.* (2001), although the food categories reported in these studies were examined with a nutritional interest, whereas the food categories in the present study were examined with an interest in food chemical exposure.

Within the field of nutrition, under-reporting in dietary surveys is flagged as an important source of bias and for that reason it has often been mooted as a potential source of error in food chemical exposure assessments. However, since energy is derived from almost all foods, it is likely that the existence of energy under-reporting in dietary surveys will have a larger impact towards biasing relationships between diet and disease. In the case of food additives, the situation is somewhat different. The percentage of total foods included in an exposure assessment of a food additive is potentially much smaller if a given additive is permitted for use in a limited number of food categories in the food supply (European Commission 1994a,b, 1995). For example, in the present analysis, the percentage contribution to total energy of foods employed in the assessment of exposure to the four food additives ranged from 0.04 (erythrosine) to

15% (annatto). Therefore, it is unlikely that energy under-reporting in dietary surveys would have an impact on exposure estimates of these food additives to the same degree as it would in the field of nutrition. However, if an additive is present in foods that make a larger contribution to overall energy, different results may be obtained.

For both consumers only and for the total population, mean additive intakes were lower amongst under-reporters compared with acceptable reporters. Statistically significant differences were observed for all food additives when expressed as total population intakes and for all additives except erythrosine, when expressed as consumer only intakes. Similarly, intakes at the 95th percentile were lower amongst under-reporters compared with acceptable reporters. This finding is not surprising, based on the results presented in table 1 where under-reporters were less likely to report the consumption of a given food and were more likely to under-estimate the frequency of consumption and the amount consumed. However, the total number of under-reporters for a given food additive exposure assessment is relatively small compared with the total number of acceptable reporters (table 2) and thus, the impact of including under-reporters in the exposure assessment is somewhat diluted.

Energy under-reporting was evaluated in the present study using the approach devised by Goldberg *et al.* (1991). This approach requires a measure of each individual's age, and body weight and is currently the most cost effective and practical approach to assess the validity of dietary data. Although uncertainty regarding the application of this approach to identify individual under-reporters has recently been acknowledged by Black (2000b), it still remains the most widely used and practical approach to assess the prevalence of energy under-reporting in large-scale dietary surveys (Briefel *et al.* 1997, Hirvonen *et al.* 1997, Price *et al.* 1997, Pryer *et al.* 1997, Johansson *et al.* 1998, Lafay *et al.* 2000, McGowan *et al.* 2001).

In the case of erythrosine, the results presented in table 3 serve to warrant caution when exposure estimates based on small sample sizes are expressed for the total population at upper percentiles. Nevertheless, the findings from the present study, would suggest that energy under-reporting does not materially influence estimates of food additive exposure for the four food additives studied and therefore, does not present a major concern for their exposure assessments. However, it would be unwise to make a blanket assumption that the current results would be applicable to all food additive exposure assessments since there are a number of situations where the existence of energy under-reporting may exert a more significant impact on resulting exposure estimates. These include (i) exposure assessments of ubiquitous food

chemicals or food additives permitted in a wide range of foods that constitute a higher percentage of total energy than observed in the present study (ii) exposure assessments of food additives permitted in a narrow range of foods that have a perceived negative health image and therefore are suspected to be more prone to under-reporting than other foods and (iii) exposure assessments based on specific population subgroups (*e.g.* over-weight and obese individuals), amongst whom energy under-reporting is well recognized (MacDiarmid and Blundell 1998). In these situations, the one should be cautious when interpreting results.

Table 5.1 Patterns of food intakes amongst subjects classified according to acceptable reporters (ARs)[1] or under-reporters (URs)[1]

Food category (number of consumers)	% contribution to total energy	% consumers			Mean (±SD) number of eating occasions per week amongst consumers			Mean (±SD) weight of food consumed (g) per eating occasion amongst consumers		
		AR	UR	Ratio AR:UR	AR	UR	Ratio AR:UR	AR	UR	Ratio AR:UR
1.Desserts (490)	1.10	55	33	1.7	2.16 (1.68)	1.75 (0.84)	1.23	93.89 (50.31)	100.98 (55.65)	0.93
2.Edible ices (20)	0.02	3	1	2	1.21 (0.71)	1 -	1.21	66.95 (27.97)	60 -	1.12
3.Extruded, puffed and/or fruit flavoured breakfast cereals (415)	1.46	44	38	1.2	3.71 (2.64)	3.26 (2.48)	1.14	40.49 (19.28)	37.70 (13.25)	1.07
4.Fine bakery wares (855)	6.31	92	79	1.2	6.48 (4.71)	3.68 (2.97)	1.76	56.13 (40.28)	42.98 (27.42)	1.31
5.Margarine, minarine, other fat emulsions and fats essentially free form water (814)	4.03	86	81	1.1	11.38 (6.42)	9.37 (5.04)	1.21	13.75 (6.61)	11.42 (5.47)	1.20
6.Processed cheese (255)	0.40	28	24	1.4	2.44 (2.19)	1.98 (1.62)	1.23	33.47 (18.81)	27.59 (12.83)	1.21
7.Ripened orange, yellow and broken white cheese (550)	1.39	60	45	1.2	2.65 (1.79)	1.76 (1.03)	1.51	38.17 (20.67)	31.41 (15.83)	1.22
8.Smoked fish (59)	0.08	7	5	1.3	1.34 (0.69)	1.33 (0.50)	1.01	108.11 (73.54)	86.56 (54.53)	1.25
9.Snacks: dry, savoury potato, cereal or starch-based snack products - extruded or expanded savoury snack products (128)	0.20	15	6	2.5	1.53 (1.16)	1.45 (0.69)	1.06	30.98 (21.61)	45.21 (25.57)	0.69
10.Candied, crystallised and glace fruit and vegetables (148)	0.02	17	8	2.2	1.77 (1.18)	1.36 (0.84)	1.30	4.67 (4.30)	6.19 (4.30)	0.75
11.Dried fruit (43)	0.07	5	4	1.2	3.03 (2.80)	2.43 (2.20)	1.25	37.13 (31.17)	49.57 (45.09)	0.75
12.Emulsified sauces with a fat content less than 60% (85)	0.05	9	7	1.3	1.54 (1.24)	1.54 (0.78)	1	16.63 (11.52)	15.31 (6.36)	1.09

Table 5.1 contd. Patterns of food intakes amongst subjects classified according to acceptable reporters (ARs)[1] or under-reporters (URs)[1]

Food category[2] (number of consumers)	% contribution to total energy	% consumers			Mean (±SD) number of eating occasions per week amongst consumers			Mean (±SD) weight of food consumed (g) per eating occasion amongst consumers		
		AR	UR	Ratio AR:UR	AR	UR	Ratio AR:UR	AR	UR	Ratio AR:UR
13.Emulsified sauces with a fat content of 60% or more (242)	0.37	28	15	1.9	2.11 (1.52)	1.69 (1.05)	1.25	16.95 (11.75)	13.85 (3.94)	1.22
14.Fat emulsions (excluding butter) with a fat content of 60% or more (685)	3.21	74	59	1.3	9.29 (6.63)	7.56 (5.10)	1.23	13.79 (6.57)	12.13 (5.36)	1.14
15.Fat emulsions with a fat content less than 60% (293) [§]	0.81	29	38	0.8	9.74 (6.60)	8.28 (5.42)	1.18	13.10 (6.69)	10.30 (5.26)	1.27
16.Fillings of ravioli and similar products (3)	0.005	0.4	0	-	1.00 (0.00)	0.00 (0.00)	-	38.00 (13.11)	0.00 (0.00)	-
17.Low-sugar jams, jellies, marmelades and similar low calorie or sugar-free products and other fruit-based spreads; mermelades (36)	0.03	4	5	0.7	4.33 (2.84)	3.44 (2.07)	1.26	22.42 (10.21)	22.67 (7.68)	0.99
18.Non alcoholic flavoured drinks (636)	1.57	69	54	1.3	4.80 (4.93)	3.91 (3.09)	1.23	279.38 (144.66)	288.15 (149.10)	0.97
19.Non heat-treated dairy-based desserts (326)	0.67	35	30	1.1	2.54 (2.14)	2.24 (1.53)	1.13	127.91 (46.42)	119.33 (36.37)	1.07
20.Non-emulsified sauces (377)	0.13	41	34	1.2	2.02 (1.57)	1.60 (1.04)	1.26	16.34 (10.35)	13.91 (9.06)	1.17
21.Olives and olive based preparations (13)	0.003	2	1	2.8	2.00 (1.48)	1.00 (0.00)	2	16.18 (6.02)	12.00 (0.00)	1.35
22.Pâté (27)	0.05	3	3	1	2.05 (1.43)	1.20 (0.45)	1.71	48.84 (23.11)	48.00 (19.24)	1.02
23.Semi-preserved fish products including fish roe products (187)	0.21	19	20	1.0	1.52 (0.96)	1.42 (0.69)	1.07	75.65 (37.23)	74.85 (27.41)	1.01
24.Unripened cheese (39)	0.04	4	2	2.0	1.68 (0.91)	1.25 (0.50)	1.34	83.45 (39.78)	90.00 (24.49)	0.93
25.Cocoa-based confectionery, including chocolate (613)	2.83	69	43	1.6	3.83 (3.80)	2.28 (1.75)	1.68	43.37 (20.12)	42.48 (20.77)	1.02
26.Candied, crystallised and glace fruit (165)	0.04	19	10	1.9	1.78 (1.22)	1.33 (0.77)	1.34	4.78 (4.33)	5.56 (3.33)	0.86

[1] Acceptable reporters: EI:BMR_{est} ≥1.05, under-reporters: EI:BMR_{est} <1.05 (Goldberg *et al.* 1991, Black 2000a).

[2] Food categories used to estimate exposure to food additives: (1-9) – annatto, (4,6, 10-24) - sorbates, (15 & 25) – polyglycerol polyricinoleate, (26) – erythrosine.

[§] Food codes used to create this food category were the same as those used to create the food category 'low and very-low fat spreads', in which polyglycerol polyricinoleate is permitted.

Table 5.2 **Comparison of consumer only additive intakes (mg/kg bw/day)[1] amongst the total sample of consumers (All) with intakes amongst acceptable reporters[2] and intakes amongst under-reporters[2]**

Additive	All (Acceptable reporters and under-reporters) (n=948)				ADI	% contribution of foods to total energy
	n	P5	Mean (±SD)	P95		
Annatto (E160b)	942	0.0028	0.0156 (0.0105)	0.0358	0.065	15
Sorbates (E200-203)	942	0.419	2.198 (1.477)	5.035	25	14
Erythrosine (E127)	163	0.0004	0.0031 (0.0031)	0.0094	0.1	0.04
Polyglycerol polyricinoleate (E476)	718	0.227	1.646 (1.829)	4.422	7.5	4
			Acceptable reporters only (n=770)	P95		Ratio AR:All @P95
Annatto (E160b)	768	0.0040	0.0173** (0.0107)	0.0376		1.05
Sorbates (E200-203)	767	0.530	2.423** (1.504)	5.206		1.03
Erythrosine (E127)	145	0.0004	0.0031^{NS} (0.0033)	0.0100		1.05
Polyglycerol polyricinoleate (E476)	602	0.238	1.792** (1.939)	4.569		1.03
			Under-reporters (n=178)	P95		Ratio AR:UR @P95
Annatto (E160b)	174	0.0014	0.0083 (0.0056)	0.0197		1.90
Sorbates (E200-203)	175	0.220	1.213 (0.799)	2.576		2.02
Erythrosine[3] (E127)	18	0.0005	0.0027 (0.0020)	-		-
Polyglycerol polyricinoleate (E476)	116	0.109	0.891 (0.725)	2.245		2.03

[1] Values are rounded to three or four decimal places.
[2] Acceptable reporters: EI:BMR_{est} ≥1.05, Under-reporters: EI:BMR_{est} <1.05 (Goldberg *et al.* 1991, Black 2000a).
**Denote differences between additive intakes amongst acceptable and under-reporters at P<0.001, Mann-Whitney U test. NS – non-significant.
[3] Insufficient sample size to calculate 95th percentile.

Mean (±SD) energy intakes MJ: All (ARs & URs)=9.56 (3.19), ARs=10.41 (2.87), URs=5.87 (1.29).
Mean EI:BMR_{est} ratio: All (ARs & URs)=1.41 (0.41), ARs=1.54 (0.35), URs=0.86 (0.15).

Table 5.3 **Comparison of total population additive intakes (All) (mg/kg bw/day)[1] with intakes amongst acceptable reporters[2] and intakes amongst under-reporters[2]**

Additive	All (Acceptable reporters and under-reporters) (n=948)				ADI	% contribution of foods to total energy
	n	P5	Mean (±SD)	P95		
Annatto (E160b)	948	0.0024	0.0155 (0.0106)	0.0357	0.065	15
Sorbates (E200-203)	948	0.375	2.184 (1.483)	5.030	25	14
Erythrosine (E127)	948	0	0.00050 (0.0017)	0.0034	0.1	0.04
Polyglycerol polyricinoleate (E476)	948	0	1.247 (1.741)	4.092	7.5	4
	Acceptable reporters only (n=770)					Ratio AR:All @P95
Annatto (E160b)	770	0.0039	0.0172** (0.0107)	0.0375		1.05
Sorbates (E200-203)	770	0.5021	2.413** (1.509)	5.204		1.03
Erythrosine (E127)	770	0	0.0006* (0.0019)	0.0041		1.20
Polyglycerol polyricinoleate (E476)	770	0	1.401** (1.867)	4.328		1.06
	Under-reporters only (n=178)					Ratio AR:UR@P95
Annatto (E160b)	178	0.0011	0.0082 (0.0056)	0.0197		1.90
Sorbates (E200-203)	178	0.183	1.192 (0.807)	2.567		2.03
Erythrosine (E127)	178	0	0.0003 (0.0010)	0.0020		2.05
Polyglycerol polyricinoleate (E476)	178	0	0.58 1 (0.723)	2.023		2.14

[1] Values are rounded to three or four decimal places.
[2] Acceptable reporters: EI:BMR_{est} ≥1.05, Under-reporters: EI:BMR_{est} <1.05 (Goldberg *et al.* 1991, Black 2000a).
* & ** Denote statistically significant differences between additive intakes amongst acceptable and under-reporters at P<0.05 (*) and P<0.001 (**), Mann-Whitney U test.

Mean (±SD) energy intakes MJ: All (ARs & URs)=9.56 (3.19), ARs=10.41 (2.87), URs=5.87 (1.29).
Mean EI:BMR_{est} ratio: All (ARs & URs)=1.41 (0.41), ARs=1.54 (0.35), URs=0.86 (0.15).

Appendix 5.1

Description of foods pertaining to food categories used in the assessment of exposure to four food additives

EU Directive food category	Description of foods in category
1. Sorbates (E200-203)	
Candied, crystallised and glace fruit and vegetables	Glace cherries
Dried fruit	Dried apricots, banana chips, figs, prunes, raisins and sultanas
Emulsified sauces with a fat content <60% fat	Dressings; caesar salad, thousand island, blue cheese, low fat, yogurt based, Italian and sandwich spread
Emulsified sauces with a fat content >60% fat	Mayonnaise
Fat emulsions with a fat content <60% fat	All fat spreads <60% fat
Fat emulsions with a fat content >60% fat	Margarine Lard Fat spreads >60% fat
Fillings of ravioli and similar products	Tortellini Egg Pasta with Filling
Fine bakery wares	Cakes Pastries Muffins Buns Gateaux Tarts Pies Biscuits Doughnuts Puddings (e.g. Christmas pudding) Crackers
Low sugar jams, jellies marmalades, and similar low calorie or sugar free products and other fruit based spreads; mermelades	Extra Fruit Jam (Fruitfield) Jam, diabetic Jam, reduced sugar Marmalade, diabetic Weight-watchers marmalade with Sweetener
Non alcoholic flavoured drinks	Carbonated soft drinks (diet and non-diet) Fruit cordials, ready to drink fruit drinks

EU Directive food category	Description of foods in category
Non emulsified sauces	Sauces; barbecue, brown, chilli, cranberry, horseradish, hot pepper, mint, redcurrant jelly, salad cream, soy, tomato ketchup and tartare
Non heat treated dairy based desserts	Cheesecake Trifle Yogurts & yogurt drinks Mousses Creme caramel Tiramisu
Olives and olive based preparations	Olives, in brine Olives, in brine, weighed with stones
Pâté	Pâté, liver Pâté, liver, in a tube Smoked salmon Pâté Tuna pate
Processed cheese	Avonmore Light low fat dairy slices Cheese Spread Reduced Fat (Laughing Cow Lite) Cheese spread, flavoured Cheese spread, plain Processed cheese (Irish) Processed cheese, plain
Semi preserved fish products including fish roe products	Canned tuna, sardines, red salmon, pink salmon, mackerel, kipper and herring (in brine or olive oil) Caviar, bottled in brine, drained
Unripened cheese	Cottage cheese; plain, reduced fat, with additions Fromage frais; plain, fruit, very low fat
2. Erythrosine (E127)	
Cocktail cherries and candied cherries	Cherries, glace Cherries, raw Cherry pie filling Dried mixed fruit[$] Fruit cocktail, canned in juice[$] Fruit cocktail, canned in syrup[$] Muffins[*], fairy cakes[*], trifle, Christmas cake, mince pies[*], mixed peel[$] $Assumed food contained 3 x 5g cherries *Assumed food contained 1x 5g cherry

EU Directive food category	Description of foods in category
3. Polyglycerol polyricinoleate (E476)	
Low and very low fat spreads and dressings*	Fat spreads less than or equal to 40% fat * No brands of dressings in INFID recorded the use of E476
Cocoa based confectionery including chocolate	Chocolate bars, chocolate gateaux, cakes, doughnuts, muffins etc.
4. Annatto (E160b)	
Edible ices	Ice lollies, does not include ice-cream
Fine bakery wares	Cakes Pastries Muffins Buns Gateaux Tarts Pies Biscuits Doughnuts Puddings (e.g. Christmas pudding) Crackers
Desserts	Ice-cream Puddings Mousses Trifle Cheesecake Custard Dream topping Tiramisu Milk pudding Rice pudding Banana split
Ripened orange, yellow and broken white cheese	Avonmore Light Cheese Slices Hard cheese, cheddar cheese; includes full fat and reduced fat, sliced and in a block
Processed cheese	Avonmore Light Low Fat Dairy Slices Cheese spread, plain and flavoured, dairy slices
Margarine, minarine, other fat emulsions and fats essentially free form water	Butter, margarine, reduced fat spreads and full fat spreads

EU Directive food category	Description of foods in category
Extruded, puffed and/or fruit flavoured breakfast cereals	All-Bran Alpen Nutty Crunch (Weetabix) Bran Buds Bran Flakes Cheerios (Nestle) Clusters (Nestle) Common Sense Oat Bran Flakes Corn Flakes Crunchy Nut Corn Flakes Frosties Fruit 'n Fibre Harvest Crunch With Almonds & Hazelnuts (Quaker) Honey Smacks Jordan's Original Crunchy Oat Clusters with Tropical Fruits Jordan's Maple Crunch Cereal Perfect Balance Breakfast Cereal (Weight-Watchers) Start Sugar Puffs
Extruded or expanded savoury snack products	Corn and starch snacks Maize and rice flour snacks Mixed cereal and potato flour snacks Popcorn Plain (Shop Bought) Puffed potato products
Smoked fish	Smoked haddock, cod, mackerel, salmon

Chapter 6

General Discussion

The procedure for the assessment of exposure to food chemicals, that has gained general acceptance at an international level, follows a 'decision tree' or tiered approach in which the methodology employed proceeds from crude screening methods to more refined methods if results from less refined methods dictate the need to do so (Nutriscan 1994, Gibney and Lambe 1996, European Commission 1998). In the case of food additives, current deterministic methods such as the Step 2 approach (European Commission 1997) that are considered refined still contain some level of conservatism since the intake of *all* the foods in which an additive is permitted is multiplied by the maximum legal concentration of the additive in those foods. Additive intakes from each food are then summed to estimate total dietary exposure to the additive. Given that an additive is not necessarily used in all the foods in which it is permitted, the development and use of a food ingredient database was proposed as a useful tool for refining crude estimates of food additive intake within the overall tiered approach for monitoring intakes (Nutriscan 1994).

As part of this thesis, an existing Irish National Food Ingredient Database (INFID) was expanded, updated and used to provide qualitative information on patterns of additive usage in the Irish food supply. Since each food in the database contains a food code, the foods can be aggregated to correspond with EU Directive food groups (European Commission 1994a,b, 1995) and this type of information can be tailored specifically to food groups relevant for food additive exposure assessments. Thus, rather than including all the food groups in which an additive is permitted in an exposure assessment, the assessment of exposure can be refined to only include the food groups in which INFID confirmed the presence of the additive. Furthermore, by monitoring trends in the pattern of additive usage in the food supply, the database may also help to focus future monitoring programmes. However, as with any database used in a food chemical exposure assessment, it is important to consider its temporal relevance for the exposure assessment in question. Thus, a food ingredient database such as INFID should be used armed with the knowledge that it pertains to a particular time period and represents a snap shot of additive usage at that time.

Whilst a food ingredient database provides a useful means of refining food additive intake estimates by identifying the food groups that can be excluded from an exposure assessment, the resulting deterministic exposure estimates still assume that the additive is present in every food within a given food group and that it is always present at its maximum legal concentration within that food group. Furthermore, no information is available to exposure assessors and risk managers on the range of possible intakes

that may occur within a population and on the proportion of the population likely to exceed a given intake level.

The application of probabilistic modelling to the estimation of food chemical intakes provides an opportunity to address these limitations and to generate a more realistic distribution of exposure together with information on the full distribution of risk. Much of the research conducted in this thesis explores some of the issues that are relevant for the novel application of this technique to food chemical exposure assessments.

Since probabilistic modelling concerns the use of distributions in place of traditional point estimates, the reliability of the results of a probabilistic analysis is largely dependent on the selection of the most appropriate distribution to represent model inputs. Indeed, one of the reasons cited for the limited use of the probabilistic technique in exposure assessments, is the lack of information on the most appropriate distribution to describe model inputs (Finley and Paustenbach 1994, Finley *et al.* 1994). One of the objectives of this thesis was to explore the type of parametric distribution that could be used to describe food consumption model inputs in a food chemical exposure assessment. Results from this exploration indicated that the lognormal distribution was most commonly accepted as a plausible distribution. However, results from a further investigation, in which the influence of using a lognormal distribution to describe food consumption model inputs on the assessment of food additive exposure was investigated, indicated some level of caution regarding the use of a lognormal distribution to describe food consumption data in probabilistic food chemical exposure assessments. This was identified as an area of research that warranted considerable further exploratory work.

Coupled with the selection of an appropriate distribution to describe exposure model inputs, the reliability of results of a probabilistic analysis is dependent on the validity of the model used in the exposure assessment. Given the flexibility of this technique, it is quite possible to generate very detailed distributions of completely invalid exposures if the validity of the underlying model is not assessed. Burmaster and Anderson (1994) quite aptly caution that the maxim *garbage in garbage out* should not become *garbage in gospel out*, when applied to probabilistic assessments. A current lack of validated models is also cited for the limited use of probabilistic techniques within the area of food chemical exposure (ILSI 1998, Petersen 2000, 2003, Kroes *et al.* 2002). To this end, one of the objectives of the Monte Carlo project was to develop and validate a simple conceptual model for the estimation of food additive intake. Modelled

intake estimates that fell below conservative deterministic estimates and above 'true' intakes were deemed to fall within a valid region. A number of interesting but important issues emerged from this validation study. Firstly, it is necessary to check the validity of individual model components before checking the validity of the full conceptual model. This ensures that exposure estimates from the full model, if valid, are valid for the correct reasons. Secondly, even if individual model components are deemed valid, the way in which these components are combined within the full model can still result in an invalid exposure estimate. Thirdly, the validity at one location on the distribution of exposure cannot automatically be extrapolated to validity at all locations on the distribution. Therefore, it is important to consider the full distribution of exposure or at least the part of the distribution that is of interest to the exposure assessment. Fourthly, for the assessment of exposure to food additives, more sophisticated models, which incorporate information on brand loyalty and/or market share into the modelling algorithms may be required. Where lack of information on these two parameters dictates the need to use simpler models, these models will only be useful if attempts are made to incorporate proxy measures of brand loyalty and market share. Fifthly, unlike deterministic methods where a single value for a given percentile of exposure is presented, the application of probabilistic modelling to food chemical exposure assessments generates a distribution of values for any given percentile. For example, a simulation of 1,000 iterations will generate 1,000 95^{th} percentiles, 1,000 97.5^{th} percentiles *etc.* For a given percentile, one can calculate the mean of the 1,000 values and any given confidence level. Therefore, one has to consider which point on the distribution of the percentiles of interest should reflect exposure. Within this study, modelled estimates were deemed valid if the upper 95% confidence level was lower than conservative deterministic estimates and if the lower 95% confidence level was higher than 'true intakes'. In the case of intense sweeteners, modelled intake estimates were deemed valid if the *mean* of the distribution of the percentile of interest was below conservative intakes and above corresponding 'true' intakes generated from a purpose built brand level food consumption database (Arcella *et al.* 2003). The different approaches adopted by Arcella *et al.* (2003) and the present study, reflect the lack of a general consensus at the present time on the most appropriate mode of presenting the results of a probabilistic food chemical exposure assessment. Clearly, this is identified as an area that requires standardisation.

The reconstruction of an existing non-brand level food consumption database to one that contained information at brand level for the purpose of calculating true

intakes was a tedious and timely process. A detailed description of the steps involved is documented elsewhere (Leclercq *et al.* 2003). It would be neither cost effective nor practical to repeat such a process for any future validation study. Therefore, alternative ways of generating data against which new models of exposure can be validated need to be considered.

A number of sources of uncertainty relating to food chemical exposure assessments were discussed in this thesis. These included, sample, temporal, spatial and measurement uncertainty. In addition, the topic of truncation was discussed in relation to the use of unbounded input distributions. Energy under-reporting, which has been identified as a critical source of uncertainty in food chemical exposure assessments, was specifically addressed in this thesis. Whilst the findings indicated that the existence of this phenomenon in dietary surveys did not appear to materially influence food additive intake estimates at upper percentiles of exposure, a number of situations were identified in which energy under-reporting may exert a more pronounced impact.

Whilst the probabilistic approach confers many advantages over traditional deterministic methods, it must be acknowledged that not every food chemical exposure assessment will require the application of this technique. The approach is more resource intensive than traditional deterministic estimates and therefore, should only be employed where necessary. Situations in which a probabilistic analysis may *not* confer any benefit are (i) when a screening level deterministic calculation indicates that exposures are negligible, (ii) where there is little variability and uncertainty in the model inputs and (iii) when the probabilities are so uncertain, that detailed probabilistic judgements are impossible.

The assessment of human exposure to chemicals present in the diet is a developing discipline. With the increasing application of probabilistic techniques to food chemical exposure assessments, there is a need to improve our understanding of this area. The research presented in this thesis will provide the exposure assessment community with a body of pertinent information that will both serve to improve existing knowledge within this area and act as a basis for future research into many of the issues that were identified during its course.

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