Chronic Dietary Exposure Assessments Conducted by UK Regulatory Authorities (FSA, HSE, and VMD)

Draft Report

Contents

1. Introduction

Background

Dietary exposure assessments are a key component of chemical risk assessments for food additives and potential food contaminants, such as pesticides or veterinary medicines; however, there can be differences in the approaches taken to these assessments in different regulatory areas and between regions internationally. There are historical reasons for this, and each area of regulation has evolved independently, based on factors such as the different regulatory contexts, the nature of the data available, or strict legislative requirements in certain areas.

Within the United Kingdom (UK), there are differences in the current approaches to assessments of chronic dietary exposure between the Health and Safety Executive's Chemicals Regulation Division for pesticides (HSE-CRD), the Veterinary Medicines Directorate (VMD) for residues of veterinary medicines, and the Food Standards Agency (FSA) for chemical contaminants and other chemicals in food. Furthermore, there are differences in how these assessments are conducted internationally for pesticides and veterinary medicines, and these differences may increase as methodologies change.

In addition, following exit from the European Union (EU), it is timely for UK regulators to consider the approaches they might wish to take in the future.

It was therefore agreed to review the current approaches to chronic dietary exposure assessments taken by HSE, VMD and FSA, accounting for the principles and aims of the exposure assessments, the reasons why differences in approach might legitimately be taken, the uncertainties associated with different approaches, and the uncertainties that exist with exposure assessments in general and how they might be reduced (if necessary).

A team of risk and exposure assessors from HSE, VMD and FSA held 10 meetings to consider this topic. The agreed terms of reference were:

- To consider approaches to chronic dietary exposure assessment, agree and set out the general principles to be followed by Government departments, and to set out a tiered system of different approaches, from simple and conservative to increasingly complex and refined, recognising that different departments may have different requirements.
- To explain the appropriate criteria for using these approaches at the different tiers and the uncertainties associated with following the different approaches.
- To capture the underlying uncertainty in food consumption and occurrence data.
- To identify potential research that would reduce uncertainties in exposure assessments.

The intention was to present the draft report to the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), the Expert Committee on Pesticides (ECP), and the Expert Committee on Pesticide Residues in Food (PRiF) for their input and feedback ahead of finalisation.

Principles of exposure assessment

Dietary exposure assessments are an essential component of the four-stage risk assessment process of hazard identification, hazard characterisation, exposure assessment, and risk characterisation. This approach is used by CODEX, international regulatory bodies, and food safety agencies, including UK Government departments. The outcomes of the first two steps of the process inform the approach required for the exposure assessment, e.g., whether chronic and/or acute dietary exposure assessments are required. The resulting exposure assessment can then be compared with a health-based guidance value (HBGV), a threshold of toxicological concern (TTC), or, alternatively, a margin of exposure could be calculated at the risk characterisation step.

There is general agreement that dietary exposure assessments should provide dietary exposure estimates that are conservative (i.e., highly protective of health) and be conducted using methods that are fit for purpose (WHO, 2020). They should address the general population, as well as specific population subgroups that have been identified as relevant from toxicological profiling (e.g., infants, children, pregnant women, older adults). The method(s) used should take into consideration non-average individuals, such as those who are disproportionately at risk to the adverse effects of the chemical under consideration, and those who are high consumers because they habitually or occasionally consume large portions of foods containing the chemical, consume many foods that contain low levels of the chemical, or habitually or occasionally consume foods with very high concentrations of the chemical (WHO, 2020).

Several approaches are available for dietary exposure assessment:

- simple deterministic or point estimates, which use single values for the concentration of a chemical in food and for the level of consumption.
- refined deterministic estimates, e.g., empirical distributions of food consumption combined with single values for the concentration of the chemical in each food, or *vice versa*.
- probabilistic/stochastic estimates, which use parametric or non-parametric techniques to generate a distribution of exposures.

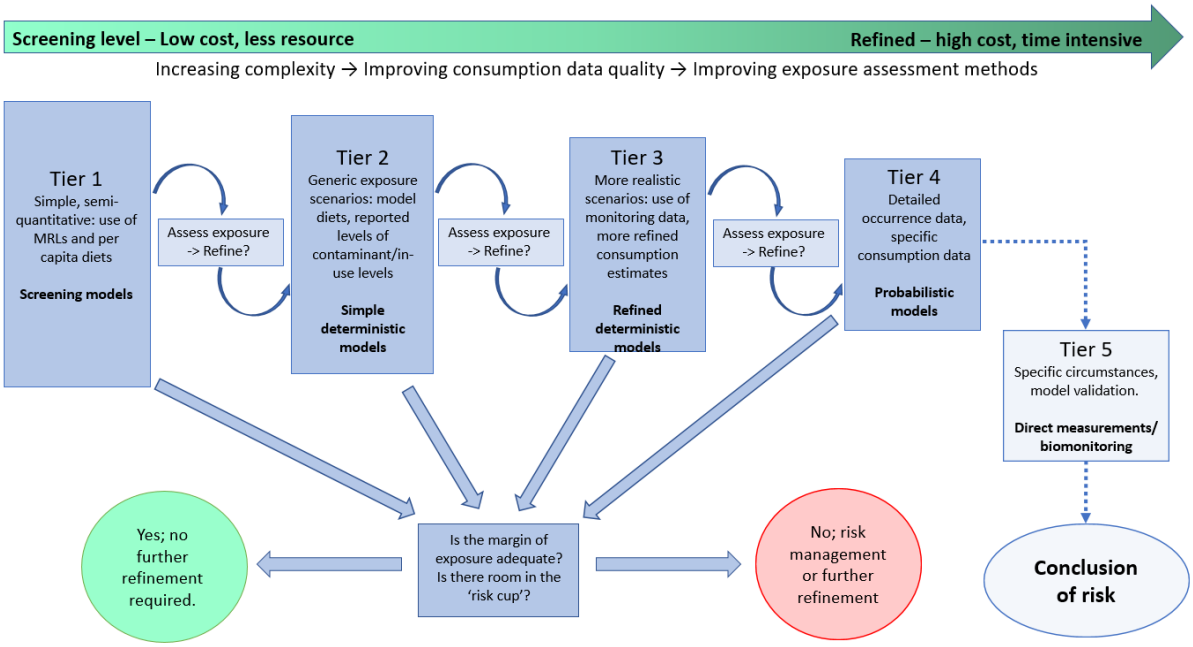
The ability to conduct refined, realistic estimates of dietary exposure depends on the available resources, so tiered approaches are often used in various stages of risk assessment, including exposure assessments (Ingenbleek et al., 2020). Tiering in exposure assessment means using simple, conservative approaches when resources, including time, are limited, or where further refinement of risk is not required (low tier), and more complex and precise approaches when further refinement is needed (higher tiers). Thus, a low tier is typically a data-poor situation involving conservative assumptions, whereas at higher tiers, more data are available, allowing assessments to become more accurate with reduced uncertainty, and eventually the potential to use probabilistic approaches (Ingenbleek et al., 2020).

Where low tier approaches are used (sometimes referred to and used as 'screening approaches'), the aim should be to overestimate the potential dietary exposure of high consumers by using conservative assumptions for food consumption and the

concentration of the chemical in food, in order to avoid situations in which dietary exposure is underestimated and the assessment erroneously indicates that there is no safety concern (WHO, 2020). Similarly, where more refined, higher tier, approaches are required, they should still be designed so that any potential high dietary exposure is not underestimated (WHO, 2020).

Taking a tiered approach means that the exposure assessment can stop, and the risk assessment concluded, without using unnecessary resources, e.g., if it can be concluded from a low tier approach that there is no significant risk to consumers. Alternatively, if a significant risk cannot be excluded from lower-tier approaches, then either risk management action may be taken at that point, or the exposure assessment may progress to higher tiers (Ingenbleek et al., 2020). See figure 1.

Figure 1: Diagram illustrating a tiered approach to dietary risk assessment



However, not all exposure assessments proceed through tiers; a more realistic estimate of exposure may be used in the first instance if the resources are available to do so (WHO, 2020). In many assessments of regulated products, the exposure assessments do not proceed from lower to higher tiers. Instead, the tier(s) applied are predetermined by the available data, the problem formulation, the regulatory context, and/or the legislation in place (Ingenbleek et al., 2020).

Exposure assessments should be clearly documented (WHO, 2020). This includes information about the dietary model and food consumption data used, the associated concentrations of the chemical in food (including the data source(s) used), the model choices, data limitations, and uncertainties.

Dietary exposure assessments may be population-based or consumer-based, depending on the purpose of the risk assessment. In this context, 'population' means all the respondents in a dietary survey, whereas 'consumers' means the subset of respondents who reported consuming foods containing the chemical of interest. If the chemical of interest is present in non-staple foods (i.e., those not consumed daily by most people), then a population-based exposure assessment may underestimate the

potential dietary exposures for regular consumers of the foods containing the chemical of interest. In this case, a consumer-based approach may be preferred, as it would lead to a more conservative estimate of high-level exposure, and thus be more protective.

The nature of dietary survey data may also affect whether a population or consumers-only approach is taken. For example, if data from a 24-hour survey are used to estimate chronic exposure, they are only considered reliable for estimating mean consumption for the total population, and not for identifying the number of consumers of a food, or for estimating exposures of consumers only. For dietary surveys conducted over multiple days, care is still needed in estimating long-term intakes, as short-term data can lead to underestimates of the proportion of the population who are consumers, and overestimates consumption by consumers on a long-term basis. Where dietary surveys are conducted over 2 or 3 days, a lower percentile (e.g., 90^{th} percentile vs. 95^{th} or 97.5^{th} percentile) can be used to represent high-level consumers, to avoid overestimating long-term exposures. This is the approach taken by, e.g., the US Food and Drug Administration (US FDA) and Food Standards Australia New Zealand (FSANZ) (WHO, 2020).

Statistical approaches are also available to estimate ‘usual’ consumption of foods, or exposures to chemicals, from short-term dietary data. These aim to remove within-person variation, resulting in distributions of exposure which are narrower. Such models can be time and resource intensive. They are usually used on a case-by-case basis, with the input of expert statistical advice. Exposures can be estimated without using a model for 'usual' intake, provided it is explained that any high percentiles of 'usual' intake are likely to overestimate the exposure on a long-term basis, to an unknown degree.

2. Description of approaches in different fields

Food additives, supplements, naturally occurring toxins, and other contaminants - FSA

General overview

FSA carries out dietary exposure assessments for a range of chemicals that can be found in foods and supplements, including food additives, pesticide and veterinary medicine residues, residues in animal feeds, contaminants, food contact materials, and naturally occurring toxins like mycotoxins.

The current FSA approach to estimating chronic exposure is to determine food consumption, multiply it by the concentration of the chemical of interest in the food, and expressing this as either a quantity per person per day, or per kg bodyweight per day (see figure 2).

Figure 2: Dietary exposure calculations

$$DietaryExposure = \sum \left(Food\ \ chemical\ \ concentration \times Food\ \ consumption \right)$$

Where: 'Food chemical concentration' is the concentration of the chemical of interest in the food and 'Food consumption' is the amount of the food that is eaten.

$$DietaryExposure = \sum \frac{\left(Food\ \ chemical\ \ concentration \times Food\ \ Consumption \right)}{BW}$$

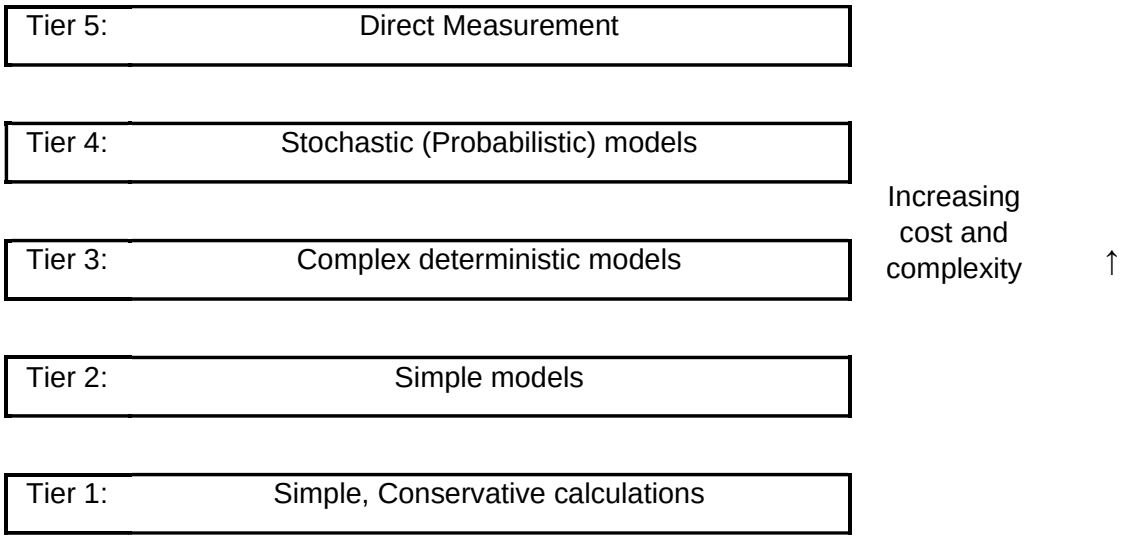
Where: 'Food chemical concentration' is the concentration of the chemical of interest in the food, 'Food Consumption' is the amount of the food that is eaten, and BW is the body weight of the consumer.

Details on how this consumption and chemical occurrence data are derived are given in the following sections.

Tiered approach to exposure assessment

Generally, FSA adopts a tiered approach to selecting the best method to carry out exposure assessment, considering factors such as sources of uncertainty, perceived risk, available time and resources, and suitability of the method. The assessment is consistent with the approach adopted by the European Food Safety Authority (EFSA). Currently, the main approach to exposure assessment has been to use deterministic and distributional methods; however, the use of more complex methodology, such as probabilistic modelling, is considered on a case-by-case basis for refining an exposure estimate. See figure 3.

Figure 3: FSA tiered approach to exposure assessment



Most FSA exposure assessments utilise Tier 1 or Tier 3 methods.

Tier 1

Tier 1 involves carrying out basic calculations based on conservative worst-case estimates of chemical occurrence and consumption data. These could be based on back calculations (e.g., knowing an established Acceptable Daily Intake (ADI) and the level of chemical in a food, then back calculating how much of that food would have to be eaten to reach the ADI, after taking account of background exposures). If the simple estimates are well within established safe limits, then the assessment will not proceed further. If the conservative estimate gives any cause for concern, the exposure estimates may be refined with additional information.

Tier 2

Tier 2 involves using mean or high-level food consumption rates taken from published summary tables of food surveys, such as the National Diet and Nutrition Survey programme (NDNS) or Diet and Nutrition Survey for Infants and Young Children (DNSIYC); see 'consumption assessment' section for more information on surveys. Calculations are carried out similarly to tier 1, but more details such as migration from food packaging, and consumption of multiple foods, will be accounted for.

Tier 3

For tier 3 assessments, FSA uses Creme Global software, which is statistical software that allows the estimation of dietary exposure from individual dietary survey records for different subgroups with single values of a chemical concentration in food. The program uses the 97.5^{th} percentile consumer to represent reasonable high-level consumption. See the section on Creme Global software for more detail.

Tier 4

Tier 4 covers the use of probabilistic modelling. Probabilistic methods represent a higher degree of complexity, allowing consideration of the full range of chemical data and/or other parameters. The models randomly sample the full distribution of chemical

concentrations in individual items of food, in addition to the distribution of consumption data provided by the NDNS; these data are combined and presented as a distribution of likely exposures. Probabilistic modelling offers the possibility of more realistic estimates of exposure and useful refinements in analysis which go beyond routine risk assessment.

Tier 5

This is a direct measure of exposure for a specific critical group, using methods such as biomarkers or duplicate diet studies.

Consumption assessment

The main source of data used by FSA for estimating dietary consumption is the NDNS. A rolling programme of the NDNS was set up in 2008 to collect data on a continuous, annual basis. The age range of participants is from 1.5 to 95 years of age and excludes pregnant/breastfeeding women and people in institutions. One of the major components of the NDNS is a detailed record of a person's diet during 4 consecutive days, via a written food diary (2008 - 2020; years 1 - 11). Up until 2020 (year 11), the NDNS used a 4-day un-weighed diary as the dietary assessment method for the rolling programme. From year 12, 'Intake 24' has been used. This was introduced in order to improve data quality and maximise value. It is a 24-hour recall method used to obtain dietary data. Participants are asked to complete 4 time-spaced recalls within 3-5 weeks using an online platform, rather than the 4-day written diary entries.

Another main source of data for FSA is the DNSIYC. This was commissioned by the Department of Health (DH) and FSA in 2011 to provide detailed information on food consumption, nutrient intakes, and nutritional status of infants and young children aged 4 - 18 months living in private households in the UK. This survey provides the only source of high-quality, nationally representative data for this age group. It was in the form of a food diary filled in by the parents of the children over 4 consecutive days.

The NDNS and DNSIYC allow flexibility in how critical groups might be considered; this is also supported by the Creme Global software. As mentioned previously, these data are entered into the Creme software and can be manipulated to give consumption or exposure assessments for specific food groups and (or) consumer groups. The data can be filtered according to age, gender, and socio-economic status, amongst other parameters. More detail on the Creme software is given later in this report.

Additionally, FSA commissioned a project for a recipe database, to help ensure that foods consumed as ingredients of other foods were accounted for in dietary exposure assessments. The initial project was carried out by the Medical Research Council's Human Nutrition Research Unit (MRC HNR) and was completed in 2015. The output was 8397 recipes with guidance notes and a project report. Recipes continue to be added each year when new data are gathered from respondents in the NDNS rolling program. This database supports the use of NDNS and DNSIYC data in consumption assessments.

Other surveys, like the Expenditure and Food Survey (EFS) (Family Food, 2007), provide supporting information on food consumption. This survey was carried out annually and provides data on food purchases at a household level. This is limited in its usefulness for assessing food safety, as the data provided are population averages.

However, as it was a continuous survey, it was useful for tracking food consumption patterns. The Expenditure and Food Survey has now been replaced by the Living Costs and Food Survey (LCF) (Living cost and food survey, 2012-2016), where food consumption is also estimated based on purchasing patterns.

Other methods of sourcing consumption data include using information from measured portion sizes, manufacturers' feeding instructions (e.g., for infant formulae), or recommended dosages (e.g., for dietary supplements) to show average exposure or to assess the number of portions required to achieve a certain level of intake. For rarely eaten foods for which there may be few, if any, recorded consumers in available surveys, typical portion sizes can be used. McCance and Widdowson's 'The Composition of Foods', Sixth Summary Edition, provides comprehensive nutrient data for over 1200 of the most commonly consumed foods in the UK (FSA, 2002). This is often used by FSA to estimate portion sizes or food composition for consumption assessments.

Occurrence data

Sources of occurrence data used by FSA vary. Data may be obtained from incidents where a particular food has been found to have a chemical concentration above a certain threshold. Data from FSA surveys have also been used for assessment of dietary exposure. Data may also be from research projects on foods or chemicals of interest. Exposure assessments are also used to interrogate the results of monitoring data during the determination of maximum allowable limits for food contaminants. Total Diet Studies (TDS) continue to provide a valuable source of data to enable the estimation of background exposure to ubiquitous food contaminants.

Examples of surveillance include surveys of chemical contaminants in food, e.g., mycotoxins or process contaminants like acrylamide, inorganic contaminants like metals, and organic environmental contaminants like dioxins. Other examples are surveys of chemical contaminants from food contact materials and articles intended to come into contact with food (e.g., cooking utensils), and food additives surveys.

A TDS is a continuous market basket-type survey, in which foods representing the average UK diet are purchased, prepared, and combined into groups of similar foods for analysis. Food samples representative of the UK diet are purchased throughout the timeframe from all around the UK. The types and quantities of food purchased are based on analysis of food consumption data recorded in surveys like the EFS/LCF, and from trade statistics. The quantities of food are updated each time to reflect changing eating habits in the UK. Population dietary exposures are estimated by multiplying the average amount of each food group consumed (based on consumption data from the NDNS or DNSIYC) by the corresponding chemical concentration in the food group from the TDS study, then summing across all food groups.

Creme Global software

Data from the NDNS (Bates et al., 2014; 2016; 2020; Roberts et al., 2018) and DNSIYC (DH, 2013) surveys, as well as the recipes database, are stored within the software (Crème Software). If an estimate of likely exposure to a chemical in a group of foods is required, Creme can retrieve information on these foods from the relevant survey; the recipes database aids this, as it allows a search for specific ingredients.

Chemical concentrations can be entered into the program for each group of foods being considered, and Creme will review each participant's dietary record for the foods specified. Where a particular food is eaten, consumption data are combined with the relevant chemical concentration for each person in the survey from all the specified foods (provided there is a sufficient number of recorded consumers of the food(s) in question). For chronic exposure, each person's average daily exposure over the length of the survey (4 days) is calculated. This software can also calculate acute exposure estimates. If exposure on a bodyweight basis is required, the software can calculate a person's exposure using their bodyweight as recorded in the survey. The full distribution of individual exposure is then plotted, and from this distribution summary statistics (e.g., mean and 97.5th percentile) are extracted.

The main summary statistics for chronic dietary exposure assessments used for FSA risk assessments are the mean and 97.5th percentile, as well as the number of consumers and the number of respondents in the population group. This is important, as consumption or exposure estimates made with a small number of consumers is unlikely to be accurate. In particular, estimates of the 97.5th percentile based on fewer than 60 consumers are treated with extreme caution, as they may not be representative of a larger number of consumers. Another summary statistic which may be used is the median, which can be compared to the mean to give an idea of the skewness of the data.

Most exposure assessments by FSA are consumer-based exposure assessments. Consumer exposure assessment, in its simplest form, involves combining chemical occurrence data with consumption data in order to estimate the amount of the chemical ingested by an individual over a fixed period of time. The benefits of consumer exposure assessment include the ability to estimate high level (e.g., 97.5th percentile) consumption and the facility to remove non-consumers of the food(s) of interest from analyses. Considering consumers only is important for foods that are consumed by a relatively small proportion of the population, allowing specific 'at risk' population sub-groups to be identified for targeted advice. Population-based exposure is where 'non-consumers' of the food(s) of interest are not removed from analyses and consumption/exposure is averaged across all participants in the population group.

The software can also calculate the serving size by taking the average amount of all meals (all amounts divided by the number of eating events). The average serving size is used to calculate the serving size for the total population and for high consumers. This may be used to compare to portion sizes given in literature and be used to estimate exposure.

Dealing with uncertainties in chronic exposure assessment

Sometimes, the chemical occurrence data available may include values below the limit of detection (LOD) or the limit of quantification (LOQ). In this case the upper and lower bound approach to exposure assessment is likely to be used.

The lower bound (LB) approach is where, if the concentration is <LOD and/or <LOQ, then the output is assumed to be 0. This results in an underestimation of the exposure. The upper bound (UB) approach is where if the concentration is <LOD then the output is assumed to be equal to the LOD and if the concentration is between the LOD and

391 the LOQ, then the output is assumed to be equal to the LOQ. This results in an
392 overestimation of the exposure. In such a case, two chemical occurrence values, the
393 LB and the UB values, will be used for the exposure assessment to give a range of
394 potential exposures.

395 Other uncertainties may be associated with the consumption data. For example, foods
396 with very few or no consumers recorded have already been mentioned. At the FSA, a
397 common approach to this type of uncertainty is either to use another similar food
398 product as a proxy, or to refer to literature or manufacturer's instructions for portion
399 size estimates, or recommended dosage (for e.g., supplements). In all cases, the
400 uncertainties associated with exposure assessments are recorded and referred to in
401 the discussion of the risk assessment.

402 Other types of uncertainty may be associated with the chemical occurrence data, for
403 example, for food contact materials, there may be limited data on migration into the
404 food product(s) of interest. In this case, we may have to assume 100% transfer which
405 would be an extremely conservative assessment. These types of assessment are
406 taken on a case-by-case basis; again, all uncertainties are recorded and discussed.

407 ***Pros and cons of the model***
408 This section has been included in the descriptions of the approaches for pesticides
409 and veterinary medicines to discuss the advantages and disadvantages of the models
410 currently used. However, the FSA does not use one single model but a range of
411 approaches, as described above.

Pesticides - HSE

General overview

The current HSE approach to the chronic consumer risk assessment of pesticides relies upon a deterministic assessment using the UK chronic model and the EFSA PRIMo rev 3.1 model (HSE, no date: Consumer exposure). The estimates of long-term exposure are calculated based on either pre-registration supervised residue trial field data, derived in accordance with Regulation 1107/2009, or monitoring data derived as part of the Great Britain and Northern Ireland monitoring programme, which is a requirement under Regulation 396/2005.

Chronic risk assessment is undertaken to determine pesticide exposure for three purposes:

a) Assessment of potential exposure at the time of active substance approval or product authorisation, based on supervised trial median residue (STMR) values from residue data for the proposed crop uses only.
b) Assessment of potential exposure for maximum residue level (MRL) setting and review (including CODEX MRLs). This will consider all authorised pesticide uses of the active substance (note: STMR values may not be available for all uses if an MRL review has not yet taken place).
c) Assessment of exposure based on monitoring data. A chronic risk assessment is undertaken on an individual commodity basis, only if sufficient samples of that commodity have been analysed for that survey (minimum of 12 is desirable) and where ≥50% of the samples for that commodity have residues of the same analyte at or above the reporting limit (RL).

To address points a) and b) above, the STMR is used for determination of individual commodity National Estimates of Dietary Intakes (NEDIs) and total dietary intake calculations (total NEDIs) using the UK model, or for determination of International Estimated Dietary Intakes (IEDI), using the EFSA PRIMo model. Alternatively, a highly conservative assessment of the Theoretical Maximum Daily Intake (TMDI) can be calculated by inserting an MRL value instead of using the STMR.

To address point c), for the monitoring programme, chronic risk assessment is currently undertaken quarterly on a case-by-case basis, using the median residue determined for an individual commodity to calculate the NEDI. The median residue is based on all samples surveyed for that commodity in that quarter, including where the residue was either not detected or was below the RL, but only where an analyte is found above the reporting level (RL) in > 50 % of samples.

To estimate chronic consumption, the UK model for long term exposure sums the two highest 97.5th percentile commodity intakes and the mean intakes across all the remaining commodities for each of the consumer sub-groups; this is known as the Rees-Day approach (HSE, 2006). The 97.5th percentile is derived from a distribution of daily food consumption that individuals have reported throughout the survey (this does not include non-consumers). See figure 4.

Figure 4: HSE Rees-Day approach to chronic risk assessment

$$\sum_{x=i}^{j} \frac{STMR_x \times P97.5_{consumption\ x}}{BW} + \sum_{y=k}^{n} \frac{STMR_y \times MC_y}{BW}$$

Where:

i, j = two raw agricultural products leading to the highest intake

k, l, m, …n = remaining raw agricultural commodities consumed

STMR = Supervised Trial Median Residue. Residue value derived from pre-registration data. Note for monitoring data, median residue of monitoring values is used.

$P97.5_{consumption}$ = 97.5th percentile consumption of the Raw Agricultural Commodity (RAC) in kg/day based on mean daily intakes of consumers only.

MC = mean consumption of RAC in kg/day derived from mean daily intakes of whole population (consumers and non-consumers).

BW = Body weight (kg)

A different calculation is used in the EFSA PRIMo rev 3.1 model, which uses mean consumption for the whole survey (based on consumers and non-consumers) to calculate chronic exposure. See figure 5.

Figure 5: EFSA PRIMo rev. 3.1 approach to chronic risk assessment

$$\sum_{x=i}^{n} \frac{\boldsymbol{STMR_x \times MC_x}}{\boldsymbol{BW}}$$

Where:

i, j, k, …n = individual raw agricultural products

STMR = Supervised Trial Median Residue. Residue value derived from pre-registration data. Note for monitoring data, median residue of monitoring values is used.

MC = mean consumption of RAC in kg/day derived from mean daily intakes of whole population (consumers and non-consumers).

BW = Body weight (kg)

The Rees-Day approach is also represented within EFSA PRIMo rev 3.1. It was included for information purposes only; there was never an intention for it to be used or relied upon for regulatory decision making by Great Britain (GB) or the EU. It can be noted that there are some differences in how EFSA has interpreted the UK consumption data (e.g., not all consumer groups are represented, and mean values were not used for swine and sheep products), which means there are differences in the calculation outcome between the EFSA and UK models.

Estimated intakes, calculated using either the UK chronic exposure model (NEDI) or the EFSA PRIMo rev. 3.1 (IEDI), are compared against the ADI for the active substance. Provided the estimated intakes are less than or equal to the ADI for that active substance, it is assumed that there is an acceptable low risk to consumer health.

It is possible to refine the risk assessment using processing data; however, refinements are only possible if a commodity is predominantly consumed after being processed, or there is sufficient consumption data available to capture the combined consumption via both the raw agricultural commodity (RAC) and any processed commodities.

In addition to chronic risk assessments undertaken for single substances, the data requirements laid out in Regulation 283/2013 also require a consideration of cumulative exposure to more than one active substance, when such methods to assess such effects are available, and where relevant. The current UK and EFSA models do not have capability built in to do this; however, HSE does consider combined chronic risk where there is a potential for combined toxicity (assumed to be additive) and there is combined exposure from two or more pesticides (or relevant metabolites). The HSE approach (HSE, 2005) to combined toxicity was prompted by the Working Group on Risk Assessment of Mixtures of Pesticides and Similar Substances (WIGRAMP), and is outlined in the Pesticide Safety Directorate (PSD) and Advisory Committee on Pesticides (ACP) guidance[1]: Approach to assessing the mammalian toxicity (and consumer/operator risk assessment) of two or more compounds in a pesticide product (formulation). The combined chronic risk assessment is undertaken using both the UK chronic and EFSA PRIMo models and follows a three-tier approach.

As part of the UK monitoring programme, a consideration of combined exposure can be undertaken on a case-by-case basis where pesticides found in combination are known to have additive effects. Generally, this assessment would be an acute exposure assessment, as the combination of pesticides rarely appear together in large numbers of samples; however, where there is a need to, i.e., where the combination of pesticides occurred in ≥50% of samples, a combined chronic risk assessment is undertaken. The specific pesticide groups for which consideration of combined exposure (acute or chronic, as required) is currently made include triazoles, organophosphates/carbamates with known acetylcholinesterase (AChE) inhibition, mepiquat/chlormequat, folpet/captan, carbendazim/thiophanate-methyl, and specific combinations of biocides used as disinfectants.

Diet/consumption data

UK chronic risk assessment model

The UK model enables the intakes of ten consumer groups from the consumption of treated agricultural commodities to be estimated. The current definition of consumer groups are adult (19-64 years old), infant (6-12 months old), toddler (18 months to 4 years old), 4–6-year-old child, 7–10-year-old child, 11–14-year-old child,15-18-year-old child, vegetarian, elderly (own home), and elderly (residential).

It should be noted that for future updates to the UK model, the definitions of consumer groups could change, as new NDNS data will not include respondents in residential institutions or allow easy separation of vegetarians from the other groups. Average

[1] PSD was the predecessor to the current Chemicals Regulatory Division (CRD) and ACP was the predecessor to the current Expert Committee on Pesticides (ECP).

bodyweights are used for each of these consumer groups, based on information submitted as part of the dietary surveys. These are detailed in the following table:

Table 1: Mean consumer bodyweights used for the ten consumer groups in the UK chronic exposure model

Consumer group	Adult 19-64 years old	Infant 6-12 months old	Toddler 18 months – 4 years old	4–6-year-old	7–10-year-old	11–14-year-old	15–18-year-old	Vegetarian	Elderly (own home	Elderly (residential)
Body weight (kg)	76	8.7	14.5	20.5	30.9	48.0	63.8	66.7	70.8	61.6

The consumption data for the ten consumer groups is provided by FSA and is based on the NDNS and the DNSIYC from 1986, 1992/93, 1994/95, 1997 & 2001; see section 2 A above for further details. The consumption data are expressed as g/kg body weight per day for both the mean and 97.5th percentile. Information on the number of consumers who have reported to have eaten a given food commodity within the survey are also included for each sub-group.

EFSA PRIMo model

This model encompasses a variety of subgroups and survey approaches. Overall, 30 Member State diets for chronic exposure assessments were considered. In addition, the relevant GEMS/Food Cluster diets relevant for the EU Member States (i.e., Cluster diet G06, G07, G08, G10, G11 and G15) were incorporated. Mean bodyweights for each consumer group are used; these data are based on the results of the different food surveys used to compile the data. These are summarised in the guidance on the use of EFSA PRIMo revision 3 (EFSA, 2018). It should be noted that the PRIMo model was later updated to revision 3.1, along with an updated guidance summarising the modifications (EFSA, 2019).

The food consumption data were provided by Member States who derived this information from national food surveys. Consumption data reported for processed and composite food was converted by the data provider to the unprocessed raw agricultural commodity (RAC). The surveys used cannot be considered fully comparable, as the surveys were performed according to different methodologies; however, the data are considered appropriate to address risk management questions, in particular to identify intake concerns for the EU population related to pesticide residues in food. The food consumption data in EFSA PRIMo revision 3.1 are structured in accordance with the current version of the food classification used to set MRLs under Regulation (EC) No 396/2005 (Annex I). The mean consumption data are expressed as g/kg body weight per day.

Occurrence data

For the purpose of conducting chronic risk assessments, the occurrence data, or pesticide residue data, originate from two main sources:

- Pre-registration data
- Monitoring data

Pre-registration occurrence data

Pesticide residue data refer to the residue of interest for a pesticide active substance. This can be either the parent compound, and/or major metabolite(s) which result from the breakdown of the active substance, or the formation of reaction products. The pesticide residue which should be quantified in a food commodity is defined by the residue definition for risk assessment (RD-RA), or the residue definition for enforcement (RD-Enf). Most of the chronic risk assessments undertaken by HSE rely on pre-registration data. These data are produced by industry to support the authorisation of a product or for the approval/renewal of an active substance.

Pre-registration data are obtained from supervised field trials. The trials should be conducted in accordance with the relevant guideline documents and the most critical good agricultural practice (GAP) in terms of field of use (e.g., indoor or outdoor), application rate, number of applications, and application timing proposed for the use of the product for which authorisation is sought.

To support the authorisation of a pesticide, either for approval/renewal of the active substance, or for a use in a new product or on additional crops, a minimum of eight supervised trials are required for major crops and a minimum of four trials are required for minor crops. Whether a crop is considered major or minor is based on daily intake contribution, relevant cultivation area, and/or production. The extrapolation guidance document[2] provides additional details on this aspect. The supervised residues trials are used to derive the STMR, which is used in the chronic risk assessment calculation for determination of the NEDI, total NEDI, or the IEDI. Where it is necessary to determine the TMDI, the MRL for the active substance is used in place of the STMR. The MRL is calculated using the OECD MRL calculator[3] and the results of the supervised residues trials. It is designed to calculate an MRL in the region of the 95th percentile of the underlying residue distribution.

Monitoring occurrence data

Pesticide residues in food (PRiF) monitoring data are generated as part of the Great Britain and Northern Ireland monitoring programmes. There is a requirement of Article 29 of the MRL Regulation 396/2005 (and the retained legislation post EU exit) to undertake a national testing programme, and to take part in a co-ordinated programme of testing for 34 foods of high consumer interest (over a three-year rolling period).

The purpose of the monitoring programme is to:

a) check that residues do not exceed the statutory MRLs.
b) back up the statutory approvals process for pesticides by checking that no unexpected residues are occurring in food.

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[2] Applicable to NI: Technical guidelines on data requirements for setting maximum residue levels, comparability of residue trials and extrapolation of residue data on products from plant and animal origin (SANTE/2019/12752); or applicable to GB: Guidance document on comparability, extrapolation, group tolerances and data requirements for setting MRLs (SANCO 7525/VI/95 Rev. 10.3)

[3] The Organisation for Economic Co-operation and Development (OECD) have developed a MRL calculator with the goal of harmonising the calculation of MRLs across the OECD: OECD Maximum Residue Limit Calculator - OECD

c) check that human dietary intakes of residues in foods are within acceptable levels.

Assessment of human dietary intakes (point c)) are relevant for consideration within this report.

Each year, a programme is drawn up to prioritise the foods under consideration. The plan is risk based and uses evidence in the public domain about the relative significance of the food in the UK diet and known incidence of non-compliance with MRLs, based on various sources, including intelligence from national and international monitoring programmes. The annual proposal is considered and developed by Defra's independent expert committee on pesticide residues in food. Comments are sought from stakeholders via informal liaison.

Each year, the monitoring programme analyses around 3350 samples for >390 different pesticides. The samples are analysed by accredited laboratories (ISO17025) and the residue results are published quarterly, as well as in an annual report. A smaller number of higher risk surveys are published monthly.

When results of the monitoring programme have been confirmed by the laboratories, HSE assesses the risk to consumer health for every sample that contains a residue at any level. Most consumer intake assessments are for short-term (acute) exposure rather than long-term (chronic) exposure. This is because the monitoring data generally shows the majority of samples contain residues below RL and so chronic exposure would not present a concern.

NB: Residues below the RL are also not screened for acute risk. The RL is generally sufficiently low enough to ensure that any acute (or chronic) risk could be identified for the active substances or metabolites included in the monitoring programme.

Description of uncertainties

There are some uncertainties common to both the UK chronic exposure model and the EFSA PRIMo model. Where an uncertainty relates only to one of the models used, this will be described under the separate sub-headings below.

Uncertainties common to both UK and EFSA models

Both models used for chronic risk assessment are deterministic; as such, they can only take limited account of variability. They use fixed values for toxicity (hazard) and exposure, producing a single measure of risk; they do not allow a prediction of the level of protection, e.g.., estimating how often a percentage of the population that exceeds a regulatory trigger will occur. Any uncertain or variable factors are fixed to worst-case values or dealt with subjectively using expert judgement. If probabilistic methods of risk assessment were used, these could take account of the variability and uncertainty that exists in the real-world situations, and potentially provide an improved basis for decision making. However, further work is needed to develop and implement probabilistic models, and these are not currently available.

The measured level of a pesticide or metabolite in a food commodity can be below the LOD or the LOQ. The data requirements (Reg. 283/2013) state that an LOQ shall be determined and reported for each analyte for the analytical methods used for risk assessment, whereas there is no legal requirement to specify the LOD. If the

concentration is >LOD but <LOQ, then the sample is positive but cannot be reliably quantified. Where the concentration is determined to be <LOQ, then the output is assumed to be at the LOQ for the purpose of chronic risk assessment.

This is likely to result in an overestimation of the exposure but is considered to be acceptable as a conservative approach to show that there will be no risk to consumers. The use of the LOQ in chronic risk assessment is considered justified, as HSE does not have robust information about authorisations in other countries which give rise to residues below the LOQ. Where an MRL is set at the LOQ, it does not necessarily mean there are no authorised uses of that pesticide on that commodity; an MRL could be set at the default LOQ (0.01 mg/kg) where there are no authorised uses, or where the authorised use leads to residues below the LOQ; hence, while assuming residues are at the LOQ is likely to overestimate the exposure, disregarding the LOQ values in the overall chronic exposure could underestimate the exposure, i.e., where a residue is present in the food above the LOD but below the LOQ.

The method of gathering consumption data can result in uncertainties relating to the representativeness of the data set, i.e., where some foods have very low numbers of consumers recorded. In this situation, as part of both the pre-registration assessment and in the monitoring programme, it is common to use a surrogate food which would be considered to have a similar range of consumers and would be consumed in a similar portion size and manner (e.g., potato may be used as a surrogate for yam due to a low number of consumers in some sub-groups for yam). A judgement on the suitability of a surrogate food would be based on literature, or through consultation with FSA.

Similarly, extrapolation between crops with similar growing practices, pest problems, and morphology can be conducted. Field trial residue data from one or several representative commodities can be extrapolated to related commodities in the same commodity group or subgroup for which trials have not been conducted. Specific extrapolations are allowed, based on the extrapolation guidelines (SANTE/2019/12752, relevant to NI, or SANCO 7525/VI/95 Rev. 10.3, relevant to GB). Where a surrogate food group or extrapolation has been used, this would be recorded within the assessment, and additional uncertainty factors would usually not be required.

For the assessment of chronic risk as part of the pre-registration process, or when using data derived from the monitoring programme, there can sometimes be small sample sizes; typically, only four residues trials are required to support an authorisation for use on a minor crop, and only eight trials for a major crop. In the monitoring programme, the number of samples analysed per quarter can sometimes be <10. This could mean that the data do not show the full range of possible residue values to which a consumer may be exposed.

For some calculations, default factors such as variability, conversion, or processing factors are used to refine the risk assessment. As these are default factors and not always specific to the active substance (or metabolite(s) where relevant) or crop, this can add to uncertainty in the calculation.

Neither the FSA nor the EFSA models can account for case-specific non-standard uncertainties. These can arise due to the available data being substandard, such as not being generated in accordance with the appropriate guidance documents, not having robust processing or conversion factors, or where analytical methods used to determine the residue present have not been fully validated for all components of the defined marker residue. The impact of the non-standard uncertainties on the outcome of the chronic exposure assessment must be assessed, usually by 'expert judgement', on the case-specific scenario.

The current procedure for conducting chronic risk assessment for pre-registration data does not routinely account for exposure to low levels of chemical mixtures which could cause adverse effects due to additive or synergistic interactions; the potential for interaction or toxic effects of different substances in combination is not regularly addressed by the standard single substance assessment approach. However, for products containing more than one active substance which are known to have a similar mode of action or target organ, a basic combined risk assessment is undertaken. There is limited understanding of human exposure to low levels and mixtures of chemicals; as such, the exposure is routinely calculated separately for each active substance. An exception to this is the risk assessment undertaken as part of the monitoring programme, where both chronic and acute combined risk assessments can be undertaken on a case-by-case basis for specific groups of active substances found in combination in a sample where there are known additive or synergistic effects.

The chronic assessment in the UK also does not account for 'aggregated risk', the risk to an individual or population group who may come into contact with a chemical from multiple sources. This could be a result of exposure of operators or by-standers during the application of a pesticide, plus any potential exposure from the consumption of the active substance (or metabolite) residues in foods.

UK chronic risk assessment model

In the UK model, some uncertainty comes from the consumption data used. The consumption data currently used are relatively old and may not account for changes to consumer habits, diets, and typical bodyweights. Detailed consumption data are not available in the UK model for all food products included in the current version of the food classification used to set MRLs for pesticides under Regulation (EC) No 396/2005 (Part 1 of the GB MRL statutory register or for the EU, Part A and B of Annex I to this regulation), including some commonly eaten and readily available foods. Where a food product is not included, it may be reasonable to use a surrogate.

It is noted that more modern consumption data are available in the form of NDNS survey data; however, at this time, the necessary steps have not been undertaken to allow incorporation of these data into the UK models.

Although refinement of consumption data is possible, it can be difficult to make meaningful refinements to the exposure assessment due to a lack of detailed consumption data, specifically considering commodities commonly consumed after processing, i.e., consumption data for raw vs. cooked foods, such as tomato, cauliflower, or carrot.

EFSA PRIMo model

Food consumption data used in the EFSA PRIMo are not fully comparable to those used in the UK model. This is due to significant differences in the design of the surveys submitted by different EU Member States when compiling the data. Differences in the statistical analyses of the consumption data, e.g., the methods used for calculation of mean or high percentile consumption, are also not standardised throughout the different surveys. This is one reason why EFSA plan to only use data from their comprehensive food database when revision 4 of the EFSA PRIMo model is developed; all survey data from all Member States will have to meet certain requirements, which will reduce some of these uncertainties.

Pros and cons of the model

Pros

The models are straightforward to use, they are not resource intensive, and they provide simple, conservative calculations which give a clear indication of whether a pesticide use will lead to an unacceptable risk to consumers.

Cons

Consumption data are not available for all food products listed in the EU food classification used for pesticides (Part A of Annex I of Regulation (EC) No 396/2005).

No detailed consumption data are available for minor food products listed in Part B of the EU food classification used for setting MRLs for pesticides.

The models do not allow for a more refined probabilistic approach to risk assessment which may be more reflective of real life.

Other international approaches

JMPR approach

The Joint FAO/WHO Meeting on Pesticide Residues (JMPR) approach to chronic risk assessment combines available residue data with cultural dietary information to estimate potential residue intake by consumers. The consumer is considered to be adequately protected when estimated dietary intake (EDI) of pesticide residues does not exceed the ADI; however, percentages above 100% of the ADI are not necessarily interpreted as giving rise to a health concern, due to the conservative assumptions of assessments.

The JMPR model (Version 4, 2019) is a deterministic model which incorporates 17 cluster diets. These cluster diets are based on food balance sheets and CODEX commodity codes and are designed to cover regions with similar dietary patterns from around the world. For information, the UK comes under the cluster G07, along with 9 other countries. The GEMs (global environmental monitoring and assessment programme) cluster diets relevant to EU countries are also included in the EFSA PRIMo model. The default adult bodyweights used in the IEDI calculations are 55 kg for cluster G09 and 60 kg for all others.

Long term dietary intakes are calculated by multiplying the residue concentrations (STMRs, STMR-Ps (STMR-processed commodities)) by the average daily per capita consumption estimated for each commodity, based on the GEMS/Food diets, and summing the intakes for each food; see figure 6.

Figure 6: JMPR approach to chronic risk assessment

$$IEDI = \sum (STMR_i \times F_i)$$

Where:

F_i = GEMS/Food regional consumption of food commodity i

Based on mean per capita intake from food balance (e.g., production minus exports plus imports).

$STMR_i$ (or STMR-P_i) = STMR (or STMR-P) for food commodity i

Using the JMPR approach, when the pesticide is also used as a veterinary medicine, and MRLs are established for animal commodities, the residues from use as a veterinary medicine should also be accounted for in the IEDI calculation.

The JMPR model is used for:

- Assessment of specific substances where there is a potential public health concern.
- Periodic review of pesticide active substance data and current MRLs.
- Assessment of potential exposure when setting new MRLs.

The JMPR can only evaluate data relating to uses that are already registered in at least one CODEX Member State.

Like the UK chronic exposure model and the EFSA PRIMo rev. 3.1 model, the JMPR approach shares the same common uncertainties, i.e., the model is deterministic, residues determined to be >LOD but <LOQ are assumed to be at the LOQ for the purpose of the calculation*, there can be limitations in the data, such as low number of consumers included in a survey, or small sample sizes, and the model cannot easily account for combined or aggregate risk (see section ‘Description of Uncertainties’, above, for further description). In addition, the JMPR approach comes with its own uncertainties.

* An exception to this is where there is evidence that there is a zero residue situation; in this case they will include zero in the calculation. JMPR only assesses exposure from the uses it has considered and recommended MRLs for; hence, if it has not recommended a CODEX Limit (CXL) then there is no automatic MRL for all other crops at the LOQ.

The model does not contain accurate information on the consumption of processed vs unprocessed foods, making any additional refinement difficult.

The model uses the GEMs cluster diets, in which the food available per capita in a country is estimated from trade balance sheets (i.e., food produced, imported, and exported). Specifically for the chronic model, only data from the GEMs cluster diets are included. These cluster diets do not give details on which population groups are consuming the food, particularly children, which are often the critical groups for exposure owing to their high consumption relative to their body weight. As such, it is not suitable for estimating children's exposure, or for assessing less than lifetime dietary exposure.

EU monitoring/EFSA – Chronic risk assessment

NB: The following chronic risk assessment scenario is discussed as it is relevant to the GB and Northern Ireland (NI) monitoring programme, which is obliged by Art. 32 of Regulation 396/2005 to conduct and publish an Annual Report on pesticide residues, including information on the analysis of chronic and acute risks to the health of consumers from pesticide residues.

Previously, the UK monitoring programme has not had to publish its own annual report, as it was part of the EU programme, and as such has not had to consider chronic exposure in the same depth as that which is covered by the EU; however, since the UK left the EU, this will be a requirement, and as such it is relevant to consider how EFSA have conducted chronic risk assessments to understand if a similar approach should be undertaken by GB and NI.

Like the GB and NI monitoring programme, there is an EU-coordinated programme (EUCP) examining pesticide residue levels in foods on the European market, in accordance with Regulation (EC) No 396/2005. To fulfil the requirement of Art. 32 of this Regulation, EFSA publishes its annual report based on data from the official national control activities carried out by EU Member States.

In the recently published annual report (EFSA, 2021), EFSA estimated the chronic exposure to pesticides for which residue concentrations were reported for all food products, using the PRIMo rev. 3.1 model.

The purpose of the chronic exposure assessment was to estimate the dietary exposure to pesticides from food over a long timeframe, with the aim of predicting lifetime exposure to pesticide residues in the diet. The calculation was based on a deterministic approach developed by JMPR (FAO, 2017), where the mean measured pesticide concentration is multiplied by the mean commodity's daily intake consumption per capita and the results for all commodities are summed within a particular dietary plan.

Three scenarios were calculated:

- The lower bound scenario, which assumes that if the residue is not quantifiable, it is not present in the food product analysed.
- The adjusted middle bound scenario, which assumes that even if not quantified, residues are present at the level of half the LOQ.
- The adjusted upper bound scenario, which assumes that even if not quantified, residues are present at the level of LOQ (for all pesticide/commodity combinations for which residues >LOQ were found in at least one sample).

Several assumptions including, but not limited to, availability of consumption data, validated LOQs of the relevant methods and residues being reported in accordance with the RD-Enf were considered by EFSA when conducting the chronic risk assessment; please refer to the 2019 EU report on pesticide residues in food (EFSA, 2021) for full details.

Veterinary Medicines – VMD

General overview

Dietary exposure assessments in the context of veterinary medicinal products (VMPs) are only conducted for the purpose of establishing MRLs for pharmacologically active substances used in VMPs for food producing species (i.e., animals raised and kept for food production). The data requirements are described in Commission Regulation (EU) 2018/782, which establishes the methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC) No 470/2009. The approach described in this Regulation is used for chronic dietary exposure only, as currently, acute exposure is not considered when establishing MRLs for VMPs in the UK.

The TMDI approach is the usual dietary exposure calculation method used by the VMD. This methodology would fit somewhere in between Tiers 1 and 2 of the r tiered approach to dietary risk assessment, as presented in Figure 1. A standard food basket is used as a model for the food consumption of a 60 kg adult, with MRLs expressed as residue concentration in those food items included in the food basket (see detailed explanation below). The individual food item TMDI is calculated for all edible tissues and commodities which have an assigned MRL, and all these individual TMDIs are then summed. The resultant total TMDI for all edible tissues and commodities must not exceed the ADI. Otherwise, lower MRLs need to be established.

MRL applications usually focus on edible tissues (i.e., muscle, fat, liver, and kidney); however, potential uses in the commodities milk, eggs, and honey, are also considered. Since it is not possible to predict with certainty the future use of a substance in other food-producing species, and with a view to increasing availability of VMPs as a general principle, it is considered that unless MRLs are proposed in all food commodities included in the standard food basket, an adequate portion of the ADI shall remain unused (i.e., it is left for use for the other commodities, should it be necessary in the future).

In the case of active substances also used as plant protection products (PPPs/pesticides), a guidance figure for the portion of the ADI that may be reserved for VMP use is 45%. Where the existing PPP authorisation allows, and sufficient data are available on intake from PPP use, it may be possible to allocate a larger portion to VMP use without exceeding the ADI. In order to identify the proportion of the ADI that is available for VMP use, the MRLs approved for the PPP use are taken into account.

For substances used as biocides in animal husbandry, the Committee for Veterinary Medicinal Products (CVMP) 'Guideline on risk characterisation and assessment of maximum residue limits (MRLs) for biocides' (CVMP, 2015) is followed. A stepwise procedure is used to determine whether an MRL assessment is required. If the estimated exposure of an animal (summed over all routes: oral, dermal, and inhalation) exceeds the trigger value of 4 µg/kg bw, established by the EU Biocides Technical Meeting, then a more detailed consideration of the potential for residues in edible products is required, and an estimation of a worst-case consumer exposure (WCCE) is undertaken and compared to the ADI. The WCCE uses worst case assumptions of the internal dose received by the animal and combines them with the standard food

basket. If it is indicated that exposure reduction measures are needed to ensure that consumer exposure remains below the ADI, then a formal MRL procedure is triggered. However, as is the case in most instances, if the total exposure is below the trigger value, or if the WCCE demonstrates that exposure reduction measures are clearly not needed to keep consumer exposure below the ADI, then there will be no need for an MRL evaluation. No biocide-specific MRLs have yet been established, either in the EU or in the UK.

A 'No MRL required' classification may be recommended in those cases where the establishment of numerical MRLs is not necessary for the protection of the consumer. In such cases, it is concluded that consumer exposure to residues will always remain at safe levels, i.e., <ADI or other alternative HBGV h (e.g., tolerable daily intakes or recommended daily allowances). Similarly, substances (most often excipients) that are demonstrated to have no pharmacological activity at the dose given to the animal(s) being treated are regarded as being out of scope of the MRL legislation, and therefore an MRL evaluation is not considered to be needed for these substances (although data are required to confirm a lack of pharmacological activity, and a regulatory procedure has been established for this). In cases where numerical MRLs are not required, dietary exposure can still be calculated using the standard food basket and a realistic worst-case estimation of the levels of residues in edible tissues/commodities after the use of a product following the recommended dosing regimen.

Diet/consumption data

It is assumed that the consumer will eat a standard food basket of animal-derived products every day. The standard food basket represents the (conservatively estimated) consumption of a 60 kg adult, which is the only age group considered when carrying out the chronic dietary exposure assessment. This standard food basket is shown in the table below:

Table 2: The standard food basket for VMPs

Mammals		**Poultry**		**Fish**		**Bees**	
Muscle	300 g	Muscle	300 g	Muscle and skin in natural proportions	300 g	Honey	20 g**
Fat	50 g*	Fat and skin in natural proportions	90 g				
Liver	100 g	Liver	100 g				
Kidney	50 g	Kidney	10 g				
Milk	1 500 ml	Eggs	100 g				
*Fat and skin in natural proportions for pigs. **JECFA[4] uses 50 g.							

MRLs are proposed for the relevant edible tissues and/or commodities, considering the proposed use of the substance that is being evaluated. For the edible tissues, it is

[4] Joint FAO/WHO Expert Committee on Food Additives

assumed that only one of the major groups is consumed per day (i.e., mammal, fish, or poultry; not all three).

Occurrence data

The levels of residues used in the risk characterisation are the MRLs for each of the different tissues/commodities.

Although the VMD administrates a residues control programme for residues of veterinary drugs in products of animal origin (POAO), the data acquired do not feed back into risk assessments, other than where there are large exceedances of the authorised MRLs, and in these cases, FSA is the responsible authority.

Theoretical Maximum Daily Intake

The TMDI is calculated using the standard food basket shown above and assumes that residues are present in all food commodities at the respective MRLs. The calculation usually includes factors to convert the concentration of residues found in the depletion studies (marker residue) to total residue concentrations (i.e., all residues, including the parent molecule and all metabolites). This is done by assigning a marker residue, which is usually the parent compound and/or one of its metabolites, and a ratio between this marker residue and the total residue. The total TMDI is calculated by summing the separate TMDIs for each tissue, which are obtained using the following equation:

$$\text{Amount per edible tissue or product} = \frac{\text{Proposed MRL} \times \text{Daily consumption}}{\text{Ratio of the marker to total residue}}$$

If the total TMDI is higher than the ADI (or the portion of the ADI reserved for veterinary use) for the substance, then lower MRLs need to be proposed, such that the total TMDI is <ADI.

Description of uncertainties

Given that neither the consumption figures nor the residue concentration values are a result of direct measurements, the uncertainty associated with this methodology comes from lack of data sampling rather than from variability in the data, or generated by the analytical methodologies, sampling techniques or population surveys. Therefore, uncertainty cannot be characterised.

In the case of dietary intake, the standard food basket is likely an overestimation of what an adult person will eat every day, although high-end consumers of a particular food item, certain age groups (e.g., infants), or consumers of edible tissues/commodities that are consumed less by the general UK population (and therefore no MRLs are established), may have their exposure underestimated using this calculation.

With regard to residue concentrations in food, the use of MRLs as the exposure level is an overestimation of the chronic dietary exposure, given that food derived from animals will generally have residue levels which are well below the established MRLs.

It is considered that, even if uncertainty cannot be characterised, in general, the TMDI approach will overestimate the dietary exposure to residues from veterinary medicines in most subpopulations, and thus be protective of the whole population.

It should be noted that there is no need to refine the dietary exposure assessment at the point of setting MRLs, as when authorising VMPs for use in food-producing species, withdrawal periods (the time between the final treatment and the day of slaughter or collection of milk/eggs/honey) are established that ensure all residues are <MRLs.

Pros and cons of the model

Pros:

The most obvious benefit of using the TMDI method is its simplicity, as no further calculations are needed for the dietary consumption figures, nor the occurrence of residues in food.

As mentioned earlier, the TMDI will generally overestimate the dietary exposure; therefore, this method is useful to estimate the worst-case dietary exposure, thus guaranteeing consumer safety with a wide margin of safety when establishing MRLs. This overestimation also enables its use as a screening methodology in a tiered approach.

Cons:

The standard food basket does not represent the real consumption as accurately as other models, usually resulting in an overestimation of the dietary intake. However, as explained above, consumers with unusual dietary habits may be under-represented with this method.

Only muscle, liver, kidney, fat, milk, eggs, and honey are considered when establishing MRLs for substances used in veterinary medicine. Other edible tissues (such as lungs or intestines) are not considered with this methodology, and minorities consuming these commodities are not represented in the exposure calculation.

Other international approaches

The Joint FAO/WHO Expert Committee on Food Additives (JECFA), which provides recommendations for MRLs to CODEX, has adopted two dietary exposure calculation approaches based on a standard food basket containing specific quantities of muscle, liver, kidney, fat, eggs, milk, and honey; the TMDI described above, and the Estimated Dietary Intake (EDI).

In addition, two new approaches to dietary exposure calculation, using actual food consumption data, the Global Estimate of Chronic Dietary Exposure (GECDE) and the Global Estimate of Acute Dietary Exposure (GEADE), have been proposed recently and are starting to be used for exposure calculations when deriving new MRLs. The GECDE is explained below; acute dietary exposure is not considered under the remit of this project.

JECFA also considers that when there are no detectable residues in a particular tissue in the depletion studies at the timepoint on the depletion curve corresponding to the MRL recommendations, the guidance MRLs (based on 2 x LOQ) should not be included in the total TMDI calculation.

JECFA uses 60 kg as the bodyweight for an adult, 15 kg as the bodyweight for a child, and 5 kg as the bodyweight for an infant.

EDI: The calculation is essentially the same as that used for the TMDI, except that the median residue concentration at the timepoint that was used to derive the MRL is used in the calculation, instead of the MRL itself. JECFA considers that the median residue is more representative of potential exposure than the upper limit represented by the MRL. This method can only be used where there are sufficient residue data for all food basket items at the timepoint associated with the MRL to provide median concentrations to use in the calculation.

GECDE: The GECDE assumes that, in the longer term, an individual would be a high-level consumer of only one category of food and that their consumption of other foods containing the residue would remain at the population average (total population). Therefore, the GECDE uses two different types of consumption data, combined with median occurrence data, to estimate chronic dietary exposure.

Firstly, the highest exposure from all the relevant foods at the 97.5th percentile of consumption is selected. This value is derived from chronic consumers of the food only, rather than from the whole population. The choice of a high percentile, such as the 97.5th, is justified by using a single commodity (instead of two, as for other food chemicals).

Secondly, the mean dietary exposures from all the other relevant foods are then added to estimate total exposure. The mean dietary exposure is derived from the total population; in other words, non-consumers of each food item are included in these calculations.

Food consumption data is estimated through food consumption surveys at an individual, household, or population level, or approximated through food production statistics at the population level only. There are several food consumption databases that can be used for this purpose, such as FAOSTAT, GEMS/Food, CIFOCOss, or GIFT. In addition to the general population and children, dietary exposure of infants can also be estimated.

3. Discussion

Differences in approach and the reasons for them

There are differences in the current approaches to chronic dietary risk assessments undertaken by FSA, HSE, and VMD, as clearly shown in Section 2. The reasons for this are partly historical. The food basket approach used by VMD originated in the early assessments of VMP residues by JECFA in the 1980s (WHO, 1988; 1989). JECFA did not have access to accurate food consumption data, particularly at the international level, considering differences in dietary habits around the world, but aimed to use high consumption figures for each edible product.

JECFA later saw limited consumption data submitted by several countries. These data were not comparable due to differences in the methodologies used; however, JECFA concluded that these data indicated that the consumption figures in the food basket were realistic but conservative (WHO, 1993). JECFA's approach was widely followed by different countries and regions of the world, which has allowed some harmonisation in approach, and in the MRLs set. This approach was seen as sufficiently conservative, and since the aim was to be protective of consumer safety, rather than to accurately assess dietary exposures, there has to date been no move away from this approach by the VMD.

The food basket approach is still used as an initial screening approach by JECFA, which has recently additionally started to use the GECDE and GEADE approaches, using consumption data, as described in Section 2. When establishing MRLs, JECFA still use the EDI approach by preference, and then confirm that the ADI will be unlikely to be exceeded, using the GECDE methodology. MRLs are not adjusted downwards in light of this.

In the case of pesticides, the JMPR has long used average food consumption data generated from food balance sheets, as this was considered the best source of data available to make international comparisons. This was reflected in WHO guidelines on exposure assessment for pesticide residues (WHO, 1989b). These guidelines recommended that, at the national level, the most relevant source of food consumption data should be used. However, they stated that an effort should be made to reflect long-term food consumption habits, and not day-to-day variations, in order to permit a valid comparison to the ADI and, therefore, recommended that average daily food consumption values be used.

These food consumption figures were multiplied by MRLs, in a TMDI approach. In later years, the TMDI approach started to be used primarily as an initial screen, to separate those pesticides for which there are no concerns for long term intake from those which require further consideration. The IEDI approach, or NEDI at the national level, which uses median residue levels from supervised trials, rather than MRL levels, is now largely used by the JMPR (WHO, 1997).

Revised WHO guidelines recommended that exposure assessments conducted at the national level should consider subgroups of the population which may be more susceptible to certain toxic effects, such as children, pregnant women, and the elderly, and that 'authorities may wish to consider possible risks to subgroups of the population

which habitually consume greater quantities of individual foods than are shown on food balance sheets' (WHO, 1997).

While other European countries continued to use mean food consumption figures from dietary surveys, the UK estimated intakes for high level consumers. In the 1990s, it developed the Rees-Day model to share with stakeholders, which would provide rapid, non-resource-intensive estimates of high-level chronic exposure. Example assessments conducted at that time showed the model provided a good estimate of the 97.5th percentile intake, estimated using complete consumption data for each consumer, similar to that currently used by FSA, and described as a more complex deterministic approach in Section 2. Most example estimates fell within 100 - 130% of the intake estimated using the more complex deterministic approach, with the full range being 90 - 180%. The model was published online, making it available to applicants and other stakeholders. It is currently available online at https://www.hse.gov.uk/pesticides/pesticides-registration/data-requirements-handbook/consumer-exposure.htm.

FSA takes a tiered approach to exposure assessment, as described in Section 2. Most assessments are either simple conservative assessments, which are not continued to higher tier assessments due to no concern being identified, or complex deterministic assessments. The latter use Creme Global software. Consumption data from dietary surveys are combined with single values for the concentration of the chemical in each food (usually the mean) to estimate intakes for each consumer in a population group. A distribution of exposures is generated from which statistics such as the mean and 97.5th percentile are extracted. The 97.5th percentile is used to represent high level consumption. Exposure assessments are conducted for different age groups depending on the requirements of the risk assessment, but usually at least for adults and young children. This approach has required investment in the dietary surveys, the development of a recipes database, and the Creme Global software. While these require significant resources, the individual exposure assessments subsequently conducted are not themselves resource intensive. The use of probabilistic modelling is considered on a case-by-case basis, but to date has not been used routinely by FSA in chronic dietary exposure assessment.

One additional difference is that HSE requires the consumption data it uses to be expressed on an RAC basis, since the pesticide residue data used in risk assessments are primarily from RACs, whereas the consumption data the FSA uses are not expressed in this way as the chemical occurrence data being used in the risk assessment are often from foods in a more processed form or from foods that have been prepared for consumption (e.g. in Total Diet Studies). Thus, food consumption data from dietary surveys must be adjusted to RAC equivalents before they can be used by HSE.

Dealing with uncertainties

There is always some uncertainty associated with an exposure assessment, e.g., a shortage of knowledge about specific factors in the exposure assessment. It is important in exposure assessment to distinguish between uncertainty and variability. Variability refers to differences within a population and cannot be reduced, whereas uncertainty refers to a lack of knowledge, which may be reduced by further

investigation. Nonetheless, variability is one of many sources of uncertainty in exposure assessment, as illustrated by several of the factors described below.

How uncertainties can differ at different tier levels

The type and complexity of the exposure assessment that is performed will determine the amount of uncertainty that occurs in the model. When performing lower-tier assessments (as described in Figure 1), the models will usually include a greater amount of uncertainty, given that the parameters used in the calculations are usually not based on sampling techniques, and therefore their variability cannot be estimated. For example, using an MRL as a chemical concentration value, or using a standard food basket as a surrogate for the dietary consumption figures, does not provide any information on how these parameters are distributed in the population. Therefore, their variability cannot be estimated or accounted for, leading to higher uncertainty in the model. By way of accounting for such uncertainty when performing lower tier assessments, uncertainty factors may be considered, or, as seen in the approach taken by the VMD when assessing consumer exposure to VMPs, conservative assumptions may be made with regard to setting (default) values used for consumption inputs (for example, with the standard food basket) and/or with regard to the potential residue levels present in the commodity (such as by assuming the MRLs are reached). Such assumptions ensure that subsequent exposure calculations represent a worst-case scenario and ensure the safety of consumers.

On the other end of the spectrum, when performing more complex dietary exposure assessments at higher-tier levels (e.g., probabilistic modelling), the variability in the data can be estimated and quantified, thereby reducing the uncertainty of the model. The uncertainty can be eliminated by performing direct measurements or using biomonitoring techniques for very specific risk assessments. The use of uncertainty factors in these cases may not be required, or if it is, these factors can be quantified using the estimated variability in the data.

Given that lower-tier assessments usually require fewer resources to be performed, these can be used as screening tools, even though they will provide less accurate results. If needed, the calculations can then be refined and uncertainty reduced by moving onto a higher tier, or by collecting higher-quality data with more sensitive methodologies. In any case, a description and, if possible, an estimation of the uncertainty of the model used should always be performed, as this can inform the risk manager whether to expend more resources to perform higher tier assessments.

Uncertainty from food consumption information

Misreporting (under-reporting is more common than over-reporting) is a well-recognised problem common to all dietary surveys. There are two aspects to misreporting, the 'observation' effect, whereby survey participants change their eating habits as a result of being asked to report their consumption, e.g., to make recording simpler, and the 'reporting' effect, whereby survey participants misreport what they actually eat. This predominantly leads to under-reporting. There is evidence that under-reporting is selective; fatty, sugary, and snack foods, and alcohol are more likely to be under-reported than are other foods, such as fruit and vegetables (DH and FSA, 2012). Foods eaten outside the home may also be subject to more under-reporting, particularly in surveys like NDNS that use a record-based methodology.

Low response rates can lead to biased data sets, as some population sub-groups may be under-represented. The age of the dietary survey data also affects the level of uncertainty around the estimates, as consumption patterns change over time.

The precision of exposure estimates is affected by the length of dietary data collection as well as the methodology used for the collection of data. Older NDNS surveys conducted for adults prior to the rolling program were carried out over 7-day periods using a weighed diary method. The data collection period used was reduced to 4 days when FSA moved towards a rolling program for collecting dietary information; this reduction is associated with a potential for underestimation of the proportion of the population who are consumers, which in turn could result in the overestimation of consumption by consumers on a long-term basis.

Since 2021, 'Intake 24' has been used for collecting NDNS data; it is a 24-hour recall method. Participants are asked to complete 4 time-spaced recalls within 3-5 weeks, using an online platform rather than the 4-day written diary entries. This shift in approach was adopted as a basis for ameliorating the uncertainties linked to the burden on respondents completing written diaries, thereby improving response rates for the survey. However, the change from a written diary method to a 24-hour recall approach is expected to result in uncertainties and challenges in interpreting trends over time.

Uncertainty from the chemical analysis of foods

Sources of analytical or occurrence data used can vary. Uncertainty in the analytical measurement is routinely characterised by laboratory performance data. Food analysis laboratories often use proficiency schemes such as FAPAS (Food Analysis Performance Assessment Scheme) to demonstrate that they are able to measure an analyte in a standardised reference material to acceptable standards. Sampling uncertainty can arise from differences in levels of a chemical within and between different batches of a foodstuff. The number of samples needed to represent the population being tested is often an important consideration.

Effects of food processing on the level or nature of chemicals in food is another source of uncertainty. Whilst it is well-established that some contaminants are generated during food processing and cooking (e.g., acrylamide, heterocyclic amines, ethylcarbamate), there is currently no clear picture of the factors that influence whether processes such as cooking will change the level or nature of other chemicals of interest in food. Chemical analysis of cooked food is sometimes problematic, and acceptable validated methods may not exist for foods in this state. Analysing cooked food also may not meet other requirements of food chemical surveys, such as the assessment of compliance with legislative levels (MRLs, CXLs, etc.) at the point of sale to the consumer.

For HSE's consumer risk assessment for pesticide residues, potential residues in processed foods and the impact on consumer intakes is an area of uncertainty, particularly where data (either processing data or consumption data) are limited. HSE currently undertakes the majority of risk assessment based on residues in the RAC; however, for some foodstuffs, these are never consumed as the RAC, and are only consumed following some form of processing. As such, it can be useful to have

additional information on the nature and magnitude of residue in a processed commodity.

There are specific data requirements which may need to be addressed, either for the approval of a pesticide active substance or authorisation of a PPP, which are intended to provide information on the nature and magnitude of a pesticide and/or its metabolites and to allow derivation of processing factors (Pfs). Pfs can be used to refine the consumer risk assessment, or to make an estimation of the level of pesticide in the RAC, based on the measured amount of a chemical in a processed food. Representative procedures of pasteurisation, baking, boiling, brewing, and sterilisation can be used to indicate the nature of the residue that is expected in a processed commodity.

Even where data are available, there can still be uncertainty; Pfs are active substance specific and both nature and magnitude studies will not cover all scenarios. Sometimes, despite data being available, they cannot always be used by HSE, as the current UK chronic risk assessment model does not contain consumption data for all types of processed commodity, or the data may be based on only a small number of consumers, and as such could be unreliable to represent a wider population. Therefore, HSE tend to use consumption data for the RAC and apply a processing factor.

Uncertainty from the methodology used to calculate the exposure estimate

Within the general framework of chemical risk assessment, a challenging step in dietary exposure assessment is the handling of concentration data reported to be below the LOD. These data are known as non-detects and the resulting distribution of occurrence values is left-censored. The difficulties associated with handling left-censored data were recognised by EFSA (EFSA, 2010). EFSA has so far treated left-censored data with widely used substitution methods, which are also used by the UK Government Departments. The appropriateness of this approach has a natural limitation in the computation of percentiles and in the application of statistical techniques. EFSA considered the accuracy of the methods currently used and proposed recommendations for more advanced alternative statistical approaches (EFSA, 2010).

In some estimates of exposure, a single assumed bodyweight is used, e.g., 60 kg. This introduces a large source of uncertainty, although erring on the precautionary side if actual body weights are higher. However, where consumption data are derived from dietary surveillance, the individuals' measured bodyweight can be used in the exposure assessment.

Uncertainty introduced by brand loyalty is more difficult to reduce, except where reliable market share data are available; these can potentially be used to augment probabilistic models.

The choice of model, the underlying data, and assumptions made about missing or incomplete data all contribute to uncertainty. As these factors rely on expert judgement, the experience and subjectivity of the individual conducting the assessment can also affect uncertainty in the exposure estimate, although this

uncertainty may be reduced by having a peer-review process (either formal or informal) in place.

Modelling exposure to food chemicals can lead to predictions that involve more uncertainty than assessments based on direct measurement, e.g., using biomarkers. However, reliable biomarkers are not available for all food chemicals of interest and their use tends to be expensive. Where direct measurement is used, it can provide a valuable way of validating exposure models.

Before action can be taken to reduce the effects of these sources of uncertainty, they need first to be quantified and then prioritised. This is required to ensure that resources are directed at reducing relatively large sources of uncertainty before lesser sources are tackled.

Consideration of a possible common approach in the future

At present, each organisation conducts chronic risk assessments mostly independently, using differing methodologies. These different approaches have evolved based on the legislative data requirements applicable to the chemical of interest, and for historic reasons within each department. However, each organisation has a shared common goal, to be protective of consumers.

As discussed in earlier sections, each organisation conducts risk assessment at different levels of the tiered approach, outlined in Figure 1, to suit the needs of the legislative requirements for that area. The level of the tiered approach, at which a risk assessment is conducted, is dependent on several factors, including but not limited to, the reason for the risk assessment being undertaken (hazard/risk potential), the regulatory requirements and associated guidance, the level of protection required, and the consumption or occurrence data available to each organisation.

As an example, HSE currently conducts risk assessment at Tier 2 for the purpose of active substance approval, MRL setting, and product authorisation assessments for pesticides. This works within the regulatory framework for pesticides where model diets based on NDNS/DNSIYC survey data are available and measured levels of residues in a food item, based on residues field trials, must be submitted by stakeholders.

Additional steps up the 'tiers' to refine the risk assessment are not routinely undertaken for pesticides. The risk assessment work undertaken as part of the residues monitoring programme, could be considered to be at Tier 3, as monitoring data are used to provide a more 'real world' estimate of exposure, based on measured residue levels found in the food available on the market. In addition, for some food commodities, more refined consumption data or calculation parameters (e.g., variability factors (VFs) or processing factors (Pfs), etc.) are considered.

For FSA, most assessments are simple conservative assessments, where no concern is identified; however, additional steps up the tiers can be taken to refine the risk assessment via complex deterministic assessments using the Creme Global software.

For VMD, assessment of chronic dietary exposure is dealt with exclusively in establishing MRLs, using a standard food basket and the TMDI approach. This

approach generally fits somewhere between Tiers 1 and 2 of the exposure characterisation process, as presented in Figure 1.

As we move towards the future, it is relevant to consider if or how we can work to develop common approaches for chronic risk assessment across the organisations, to provide consistency and transparency in the process; this consideration forms one of the purposes of this working group and report.

Some key areas have been identified for further discussion:

- The use of one shared food consumption database which can be utilised by all organisations.
- The use of the same consumer groups within the risk assessment (i.e., infant, toddler, adult groups etc).
- The potential to have a shared model capable of performing chronic exposure assessment calculations suitable for all organisations.
- A shared guidance on how chronic intake assessments are conducted.
- The use of the same active substance endpoints (e.g., toxicological reference values, ADIs, MRLs, and residue definitions).

The latter will be discussed in the next section, where multiple use substances are considered.

Consumption data

Currently, the consumption data used by each organisation differs in several aspects, including but not limited to the age of the data, format (food basket/food as consumed/RAC) and range of commodities considered.

FSA currently holds the most up to date consumption data for UK consumers, based on the latest NDNS/DNSIYC survey data and recipes database. These data cannot automatically be used by VMD and HSE, due to the format in which the data are held within the Creme software. The Creme software holds consumption data for foods directly consumed by individuals, whereas the VMD and HSE need data for the RAC. Recipes and reverse yield factors need to be applied, which is a complex process. However, the development of a tool by which each organisation could access and use recent dietary survey data originating from one source could be a project to investigate further.

Consumer groups

The consumer groups currently used by each organisation differ. These differences are built into the chronic risk assessment models used by each organisation.

VMD currently use a standard food basket approach, representing the (conservatively estimated) consumption of a 60 kg adult, which is the only age group considered.

HSE conduct chronic risk assessment for 10 separate consumer groups, with specified age ranges and mean bodyweights.

FSA have survey data for participants ranging from 4 months to 95 years of age and have flexibility in how critical groups might be considered.

If a project were to be undertaken to move towards a common approach for chronic risk assessment, where each organisation utilises consumption data from one source,

it would make sense to consider the implications of using the same or similar ranges for the consumer groups considered in the risk assessment.

Chronic risk assessment model

There are significant barriers to having the same chronic risk assessment model across organisations, including the current differences in consumption data, consumer groups, calculation methods, and legislative need of each organisation.

Discussion has taken place regarding the use of shared consumption data and the same consumer groups; a natural progression from this would be to consider the opportunity to develop a complex model, capable of performing chronic risk assessment estimations utilising the different calculation methods used by each organisation. This would be a highly aspirational concept and would require significant resource to develop and validate a model that would have the capability to allow both simple and complex modelling (either deterministic or probabilistic) which would suit the needs of each organisation.

Shared guidance

As discussed in Section 1, risk assessment is undertaken at differing levels of cost and complexity, depending on the available data and regulatory need. Chronic risk assessments are unlikely to proceed through the tiers if it can be concluded at an early tier that there is no significant risk to consumers, or reasonable risk management action can be taken to mitigate any risks identified.

A project looking into the development of a shared guidance document, which can be utilised by each organisation, focusing on the tiered approach outlined in Figure 1, could be a worthwhile project to consider in working towards a common approach. The guidance document could discuss scenarios of when or how it would be appropriate to either continue with increasing refinement of the risk assessment, or whether risk management options would be more appropriate.

Any project looking into the development of such guidance would need to consider how the specific legislation for each organisation could be accommodated and have scope for case-by-case deviation from the guidance where this could be justified (or there is industry need).

Possibility of a combined approach for multiple use substances

Some chemicals considered by FSA, HSE and VMD have multiple uses, e.g., iodine, which has uses in biocides, VMPs, and food and feed additives, or copper, which has uses in pesticides, VMPs, and food supplements.

At present, although there is an awareness of these substances and some aspects of joined up working do take place, the different organisations do not regularly work together on the chronic risk assessments for these substances, unless there is a specific concern identified. A brief discussion around the current combined approaches for specific scenarios is given here, along with discussion around potential changes which could be implemented for the future.

Current combined approaches

Pesticides/veterinary medicines

HSE and VMD hold regular liaison meetings which provide an opportunity to discuss new and upcoming guidance documents, any challenges facing each organisation (e.g., regarding legislation) or 'hot topics' within risk assessment which could be relevant to both organisations.

Historically, MRLs for POAO for dual pesticide/veterinary medicine active substances have been set at different levels under the different legislations for pesticide residues and VMPs. As outlined below, steps to resolve this issue have already been implemented.

HSE and VMD share relevant information about current and future assessments of active substances which could have dual pesticide/VMP uses. Sharing this information at an early stage allows any concerns with regards consumer exposure and MRL setting to be considered and, if required, discussion around appropriate endpoints can take place.

Vitamins/food and feed supplements and biocides

Consumer exposure assessments for vitamins/supplements and biocides can overlap between VMD, FSA and HSE. These are all complex areas and risk assessments are undertaken by different organisations for different reasons, led by the circumstances, resulting from the legislative requirements for each organisation.

Biocides cover 22 diverse product types and most authorisations do not lead to residues in food or feed. However, the use patterns of product types 3, 4, 5, 18 and 19 cover disinfectants used for veterinary hygiene, for the disinfection of food and feed areas, for the disinfection of drinking water, and products used for the control of arthropods. All of these can include uses that may lead to residues in food and feed. Furthermore, the use patterns of these can be complex and hence require different approaches to the consumer exposure, including first tier theoretical calculations.

Despite the purpose of risk assessment for each scenario being different, there are opportunities to consider a combined approach using agreed active substance specific endpoints (e.g., toxicological reference values (TRVs), ADIs) within the risk assessment. Furthermore, the three organisations will need to work together, as there is no single regulation that covers setting MRLs for biocides. MRLs for biocides will be established under different legislation depending on the nature of the active substance:

a) MRLs for biocides that are used in animal husbandry should be set under veterinary medicines legislation.
b) MRLs for biocides that are, or have been, plant protection products should be set under the MRL regulation for pesticides.
c) Biocides that may migrate into food/feed from treated packaging should be set under the food contact materials legislation.
d) MRLs for biocides that do not fall under the three criteria above, should be set under the contaminants legislation.

At the time of writing, no MRLs have been set for biocides in GB (or the EU). However, it is clear, based on the range of different biocides, the complex use patterns, and the

different legislation that may be used to set MRLs, that HSE, FSA and VMD will need to consult together on the risk assessments and the setting of MRLs for biocides.

Mechanisms are already in place for discussion between HSE/FSA and HSE/VMD for biocides, with HSE having consulted with FSA on active substance dossiers and products when required.

This is an area in which we would continue to encourage the organisations to work together where there are common sources of exposure, to ensure that endpoints used in the assessment are aligned, where appropriate, and to note these as examples for reference in future assessments.

It should be noted that the process of aligning endpoints may not be straightforward, and could take time to address, due to the legislation under which they have been set. It would be expected that ADIs, Acute Reference Doses (ARfDs), and (marker) residue definitions could be the same; however, should any of these need to be changed under any of the regulatory regimes, a formal assessment would be required; new endpoints cannot just be used in an assessment, they would have to be formally adopted. There is further discussion of TRVs below.

Looking to improve combined approaches

In each of the above scenarios, it is apparent that steps are being taken to start working on combined approaches for multiple use substances, but this is without any specific guidance and is often conducted on an *ad hoc* basis. It is apparent that a big step forward in considering multiple use substances would be the consistent and transparent use of agreed active substance hazard endpoints across all organisations.

Toxicological reference values

In the context of this document, for the purpose of chronic risk assessment for multiple use substances, the collective term toxicological reference value (TRV) is being used to refer to ADIs, upper tolerance limits (UTLs), TTCs or other TRVs relevant to the nature or use of the chemical.

At present, although some substances have multiple uses, the TRV applicable for that substance can differ between the regulatory areas. This results in the chronic risk assessment for different organisations being conducted against different endpoints. This makes it difficult to compare results between organisations and adds a layer of complexity for anyone trying to understand the exposure assessment.

A project which investigates aligning and agreeing a set of TRVs, which could be stored within a central database for use in consumer risk assessment by all organisations, could be a valuable step in ensuring consistency of assessment. It would also provide transparency on the risk assessment for applicants, or others, who are attempting to submit consumer risk assessments as part of regulatory dossiers.

A project looking to align and develop a database for TRVs would need to consider the legislative requirements, i.e., any new TRV would need to be assessed and endorsed under the different regulatory regimes. Establishing new TRVs may take time to coordinate between the agencies, and a move to change endpoints may not be considered a priority.

Additionally, for TRVs to be harmonised, it may be necessary to consider whether the core data requirements of the organisations involved would require alignment so as to enable TRVs to be established based on the same data, and whether such alignment would be possible.

It would need to be considered whether the above points would need to be resolved ahead of a project to develop a database of agreed TRVs, i.e., would it be preferable to have TRVs aligned before a shared database was developed, or is the alignment of TRVs an issue that could be resolved over time and hence mechanisms could be put in place to ensure when delivering decisions, dual uses are taken note of, and ensure there is agreement on common TRVs.

MRLs and residue definitions/marker residues

Alignment of MRLs (in animal produce) for dual use VMP and pesticide active substances would ensure that there is clarity over the applicable MRL, for compliance and enforcement purposes, for that particular substance/commodity combination.

Some steps in improving consistency in this area are already being undertaken for MRLs for substances with dual pesticide/VMP uses. There has been a drive, both in the UK and EU, to ensure that where this is the case, a consideration of consumer intakes originating from both sources can be taken into account.

Now that there is an independent regime for GB MRLs, HSE intend to take into account any VMP MRLs within the consumer risk assessment for MRL setting of dual pesticide/VMPs. VMD already take pesticide uses into account when setting MRLs for VMPs.

It is important to note that for historic cases this approach was not taken and the MRLs set for dual pesticide/VMPs may be different. The alignment of MRLs is likely to take time.

Currently, as an interim approach, if it is identified that either organisation (VMD/HSE) is proposing to set new MRLs for products of animal origin, then a check should be conducted to compare and contrast the current MRLs established under both Regulations with the newly proposed ones; if no consumer risk issues are identified, then the higher MRLs will be recommended, thus aligning the MRLs.

As a longer-term approach, the various points discussed above would need to be resolved, along with any legislative barriers. For this approach to work, it would be necessary for the same residue definition for enforcement (marker residue) to be established, or if this was not agreed, then a simple way of converting measured residues to check compliance with MRLs would be required.

At present, when VMD propose a new MRL for VMP use, a conservative approach is used for the risk assessment whereby 55% of the ADI for the active substance is reserved for the use of a substance as a pesticide. A suggestion to improve and refine this process would be for HSE to provide VMD with specific consumer intake estimates based on the authorised pesticide uses.

Alternatively, if VMD proposes new MRLs for POAO for a dual pesticide/VMP active substance, a process could be established where VMD provide, as a minimum, the proposed MRLs, Highest Residues (HR) and STMRs (residue depletion study data) to

HSE, to assess whether the new MRLs can be adopted using HSE's consumer risk assessment approach. It should be noted that there is a mechanism currently in place that allows HSE and FSA to comment on VMD MRL assessments at the initial assessment stage, via attendance at the monthly Scientific Secretariat (SciSec) meetings held at VMD.

For either option, mechanisms would need to be put in place to allow this to occur consistently, such as specific guidance documents, known contact points within each organisation to allow the discussions to take place and, aspirationally, a shared database of consumption data and agreed TRV endpoints. Even where agreed TRVs are not in place, it would be possible for HSE to provide VMD with exposure assessments for the pesticide uses, which could be added to the exposure scenarios from the VMP uses and compared to an established TRV, and *vice versa*. A problem which would make this more challenging would be where different residue definitions (marker residues) are established across the two regimes, resulting in the exposure assessment being conducted based on different approaches.

As such, it would also be useful to have agreed residue definitions or marker compounds, in much the same way as for TRVs and MRLs, to allow the appropriate analytical determination of residues arising from the use of multiple use substances. Having consistent residue definitions agreed across organisations would ensure that where a risk assessment calculation has been carried out, the appropriate (total) residue has been identified.

Overall, it is considered that to improve consistency and transparency in the risk assessment of multiple use substances, there is a clear need to agree on, and use, the same active substance specific endpoints across organisations.

For this to be possible, it firstly needs to be considered whether, legislatively, a position can be agreed allowing the adoption of the same TRVs and residue definitions for different regulatory regimes; for example, at this time it is not thought to be possible that an assessment undertaken by VMD to establish residue definitions or TRVs could be automatically adopted by HSE, and *vice versa*, due to the differences in the data requirements for the different regimes. As such, it would need to be decided how an active substance could be jointly reviewed and a common set of endpoints established; this should account for the various timelines involved in active substance assessment for each regime (e.g., active substance renewal assessments), which may differ.

If this can be resolved, further work would be required to develop an agreed database of endpoints, and to develop guidance on how chronic risk assessment should be undertaken involving collaborative working across organisations.

Considerations regarding cumulative effects and aggregate exposure

Commission regulation (EU) No. 283/2013, which sets out the data requirements for pesticide active substances[5] states:

[5] As retained EU law relevant to GB and amended by the appropriate statutory instrument (SI) The Plant Protection Products (Miscellaneous Amendments) (EU Exit) Regulations 2019 (legislation.gov.uk)

'Where relevant, the possible presence of pesticide residues arising from sources other than current plant protection uses of active substances (for example use of active substances resulting in common metabolites, use as biocide or veterinary drug), and their aggregate exposure shall be taken into account. In addition, the cumulative exposure to more than one active substance shall, where relevant, be considered.'

Aggregate exposures

Aggregate exposure and risk assessment is considered to be exposure to a single chemical by multiple pathways and routes of exposure, e.g., from consumption of chemicals in food or water in combination with residential or occupational exposure routes.

Aggregate exposure assessments are highly challenging. Other than setting aside a proportion of the ADI when establishing MRLs in veterinary medicine for dual use substances, the UK does not conduct aggregate exposure assessments for pesticides or VMPs. This is not a requirement as, at present, there are no guidelines or suitably validated models available to allow aggregate exposure assessments to be conducted.

Aggregate exposure assessments are an area of pesticide risk assessment which is under regular review within the EU. A notable project in this regard is the EuroMix project (Funded by EU Horizon 2020), which aimed to develop relevant methods and tools for risk assessment for chemical mixtures, including from multiple sources (Kennedy et al., 2019).

At the current time, aggregate exposure assessments are not carried out routinely in the EU, however some Member States have performed dietary mixture exposure assessment using EuroMix data and models, and three case studies addressing multiple exposure routes of bisphenols and pesticides, are planned to be published.[6]

In the USA, the Environmental Protection Agency (EPA) does undertake some level of aggregate exposure assessment within their pesticide regulatory regime. The US EPA General Principles for Performing Aggregate Exposure and Risk Assessments for Pesticides (EPA, 2021) highlights that 'All potential, relevant routes of exposure are analysed within an aggregate exposure assessment. These include the oral, dermal (absorption), and inhalation routes of exposure.' According to the general principles, this is carried out using a combination of data, models, and reasonable judgements, to represent each potentially exposed 'individual' in the population over time.

FSA does on occasion conduct some level of aggregate exposure assessments, e.g. combining exposures from food with water and with those from dust/soil (COT, 2016). These aggregate exposure assessments are only considered on a case-by-case basis, where required.

Cumulative exposures

Cumulative exposures, also referred to as combined exposures, refer to the potential exposure effects from two or more chemicals that may have the same/similar or

[6] The truth about our exposure to chemical cocktails and its impact on our health | EuroMix Project | Results in brief | H2020 | CORDIS | European Commission (europa.eu)

interlinked modes of action. Effects resulting from exposure to multiple chemicals is sometimes termed the 'cocktail effect'.

Cumulative risk assessment requires consideration of complex interacting sets of data which cover toxicology, residues, and risk management issues; it represents another challenging area of risk assessment. Methodologies and research activities developed so far mainly focus on combined exposure to predefined groups of chemicals within a specific regulatory domain (e.g., pesticides, biocides). These often do not cover mixtures of chemicals across different regulatory domains/sectors, nor do they account for all the chemicals humans may be potentially exposed to.

A challenge to doing this, is that for groups of chemicals that have a strong evidence base in terms of hazard and exposure data (e.g., pesticides), it is difficult to combine the information with other risk assessment areas where less information or a more pragmatic approach is recommended, such as the mixture assessment (or allocation) factor (MAF).

Within the UK and EU, there currently are no guidelines, or models, for cumulative exposure assessment, either chronic or acute, to be routinely conducted across any of the regulatory regimes. EFSA are working to develop new approaches and tools for harmonising how risks to humans (and the environment) from combined exposure to multiple chemicals can be assessed. EFSA's scientific committee published a guidance document on methodologies for risk assessment of combined exposure to multiple chemicals in 2019 (EFSA, 2019b).

EFSA held an international workshop in October 2021 on the risk assessment of chemical mixtures[7], following which they finalised and published guidance on the scientific criteria for grouping chemicals into assessment groups for risk assessments, assuming dose addition (EFSA, 2021b).

Chemicals are to be grouped based on a common mode of action (MoA) or Adverse Outcome Pathway (AOP). In cases where the MoA or AOP is unknown, chemicals are to be grouped based on a common adverse outcome, or if that is unknown, a common target organ or system.

In 2019, a Joint FAO/WHO Expert Consultation was held, which proposed an approach to the risk assessment of combined exposure to multiple chemicals. This approach is now being trialled for VMPs and pesticides by JECFA and JMPR (WHO, 2020b; FAO and WHO, 2020). As a pragmatic cut-off, it was proposed that if the estimated dietary exposure for a substance is less than or equal to 10% of its HBGV for all population groups assessed, it does not need to be considered in a risk assessment of combined exposure. If exposure is greater than 10% of its HBGV, then the need to include the substance in a risk assessment of combined exposure to multiple chemicals should be considered.

A weight of evidence approach should be used to determine whether there is evidence for combined effects of the substance with other substances, taking into account structural similarities, modes of action or adverse outcome pathways, and shared

[7] EFSA International Workshop on Risk Assessment of Combined Exposure to Multiple Chemicals | EFSA (europa.eu)

adverse effects. The default assumption should be dose addition, but the possibility of synergistic interactions should be considered on a case-by-case basis. It is anticipated that joint assessments of groups of pesticides and VMPs will be conducted in the future if required.

For pesticide product authorisation, HSE conducts a simple assessment of combined chronic (and acute) exposure where a PPP contains two or more pesticides. The assessment is limited and basic in nature, as it only considers combined exposure where they are approved for use together in the same product; no consideration of cumulative exposure from other scenarios (e.g., tank mixtures) is considered.

Initially, the exposure assessment is carried out on a tier 1 assumption of combined toxicity. Assumed combined toxicity saves resource (initially) and is conservative, and therefore protective of consumers. It allows scope for refinement if there is an indication of potential risk, by determining whether there are true AOPs common to both chemicals which could result in combined/synergistic toxic effects. This requires input from toxicologists. If there is an indication of risk based on a tier 1 assumption of combined toxicity, and it is later confirmed that there are no common adverse effects, then the cumulative risk assessment can be refined.

Cumulative risk assessments are also considered as part of the PRiF monitoring programme. A combined risk assessment is conducted for substances which are known to belong to the same cumulative assessment groups (CAGs), such as triazoles, or AChE inhibitors, where they are detected above the reporting limit within the same sample. The approach to cumulative risk assessment is limited, as it is considered on a single commodity basis. Due to the nature of the PRiF risk assessments, generally only acute risk is considered in the cumulative assessment; however, on a case-by-case basis, where two or more chemicals from the same CAG are found in >50% of samples, combined chronic risk is also considered.

Chronic risk from aggregate and cumulative exposure is an uncertainty at present. This could be considered an area where future research could potentially seek to develop methodologies to address these challenges in chronic risk assessment.

Less than lifetime approach

There has recently been a programme of work to harmonise the approaches of JMPR and JECFA to chronic dietary exposure assessment (Arcella et al., 2019). The JMPR model, which uses per capita estimates of food consumption, was considered to estimate lifetime exposure, whereas the models used by JECFA, which consider exposure separately for children and adults, and for mean and high-level consumers, were considered to estimate less than lifetime exposures. A decision tree was created in order that the appropriate dietary exposure assessment model could be used in risk assessment, depending on the toxicological profile of the chemical.

The approach currently taken by HSE for pesticides, and by FSA for contaminants, would be considered a less than lifetime approach, as it assesses the exposures of different population subgroups and high-level consumers and compares them to the HBGV that has been established to be protective for long-term exposure. In contrast, the current approach used by the VMD does not assess exposures for children, though for adults, the model diet used aims to cover high level consumers.

The Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) has recently produced a set of principles on assessing risks from less than lifetime exposure to carcinogens (COC, 2019), and the COT has also produced a statement on assessing risks from less than lifetime exposure (COT, 2021). The COT preferred the term 'less than lifetime or variable exposure over a lifetime', since for most food chemicals the exposure is not shorter than a lifetime and then ceases, but rather the exposure is over a lifetime but varies over that lifetime, being substantially higher for a certain portion of it.

The COT statement recommends that less than lifetime exposures, or exposures in the window of raised exposure, should initially be compared to a HBGV that has been established to be protective for long-term exposure, which is consistent with the approaches currently undertaken by HSE and FSA. However, if required, it recommends approaches that may be taken to refine the risk assessment in cases where exposure averaged over a time frame relevant to the basis upon which the HBGV is established is less than the HBGV, but shorter-term exposure exceeds it.

For chemicals without established HBGVs, margins of exposure (MOEs) may be calculated. Similarly, calculating the MOE for the less than lifetime exposure or the window of raised exposure, the COT principles, and the COC principles in the case of non-genotoxic carcinogens, recommend considerations that may be applied in refining the risk assessment if this initially calculated MOE is insufficiently large to conclude there is no safety concern. For chemicals which are genotoxic and carcinogenic, the MOE is also initially calculated based on the less than lifetime exposure or exposure in the window of raised exposure, but there are specific considerations for these in the COC principles (COC, 2019).

Acute exposure

The focus of this report is on approaches to chronic dietary exposure assessment. However, FSA and HSE also undertake acute dietary exposure assessments for chemicals for which there is the potential for a single exposure to cause adverse effects. In most cases this involves comparing the estimated exposures to established acute reference doses (ARfDs), while in other cases margins of exposure may be calculated to point of departure relevant to acute exposure in the absence of an established ARfD. Acute dietary exposure assessments are commonly either deterministic assessments, based on high percentiles of residue concentration and high percentiles of consumption, or probabilistic modelling.

VMD does not generally assess acute dietary exposures for VMPs, but this would become of greater importance if a more refined, higher tier approach were to be taken to chronic dietary exposure assessments, such as when considering the potential for VMP residues to cause acute adverse effects in humans, e.g., following ingestion of the injection site. Since the change by JECFA to the GECDE and GEADE approaches to chronic and acute exposure assessments for VMP residues, respectively, JECFA has begun to establish ARfDs for VMPs, and has published guidance on when it is necessary to, and how, to establish ARfDs for VMPs (WHO, 2017).

4. Conclusions and recommendations for future work

Approaches to exposure assessments

FSA, HSE, and VMD have different remits under their respective legislation, and have different expectations for their respective outputs. For example, VMD establishes conservative MRLs for VMP active substances, which are protective of adult high-level consumers of POAOs, but may not, on the face of it, be as protective for, e.g., toddlers/infants. These assessments are considered to be a low tier approach but are not the final level of consumer protection; risk mitigation measures in the form of product- and species- specific withdrawal periods are established when VMPs are authorised. Withdrawal periods are defined as the time that elapses between the final treatment of an animal, and the time when that animal can be slaughtered and enter the human food chain, or commodities such as milk or eggs can be taken for human consumption. This allows time for the animals' normal metabolic processes to break down and eliminate the chemicals of concern before the consumer is exposed. In practice, VMPs are not always given to the animals at a time when they are close to slaughter, or are ready to start producing milk, and so there are multiple factors that reduce the real-world exposure to VMPs. This approach is not possible for either HSE or FSA, since withdrawal periods cannot be established for other types of contaminants in the same way.

For example, when animals consume pesticide residues as part of their feed, they cannot be put on a withdrawal period, as it is unknown at the time of feeding what contaminants are in their feed (and they still need to eat); as such, levels must be controlled at an earlier stage in the process.

Both HSE and FSA use lower tier approaches for screening purposes, and higher tier approaches where more accurate calculations are required. This tiered approach allows for management of resources and focusses on the higher-priority risks.

For all agencies, the priority is the protection of consumers that may be exposed to contaminants in their foods.

Exposure assessments generally should take account of high-level consumers and all subgroups of the population considered relevant from toxicological data that are used to establish the HBGVs, e.g., infants, children, pregnant women, and older adults.

No matter what approach is taken, it should be ensured that conservative assumptions are made so that any potential dietary exposures are not underestimated. Where higher tier approaches are used, it should still be ensured that these do not underestimate high dietary exposures.

Transparency of assessments

For any chemical risk assessment, the key uncertainties in the dietary exposure assessment should be communicated as part of the risk assessment.

Collaboration between agencies

Although each agency has different regulatory remits and different consumer protection goals, there are areas where collaboration could take place. For example, consideration should be given to using a common source of dietary consumption data, and in the longer term, consideration should be given to conducting a single chronic

dietary exposure assessment for chemicals with multiple uses (e.g., those used as both a VMP and a pesticide), covering all sources of dietary exposure, where feasible.

Since assessment groups for combined exposure may cross regulatory boundaries, it is recommended that discussions be held between FSA, HSE and VMD on the methodologies for combined chemical dietary exposure assessment for chronic exposure. Cross-department/agency working may be required on combined risk assessments.

International considerations

In order to trade effectively with other nations and regulatory regions, the UK needs to collaborate with international standard-setting authorities, such as CODEX, to establish internationally recognised safe levels of contaminants in foods and feeds. There is already extensive interaction with standard-setting committees, such as JMPR and JECFA, from all three agencies. It may be appropriate in the future to move towards using the same methodologies as these committees, so that a) we become experts in said methodologies and can use that expertise to influence the recommendations made, and b) make it more likely that UK standards harmonise with international standards.

Future work

The exposure assessment methodologies used in regulatory contexts should be periodically reviewed for fitness for purpose and their uncertainties considered.

There are already nascent collaborations between the Government departments and agencies to consider the establishment of common HBGVs and MRLs, but this could be progressed and be established as routine, and even go further and be established in legislation and/or guidance.

To have sufficient confidence in the consumption data available, progress on acquiring comprehensive, regular, up-to-date consumption data is a priority, alongside the establishment of a more comprehensive commodity list for HSE and review of calculation approaches. In addition, there should be a central database to which all UK regulators have access and thorough training on the use of. This should act to reduce some of the uncertainties inherent in the exposure assessments.

Further research is needed to develop methods to allow chronic risk from aggregate and cumulative exposures to chemicals, or groups of chemicals of concern to be assessed.

Glossary

ACP: Advisory Committee on Pesticides

ACP was the predecessor to the current Expert Committee on Pesticides.

ADI: Acceptable Daily Intake

An estimate of the amount of chemical that can be ingested daily over a lifetime without an appreciable health risk to the consumer. It is applied to residues of pesticides and veterinary drugs, as well as food additives, and is usually expressed on body weight basis (mg/kg bw/day).

Aggregate exposure:

The combined exposure to a single chemical substance across multiple routes (oral, inhalational, dermal) and pathways (food, drinking water) of exposure.

AOP: Adverse Outcome Pathway

A sequence of events, commencing with initial interactions of a stressor with a biomolecule in a target cell or tissue (molecular initiating event), progressing through a dependent series of intermediate events and culminating with an adverse outcome.

ARfD: Acute Reference Dose

BW: Body weight

CAG: Cumulative assessment groups

COC: Committee on Carcinogenicity of Chemicals in Food, Consumer Products, and the Environment

CODEX: Established in 1963 by the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO), the Codex Alimentarius Commission (CAC) is the body responsible for all matters regarding the implementation of the Joint FAO/WHO Food Standards Programme.

COT: Committee on Toxicity of Chemicals in Food, Consumer Products, and the Environment

Cumulative exposure:

Cumulative exposures, also referred to as combined exposures, refer to the potential exposure effects from two or more chemicals that may have the same/similar or interlinked modes of action.

CVMP: Committee for Medicinal Products for Veterinary Use; A committee of the European Medicines Agency (EMA)

CXL: CODEX limit

DH: Department of Health

The Department of health (DH) has since become the Department of Health and Social Care (DHSC), Jan 2018.

DNSIYC: Diet and Nutrition Survey for Infants and Young Children

The DNSIYC survey was commissioned by the Department of Health (DH) and the Food Standards Agency (FSA) in 2011 to provide detailed information on the food consumption, nutrient intakes and nutritional status of infants and young children aged 4 up to 18 months living in private households in the UK.

Dual (or multiple) use substance:

A substance that could be used in multiple regulatory areas, e.g., some pesticides can also be used as veterinary medicines.

Deterministic:

if something is deterministic, you have all the data necessary to predict (determine) the outcome with 100% certainty. The process of calculating the output is called a deterministic process or procedure.

ECP: Expert Committee on Pesticides

EDI: Estimated Dietary Intake

The estimated amount of a substance ingested by a person as part of their diet (via food, water, beverages, and supplements)

EFS: Expenditure and Food Survey

EFSA: European Food Safety Authority

EPA: Environmental Protection Agency

EU: European Union

EUCP: European union coordinated programme

FAO: Food and Agriculture Organization of the United Nations

FAPAS: Food Analysis Performance Assessment Scheme

FSA: UK Food Standards Agency

GAP: Good agricultural practice

GEADE: Global Estimate of Acute Dietary Exposure

GECDE: Global Estimate of Chronic Dietary Exposure

GEMs: Global Environmental Monitoring and assessment programme

HBGV: Health Based Guidance Value

A numerical value derived by dividing a point of departure, e.g., benchmark dose lower confidence limit, $BMDL_{10}$, by a composite uncertainty factor, to determine the levels of a substance that can be ingested over a defined period without an appreciable risk to health.

HR: Highest Residue

The highest residue determined in a study conducted in accordance with the critical dose regimen or application procedure.

HSE: Health and Safety Executive

IEDI: International Estimated Dietary Intakes

JECFA: Joint FAO/WHO Expert Committee on Food Additives

JMPR: Joint FAO/WHO Meeting on Pesticide Residues

LB: Lower bound

Where the concentration is <LOD and/or <LOQ, then the output is assumed to be 0

LCF: Living Costs and Food Survey

LD_{50}: Median lethal dose

A dose at which 50% of exposed subjects are expected to die.

LOD: Limit of Detection

The minimum concentration of an analyte in a sample that can be quantitatively detected, but cannot be quantitatively determined, under a pre-established set of analytical conditions

LOQ: Limit of Quantification

The minimum concentration of a component that can be determined quantitatively with acceptable accuracy and consistency.

MAF: Mixture assessment factor

MC: Mean consumption

Mean:

Suppose we have observed n values $x_1, x_2, ..., x_n$.

The mean value of the n observations is calculated as:

$$\bar{x} = \frac{\sum_{i=1}^{n} x_i}{n} = \frac{x_1 + x_2 + \cdots + x_n}{n}$$

Median:

The median is the middle number in a sorted, ascending, or descending list of numbers and can be more descriptive of that data set than the mean. It is the point above and below which half (50%) the observed data falls, and so represents the midpoint of the data.

MoA: Mode of Action

A biologically plausible sequence of key events in an organism leading to an observed effect, commonly supported by robust experimental observations and mechanistic data

MOE: Margin of exposure

MRC HNR: Medical Research Council's Human Nutrition Research Unit

MRL (PPPs): Maximum Residue Level

An MRL is the maximum concentration of a pesticide residue in or on food or feed that is legally tolerated when a plant protection product (PPP) is applied correctly (following good agricultural practice). MRLs are regulated in GB and the EU under Regulation (EC) 396/2005. They are a trading limit, not a safety limit.

MRL (VMPs): Maximum Residue Limit

The maximum allowed concentration of residue in a food product obtained from an animal that has received a veterinary medicine or that has been exposed to a biocidal product for use in animal husbandry.

NDNS: National Diet and Nutrition Survey programme

The NDNS rolling programme is a continuous, cross-sectional survey designed to collect detailed, quantitative information on the food consumption, nutrient intake and nutritional status of the general population aged 1.5 years and over living in private households in the UK.

NEDI: National Estimates of Dietary Intakes

97.5th percentile:

The percentile is the value of a variable below which a certain percentage of observations fall. The 97.5th percentile is the value of exposure below which 97.5% of the population falls. If n=100 people and the values are sorted in ascending order, the 97.5th percentile falls between the 97th and 98th person.

OECD: Organisation for Economic Cooperation and Development

PFs: Processing factors

POAO: Products of animal origin

PPP: Plant Protection Products

PRiF: Expert Committee on Pesticide Residues in Food

PRIMo: Pesticide Residue Intake Model

Probabilistic:

Probabilistic actions, methods, or arguments are based on the idea that you cannot be certain about results or future events, but you can judge whether or not they are likely, and act on the basis of this judgment.

PSD: Pesticide Safety Directorate

PSD was the predecessor to the current Chemicals Regulatory Division (CRD).

RAC: Raw Agricultural Commodity

RD-Enf: Residue definition for enforcement

RD-RA: Residue definition for risk assessment

RL: Reporting limit

Used in the PRiF monitoring program. Used to describe the limit of determination that is the lowest levels our tests are set to measure. The RL can vary for different analytes or commodities.

STMR: Supervised Trials Median Residues

STMR-P: Supervised Trials Median Residues – processed commodities

TDS: Total Diet Studies

TMDI: Theoretical Maximum Daily Intake

TRV: Toxicological reference value

TTC: Threshold of Toxicological Concern

UB: Upper bound

Where the concentration is <LOD then the output is assumed to be equal to the LOD and if the concentration is between the LOD and the LOQ, then the output is assumed to be equal to the LOQ.

UK: United Kingdom

US: United States

UTL: Upper Tolerance Limits

VFs: Variability factors

VMD: Veterinary Medicines Directorate

VMP: Veterinary Medicinal Product

WCCE: worst-case consumer exposure

WHO: World Health Organization

WIGRAMP: Working Group on Risk Assessment of Mixtures of Pesticides and Similar Substances

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ANNEX 1 – Summary of current approaches to chronic dietary exposure assessment for pesticides and veterinary medicines

Area of concern	**Pesticides**		
Organisation	**HSE**		**JMPR**
Uses	• Assessment of potential exposure at active substance approval or product authorisation, based on median residue values (STMR) from residue trial data for the proposed crop uses only. • Assessment of potential exposure for MRL setting and review. This will consider all authorised pesticide uses of the active substance (note STMR values may not be available for all uses if an MRL review has not yet taken place). • Assessment of exposure based on monitoring data. Note this currently occurs on a commodity basis (if >50% of the samples for a particular commodity have determinable residues of the same active substance).		Assessment of specific potential public health concern. Periodic review of pesticide active substance data and MRLs. Assessment of potential exposure for new MRL setting or MRL review. The JMPR can only evaluate data relating to uses that are already registered in at least one country.
Model/ Calculation tool	UK Chronic model	EFSA PRIMO v 3.1	Template for the evaluation of chronic exposure(IEDI) xlsm, 1.55Mb Version 04, 2019

Area of concern	**Pesticides**		
Organisation	**HSE**		**JMPR**
Origin of substance data	Pre-registration supervised residue trial field data derived in accordance with Reg EC 1107/2009. OR Monitoring data derived as part of the PRiF programme		Supervised residue trial field data.
Assumptions	IEDI < ADI is acceptable Chronic exposure is considered per active substance.	IEDI < ADI is acceptable Chronic exposure is considered per active substance.	IEDI < ADI is acceptable Chronic exposure is considered per active substance. Percentages above 100% not necessarily interpreted as giving rise to a health concern due to the conservative assumptions of assessments. Where the ADI is exceeded, JMPR indicates parts of the risk assessment leaving room for refinement. At the National level, potential refinements include taking into account more detailed information on food consumption, monitoring and surveillance data, total diet or reliable data on the percentage of crop treated and percentage of crop imported.
Consumption data	NDNS and DNSIYC.	From a variety of EU member states and WHO. Calculation back to RAC performed at member state level.	WHO cluster diets based on Food Balance sheets and Codex commodity codes

Area of concern	**Pesticides**		
Organisation	**HSE**		**JMPR**
	Based on 7 day food diaries (4 days toddler and elderly).		
Approach	Rees- day approach $\sum_{x=i}^{j} \frac{STMR_i \times P97.5consumption_i}{BW} + \sum_{x=k}^{n} \frac{STMR_k \times MC_k}{BW}$ i, j: two raw agricultural products leading to the highest intake; k, l, m, . . .n: remaining raw agricultural commodities consumed P97.5consumption= 97.5th percentile consumption of RAC in kg/day based on mean daily intakes of consumers only. MC = mean consumption of RAC in kg/day derived from mean daily intakes of whole population (consumers and non consumers). STMR= Supervised Trial Median Residue. Residue value derived from pre-registration data. Note for monitoring data, median residue of monitoring values is used.	$\sum_{x=i}^{n} \frac{STMR_i \times MC_i}{BW}$ i, j, k,. . ..n: individual raw agricultural products Calculation of mean consumption is not standardised across the consumption data used. Also includes Rees- day approach but not relied upon for regulatory decision making (by GB or EU).	$IEDI = \sum (STMR_i \times F_i)$ Fi:GEMS/Food regional consumption of food commodity i Based on mean per capita intake from food balance (e.g., production minus exports plus imports). STMRi (or STMR-Pi): STMR (or STMR-P) for food commodity i When the pesticide is also used as veterinary drug and MRLs were established for animal commodities, the veterinary drug residues should also be taken into account in the IEDI calculation.
Consumer groups/	Adult, infant, toddler, 4-6 years, 7-10 years, 11-14 years, 15-18 years, vegetarian, elderly (own home), elderly (residential)	Encompasses a variety of sub groups and survey approaches (e.g., 7 day	No consumer groups. Seventeen cluster diet groupings covering regions with similar dietary patterns.

Area of concern	**Pesticides**		
Organisation	**HSE**		**JMPR**
critical groups	Note requirement for consideration of vulnerable groups pregnant women, infants and children.	diets, WHO cluster diets, Swedish 90th centile consumption). Use of EFSA Pesticide Residue Intake Model (EFSA PRIMo revision 3) (wiley.com)	
Body weights	Adult (76 kg), infant (8.7 kg), toddler (14.5 kg), 4-6 years (20.5 kg), 7-10 years (30.9 kg), 11-14 years (48 kg), 15-18 years (63.8 kg), vegetarian (66.7 kg), elderly-own home (70.8 kg) , elderly- residential (61.6 kg)	Variety of standard bodyweights used depending on consumption data source.	All 60 kg except for G09 diet 55kg.
Refinement	Processing data can be used to refine the assessment. However, refinements only possible if a commodity is predominantly consumed processed or sufficient consumption data is available to capture the combined consumption via RAC and any processed commodities.	Processing data can be used to refine the assessment. However, refinements only possible if a commodity is predominantly consumed processed or sufficient consumption data is available to capture the combined consumption via RAC and any processed commodities.	Processing data can be used to refine the assessment. See also assumptions above.

Area of concern	**Pesticides**		
Organisation	**HSE**		**JMPR**
LOQ values[1]	Currently considered for risk assessment at the LOQ.	Currently considered for risk assessment at the LOQ.	STMR value would be assumed to be at the LOQ, unless there is scientific evidence that residues are "essentially zero"- exaggerated dose trials etc.
Uncertainties	There are 'standard' uncertainties within the exposure assessment as well as other, non-standard uncertainties. 1. (Standard uncertainty) The toxicological reference values are established from the thresholds derived from the dose response curves. A standard uncertainty factor of 100 is applied; an uncertainty factor of 10 to take into account the toxicological studies are undertaken on laboratory animals and an uncertainty factor of 10 to take into account variations in response that may occur for different individuals in the population. Additional uncertainty factors may be applied if the studies do not fully comply with the guidelines/guidance. 2. (Standard uncertainty) Uncertainties relating to the representativeness of the data set e.g. small sample sizes not giving the entire range of possible residue values; the use of default factors (variability and processing factors); extrapolation	Uncertainties 1, 2, 4, 5, 6 and 7 listed for the HSE model would also apply to the EFSA PRIMo model. The following additional points are noted: Food consumption data used in the EFSA PRIMo are not fully comparable; the design of the surveys may differ significantly; the statistical analysis of the consumption data (e.g. calculation of mean or high percentile consumption) is not standardised.	Uncertainties 1, 2, 4, 5, 6 and 7 listed for the HSE model would also apply to the JMPR models. The following additional points are noted: The JMPR models rely on consumption data being provided from member countries. The design of the surveys may differ significantly; the statistical analysis of the consumption data (e.g. calculation of mean or high percentile consumption) is not standardised. The models also do not contain accurate information on the consumption of processed vs unprocessed foods. The Models use the GEMs (global environmental monitoring and assessment programme) cluster diets in which the food available per capita in a country is estimated from trade balance sheets (i.e. food produced, imported and exported). Specifically for the chronic model, only data from the GEMs Cluster diets is included. The cluster diets do not give details on which population groups are consuming the food, particularly children which are often the critical groups for exposure

Area of concern	Pesticides		
Organisation	**HSE**		**JMPR**
	uncertainty where data for one crop/crop group are extrapolated to other crops. 3. (Standard uncertainty) UK models are based on relatively old consumption data and may not account for changes to consumer habits, diets and typical bodyweights. Detailed consumption data aren't available for all food products, including some commonly eaten and readily available foods. It can be difficult to make meaningful refinements to the exposure assessment due to a lack of detailed consumption data, specifically considering commodities eaten following processing (i.e. consumption data for raw vs. cooked vegetables such as cauliflower or carrots). 4. Models don't assess/account for case specific non-standard uncertainties (i.e. where there are some inadequacies in the data or where data are non-standard/not fully in accordance with the guidance such as the impact of not having robust CF/PF or resulting from measurement uncertainty, in situations where the analytical methods used for the determination of input values are not fully validated for all components in the residues definition for risk assessment). The impact of the		owing their high consumption relative to their body weight. As such it is not suitable for estimating children's exposure or for assessing less than lifetime dietary exposure. For info, the GEMs cluster diets relevant to EU countries are also included in the PRIMo model.

Area of concern	Pesticides		
Organisation	**HSE**		**JMPR**
	non-standard uncertainties on the result of a standard assessment must be judged, usually by 'expert judgement' using case-specific assessment of the available data/scenario. 5. Doesn't account for exposure to low levels of chemical mixtures which could cause toxicological effects due to additive or synergistic interactions; the potential for interaction or toxic effects of different substances in combination is not routinely addressed by the standard single substance assessment approach. There is limited understanding of human exposure to low-levels and mixtures of chemicals. The exposure is calculated separately for each pesticide. The calculation of cumulative exposure resulting from more than one pesticide is not determined. 6. The models are not able to account for combined exposure resulting from operator/by-stander exposure i.e. aggregated risk. 7. Models are deterministic and as such they do not allow a prediction of the level of protection i.e. the percentage of the population that exceeds a certain exposure level defined by risk managers.		

[1] – Consideration of approaches to LOQ values (will be of significance for cumulative exposure). EFSA approaches (EFSA, 2019c) have been to use upper (assuming LOQ) or lower bound (assuming zero).

Area of concern	**Veterinary Medicines**		
Organisation	**VMD**	**JECFA**	
Uses	Assessment of potential exposure for MRL setting and review.	Assessment of potential exposure for MRL setting and review.	
Model/ Calculation tool	Theoretical maximum daily intake (TMDI)	EDI	GECDE
Origin of substance data	Residue depletion data in line with VICH guidance. Doses administered to animals at the highest proposed/recommended dosage regimen.	All available residue depletion data.	
Assumptions	TMDI < ADI is acceptable Chronic exposure only. If substance also used as a pesticide, then TMDI has to be below 45% of the ADI.	EDI < ADI is acceptable Chronic exposure only.	GECDE < ADI is acceptable Less than lifetime exposure should be considered for relevant populations (e.g. children or pregnant women) When the ADI/ARfD is based on an acute exposure toxicological endpoint the GEADE is calculated
Consumption data	Food basket approach	Food basket approach	Individual national survey from different countries (CIFOCOss, based on FoodEx2).

Approach	Residue levels at the MRL are multiplied by the consumption factor of each commodity, and the result is summed up to compare with the ADI. MRLs are usually derived using the upper tolerance limit (UTL 95/95) at the expected withdrawal period for the substance according to the proposed used.	Median residue concentrations associated with the MRL (at the expected withdrawal period for the substance according to the proposed used), are multiplied by the consumption factor of each commodity, and the result is summed up to compare with the ADI.	GECDE = Highest exposure from one animal product + Total mean exposure from all other products (Highest 97.5th percentile consumption plus the highest mean across surveys from different countries). Residue levels used are median values at the expected withdrawal period according to good veterinary practice.
Consumer groups/ critical groups	No consumer groups. Only adults are considered.	No consumer groups. Only adults are considered.	At the moment, exposure estimates for all potentially relevant subpopulations (e.g. children, general population and pregnant women [or a suitable surrogate])
Body weights	Adult (60 kg)	Adult (60 kg)	Adult = 60 kg Children = 15 kg Infant = 5 kg
Refinement	If TMDI > ADI, then lower MRLs are proposed based on residue concentrations at later timepoints on the residue depletion studies.	When the residue data are insufficient to calculate the EDI, the TMDI calculation is used instead.	Instead of using the highest mean and the highest 97.5th percentile consumption across surveys, calculation can be made using the mean and the highest reliable percentile for each individual national survey from available datasets (CIFOCOss) from which data

			can be obtained. The mean and the range of these estimates is compared with the ADI.
LOQ values	Usually values < LOQ are considered as 1/2LOQ.	Usually values < LOQ/LOD are considered as ½ LOQ/LOD. When there are no detectable residues in the depletion studies with radiolabelled and non-radiolabelled drug in the tissue at the timepoint on the depletion curve corresponding to the MRL recommendations, MRLs based on 2xLOQ should not be included in the calculation.	Usually values < LOQ/LOD are considered as ½ LOQ/LOD.
Uncertainties			

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