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Committee for Veterinary Medicinal Products

Draft report on development of a harmonised approach to exposure assessment methodologies for residues from veterinary medicinal products, feed additives and pesticides residues in food of animal origin

Draft report from the Working Group

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Comments should be provided using this template. The completed comments form should be sent to Vet-Guidelines@ema.europa.eu

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1. Introduction and problem statement

A number of active substances can be used for different purposes, such as veterinary medicinal products (VMP), feed additives, pesticides and biocides. Those substances are regulated under different sectoral legislation and are assessed separately by European Medicines Agency (EMA) and/or European Food Safety Authority (EFSA) and/or European Chemicals Agency (ECHA) in the context of this sectoral legislation. Currently, different risk assessment methodologies are used with the potential for different outcomes when conducting risk assessments on the same active substance. While it is acknowledged that there are a number of factors that may lead to different risk assessment outcomes (e.g. different data requirements in view of the different purposes of the studies, different assumptions and approaches to hazard assessment, etc.), some of the different outcomes could be avoided by aligned procedures, especially with regard to the exposure assessment procedures used (input data and models) which often are the critical starting point in the risk assessment.

For veterinary medicinal products, EMA uses the Theoretical Maximum Daily Intake (TMDI) model to estimate the risk from life-long consumer exposure to residues from animals treated with veterinary medicinal products. This model was formerly also used by EFSA (EFSA's Panel on Additives and Products or Substances used in Animal Feed - FEEDAP Panel) and by JECFA, but both EFSA and JECFA have now moved away from the TMDI model, in favour of alternative models in accordance with the development of scientific and computational tools in this field.

EFSA developed models for the assessment of consumer exposure of feed additives and pesticide residues (FACE/PRIMo 4) allowing for age-dependent exposure scenarios based on individual food consumption data whereas JECFA developed the Global Estimated Chronic Dietary Exposure (GECDE) model.

Similarly, for substances with dual uses as VMPs and pesticides, maximum residue limits/levels (MRLs) may be different for the same substance in the same animal commodity (muscle, fat, liver, kidney, eggs or milk) or may have different residue definitions depending on different assumptions used and different legislative frameworks under which the MRLs were established. This has led to uncertainties for EU enforcement authorities as to the appropriate enforcement level and residue definition as a basis to take enforcement action.

In view of these potential difficulties resulting from use of different exposure calculation models, the European Commission mandated EFSA and EMA (in 2020) to provide scientific and technical assistance in order to develop a common approach on exposure assessment methodologies for residues from veterinary medicinal products, feed additives and pesticides residues in food of animal origin.

If other elements of possible harmonisation of risk assessment methodologies that could be pursued to achieve their better alignment across the concerned sectors are identified, this should also be highlighted in the Technical Report for further follow up by the Commission.

As Codex maximum residue limits are systematically considered in EU food legislation, the ongoing developments at international level should also be considered in this mandate, namely the outcome of the work carried out by the 2018 WHO/FAO joint working group of experts that dealt with harmonisation issues for dual use substances. The outcome of this working group was a partial alignment of exposure assessment methodology, which is now reflected in the revised Chapter 6 of the draft EHC guidelines[1] and was welcomed by the EU as a step forward.

[1] FAO/WHO. Chapter 6 dietary exposure assessment of chemicals in food. In FAO/WHO. Principles and methods for the risk assessment of chemicals in food. Geneva: WHO; 2009

2. Terms of reference as provided to EFSA and EMA

The European Commission requested EFSA and EMA, to develop a common approach on exposure assessment methodologies for residues from veterinary medicinal products, feed additives and pesticides in a stepwise approach as detailed below:

1. By 31.12.2021,

a. Assess currently available exposure assessment models routinely used in the EU and on an international level in Codex Alimentarius for veterinary medicinal products (VMPs), feed additives and pesticides residues for their suitability for use in routine risk assessment in these areas and describe their advantages and limitations overall and per area. Discuss whether alignment of existing models would be possible and under which circumstances. Exemplary calculations on the same data sets (e.g. for ongoing real assessments) should be considered to assess impacts of a change of methodology.

b. Assess in how far the jointly developed approach by JECFA and JMPR – once adopted - laid down in Chapter 6 of the EHC risk assessment guidelines could be integrated, and under what circumstances. Describe advantages and limitations.

2. By 30.11.2022,

a. Recommend a common approach for exposure assessment compatible with current scientific knowledge for future use by EMA and EFSA in their routine assessments of VMPs, feed additives and pesticides residues. The compatibility of the approach with internationally used approaches in these areas should also be ensured.

3. Background information on concepts, data and models

In the regulatory framework for the establishment of residue limits related to veterinary medicinal products (Regulation (EC) No 470/2009) and for feed additives (Regulation (EC) No 1831/2003), the Maximum Residue Limit (MRL) is defined as the concentration of a residue from a pharmacologically active substance which may be permitted in a particular foodstuff of animal origin. In the area of pesticide residues (Regulation (EC) No 396/2005), the MRL stands for "Maximum Residue Level" which is defined as the upper legal level of a concentration for a pesticide residue in or on food or feed set in accordance with this Regulation, based on good agricultural practice (GAP) and the lowest consumer exposure necessary to protect vulnerable consumers.

The MRLs are established such that substances in products used under authorised conditions do not pose an unacceptable risk to consumers. The consumer risk assessment follows the same principles in all regulatory sectors[2] and considers the metabolism and depletion of pharmacologically active substances in relevant animal species, the type of residues and the amount thereof, that may be ingested by human beings without an appreciable health risk. Points of reference in the risk characterisation are typically based on a comprehensive hazard assessment and are expressed in terms of an acceptable daily intake (ADI), acute reference dose (ARfD) or an alternative health based guidance value (HBGV) (see Regulation (EC) No 470/2009, Regulation (EC) No 1831/2003 and Regulation (EC) No 429/2008).

[2] E.g. as described in WHO/IPCS (World Health Organization/International Programme on Chemical Safety), 2009. Principles and Methods for the Risk Assessment of Chemicals in Food, International Programme on Chemical Safety,Environmental Health Criteria 240. Availableonline:http://www.who.int/ipcs/food/principles/en/index1.html

3.1. Hazard assessment

The hazard assessment follows comparable internationally established principles and study requirements laid down in certain guidelines (e.g. EHC 240, OECD or also specific EU guidelines).

For the establishment of HBGVs for chronic exposure, similar approaches are used by EMA, EFSA, JMPR and JECFA. In short, data on pharmacological and toxicological activity of the particular active compound are assessed and dose-response relationships are modelled. In case of microbiologically active compounds, data on microbiological properties are also taken into account. These data are used to identify No Observed Adverse Effect Levels (NOAELs) or benchmark dose levels (BMDL) (or No Observed Effect Concentrations (NOEC) for in vitro endpoints) and to establish a HBGV, typically an ADI or a tolerable upper intake level (UL), depending on the nature of the substance under assessment. To derive suitable HBGVs, NOAELs or BMDLs are adjusted by uncertainty factor(s) (typically 100) to cover intra- and interspecies variation.

If necessary, EFSA, JMPR and JECFA establish ARfDs based on the same principles as described above for ADIs. Only short-term effects are taken into account. Currently no ARfDs are derived by EMA, but endpoints for certain ADIs are based on short-term effects (e.g. pharmacological effects).

3.2. Considerations regarding exposure and risk characterisation

The experimental studies required for exposure assessment of veterinary medicinal products, pesticides and feed additives are defined in Commission Regulation (EU) 2018/782, Regulation (EC) No 1107/2009[3] and Commission Regulation (EC) No 429/2008. The aim of the studies is to first evaluate the nature and fate of the substance. This is most often accomplished in studies using radiolabelled substances. Other specific studies may also be designed to quantify the residue concentrations in the edible tissues/food commodities from target animals. Depending on the specific requirements, the latter studies will investigate different dosing regimens/levels and/or depletion times.

The residue considered in the dietary exposure assessment is the relevant "residue of concern" (RoC)[4]. When determining RoC [5], the most common approach (e.g. when evaluating substances used in VMPs) is to assume, by default, that all metabolites have the same pharmacological/toxicological potential as the parent compound. In this case, the RoC would be the total residue (sum of residue components). Yet, for the purpose of residue monitoring, it may not be feasible to measure concentrations for all compounds considered in the RoC, and a marker residue[6] may need to be defined.

The risk is characterised by a comparison of the estimate of dietary exposure to the RoC with the appropriate HBGV (ADI in case of chronic risk and ARfD in case of acute risk). In the framework of a pre-authorisation assessment (i.e. in view of authorising a VMP, feed additive or pesticide), robust information on the frequency of use of a chemical and its actual occurrence in food may not (yet) be available. Hence, for the dietary exposure assessment, it is assumed by default that all animals are treated with or exposed to the chemical.

[3] In particular, in the related Regulations on data requirements.
[4] partly different terminology is used for this concept in the various fields (e.g. residue definition for risk assessment for pesticide residues).
[5] = absence of concern that metabolites have a higher toxicity
[6] The marker residue is the residue selected for residue monitoring and is in a known relationship to total residues in edible products

3.3. Studies used and requirements to derive residue (occurrence) data

This chapter is intended to give an overview of the residue studies and guidelines used in the different jurisdictions. The overview is given in table 1

Table 1: Overview of residue studies used in the different fields and different organisations

		Veterinary Medicinal Products			**Feed Additives**		**Pesticides**
		EMA		***JECFA***	***EFSA***		***JMPR, EFSA***
		MRL *(VICH[7] GL46, GL56, GL57)*	***Withdrawal Period**** *(VICH GL48, GL56, GL57)*	***MRL***	***TR study*****	***MR*****	***Accumulating feeding studies*** *(OECD TG 505 /a)*
Meat and offal	*Mammals*	*≥3 animals/time point*	*Minimum 4 animals/time point at a minimum of 4 time points 6 animals for 0-day WP (i.e. one time point study)*	*JECFA is mostly reusing data from regional product authorisations, e.g. EMA/FDA/JMAFF, other Ideally data acc. to VICH GL46, GL56, GL57, GL48, GL56, GL57 are available For example studies as mentioned for EMA*	*≥3 dairy cows, sows ≥4 cattle, pigs, rabbits*	*≥4 dairy cows, cattle, pigs, sows, rabbits*	*Dairy cattle (rarely beef cattle, goat or swine) 3 animals per dose group, 3 dose groups, at least 28d dosing Sampling of tissues after last administration Depuration for up to +2 weeks optional*
	Poultry	*≥3 animals/time point*	*6 animals/time point minimum of 4 time points 12 animals for 0-day WP (i.e. one time point study)*		*≥ 3 laying hens ≥4 poultry and related minor species*	*≥6 poultry*	*Laying hens (rarely broiler chicken) 5 animals per dose group, 3 dose groups, at least 28d dosing Sampling of eggs (all days) Sampling of tissues after last administration Depuration for up to +2 weeks optional*

[7] VICH is a trilateral (EU/EMA-Japan-USA) programme aimed at harmonising technical requirements for veterinary product registration.

	Fish	*10 animals/time point*	*10 animals/time point minimum of 4 time points 15 animals for 0-day WP (i.e. one time point study)*		*≥10 salmonids and other aquatic species*	*≥10 salmonids and other aquatic species*	*No agreed guideline yet, not considered in JMPR*
Milk		*≥8*	*least 20 animals for a sufficient time period*		at least eight cows (24 h pooled milk)	at least eight cows (24 h pooled milk)	*Same study as for meat and offal: Dairy cattle (rarely goat) 3 animals per dose group, 3 dose groups, at least 28d dosing Sampling of milk (all days)*
Eggs		*≥10 eggs/day for laying birds over a sufficiently long time period.*	*At least 10 eggs per time point*		sufficient number of laying hens to collect 10 eggs	sufficient number of laying hens to collect 10 eggs	*Same study as for meat and offal: Laying hens 5 animals per dose group, 3 dose groups, at least 28d dosing Sampling of eggs (all days)*
Honey		*6 colonies per site, 4 sites*	*6 colonies per site, 4 sites*		six bee hives	six bee hives	*No agreed guideline yet, not considered in JMPR*

** These studies are normally only available in the marketing authorisation procedures and only the marker residue is measured. However, if such studies are available in a MRL procedure, they will be used in the assessment.*[2]

/a: Feeding studies for pesticides only become necessary when significant feed levels (0.004 mg/kg bw or 0.1 mg/kg feed DM) are reached. Often, estimations need to be based on radioactive metabolism studies on goat and laying hens according to OECD TG 503 instead. These studies involve less animals and shorter dosing periods.

*** TR=Total residue; Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017): A study of total residues should be made with the labelled active substance, administered until metabolic equilibrium in tissues is reached. The parent compound and identified metabolites (see Section 2.1.1.1) should be determined in edible tissues and products. The marker residue should be selected from this study, and the ratios marker to total residues should be established.*

**** MR=Marker Residue; Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017): The minimum administration period of the additive should be 28 days, for animals for fattening for the 28 days prior to slaughter. The samples should be collected at the end of the administration period. Measurements of the marker residue concentration (MRC) should use a validated analytical method with sufficient sensitivity.*

*# Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017): For those additives in which the consequences of the rate of depletion on residue concentration are needed (e.g. when MRLs are considered necessary), residues in tissues should be measured at additional sampling points after withdrawal (preferably three), spaced according to the rate of depletion from tissues. The same number of animals as listed in ** and *** applies for each time point, respectively.*

3.4. Exposure models used

Exposure is generally estimated by combining occurrence data (residues concentration) with data for consumption of the respective foods/products.

Different models are currently used for dietary exposure estimation in various jurisdictions and by different scientific bodies. The differences lie mainly in the data and assumptions used for daily food consumption (e.g. default data, empirical data, individual data/summary data) and also in the summary statistic from residue distributions used as input for the RoC (e.g. median/mean, upper percentile/tolerance limits). For the acute exposure, typically the food commodity/RoC combination leading to the highest exposure is used.

3.4.1. Veterinary medicinal Products

3.4.1.1. TMDI - Theoretical Maximum Daily Intake (EMA/CVMP)

The estimate of chronic dietary exposure to residues of veterinary medicinal products is based on a specific model diet for the daily intake (standard food basket (SFB)[8] made up of 300 g of muscle, 100 g of liver, 50 g each kidney and fat, 1500 g milk, 100 g eggs, 20 g honey) and maximum residues of concern (RoC), typically 95/95 tolerance limits (i.e the upper one-sided 95% confidence limit over the 95th percentile of residue concentration) or MRL (both corrected with the respective MR:TR ratio)[9].

A standard body weight of 60 kg for a person is used in the calculation. This includes the assumption that children are also protected by the high consumption figures.

No specific calculation is done for acute exposure estimates. However, the TMDI is assumed to be conservative enough to also cover acute exposure (the term ADI is generally used, although, strictly speaking, the pharmacological ADI is most often based on an acute endpoint).

3.4.1.2. GECDE/GEADE approach (JECFA)

For assessment of veterinary medicinal products by JECFA, the chronic dietary exposure model used is the Global Estimate of Chronic Dietary Exposure (GECDE). The GECDE uses the median residue concentration combined with two different types of consumption estimates to estimate chronic exposure from foods in relation to which MRLs exist or are being sought. The approach assumes that, in the longer term, an individual would be a high-level consumer of only one category of food and that consumption of the other foods would remain at the population mean.

The GECDE is calculated from the sum of the highest single food dietary exposure (computed using the highest reliable percentile (HRP) consumption of each food containing the residues of interest) plus the population mean dietary exposure from all the other relevant foods.

While the GECDE initially specified the use of the 97.5th percentile consumer, as a measure of an individual with habitually high consumption of a single food, this percentile is inappropriate when the number of consumers of a food is small. The HRP is the highest percentile that is consistent with the reported number of consumers and may be the 97.5th, 95th, 90th or 50th percentile. The consumption

[8] For pigs, Fat = "Fat and skin in natural proportions"; For poultry, SFB = 300 g of muscle, 100 g of liver, 10 g of kidney and 90 g of "Fat and skin in natural proportions"; For fish, SFB = 300 g of muscle and skin in natural proportions

[9] For reasons of simplicity and to ensure better comparability across models no such corrections for the RoC acc. to MR:TR ratios have been made in the example calculations in Section 4

data are derived from the FAO/WHO Chronic Individual Food Consumption[10] – summary statistics (CIFOCOss).

The GECDE uses the highest consumer HRP, and highest population mean food consumption figures across all surveys in CIFOCOss. Since 2017, country/survey specific estimates of chronic dietary exposure, based on the GECDE methodology, have also been derived.

Possible population subgroups of concern, such as women of childbearing age, infants and children, can be considered, as CIFOCOss contains food consumption data for a range of population subgroups.

The CIFOCOss database currently contains summary statistics of 289 survey/population groups from 32 countries, with further studies added on an ongoing basis. To be included in CIFOCOss, a food consumption survey must have collected food consumption data from individuals on at least two separate days.

The GECDE uses median RoC values as the concentration inputs for dietary exposure calculations.

In summary, the GECDE is the highest exposure calculated using the HRP consumption for a single food selected from all the foods plus the mean dietary exposure from all the other relevant foods.[11]

The Global Estimated Acute Dietary Exposure (GEADE), is an explicit estimate of acute dietary exposure. The GEADE considers high-level exposure from each relevant food of animal origin, individually. The concurrent occurrence of the selected high residue concentration in each food to which a consumer might be exposed (e.g., an MRL or high residue concentration derived from depletion studies, such as the upper one-sided 95% confidence limit over the 95th percentile residue concentration) is combined with a high daily consumption (97.5th percentile, FAO/WHO large portion database) of that food (meat, offal, milk, others). In cases where there is insufficient data to derive a percentile, the maximum consumption may be used to obtain a worst-case exposure estimate. When calculating the GEADE, instead of the amounts of food consumed set out in a model diet, more detailed consumption data are used to estimate acute dietary exposure. The GEADE is reported as the highest of the individual estimates for the relevant foods of animal origin. The GEADE is then used to calculate the percentage exposure of the ARfD.

3.4.2. Feed Additives

3.4.2.1. FACE Tool approach (EFSA)

The FACE calculator[12] was developed by EFSA and is used to estimate chronic and acute dietary exposure to residues of feed additives and their metabolites present in food of animal origin. The tool relies on food consumption data collected from EU Member States (stored in the EFSA Comprehensive European Food Consumption Database[13]). The database includes consumption data for foods as consumed, such as composite foods (e.g. pizza) and other single foods or ingredients (e.g. cheese). Although Member States are encouraged to disaggregate consumption of composite food into single components, the level of disaggregation may differ among dietary surveys. As some of these data cannot be used in exposure assessment when the occurrence data are measured in raw primary commodities (RPCs), EFSA converted the Comprehensive Database into a new database (RPC Consumption Database), where both RPC and RPC derivatives (RPCD) data are present, using the

[10] mainly includes composite dishes, household recipes are commonly disaggregated into the main ingredients (e.g. whole pasta, cheese) but rarely to the RPC (e.g. grains, milk)

[11] http://www.fao.org/fileadmin/user_upload/agns/pdf/jecfa/Dietary_Exposure_Assessment_Methodologies_for_Residues_of_Veterinary_Drugs.pdf

[12] https://dwh.efsa.europa.eu/bi/asp/Main.aspx?rwtrep=FACE

[13] https://www.efsa.europa.eu/en/food-consumption/comprehensive-database

RPC[14] model. RPCDs are single-component foods whose nature has been physically changed through processing (e.g., grilled meat, cheese, etc.). The RPC consumption data for foods of animal origin are used in the FACE calculator, noting that specific consumption data for muscle are not available. Food consumption of muscle is considered part of the meat consumption, which includes certain amounts of trimmable fat (and skin in the case of poultry). Likewise, consumption data for kidney were very limited and integrated in the consumption of other offal.

Residue data used for the assessment are the high-end residues of the distribution of relevant residues in the food commodities (i.e. the arithmetic mean plus two standard deviations or the highest single value in case of fewer than six animals)[15]. To account for the uncertainty on the composition of meat reported above, residue concentrations for muscle and fat are applied to the intake of meat according to the following proportions: 80% muscle and 20% fat for mammals and 90% muscle and 10% fat (incl. skin) for poultry. The residue concentration in kidney is applied to the intake of other offal. When assessing feed additives intended for multispecies use, the value for the species with the highest concentration of residues in a given tissue of poultry, mammals and fish will be taken as representative for that specific food commodity in all poultry, mammals and fish, respectively.

To obtain chronic exposure estimates, residue data are combined with the average daily consumption of the corresponding food commodity, and the resulting exposures per food are summed to obtain total chronic exposure at the individual level. Distributions of the individuals' exposures are estimated for the different European countries and age classes, and reported using summary statistics, representing mean and high-level exposure (i.e. the 95th percentile of exposure distribution). The tool also indicates how different food commodities contribute to the overall exposure. Acute exposure estimates are obtained similarly based on the consumption of a food commodity within a single day (instead of average daily consumptions).

The FACE calculator contains consumption data from 33 dietary surveys, which allows to obtain exposure estimates for 17 countries in 7 age classes (infants, toddlers, other children, adolescents, adults, elderly and very elderly).

For further information, please consult "Guidance on the assessment of the safety of feed additives for the consumer", EFSA Journal 2017;15(10):5022[16]

3.4.3. Pesticides

3.4.3.1. IEDI/IESTI approach (JMPR)

The assessment of residues in foods by JMPR following the use of pesticidal active substances is conducted considering the long-term (chronic) and, if the substance under review has acute toxic properties, the short-term (acute) dietary exposure. The consumer is considered to be adequately protected when estimated dietary intake of pesticides residues do not exceed the acceptable daily intake (ADI) or the acute reference dose (ARfD). Details on the methodology can be found in the 3rd Revision of the FAO Manual on the Submission and Evaluation of Pesticide Residues Data[17].

For the chronic dietary exposure assessment, the International Estimated Daily Intakes (IEDIs) are estimated based on the residue definition for dietary risk assessment derived by the JMPR, which includes all compounds (pesticidal active substance and their metabolites/degradates) significantly

[14] https://www.efsa.europa.eu/en/supporting/pub/en-1532
[15]https://doi.org/10.2903/j.efsa.2017.5022
[16] https://www.efsa.europa.eu/en/applications/feedadditives/tools
[17] https://www.fao.org/3/i5452e/i5452e.pdf) and in Chapter 6 of Environmental Health Criteria 240 (EHC 240, https://cdn.who.int/media/docs/default-source/food-safety/publications/chapter6-dietary-exposure.pdf?sfvrsn=26d37b15_6

contributing to the risk. The IEDI Model is based on the WHO GEMS Food Cluster diets, estimating average per capita consumption figures based on international trade and production statistics of foods[18]. Occurrence input parameters are estimated by the JMPR on the basis of registered uses of plant protection products with the active substance of interest. From all supervised field trial and animal feed studies available, median residue concentrations are identified for each food. In addition, quantitative information on the behaviour during industrial processing are taken into account. The IEDI represents the sum of average exposures from all individual food items – plant and animal based – expressed in µg/kg bw per day. It is compared with the ADI value of the active substance and addresses the long-term (lifelong) dietary risk. No stratifications e.g. concerning sub-populations, age groups, specific diets are taken into account. Also, no refinements related to use frequencies of plant protection products are considered.

In addition, when an active substance shows acute toxic properties and an ARfD becomes necessary, the International Estimate of the Short-Term Intake (IESTI) is assessed. The principles of the IESTI Methodology were revised several times and the current approach is also described in the documents cited for the IEDI. The IESTI addresses the dietary risk arising from a single high exposure within 24h via foods. In contrast to the IEDI, actual consumption data based on national dietary surveys are considered in a deterministic model consisting on three cases. The IESTI calculates the exposure using 4 different equations (case 1, 2a, 2b, 3) considering the amount of large portion consumed, edible unit weight and the bulking/blending of the commodities, but only the case 1 and case 3 calculations are considered relevant for food of animal origin. The target consumption value is defined as large portion "LP", which represents the 97.5th percentile of the portion size from all individuals which consumed the respective food item (consumers only). Input parameters for the occurrence data are either the highest residues (HR) observed in supervised field trial and animal feed studies for unblended commodities (e.g. pieces of fruit or vegetables, meat, eggs) or the median residue for blended commodities (e.g. cereal grains, pulses, oilseed, milk). Again, quantitative information on the behaviour during industrial processing is considered and a variability factor is considered for some cases describing the heterogenicity of residues in composite samples. The IESTI Methodology considers each food commodity individually – no aggregation with other foods is foreseen. The IESTI Model currently used by JMPR represents a compilation of national or supra-national IESTI models (e.g. EFSA PRIMo) and LP data submitted to WHO directly. From all data available, the most critical case leading to the highest exposure per kg bodyweight is identified and considered by JMPR to estimate the acute dietary exposure, which is compared to the ARfD. Since the IESTI model is based on consumption data sub-populations (general population, children, women in childbearing age) are specifically addressed.

The latest versions of the IEDI and IESTI Model used by JMPR can be obtained from the WHO GEMS Food Website[19].

In summary, JMPR uses two different approaches to assess the dietary risk for consumers. The IEDI model based on trade/production statistics represents the average long-term dietary exposure over a lifetime while the IESTI aims at a single high exposure event within 24h. To exclude potential dietary risks for consumers, the exposure from both approaches should not exceed the ADI and/or the ARfD.

3.4.3.2. PRIMo approach (EFSA)

Since 2007, the EFSA Pesticide Residue Intake Model (PRIMo) is the standard tool used at EU level to perform the dietary risk assessment for pesticide residues in food of plant and animal origin, i.e. to estimate the short- and long-term dietary exposure and compare those exposures to the relevant

[18] https://www.who.int/data/gho/samples/food-cluster-diets
[19] https://www.who.int/teams/nutrition-and-food-safety/databases/global-environment-monitoring-system-food-contamination

toxicological reference values (ADI and ARfD, respectively). It is a deterministic model that uses internationally agreed methodologies for the assessment of pesticide residues and it is mainly used under the regulatory framework of Regulation (EC) No 396/2005 and Regulation (EU) No 1107/2009.

Revision 4 of PRIMo is currently under development by EFSA. As in the case of FACE, PRIMo 4 will rely on food consumption data from the RPC Consumption Database, where both RPC and RPC derivatives (RPCD) data are present. RPCDs are single-component foods whose nature has been physically changed through processing (e.g. grilled meat, cheese, etc.).

Unlike FACE, in PRIMo 4 the classification of foods is more refined, allowing to also perform an assessment at the level of RPCDs and a further distinction between different types of mammals (i.e. cattle, goats, sheep and pigs).

Within the chronic exposure assessment, occurrence data are combined with the average daily amount of food consumed and the exposure calculated for the different commodities is then summed up by subject. Summary statistics (i.e. mean, percentiles) are then calculated for the total population of the different European countries, surveys and age classes. Although in the area of pesticide residues risk managers now mainly refer to the mean exposure, EFSA will introduce the use of the highest reliable percentile (HRP) for chronic risk assessment in PRIMo 4, to promote possible harmonisation with other domains of activity. The HRP is the highest percentile of exposure that can be obtained based on the number of subjects included in the dietary survey. While in FACE the HRP is only derived up to the 95th percentile, in the case of pesticides HRP estimates are derived up to the 97.5th. However, the mean exposure estimates will still be reported in the outputs.

Acute estimates are obtained similarly, firstly applying the International Estimated Short-Term Intake (IESTI) formulae[20] and considering the exposure to a certain commodity consumed within a single day. The IESTI calculates the exposure using 4 different equations (case 1, 2a, 2b, 3) considering the amount of large portion consumed, edible unit weight and the bulking/blending of the commodities, but only the case 1 and case 3 calculations are considered relevant for food of animal origin. The HRP (up to the 97.5th percentile) of exposures based on the consuming days is then calculated for each RPCD, dietary survey and age class separately. The most critical estimate among the different RPCDs is considered for decision making.

As for the FACE calculator, PRIMo 4 will contain consumption data from 33 dietary surveys, which allows to obtain exposure estimates for 17 countries in 7 age classes (infants, toddlers, other children, adolescents, adults, elderly and very elderly).

[20] https://www.who.int/foodsafety/chem/guidance_for_IESTI_calculation.pdf

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		Veterinary Medicinal Products		**Feed Additives**	***Pesticides***	
		EMA	***JECFA***	***EFSA***	***EFSA***	***JMPR***
Commodities		Raw commodities	Raw commodities (no incl. of processed commodities at the moment)	Raw commodities (processed foods converted to raw primary commodity (RPC))	Raw commodities (processed foods converted to raw primary commodities (RPCs) and raw primary commodity derivatives (RPCDs))	Mainly raw commodities (processed foods converted to raw commodity (RPC)). Major processed foods (e.g. juices, wine, beer) considered processed.
Consumption data		Standard Food basket	EU food consumption data (summary statistics) (g/person) (CIFOCOss EU data)	EU food consumption data (individual dietary records) (g/kg bw)	EU food consumption data (individual dietary records) (g/kg bw)	GEMS Food Cluster diets (trade/production statistics) (g per capita per day)
Age classes considered		Adult (60 kg)	General (total) population (subgroups if needed based on toxicology)	Infants, toddlers, other children, adolescents, adults, elderly and very elderly	Infants, toddlers, other children, adolescents, adults, elderly and very elderly	Adult (60 to 65 kg)
Occurrence data		Residue studies target animal	Residue studies target animal	Residue studies target animal	Residue studies target animal	Residue studies target animal
residue definition/ residue for dietary risk assessment		*Total residues (by default, exceptions possible when*	Total residues (by default, exceptions possible when toxicological properties	*Depending on the nature of the feed additive, total residues and/or marker residue[21] (by*	Enforcement: Suitable marker residue (pref. parent or single substance, analysed by multi-methods, same in all commodities)	Enforcement: Suitable marker residue (pref. parent or single substance, analysed by multi-methods, same in all commodities)

[21] *Guidance on the assessment of the safety of feed additives for the consumer (EFSA FEEDAP Panel, 2017): For the following substances, the requirement for residue data is limited to marker residue (Section 2.1.2.2) concentrations comparing the tissue/products levels in an untreated group and in the group supplemented with the highest proposed concentration without a withdrawal time:
• substances which are a natural constituent of body fluids or tissues or are naturally present in food or feedingstuffs if the use of the additive substantially increases the intake or tissue retention;

		toxicological properties residue are well-defined)	residue are well-defined)	*default, exceptions possible when toxicological properties residue are well-defined)*	Risk Assessment: Set of defined substances covering a significant amount of the residue (currently parent and major metabolites, if quantitatively relevant, plus substances with known higher toxicity. In addition, compounds with individual HBGVs may be assessed in separate residue definition (RDs.)	Risk Assessment: Set of defined substances covering a significant amount of the residue (currently parent and major metabolites, if quantitative relevant, plus substances with known higher toxicity. In addition, compounds with individual HBGVs may be assessed in separate RDs.)
Input occurrence data	chronic	MRL or UTL (95/95 upper tolerance limits)	Median	Mean + 2xSD or highest residue (dep. on the animal number)	Mean	Median/mean
	acute	Not applicable[22]	Upper 95/95 residue	Mean + 2xSD or highest residue (dep. on the animal number)	For unblended commodities (i.e. tissues & eggs), highest residue (HR) at the maximum livestock dietary burden. For blended commodities (i.e. milk), mean residue at the maximum livestock dietary burden	highest residue (HR) for unblended commodities (e.g. fruits, vegetables, tissues) and median/mean residue (STMR) for blended commodities (juice, grains, milk etc.)
Exposure output	**(chronic)**	TMDI (sum of MRL x food baskets components)	GECDE (here based on EU data) the highest exposure from	Distribution of chronic exposure estimates for the total population, characterised by	Distribution of chronic exposure estimates for the total population, characterised by the mean and 97.5th percentile	IEDI (sum of all food commodities using mean/median residue and average consumption)

• for colourants which add colour to food of animal origin;
• 'vitamins, pro-vitamins and chemically well-defined substances, having similar effect' that have a potential for accumulation in the tissues/products which are not already authorised;
• 'compounds of trace elements' not already authorised;
• additives already authorised in food for which a health-based guidance value is established.

[22] Normally no acute estimate is done, however, as TMDI is assumed to be conservative enough also for acute endpoints, the same input parameters as for chronic estimates are used here.

			one animal product (highest 97.5th percentile or other HRP, consumers only) plus mean highest total population exposure from all other products	the mean and 95th percentile exposure (or other HRP) per country and age class	exposure (or other HRP) per country and age class	
	acute	Not applicable[11]	GEADE The concurrent occurrence of the selected high residue concentration in each food to which a consumer might be exposed is combined with a high daily consumption (97.5th percentile) of that food. The highest exposure of an individual food is selected	Distribution of acute exposure estimates for consumers only, characterised by the mean and 97.5th percentile exposure (or other HRP) per country, age class and RPC.	Distribution of acute exposure estimates for consumers only, characterised by the mean and 97.5th percentile exposure (or other HRP) per country, age class and RPC.	IESTI (if ARfD necessary based on tox. effects), single commodity wise
Estimating exposure from multiple species/products	**chronic**	TMDI includes the highest residue concentration for muscle, liver, kidney and fat (from all species) + milk + eggs + honey	Combined GECDE over all animal species and food commodity (meat+ fat + edible offal + milk + eggs + honey)	Combined exposure, e.g. as the sum of consumption from all animals within a group (e.g. cattle, sheep, etc…) using occurrence data at the highest residue	Combined over all animal species and food commodities (i.e. meat+ fat + edible offal + milk + eggs + fish + honey)	IEDI always considers combined exposure from all animal and plant based foods

				concentration observed (e.g. highest mammal) + consumption from all animals within another group (e.g. poultry/chicken or fish) + milk + eggs + honey		
	acute	Not applicable[11]	Acute exposure is estimated for each species and product separately; the most critical estimate is selected and considered sufficiently protective to cover all products and species.	Acute exposure is estimated for each species and product separately; the most critical estimate is selected and considered sufficiently protective to cover all products and species.	Acute exposure is estimated for each species and product separately; the most critical estimate is selected and considered sufficiently protective to cover all products and species.	Acute exposure is estimated for each species and product separately; the most critical estimate is selected and considered sufficiently protective to cover all products and species.
Other dietary exposure estimates[23]		None	YES short term (if needed based on toxicology) Injection site	None	None	None
Hazard endpoint	chronic	ADI	ADI (specific endpoints for subgroups, if necessary)	ADI or UL (depending on the nature of the feed additive)	ADI	ADI
Hazard endpoint	acute	None (however, pharm/micro ADI)	ARfD	ARfD	ARfD	ARfD

[23] Not falling under current mandate. Mentioned for completeness.

Hazard endpoint	short term	none	short-term endpoint(s), as required	none	none	ADI (if short-term effects are identified in tox. studies)

393

4. Exercise to compare the estimates of dietary exposure from different models

To explore and better understand quantitative differences between the various exposure models described above (i.e. TMDI, FACE, PRIMo 4[24] and GECDE/GEADE, IEDI/IESTI), different sets of residue data were applied. These data were derived from real residue studies of VMPs (slightly modified e.g. filling data gaps with simulations, for the calculations to generate sufficient data to conduct the estimates). For each dataset (i.e. bovine meat and offal as well as milk, chicken meat and offal as well as eggs, fish and honey), anonymised (i.e. deleting any information relating to the substance or protected data, which allow to identify the substance and or the product) individual residue data, as well as summary statistics of these data, were provided to the experts, who then conducted the estimates for 'their' dietary exposure models (i.e. EFSA experts for FACE and PRIMo 4, JECFA- experts for GECDE/GEADE, JMPR experts for IEDI/IESTI and EMA experts for TMDI). In all exercises, the so-called "marker residue" (parent compound) was used without considering any corrections for potentially relevant metabolites and marker/total ratios (residues of concern, respectively) or other factors[25,26]. Although this is perfectly acceptable for relative quantitative comparisons of the models, such factors would need to be taken into account in a final exposure estimate used in the risk characterisation.

It is noted that certain elements in the design of residue studies may differ between the veterinary, feed additive and pesticide field which may influence the type and amount of data available. For a direct comparison of the output of the various exposure models the study design is not considered relevant and therefore it is acceptable to use the residue data from VMPs in this exercise. However, the question of study design can play a role in connection with the type/quantity and choice of available input data.

4.1. Model data sets

Residue depletion data from the "Guideline on the determination of withdrawal periods for edible tissues" (EMA/CVMP/SWP/735325/2012) and from other residue depletion studies (for veterinary medicinal products) were used as model data sets.

Measures of central tendency and measures of variation as listed in the table below were derived from the residue depletion data in relevant edible tissues as a basis for use in the dietary exposure models.

Additional values for meat were calculated based on residue concentrations in muscle and fat at proportions of 80% and 20%, respectively to be used with the FACE and PRIMo 4-models.

[24] PRIMo4 is currently under development
[25] As these factors are applied multiplicatively and they would not change the relative comparisons.
[26] Consideration of metabolites and various toxicologically derived residue definitions, is not part of the calculations of Chapter 4, but needs to be discussed in view of further harmonization of risk characterization models at a later stage.

425 ***Table 2: Summary statistics of residue data for bovine meat and offal***

Tissue/ Day	Ari. Mean* µg/kg	+/- SD µg/kg	Mean + 2 SD**** µg/kg	Geom. Mean** µg/kg	+/- SD µg/kg	Median µg/kg	Upper 95/95 Tolerance*** µg/kg	Maximum µg/kg
Liver								
Day 7	119.1	56.2	231.5	102.6	1.9	127.2	797.5	198.0
Day 14	32.5	19.1	70.7	23.6	3.1	25.9	232.1	60.8
Day 21	19.7	29.6	78.9	9.9	3.3	9.0	74.9	108.0
Day 28	4.9	4.4	13.7	3.2	2.7	3.4	26.8	13.5
Kidney								
Day 7	29.8	17.1	64	24.9	2.0	28.15	133.9	60.8
Day 14	8.7	6.4	21.5	6.3	2.5	7.9	45.2	20.3
Day 21	4.4	3.6	11.6	3.4	2.1	2.3	18.5	11.3
Day 28	1.7	1.1	3.9	1.5	1.7	1.0	8.4	4.5
Fat								
Day 7	177.3	104.4	386.1	151.8	1.8	176.65	969.7	450.0
Day 14	29.2	23.3	75.8	17.7	3.7	23.65	260.1	78.8
Day 21	11.7	11.0	33.7	8.3	2.5	9	77.7	40.5
Day 28	5.0	4.0	13.0	3.5	2.7	4.5	25.8	13.5
Muscle								
Day 7	15.5	7.7	30.9	13.2	2.0	16.3	65.9	24.4
Day 14	5.1	3.6	12.3	4.0	2.2	5.4	24.0	13.6
Day 21	2.4	2.2	6.8	1.9	1.9	2.2	10.4	9.0
Day 28	1.2	0.5	2.2	1.1	1.3	1.0	5.0	2.8
Meat****								
Day 7	47.86		101.9					109.52
Day 14	9.92		25.0					26.64
Day 21	4.26		12.1					15.3
Day 28	1.96		4.4					4.94

426 *N=12 treated animals per day; *arithmetic mean, ** geometric mean, ***95% tolerance level with 95%*
427 *confidence, calculated via linear regression analysis as described in the Guideline on determination of withdrawal*
428 *periods for edible tissues*[27]
429 ***** For calculation with the FACE and PRIMo 4-model, residue concentrations in muscle and fat were applied to*
430 *the intake of meat according to the following proportions: mammals 80% muscle and 20% fat.*

[27] https://www.ema.europa.eu/en/approach-towards-harmonisation-withdrawal-periods-edible-tissues

Table 3: Summary statistics of residue data for milk

Hours	Ari. Mean* µg/kg	+/- SD µg/kg	Mean + 2 SD**** µg/kg	Geom. Mean** µg/kg	+/- SD µg/kg	Median µg/kg	Upper 95/95 Tolerance*** µg/kg	Maximum µg/kg
24	0.9	0.8	1.44	0.7	3.0	0.9	No of animals too low	1.4
36	3.6	4.3	6.62	1.9	5.7	3.6	No of animals too low	6.6
48	4.3	0.1	4.5	3.3	2.2	3.3	20.6	11.4
60	4.9	0.1	5.1	4.0	1.9	3.9	19.7	11.3
72	5.0	0.5	6.0	4.2	1.9	4.4	18.7	11.0
84	4.5	0.1	4.7	4.0	1.7	4.2	13.9	9.2
96	3.8	0.4	4.6	3.4	1.6	3.4	10.4	8.6
120	2.8	0.2	3.2	2.6	1.5	2.7	7.1	6.9
144	2.5	0.2	2.9	2.2	1.6	2.3	6.7	5.5
168	1.9	0.2	2.3	1.8	1.5	1.7	4.9	3.4
192	1.3	0.0	1.3	1.2	1.6	1.2	3.5	2.4
216	0.9	0.1	1.1	0.8	1.6	0.8	2.5	2.0

*N=20 treated animals per day (at 24 and 36 hours only N=2 treated animals); *arithmetic mean, ** geometric mean, ***95% tolerance level with 95% confidence, calculated as described in the Guideline on determination of withdrawal periods for milk[28]*

***** If the number of animals is < 6, the highest value is used.*

[28] https://www.ema.europa.eu/en/determination-withdrawal-periods-milk#current-version---currently-under-revision,-see-below-section

436 ***Table 4: Summary statistics of residue data for chicken meat and offal***

Tissue/ Day	**Ari. Mean*** µg/kg	**+/- SD** µg/kg	**Mean + 2 SD****** µg/kg	**Geom. Mean**** µg/kg	**+/- SD** µg/kg	**Median** µg/kg	**Upper 95/95 Tolerance***** µg/kg	**Maximum** µg/kg
Liver								
Day 1	1301.1	341.6	1984.3	1266.7	1.3	1219.0	2268.0	1963.0
Day 2	1002.5	231.3	1465.1	980.3	1.3	946.6	1808.2	1345.0
Day 4	694.9	108.1	911.1	688.0	1.2	679.6	1160.0	846.0
Day 7	378.4	124.7	627.8	363.1	1.4	365.1	614.0	621.1
Day 10	188.4	80.1	348.6	177.0	1.4	151.9	334.5	348.6
Kidney								
Day 1	841.2	192.8	1226.8	823.3	1.2	784.1	1470.0	1203.0
Day 2	661.1	168.7	998.5	645.5	1.3	630.3	1176.3	1013.0
Day 4	448.7	78.6	605.9	443.1	1.2	417.9	760.3	563.9
Day 7	242.9	74.5	391.9	233.9	1.3	236.5	407.0	380.1
Day 10	129.8	60.0	249.8	120.8	1.5	101.8	224.3	253.5
Skin + Fat								
Day 1	1275.8	204.6	1685	1261.1	1.2	1309.0	2360.5	1526.0
Day 2	984.8	216.7	1418.2	966.2	1.2	887.3	1877.7	1336.0
Day 4	695.0	251.1	1197.2	656.7	1.4	667.5	1200.7	1036.0
Day 7	332.6	91.5	515.6	322.7	1.3	319.4	634.6	508.2
Day 10	197.7	103.1	403.9	181.2	1.5	164.5	346.5	418.1
Muscle								
Day 1	108.2	25.2	158.6	105.8	1.3	100.0	175.8	152.2
Day 2	84.7	19.8	124.3	82.7	1.3	87.2	145.9	113.8
Day 4	59.4	10.8	81	58.6	1.2	55.1	101.4	76.2
Day 7	39.8	8.2	56.2	39.1	1.2	39.6	60.4	49.7
Day 10	21.4	8.8	39	20.3	1.4	17.4	36.9	40.4
Meat******								
Day 1	224.96		311.2					289.58
Day 2	174.71		253.7					236.02
Day 4	122.96		192.6					172.18
Day 7	69.08		102.1					95.55
Day 10	39.03		75.5					78.17

437 *N=7 treated animals per day; *arithmetic mean, **geometric mean, ***95% tolerance level with 95% confidence,*
438 *calculated via linear regression analysis as described in the Guideline on determination of withdrawal periods for*
439 *edible tissues*[27]
440 ***** For calculation with the FACE and PRIMo 4-model, the residue concentration in muscle and fat will be applied*
441 *to the intake of meat according to the following proportions: poultry 90% muscle and 10% skin+fat.*

442 *Table 5: Summary statistics of residue data for eggs*

	Number of samples	Ari. Mean* µg/kg	+/- SD µg/kg	Mean + 2 SD**** µg/kg	Geom. Mean** µg/kg	+/- SD µg/kg	Median µg/kg	Upper 95/95 Tolerance*** µg/kg	Maximum µg/kg
Day		**µg/kg**	**µg/kg**		**µg/kg**	**µg/kg**	**µg/kg**	**µg/kg**	µg/kg
5	14	420.2	125.5	671.2	396.9	1.5	452.6	1071	570.1
6	15	519.7	109.6	738.9	504.4	1.3	525.4	1038.8	667.4
7	12	576.1	145.9	867.9	551.2	1.4	571.5	1429.7	763.1
8	14	552.4	65.9	684.2	549	1.1	539.4	741.8	703.5
9	11	546.4	113.1	772.6	535.6	1.2	555.2	971	707.3
10	14	594.5	83.8	762.1	589.1	1.2	579.7	849.8	730.0
11	14	709.2	120.1	949.4	699.5	1.2	694.9	1103.1	899.6
12	14	783.9	101.2	986.3	777.9	1.1	758.6	1091.8	958.0
13	12	812.6	115.1	1042.8	805.6	1.1	790.4	1167.9	1072.0
14	13	828.4	133.3	1095	818.9	1.2	784	1245.5	1065.0
15	14	734.5	114.2	962.9	725.8	1.2	748	1110.4	915.5
16	15	621.1	147.5	916.1	596.6	1.4	641.1	1397	853.8
17	12	502.9	130.7	764.3	482.6	1.4	511.3	1177.5	671.4
18	15	387.2	147.2	681.6	357	1.5	430.6	1095.2	636.9

443 **arithmetic mean **Geometric mean and standard deviation are estimated by Maximum Likelihood Optimization*
444 *assuming a log-normal distribution of residues censored at LOQ. This is only applicable to time points with values*
445 *BLQ.; ***95% tolerance level with 95% confidence, calculated via linear regression analysis as described in the*
446 *Guideline on determination of withdrawal periods for milk*[28]
447

448 *Table 6: Summary statistics of residue data for fish (n=10 samples per day)*

Tissue/ Day	Ari. Mean* µg/kg	+/- SD µg/kg	Mean + 2 SD**** µg/kg	Geom. Mean** µg/kg	+/- SD µg/kg	Median µg/kg	Upper 95/95 Tolerance*** µg/kg	Pointwise 95/95 UTL **** µg/kg	Maximum µg/kg
Muscle									
Day 1	307.2	60.3		302.7	1.2	296.5	512.2	501.6	463.0
Day 7	48.0	8.9		47.2	1.2	48.9	81.8	82.5	64.7
Day 14	6.3	2.0		6.0	1.4	6.1	10.3	15.1	10.5
Skin									
Day 1	249.4	46.4		245.9	1.2	242.0	481.3	408.2	355.0
Day 7	36.2	7.7		35.4	1.3	36.9	70.0	68.0	49.1
Day 14	4.4	1.7		4.1	1.5	4.1	8.0	14.3	7.6
Filet (Muscle+Skin)									
Day 1	301.9	54.2	410.3	298.2	1.2	290.5	526.8	475.7	437.0
Day 7	50.0	11.7	73.4	48.7	1.3	51.0	84.3	97.6	73.5
Day 14	6.3	2.0	10.3	6.0	1.4	6.2	10.6	15.3	9.6

449 **arithmetic mean; ** geometric mean; ***95% tolerance level with 95% confidence, calculated via linear*
450 *regression analysis as described in the Guideline on determination of withdrawal periods for edible tissues*[27]*;*
451 *****95% tolerance level with 95% confidence, calculated as described in the Guideline on determination of*
452 *withdrawal periods for milk*[28]
453

Table 7: Summary statistics of residue data for honey

Location/ Treatment/ Day	Number of samples	Ari. Mean* µg/kg	+/- SD µg/kg	Mean + 2 SD**** µg/kg	Geom. Mean** µg/kg	+/- SD µg/kg	Median µg/kg	Upper 95/95 Tolerance*** µg/kg	Maximum µg/kg
TG1 (B)									
Day 7	4	1365.5	810.6	2986.7	1129.1	2.2	1383.3	65144.3	2323.6
Day 16	4	1017.0	737.5	2492.0	695.9	3.4	1025.5	354603.4	1896.2
TG1 (D)									
Day 7	6	1465.1	1067.4	3599.5	988.9	3.1	1567.0	63562.9	2863.1
Day 16	6	1237.9	1033.7	3305.3	803.4	3.2	998.3	58332.7	2694.4
TG2 (B)									
Day 7	5	1674.0	741.6	3157.2	1527.0	1.7	1471.6	12633.9	2589.9
Day 16	5	1613.0	605.1	2823.2	1540.3	1.4	1412.1	5993.4	2671.7
TG2 (D)									
Day 7	5	1211.8	792.5	2796.8	974.1	2.2	997.8	28660.9	2353.7
Day 16	5	1066.3	713.4	2493.1	827.4	2.4	825.4	34557.5	1955.8

*B, D = location; TG = different types of hives; *arithmetic mean; ** geometric mean, ***95% tolerance level with 95% confidence, calculated as described in the Guideline on determination of withdrawal periods for milk*[28]

4.2. Chronic Exposure

To derive estimates for chronic exposure, TMDI uses the consumption data from the SFB and the upper 95/95 tolerance interval of the residue depletion data (3.4.1).

Both EFSA models, FACE and PRIMo 4, use the individual consumption figures from the RPC consumption database. For the occurrence data, the first uses the mean +2 SD from the residue depletion data (3.4.2.1.), whereas the second uses the arithmetic mean of the residue data (3.4.3.2.). Although PRIMo 4 allows to calculate exposure for the different types of mammals (i.e. equine, sheep, goat, swine, bovine, other farmed terrestrial animals), the calculations presented in this section were performed for all mammals. The food classification used in PRIMo also makes a distinction between liver, kidney and other offal and slaughtering products. For the latter category, the residue concentration was assigned taking the highest occurrence value from liver and kidney.

Median residue concentrations were used to calculate the GECDE. At all time points, dietary exposure estimates based on liver highest reliable percentile was the highest contributor to estimated dietary exposure. For all other food commodities, the highest mean was used (3.4.1.2.). To allow for better comparability, only European food consumption data were used for this exercise.

The IEDI uses mean/median residue values and processing factors (if applicable). Furthermore, the IEDI is based on 17 GEMS food cluster diets. Each diet contains individual values for each food commodity, but only the totals from each cluster are considered for chronic exposure. In the following tables, the highest exposure per commodity from European clusters is listed. However, if another (Non-European) cluster results in higher exposure the highest exposure estimate from all 17 clusters (as normally used in IEDI) is given in brackets (3.4.3.1.).

4.2.1. Bovine meat and offal and milk

Meat and offal

Chronic dietary exposure estimates for bovine meat and offal calculated based on the five models are summarised in Table 8.

Table 8: Chronic exposure estimates for bovine (mammals) meat and offal expressed as µg/kg bw per day

Day	TMDI[1]	FACE[2]							PRIMo 4[2]							GECDE[1]	IEDI[3]
		Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		
7	***2.58***	***0.84***	***1.04***	***1.05***	***0.93***	***0.67***	***0.47***	**0.45**	**0.47**	**0.54**	***0.60***	**0.49**	**0.43**	**0.29**	**0.21**	***0.18***	***0.18***
14	0.76	0.20	0.24	0.26	0.21	0.16	0.12	0.10	0.09	0.11	0.11	0.10	0.09	0.06	0.05	0.04	0.04
21	0.26	0.11	0.13	0.13	0.11	0.08	0.06	0.07	0.04	0.05	0.05	0.04	0.04	0.03	0.02	0.01	0.02
28	0.10	0.04	0.04	0.04	0.04	0.03	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.01	0.01	0.01	0.01

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) HRP calculated at individual body weights, to note: PRIMo 4 normally distinguishes between cattle and other mammalian species, however for better comparison with FACE, the values for mammalian species were used here; 3) average bodyweights are assumed; green-red = lowest-highest value in a row; in bold: highest value in a column

From Table 8 it can be seen that the highest values at all time points result from the TMDI model. Concentrations at each time point are at least 2 times above concentrations resulting from all other models/age groups, showing that TMDI leads to very conservative estimates for edible tissues. This may largely be attributed to the upper 95/95 tolerance limit used in the TMDI calculation. As shown in Table 2, the upper 95/95 tolerance levels were up to 3 times higher than the mean + 2 SD (as used by FACE), up to 9-fold higher than the mean (as used by PRIMo 4) and up to 11-fold the median (as used by GECDE and IEDI).

The second highest values were obtained using the FACE model for the groups of toddlers and children ≥36 months to <10 years. Results from GECDE and IEDI calculations were roughly one order of magnitude lower than results from the FACE model. PRIMo 4 results in approximately half of the exposure value of FACE in all subgroups. Looking at the residue concentrations used for the estimation, the mean used by PRIMo is about half of the value of mean + 2 SD as used by FACE, explaining the differences between these two models.

The different consumption assumptions used might also contribute to the differences mentioned above; TMDI uses the sum of residue concentrations for all relevant tissues in a standard food basket (i.e. it assumes that each person consumes the same amount from each food commodity each day). In contrast, the FACE and PRIMo 4 tools consider food commodities at an individual level, which means, for example, that a person may eat a considerable amount of meat but not necessarily eat liver (or the other way around). The GECDE is the sum of the highest dietary exposure calculated using the highest reliable percentile (HRP) consumption of a single food, plus the population mean dietary exposure from all the other relevant foods. IEDI uses supply (or portion) in g/d and person of each food obtained by dividing the quantity for each country by its population from economy statistics (food production, import, export).

Milk

The outcome of the chronic dietary exposure estimates for milk with the five models are summarised in Table 9.

Table 9: Chronic exposure estimates for bovine (mammals) milk expressed as µg/kg bw per day

Hrs	TMDI	FACE							PRIMo 4							GECDE	IEDI
		Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		
24	n.d.	0.18	0.18	0.23	0.08	0.05	0.04	0.05	0.12	0.12	0.15	0.06	0.04	0.03	0.04	0.02	0.01
36	n.d.	***0.82***	***0.81***	***1.07***	***0.39***	***0.22***	***0.19***	**0.22**	0.49	0.46	0.59	0.24	0.16	0.12	0.14	0.07	n.c.
48	***0.52***	0.56	0.55	0.72	0.26	0.15	0.13	0.15	0.59	0.55	0.70	0.28	0.19	0.15	0.17	0.06	0.03
60	0.49	0.63	0.62	0.82	0.30	0.17	0.15	0.17	0.67	0.63	0.80	0.32	0.22	0.17	0.19	0.07	n.c.
72	0.47	0.74	0.73	0.97	0.35	0.20	0.17	0.20	**0.68**	**0.64**	***0.82***	**0.33**	**0.23**	**0.17**	**0.20**	***0.08***	***0.04***
84	0.35	0.58	0.58	0.76	0.28	0.15	0.14	0.15	0.61	0.58	0.73	0.29	0.20	0.15	0.18	0.08	n.c.
96	0.26	0.57	0.56	0.74	0.27	0.15	0.13	0.15	0.52	0.49	0.62	0.25	0.17	0.13	0.15	0.06	0.03
120	0.18	0.40	0.39	0.52	0.19	0.10	0.09	0.10	0.38	0.36	0.46	0.18	0.13	0.10	0.11	0.05	n.c.
144	0.17	0.36	0.35	0.47	0.17	0.10	0.08	0.09	0.34	0.32	0.41	0.16	0.11	0.09	0.10	0.04	0.02
168	0.12	0.29	0.28	0.37	0.14	0.08	0.07	0.08	0.26	0.24	0.31	0.12	0.09	0.07	0.07	0.03	0.02
192	0.09	0.16	0.16	0.21	0.08	0.04	0.04	0.04	0.18	0.17	0.21	0.08	0.06	0.04	0.05	0.02	0.02
216	0.06	0.14	0.13	0.18	0.06	0.04	0.03	0.04	0.12	0.12	0.15	0.06	0.04	0.03	0.04	0.02	0.01

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) HRP calculated at individual body weights; to note: PRIMo 4 normally distinguishes between cattle and other mammalian species, however for better comparison with FACE, the values for mammalian species were used here; 3) average bodyweights are assumed; green-red = lowest-highest value in a row; in bold: highest value in a column; n.c. = not calculated

For milk, the TMDI did not result in the highest dietary exposure values expressed on a µg/kg bw base. The highest dietary exposure values were derived for children up to an age of 10 years (approximately 2 times higher compared to TMDI results), calculated with the FACE model. Adolescents up to 18 years have dietary exposure values similar to the estimations based on the TMDI model.

Also for milk, the residue concentrations used by TMDI (upper 95/95 tolerance) were higher (up to 4.5 fold) compared to other models, e.g. the concentration used by FACE (mean + 2 SD), up to 5-fold the concentrations (mean) used for PRIMo 4 and 6 fold higher than the median used by GECDE (see Table 3). This may to a large extent explain the higher exposure value for the TMDI compared to GECDE, FACE and PRIMo 4-models for adolescents, adults, elderly and very elderly as the consumption figures do not differ significantly for these age groups. On a bodyweight basis, children consume much more milk than adults, and the consumption figure was also much higher compared to the value used in TMDI (which uses a standard assumption of 25 g milk per kg bw for a 60 kg adult).

The really low exposure levels for IEDI cannot be explained by different residue input values, but may be explained by the different approach of using consumption figures, i.e. food balance sheets instead of actual food consumption surveys (3.4.3.1.).

Estimates obtained for adults with FACE and PRIMo 4 are approximately 2-3 times higher compared to estimates obtained with GECDE for the general population. This is mainly due to the difference in residue concentrations used (mean + 2 SD, mean vs median) and a different use of the consumption data. Although the above-mentioned models are based on the same European food consumption data sets in these estimations, these data are used in different ways. Specifically, both FACE and PRIMo 4 models use consumption data of dairy food that was converted to the RPC (RAC, milk in this case), while GECDE considered consumption of liquid milk only. Additional calculations were carried out with GECDE demonstrating that, when input values for GECDE are better aligned with the EFSA models (i.e. using milk equivalence instead of cheese and butter or using mean+2SD instead of the median) FACE and PRIMo 4, the obtained results are more comparable (see Table 10).

Considering that the conversion into raw primary commodities assumes no loss of the chemical during the preparation of the processed food, the use of FACE and PRIMo 4 might overestimate the exposure. For example, exposure to lipophilic compounds in cream might be adequately assessed whereas exposure to a water-soluble compound in the same food will likely be overestimated.

539 ***Table 10: Indicative comparisons of TMDI, FACE, PRIMo 4 and GECDE for bovine milk***

Hrs	TMDI	FACE[1]	FACE[2]	PRIMo 4[1]	PRIMo 4[2]	GECDE					
						Median conc	Mean+2SD conc	Mean+2SD conc (cheese, butter adjusted)	Median conc (cheese, butter adjusted)	Median conc (cheese, butter adjusted), mean consumption	Mean+2SD conc (cheese, butter adjusted), mean consumption
24	n.d.	0.0233	0.0472	0.0145	0.0405	0.017	0.027	0.064	0.040	0.012	0.020
36	n.d.	0.1865	0.2168	0.0581	0.1621	0.068	0.125	0.294	0.160	0.050	0.091
48	0.52	0.0729	0.1474	0.0694	0.1937	0.062	0.085	0.200	0.146	0.046	0.062
60	0.49	0.0826	0.1670	0.0791	0.2207	0.074	0.096	0.226	0.173	0.054	0.070
72	0.47	0.0972	0.1965	0.0807	0.2252	0.083	0.113	0.266	0.195	0.061	0.082
84	0.35	0.0761	0.1539	0.0727	0.2027	0.079	0.089	0.209	0.186	0.058	0.065
96	0.26	0.0745	0.1506	0.0614	0.1711	0.064	0.087	0.204	0.151	0.047	0.063
120	0.18	0.0518	0.1048	0.0452	0.1261	0.051	0.060	0.142	0.120	0.037	0.044
144	0.17	0.0470	0.0950	0.0404	0.1126	0.043	0.055	0.129	0.102	0.032	0.040
168	0.12	0.0373	0.0753	0.0307	0.0856	0.032	0.043	0.102	0.075	0.023	0.032
192	0.09	0.0211	0.0426	0.0210	0.0585	0.023	0.025	0.058	0.053	0.017	0.018
216	0.06	0.0178	0.0360	0.0145	0.0405	0.015	0.021	0.049	0.035	0.011	0.015

540 *1 Adult maximum mean; 2 Adult maximum HRP*

4.2.2. Chicken (poultry) meat and offal and eggs

Meat and offal

The outcome of the chronic exposure estimates for chicken meat and offal with the five models are summarised in Table 11.

Table 11: Chronic exposure estimates for chicken (poultry) meat and offal expressed as µg/kg bw per day

Day	TMDI[1]	FACE[2]							PRIMo 4[2]							GECDE[1]	IEDI[3]
		Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old	Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old		
1	***8.44***	***2.12***	***2.58***	***2.33***	***1.44***	***1.02***	***0.74***	0.70	1.60	***2.31***	2.03	1.19	0.86	0.57	0.51	***2.00***	*0.34* (0.605 /n)
2	6.76	1.72	2.06	1.88	1.18	0.80	0.60	0.57	1.24	1.80	1.58	0.92	0.67	0.44	0.39	1.60	0.26 (0.469 /n)
4	4.37	1.31	1.56	1.40	0.88	0.56	0.45	0.43	0.87	1.26	1.11	0.64	0.47	0.30	0.28	1.10	0.18 (0.329 /n)
7	2.35	0.69	0.83	0.75	0.47	0.33	0.24	0.23	0.49	0.71	0.62	0.35	0.26	0.17	0.16	0.60	0.10 (0.422)
10	1.30	0.51	0.61	0.54	0.35	0.22	0.18	0.17	0.28	0.40	0.35	0.20	0.14	0.10	0.09	0.30	0.06 (0.400)

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) HRP calculated at individual body weights; 3) average bodyweights are assumed, for comparison with the other models, the EU-Cluster are given, but the values normally used by JMPR are mentioned in brackets (n: For these days no data on eggs were available.); green-red = lowest-highest value in a row; in bold: highest value in a column

From the calculations it can be seen that, as for bovine meat and offal, the highest values result from the TMDI. This approach uses the highest residue values (upper 95/95 tolerance limit), as can be seen in section 4.2.1.1, the upper 95/95 tolerance limit is up to 1.4-fold times higher than the mean + 2 SD (used by FACE), up to 1.9-fold higher than the mean (as used in PRIMo 4) and up to 2.2-fold the median (used by GECDE).

In addition, consumption data used in the FACE and PRIMo 4 are lower than for the TMDI, at least for adults.

Furthermore, TMDI is adding the whole portion for all tissues while FACE and PRIMo 4 add the food commodities at an individual level, which means, that a person may eat a considerable amount of meat but not necessarily eat liver (or the other way round).

Again, the really low exposure levels for IEDI may be explained by the different approach to deriving consumption input data, using import, export and production data instead of consumption surveys (3.4.3.2.).

Eggs

The outcome of the chronic exposure estimates for eggs with the five models is summarised in Table 12.

Table 12: Chronic exposure estimates for chicken eggs expressed as µg/kg bw per day

Day	TMDI[1]	FACE[2]							PRIMo 4							GECDE[1]	IEDI[3]
		Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		
5	1.80	2.30	2.62	2.81	1.80	0.99	0.86	1.09	1.53	2.00	2.06	1.26	0.75	0.63	0.68	1.10	0.26
6	1.70	2.54	2.89	3.09	1.99	1.09	0.95	1.20	1.90	2.48	2.54	1.56	0.93	0.78	0.85	1.30	0.32
7	***2.40***	2.98	3.39	3.63	2.33	1.28	1.11	1.41	2.10	2.74	2.82	1.73	1.03	0.86	0.94	1.40	0.35
8	1.20	2.35	2.67	2.86	1.84	1.01	0.88	1.11	2.02	2.63	2.70	1.66	0.99	0.82	0.90	1.30	0.34
9	1.60	2.65	3.02	3.23	2.08	1.14	0.99	1.25	1.99	2.60	2.68	1.64	0.98	0.82	0.89	1.40	0.33
10	1.40	2.62	2.98	3.19	2.05	1.12	0.98	1.23	2.17	2.83	2.91	1.79	1.06	0.89	0.97	1.40	0.36
11	1.80	3.26	3.71	3.97	2.55	1.40	1.22	1.54	2.59	3.38	3.47	2.13	1.27	1.06	1.15	1.70	0.43
12	1.80	3.39	3.85	4.13	2.65	1.45	1.27	1.60	2.86	3.74	3.84	2.35	1.40	1.17	1.28	1.90	0.48
13	1.90	3.58	4.07	4.36	2.80	1.53	1.34	1.69	2.97	3.87	3.98	2.44	1.45	1.21	1.32	***2.00***	0.49
14	2.10	***3.76***	***4.28***	***4.58***	***2.94***	***1.61***	***1.41***	1.77	3.02	3.95	***4.06***	2.49	1.48	1.24	1.35	***2.00***	***0.50***
15	1.90	3.31	3.76	4.03	2.59	1.42	1.24	1.56	2.68	3.50	3.60	2.21	1.31	1.10	1.19	1.90	0.45
16	2.30	3.14	3.58	3.83	2.46	1.35	1.18	1.48	2.27	2.96	3.04	1.87	1.11	0.93	1.01	1.60	0.38
17	2.00	2.62	2.99	3.20	2.05	1.12	0.98	1.24	1.84	2.40	2.46	1.51	0.90	0.75	0.82	1.30	0.31
18	1.80	2.34	2.66	2.85	1.83	1.00	0.88	1.10	1.41	1.84	1.90	1.16	0.69	0.58	0.63	1.10	0.24

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) HRP calculated at individual body weights; 3) average bodyweights are assumed; green-red = lowest-highest value in a row; in bold: highest value in a column

For eggs (similarly as for milk) the TMDI did not result in the highest dietary exposure value expressed on a µg/kg bw base. The highest dietary exposure values were derived for children up to an age of 10 years, calculated with the FACE model. For exposure estimates calculated with PRIMo 4 model, the age class for "other children" resulted in the highest dietary exposure value, directly followed by toddlers.

For adults, elderly and very elderly the consumption figures do not differ significantly but, on a bodyweight basis, children consumed much more eggs per kg bw than adults, and the consumption was also much higher compared with the value used in TMDI (which uses a standard assumption of 1.66 g egg per kg bw for a 60 kg adult).

With a look at the really low exposure levels for IEDI these cannot be explained by different residue input values only (especially in comparison to GECDE), but may be explained by the different approach to deriving consumption input data, using import, export and production data instead of real consumption surveys (3.4.3.1.).

4.2.3. Fish

The outcome of the chronic exposure estimates for fish with the five models is summarised in Table 13

Table 13: Chronic exposure estimates for fish expressed as µg/kg bw per day

Day	TMDI[1]	FACE[2]							PRIMo 4[2]							GECDE[1]	IEDI[3]
		Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		
1	***2.63***	***0.87***	***2.35***	***1.63***	***1.16***	***0.97***	***0.90***	**0.68**	**0.88**	***1.85***	**1.76**	**1.28**	**1.08**	**0.86**	**0.64**	***1.25***	**0.206 (0.352)**
7	0.42	0.16	0.42	0.29	0.21	0.17	0.16	0.12	0.15	0.31	0.29	0.21	0.18	0.14	0.11	0.21	0.032 (0.055)
14	0.05	0.02	0.06	0.04	0.03	0.02	0.02	0.02	0.02	0.04	0.04	0.03	0.02	0.02	0.01	0.03	0.004 (0.007)

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) HRP calculated at individual body weights; 3) average bodyweights are assumed, for comparison with the other models, the EU-Cluster are given, but the values normally used by JMPR are mentioned in brackets;
green-red = lowest-highest value in a row; in bold: highest value in a column

TMDI leads to the highest exposure estimate for fish. It seems that the differences can be explained by the different residue input values, which are in case of TMDI up to 1.8-fold higher than for the other models (see also Table 6).

Again, the really low exposure levels for IEDI in comparison to the other models, may be explained by the different approach to deriving consumption input data, using import, export and production data instead of real consumption surveys (3.4.3.1.).

583 ## 4.2.4. Honey

584 The outcome of the chronic exposure estimates for honey with the five models is summarised in Table 14.

585 *Table 14: Chronic exposure estimates for honey expressed as µg/kg bw per day*

TG1 (B)	TMDI[1]	FACE[2]							PRIMo 4[2]							GECDE[1]	IEDI[3]
		Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		
Day 7	21.71	***0.09***	***1.15***	***1.45***	***0.87***	***0.75***	***0.97***	**0.93**	**0.06**	**0.71**	***1.14***	**0.63**	**0.49**	**0.67**	**0.66**	***1.26***	***0.05***
Day 16	***118.20***	0.08	0.96	1.21	0.72	0.62	0.81	0.78	0.04	0.53	0.85	0.47	0.37	0.50	0.49	0.93	0.04
TG1 (D)	**TMDI[1]**	**FACE[2]**							**PRIMo 4[2]**							**GECDE[1]**	**IEDI[3]**
		Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		
Day 7	***21.19***	***0.11***	***1.39***	***1.75***	***1.04***	***0.90***	***1.17***	**1.12**	**0.06**	**0.76**	***1.22***	**0.67**	**0.53**	**0.72**	**0.70**	***1.43***	***0.054***
Day 16	19.44	0.10	1.28	1.61	0.96	0.83	1.07	1.03	0.05	0.64	1.03	0.57	0.45	0.61	0.60	0.91	0.046
TG2 (B)	**TMDI[1]**	**FACE[2]**							**PRIMo 4[2]**							**GECDE[1]**	**IEDI[3]**
		Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		
Day 7	***4.21***	***0.10***	***1.22***	***1.54***	***0.91***	***0.79***	***1.03***	**0.99**	**0.07**	**0.87**	***1.40***	**0.77**	**0.61**	**0.83**	**0.80**	***1.34***	***0.062***
Day 16	2.00	0.09	1.09	1.37	0.82	0.71	0.92	0.88	0.07	0.84	1.34	0.74	0.58	0.80	0.78	1.29	0.060

TG2 (D)	TMDI[1]	FACE[2]							PRIMo 4[2]							GECDE[1]	IEDI[3]
		Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		
Day 7	9.55	***0.08***	***1.08***	***1.36***	***0.81***	***0.70***	***0.91***	**0.87**	**0.05**	**0.63**	***1.01***	**0.56**	**0.44**	**0.60**	**0.58**	***0.91***	***0.045***
Day 16	***11.52***	0.08	0.96	1.21	0.72	0.63	0.81	0.78	0.05	0.55	0.89	0.49	0.39	0.53	0.51	0.75	0.039

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) HRP calculated at individual body weights; 3) average bodyweights are assumed; green-red = lowest-highest value in a row; in bold: highest value in a column

The impact of different residue input values becomes apparent in this example. The residue concentrations of the hives are very different, resulting in huge tolerance limits (used by TMDI), which are 2- 142-fold above the values used by FACE, 4 to 349-fold higher than those used in PRIMo 4 and between 4.2 and 346-fold above the values used by GECDE/IEDI.

However, as for the other food commodities, the really low exposure levels for IEDI may be explained by the different approach to deriving consumption input data, using import, export and production data instead of real consumption surveys (3.4.3.1.).

4.2.5. Combined exposure for a substance used in all food producing species

As discussed above, there are differences in the data inputs used in the different exposure models. Specifically, different residue input data are taken (upper tolerance limit, mean + 2 SD, mean or median), and different consumption figures are used (see 3.3.). Also, the approaches for combined exposure from multiple species are slightly different.

The data sets for cattle (mammals), chicken (poultry), fish and honey were combined, and exposure estimates were calculated for the purpose of evaluating the impact of the different procedures.

For the combined (chronic) exposure it would seem to make sense that the same time points will be used in each model. For this exercise, it was proposed to calculate at least one scenario using residue values from day 7 for cattle tissues and day 1 for chicken and day 1 for fish (based on the earliest time points/tentatively highest mean values). For honey and milk, it was suggested to take the time point of the highest mean values (i.e. milk 72 h and honey day 7, i.e. the values for TG2 (B)). For eggs, it was suggested to use residue data from day 7 (highest UTL).

Table 15 Combined chronic exposure estimates for cattle (incl. milk), chicken (incl. eggs), fish and honey expressed as µg/kg bw per day

TMDI[1]	FACE[2]							PRIMo 4[2]							GECDE[1]	IEDI[3]
	Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		
17.26	*5.13*	*6.30*	*5.82*	*3.55*	*2.44*	*2.42*	2.35	3.73	*5.06*	4.82	2.98	1.98	1.82	1.56	*3.1*	***1.05***

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) HRP calculated at individual body weights; 3) average bodyweights are assumed; green-red = lowest-highest value in a row;
** Includes adjustment for inclusion of cheese and butter in milk description (see 4.1.2.4)*

It can be seen that in this example TMDI leads to the highest chronic dietary exposure estimate for all population subgroups. The reason might be that TMDI uses the standard food basket with consumption figure of 0.3 kg muscle (highest of chicken, bovine or fish), 0.1 kg of liver (highest of chicken, bovine), fat (highest of 0.09 kg skin+fat from chicken or 0.05 kg for bovine), kidney (highest of 0.01 from chicken or 0.05 kg for bovine), milk and eggs for a 60 kg person. It is calculated for each day as: TMDI = Σ consumption figure x 95/95 upper tolerance limit (for milk, eggs and honey pointwise UTL)

In contrast, for the GECDE dietary exposure estimate including all tissues, the main contributor to dietary exposure was eggs – the exposure estimate included the contribution from eggs for a 97.5th percentile consumer and contributions from all other matrices at the maximum population mean. The contribution from eggs accounted for 90% of the total GECDE. 'Mean dietary exposure' for GECDE has been calculated using the highest population mean consumption values for each food type.

For FACE and PRIMo 4 individual consumption figures were used, which means, for example, that a person may eat a considerable amount of meat not necessarily eat liver (or the other way around). Additionally, for FACE the residue input value is the mean+2SD and for PRIMo 4 it is equal to the mean, which are typically lower than the 95/95 upper tolerance limit used by TMDI.

IEDI uses import, export and production data instead of real consumption surveys. Therefore, a direct comparison with the other models is difficult.

4.3. Acute Exposure

No specific calculation is done to estimate acute exposure in the TMDI. To derive exposure estimates, TMDI uses the consumption data from the SFB and the upper 95/95 tolerance of the residue depletion data (3.4.1). TMDI is assumed to be conservative enough to also (partly) cover acute exposure (the term ADI also includes acute endpoints such as the pharmacological ADI). The values are in principle the same as for the chronic exposure (i.e. referring to the sum of tissues/exposures and not a single tissue).

FACE uses the individual consumption figures of the RPC Consumption Database based on the consumption of a food commodity within a single day and the mean +2SD from the residue depletion data (3.4.2.1.).

In PRIMo revision 4, acute exposure is calculated by combining individual food consumption data within a single day from the RPC consumption database with the high residue concentration (HR) of the residue data (3.4.3.2.). The HR corresponds to the highest measured residue concentration in each commodity.

For GEADE, upper 95/95 residue and highest 97.5th percentile single day consumption (large portion database) are used. Large portions used included values from Bulgaria (muscle), Bulgaria and Thailand (liver), France and Greece (kidney) and China and Poland (fat). Calculations are carried out for each tissue type and the highest individual exposure value is used as GEADE – assumed that a person will not consume large portion with high residue of more than one tissue type on the same day. Consumption is expressed in g/kg bw. (3.4.1.2.).

The IESTI-Model is based on consumption data/models from various Codex Member Countries. In the spreadsheet, only the single diet/model resulting in the highest exposure is calculated. This may either be a specific population group (e.g. Children, 1-6 yrs, CN) or a supranational model (EFSA PRIMo.rev.3, FR adult)(3.4.3.1.).

4.3.1. Bovine (mammals) meat and offal and milk

Meat and offal

The outcome of the acute dietary exposure estimates for bovine meat and offal with the five models are summarised in Table 16.

Table 16: Acute exposure estimates for bovine meat and offal expressed as µg/kg bw

Day	TMDI[1]	FACE[2]							PRIMo 4[2]							GEADE[1]		IESTI[3]
		Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old	Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old	GP*	CH	**
7	*2.58*	*1.07*	*1.15*	*1.65*	*1.10*	*0.87*	*0.63*	0.65	1.07	1.30	1.68	1.34	1.55	1.02	0.76	*6.60*	*7.30*	*1.86*
14	0.76	0.26	0.28	0.40	0.27	0.26	0.15	0.16	0.24	0.40	0.52	0.33	0.48	0.31	0.23	1.90	2.10	0.57
21	0.26	0.27	0.21	0.41	0.22	0.30	0.14	0.13	0.40	0.71	0.92	0.52	0.85	0.56	0.41	0.62	0.68	1.051
28	0.10	0.05	0.05	0.07	0.05	0.05	0.03	0.03	0.05	0.09	0.11	0.06	0.11	0.07	0.05	0.22	0.24	0.127

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) calculated at individual body weights; to note: PRIMo 4 normally distinguishes between cattle and other mammalian species, however for better comparison with FACE, the values for mammalian species were used here; 3) average bodyweights are assumed;
green-red = lowest-highest value in a row;
** consumption data of Bulgaria and Thailand (liver); ** consumption data of South Africa, China and Primo.rev.3-FR*
GP=general population, CH=children

The models using world-wide data (GEADE, IESTI) lead to higher exposure estimates compared to the European models. One reason for this might be that consumption figures from third countries are at least for some commodities higher than those for European countries. E.g. for GEADE the highest exposure results were associated with consumption of liver based on data from Thailand. It needs to be discussed in how far those data are representative for food consumption habits in Europe and hence if they should be considered or not. A comparison of acute consumption figures can be found in chapter 5.2.

Milk

The outcome of the acute dietary exposure estimates for milk with the five models are summarised in Table 17.

Table 17: Acute exposure estimates for milk expressed as µg/kg bw

Hrs	TMDI[1]	FACE[2]							PRIMo 4[2]							GEADE[1]		IESTI[3]
		Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**GP***	**CH****	*******
24	n.d.	0.19	0.18	0.26	0.09	0.05	0.05	0.05	0.12	0.09	0.28	0.13	0.13	0.03	0.03	ND	ND	0.112
36	n.d.	***0.89***	***0.84***	***1.19***	***0.42***	***0.24***	***0.21***	**0.23**	0.49	0.37	1.12	0.53	0.50	0.11	0.13	ND	ND	n.c.
48	***0.52***	0.61	0.57	0.81	0.29	0.16	0.15	0.15	0.59	0.45	1.33	0.63	0.60	0.13	0.16	1.30	***2.3***	0.534
60	0.49	0.69	0.65	0.92	0.32	0.18	0.17	0.17	0.67	0.51	1.52	0.72	0.69	0.15	0.18	**1.30**	2.2	n.c.
72	0.47	0.81	0.76	1.08	0.38	0.21	0.19	0.20	**0.69**	**0.52**	***1.55***	**0.74**	**0.70**	**0.15**	**0.18**	1.20	2.1	***0.621***
84	0.35	0.63	0.59	0.84	0.30	0.17	0.15	0.16	0.62	0.47	1.40	0.66	0.63	0.14	0.16	0.89	1.5	n.c.
96	0.26	0.62	0.58	0.83	0.29	0.16	0.15	0.16	0.52	0.40	1.18	0.56	0.53	0.11	0.14	0.66	1.2	0.472
120	0.18	0.43	0.40	0.57	0.20	0.11	0.10	0.11	0.38	0.29	0.87	0.41	0.39	0.08	0.10	0.45	0.79	0.348
144	0.17	0.39	0.37	0.52	0.18	0.10	0.09	0.10	0.34	0.26	0.78	0.37	0.35	0.08	0.09	0.43	0.74	0.311
168	0.12	0.31	0.29	0.41	0.15	0.08	0.07	0.08	0.26	0.20	0.59	0.28	0.27	0.06	0.07	0.31	0.54	0.236
192	0.09	0.17	0.16	0.23	0.08	0.05	0.04	0.04	0.18	0.14	0.40	0.19	0.18	0.04	0.05	0.22	0.39	0.161
216	0.06	0.15	0.14	0.20	0.07	0.04	0.04	0.04	0.12	0.09	0.28	0.13	0.13	0.03	0.03	0.16	0.28	0.112

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) calculated at individual body weights; to note: PRIMo 4 normally distinguishes between cattle and other mammalian species, however for better comparison with FACE, the values for mammalian species were used here; 3) average bodyweights are assumed; green-red = lowest-highest value in a row;
** consumption data of Finland; ** consumption data of Canada, *** consumption data of Primo.rev.3-UK*
GP=general population, CH=children

Also, for milk, the international models result in higher exposure estimates, at least for the adult population but also for children with the GEADE. This is interesting as only GEADE for children uses consumption figures from a third country (here Canada). The comparison of the residue input value (upper 95/95 tolerance limit vs mean+2SD, upper 95/95 tolerance limit vs mean) shows that the value used by TMDI and GEADE is up to 4.6-fold higher than the value used by FACE and up to 2-fold higher than that used by PRIMo 4. As TMDI and GEADE use the same residue input value, the difference in the exposure estimate might be mainly in the consumption figures used.

With a look at the European population, it becomes evident, that regarding residues in milk, children are of special importance. Infants, toddlers and other children exposure calculated with FACE and PRIMo 4 models are higher than the values estimated with the TMDI (based on a body weight base).

4.3.2. Chicken (poultry) meat and offal and eggs

Meat and offal

The outcome of the acute dietary exposure estimates for meat and offal from chicken with the five models are summarised in Table 18.

Table 18: Acute exposure estimates for meat and offal from chicken (poultry) expressed as µg/kg bw

Day	TMDI[1]	FACE[2]							PRIMo 4[2]							GEADE[1]		IESTI[3]
		Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old	Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old	GP	CH	*
1	***8.44***	***3.71***	***3.47***	***10.91***	***5.86***	***9.62***	***2.36***	**1.65**	**4.05**	**5.18**	***11.31***	**7.02**	**9.68**	**4.71**	**4.69**	***16.30***	**12.70**	***12.75***
2	6.76	3.03	2.83	8.06	4.32	7.10	1.74	1.34	3.06	3.55	7.75	4.81	6.63	3.22	3.21	13.00	10.10	8.73
4	4.37	2.30	2.15	5.01	2.69	4.42	1.08	1.02	2.23	2.47	4.87	3.02	4.17	2.03	2.02	8.40	6.50	5.49
7	2.35	1.22	1.14	3.45	1.85	3.04	0.75	0.54	1.28	1.64	3.58	2.22	3.06	1.49	1.48	4.40	3.40	4.03
10	1.30	0.90	0.84	1.92	1.03	1.69	0.42	0.40	1.01	1.12	2.01	1.25	1.72	0.84	0.83	2.40	1.90	2.26

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) calculated at individual body weights; 3) average bodyweights are assumed; green-red = lowest-highest value in a row;
** consumption data of China, Canada and Primo-UK*
GP=general population, CH=children

The comparison of the international and European estimates led to similar conclusions as for bovine (mammalian) meat and offal. However, unlike bovine (mammalian) meat and offal, the highest exposure estimate is obtained for GEADE European data (Germany and Poland (poultry offal)). The differences might be explained as GEADE uses only summary statistics whereas FACE and PRIMo 4 use individual consumption data. Further on, the residue input value used by GEADE is up to 1.4- and 1.5-fold higher than the values used by FACE and PRIMo 4, respectively.

Comparing the European models for adults similar results are obtained, while the "other children" age class has slightly higher exposure estimates and the other sub populations lower exposure estimates.

Eggs

The outcome of the acute dietary exposure estimates for eggs with the five models are summarised in Table 19.

Table 19: Acute exposure estimates for eggs expressed as µg/kg bw

Day	TMDI[1]	FACE[2]							PRIMo 4[2]							GEADE[1]		IESTI[3]
		Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old	Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old	GP	CH	*
5	1.80	5.06	4.74	4.30	2.55	1.82	1.87	1.63	6.57	7.38	6.64	3.04	3.37	2.60	2.98	7.80	13.00	7.08
6	1.70	5.57	5.21	4.74	2.81	2.01	2.06	1.80	7.69	8.64	7.78	3.56	3.94	3.04	3.49	7.60	12.60	8.29
7	***2.40***	6.54	6.12	5.56	3.30	2.36	2.42	2.11	8.80	9.88	8.89	4.07	4.51	3.48	3.99	**10.40**	***17.30***	9.47
8	1.20	5.16	4.83	4.39	2.60	1.86	1.91	1.66	8.11	9.11	8.20	3.75	4.16	3.21	3.67	5.40	9.00	8.73
9	1.60	5.82	5.45	4.95	2.94	2.10	2.15	1.88	8.15	9.16	8.24	3.77	4.18	3.23	3.69	7.10	11.70	8.78
10	1.40	5.74	5.38	4.88	2.90	2.07	2.12	1.85	8.41	9.46	8.51	3.89	4.31	3.33	3.81	6.20	10.30	9.06
11	1.80	7.16	6.70	6.08	3.61	2.58	2.65	2.31	10.37	11.65	10.48	4.79	5.31	4.10	4.70	8.10	13.30	11.17
12	1.80	7.43	6.96	6.32	3.75	2.68	2.75	2.40	11.04	12.41	11.17	5.11	5.66	4.37	5.00	8.00	13.20	11.89
13	1.90	7.86	7.36	6.68	3.96	2.84	2.91	2.53	**12.36**	***13.88***	**12.49**	**5.71**	**6.33**	**4.89**	**5.60**	8.50	14.10	***13.31***
14	2.10	***8.25***	***7.73***	***7.02***	***4.16***	***2.98***	***3.05***	**2.66**	12.28	13.79	12.41	5.68	6.29	4.86	5.56	9.10	15.10	13.22
15	1.90	7.26	6.79	6.17	3.66	2.62	2.68	2.34	10.55	11.86	10.67	4.88	5.41	4.17	4.78	8.10	13.40	11.37
16	2.30	6.91	6.46	5.87	3.48	2.49	2.55	2.23	9.84	11.06	9.95	4.55	5.04	3.89	4.46	10.20	16.90	10.60
17	2.00	5.76	5.39	4.90	2.90	2.08	2.13	1.86	7.74	8.70	7.82	3.58	3.97	3.06	3.51	8.60	14.20	8.34
18	1.80	5.14	4.81	4.37	2.59	1.85	1.90	1.66	7.34	8.25	7.42	3.39	3.76	2.90	3.33	8.00	13.30	7.91

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) calculated at individual body weights; 3) average bodyweights are assumed,;
green-red = lowest-highest value in a row;
** consumption data of UK*
GP=general population, CH=children

Again, differences in the exposure estimates might be explained mainly by different consumption figures. For GEADE, large portion data for egg consumption are from France (adults) and China (children), whereas IESTI uses data from UK. Therefore, differences in comparison to FACE and PRIMo 4 cannot be explained by different consumption figures only. But again, the residue input value is up to 1.2-fold higher compared to the two EFSA models with both differences together leading to the different exposure estimates.

Despite the fact that the residue value for TMDI is higher than for FACE, it results in similar exposure values for adult and older population subgroups. For PRIMo 4, the exposure estimates are higher than those calculated with the TMDI also for the adults, elderly and very elderly age classes (up to 3-fold),

despite the lower input occurrence values used for the European model. However, it can be seen that exposure estimates (based on a kg body weight base) for infants, toddlers and children is 2.3-4.3 fold higher with FACE than for TMDI.

4.3.3. Fish

The outcome of the acute dietary exposure estimates for fish with the five models are summarised in Table 20.

Table 20: Acute exposure estimates for fish expressed as µg/kg bw

Day	TMDI[1]	FACE[2]							PRIMo 4[2]							GEADE[1]		IESTI[3]
		Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**GP***	**CH****	**
1	*2.63*	*3.33*	*4.85*	*4.20*	*3.88*	*2.77*	*2.13*	*1.94*	4.82	4.99	*5.05*	3.19	3.11	2.95	2.14	*14.20*	*16.00*	*14.47*
7	0.42	0.60	0.87	0.75	0.69	0.50	0.38	0.35	0.81	0.84	0.85	0.54	0.52	0.50	0.36	2.30	2.60	2.02
14	0.05	0.08	0.12	0.11	0.10	0.07	0.05	0.05	0.11	0.11	0.11	0.07	0.07	0.06	0.05	0.29	0.32	0.33

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) calculated at individual body weights; 3) average bodyweights are assumed;
green-red = lowest-highest value in a row;
**consumption data of Slovakia; **consumption data of Canada*
GP=general population, CH=children

There are really big differences between the international and the European models for the exposure estimates for fish. These differences cannot be explained by the different input values, which differ only up to 1-2 fold. The consumption figures for IESTI and GEADE (children) are from Canada, which might explain the differences. However, the data for GEADE (general population) are from a European country, therefore other differences (e.g. summarised statistic instead of individual consumption figures) might be the reason for the different exposure estimate.

4.3.4. Honey

The outcome of the acute dietary exposure estimates for honey with the five models are summarised in Table 21.

Table 21: Acute exposure estimates for honey expressed as µg/kg bw

TG1 (B)	TMDI[1]	FACE[2]							PRIMo 4[2]							GEADE[1]		IESTI[3]
		Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**GP**	**CH**	*
Day 7	21.71	***2.49***	***4.27***	***5.27***	***3.38***	***3.51***	***2.46***	2.41	2.09	4.04	***4.10***	2.90	3.87	3.06	1.94	n.c.	n.c.	***8.45***
Day 16	***118.20***	2.07	3.56	4.40	2.82	2.93	2.06	2.01	1.70	3.30	3.35	2.37	3.16	2.50	1.58	n.c.	n.c.	6.9

TG1 (D)	TMDI[1]	FACE[2]							PRIMo 4[2]							GEADE[1]		IESTI[3]
		Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**GP**	**CH**	*
Day 7	***21.19***	***3.00***	***5.14***	***6.35***	***4.07***	***4.23***	***2.97***	2.90	2.57	4.98	***5.05***	3.58	4.77	3.77	2.39	n.c.	n.c.	***10.41***
Day 16	19.44	2.75	4.72	5.83	3.74	3.89	2.73	2.67	2.42	4.69	4.75	3.37	4.49	3.55	2.25	n.c.	n.c.	9 8

TG2 (B)	TMDI[1]	FACE[2]							PRIMo 4[2]							GEADE[1]		IESTI[3]
		Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**GP**	**CH**	*
Day 7	***4.21***	***2.63***	***4.51***	***5.57***	***3.57***	***3.71***	***2.60***	2.55	2.33	4.50	4.57	3.24	4.32	3.41	2.16	n.c.	n.c.	9.42
Day 16	2.00	2.35	4.03	4.98	3.20	3.32	2.33	2.28	2.40	4.65	***4.71***	3.34	4.45	3.52	2.23	n.c.	n.c.	***9.72***

TG2 (D)	TMDI[1]	FACE[2]							PRIMo 4[2]							GEADE[1]		IESTI[3]
		Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**GP**	**CH**	*
Day 7	9.55	***2.33***	***4.00***	***4.94***	***3.17***	***3.29***	***2.31***	2.26	2.12	4.09	***4.15***	2.94	3.92	3.10	1.97	n.c.	n.c.	***8.56***
Day 16	***11.52***	2.08	3.56	4.40	2.82	2.93	2.06	2.01	1.76	3.40	3.45	2.44	3.26	2.57	1.63	n.c.	n.c.	7.11

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) calculated at individual body weights; 3) average bodyweights are assumed;
green-red = lowest-highest value in a row;
**consumption data from China*
GP=general population, CH=children

It should be noted that (as explained in 4.2.4) the residue concentrations of the different hives are very diverse, resulting in huge tolerance limits and TMDIs which are 2- to 142-fold above the value used by FACE, 2- to 187-fold those used by PRIMo 4 and up to 4.2-187-fold above the value used by IESTI. Because of these differences JECFA Experts decided not to use these data for an exposure estimate. However, as these were data from a real residue depletion study the exposure estimates was calculated for the remaining models.

Interestingly, although TMDI uses higher residue input values than the other models it does not result in the highest estimates at every time point, leading to the assumption that the consumption figure used by TMDI is lower than for the other models.

5. Exercise to compare consumption figures of different models, using a default residue value of 1 mg/kg

After comparison of exposure estimates as used by EFSA, EMA, JECFA and JMPR by using real residue data (see Section 4), it becomes evident that differences cannot only be explained by different residue input data. Therefore, the influence of the different consumption figures/assumptions used in the models were evaluated. For the JECFA and JMPR models, for comparison reasons, European data were used where possible. However, in both cases this is only possible for the chronic estimate.

Therefore, calculations were conducted using a unique default residue value of 1 mg/kg (1000 µg/kg) and consumption figures as used normally in the different models.

5.1. Chronic exposure

The outcome of the chronic exposure models is summarised in tables 22-26.

Table 22: Chronic exposure estimates for bovine (mammalian) meat and offal and milk expressed as µg/kg bw per day

Tissue

	TMDI[1]	FACE[2]							PRIMo 4[2]							GECDE[1]	IEDI[3]
		Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old	Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old		*
Liver	1.67	0.48	0.55	0.41	0.21	0.39	0.24	0.26	0.67	0.72	0.68	0.36	0.58	0.52	0.30	1.30	0.25
Kidney	0.83	0.00	0.09	0.68	0.58	0.92	0.48	0.29	0.00	0.00	0.00	0.00	0.00	0.18	0.00	0.74	0.25
Fat	0.83	0.76	0.92	0.72	1.00	0.59	0.40	0.37	0.95	1.07	1.02	1.19	0.71	0.45	0.40	0.26	0.31
Muscle	5.00	4.64	7.66	8.56	6.83	4.75	3.58	3.44	5.48	8.76	8.87	7.70	5.33	3.97	4.01	4.23	2.51
Tissue (total)	8.33	5.63	7.99	8.63	6.96	5.42	3.65	3.52	6.65	8.76	9.28	8.16	6.16	4.11	4.17	4.29	2.86

*IEDI gives only one value for "offal", for illustrational reasons used for liver and kidney

Milk

TMDI[1]	FACE[2]							PRIMo 4[2]							GECDE[1]	IEDI[3]
	Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old	Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old		
25.00	124.11	122.34	161.01	58.70	32.74	28.96	32.68	136.62	128.68	163.21	65.32	45.04	34.33	39.32	44	7.81

Combination of cattle (mammalian) tissue and milk

TMDI[1]	FACE[2]							PRIMo 4[2]							GECDE[1]	IEDI[3]
	Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old	Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old		

33.00	124.11	126.38	162.29	61.62	34.02	31.17	33.97	136.62	136.19	164.96	70.01	46.49	35.62	40.62	46	10.18

738 *1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) HRP calculated at individual body weights; to note: PRIMo 4 normally distinguishes between*
739 *cattle and other mammalian species, however for better comparison with FACE, the values for mammalian species were used here; 3) average bodyweights are assumed*
740 *green-red = lowest-highest value in a row;*
741

742 ***Table 23 Chronic exposure estimates for chicken (poultry) meat and offal and eggs expressed as µg/kg bw per day***

Tissue

	TMDI[1]	FACE[2]							PRIMo 4[2]							GECDE[1]	IEDI[3]
		Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		*
Liver	1.67	0.00	0.19	0.26	0.05	0.29	0.04	0.12	0.00	0.35	0.42	0.09	0.44	0.34	0.12	1.54	0.02
Kidney	0.17	0.00	0.00	0.00	0.00	0.00	0.00	0.00								-	0.02
Fat	1.50	0.00	0.15	0.21	0.04	0.03	0.02	0.02	0.00	0.33	0.37	0.06	0.05	0.08	0.02	0.02	0.01
Muscle	5.00	6.53	7.71	6.35	4.33	2.26	1.99	2.07	6.88	9.13	7.86	4.79	2.70	2.10	2.08	5.36	1.45
Tissue (total)	8.33	6.60	7.71	6.45	4.33	2.35	2.07	2.07	7.09	9.13	7.86	4.79	2.73	2.10	2.08	5.50	1.46

*IEDI gives only one value for "offal", for illustrational reasons used for liver and kidney;

Eggs

TMDI[1]	FACE[2]							PRIMo 4[2]							GECDE[1]	IEDI[3]
	Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		
1.67	3.43	3.91	4.18	2.69	1.47	1.28	1.62	3.65	4.76	4.90	3.00	1.79	1.49	1.63	2.50	0.61

Combination of chicken (poultry) tissue and eggs

TMDI[1]	FACE[2]							PRIMo 4[2]							GECDE[1]	IEDI[3]
	Infants < 12 months old	**Toddlers** ≥ 12 months to < 36	**Other children** ≥ 36 months	**Adolescents** ≥ 10 years to	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36	**Other children** ≥ 36 months	**Adolescents** ≥ 10 years to	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		

		months old	to < 10 years old	< 18 years old					months old	to < 10 years old	< 18 years old					
10.00	8.34	9.94	8.57	5.04	3.17	3.03	2.86	9.01	11.86	10.07	6.01	3.63	3.04	2.86	6.30	2.01

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) HRP calculated at individual body weights; 3) average bodyweights are assumed; green-red = lowest-highest value in a row

Table 24: Chronic exposure estimates for fish meat expressed as µg/kg bw per day

TMDI[1]	**FACE[2]**							**PRIMo 4[2]**							**GECDE[1]**	**IEDI[3]**
	Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		
5.00	2.13	5.73	3.98	2.82	2.35	2.19	1.66	2.93	6.12	5.83	4.22	3.57	2.84	2.11	4.00	0.72

**highest value of Freshwater fish (e.g. tilapia), Diadromous fish (e.g. salmon, trout) or Marine fish used*

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) HRP calculated at individual body weights; 3) average bodyweights are assumed; green-red = lowest-highest value in a row

Table 25: Chronic exposure estimates for honey expressed as µg/kg bw per day

TMDI[1]	**FACE[2]**							**PRIMo 4[2]**							**GECDE[1]**	**IEDI[3]**
	Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		
0.33	0.03	0.39	0.49	0.29	0.25	0.32	0.31	0.04	0.52	0.83	0.46	0.36	0.49	0.48	0.90	0.037

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) HRP calculated at individual body weights; 3) average bodyweights are assumed; green-red = lowest-highest value in a row

Table 26: Combined chronic exposure estimates for cattle (incl. milk), chicken (incl. eggs), fish and honey expressed as µg/kg bw per day

TMDI[1]	FACE[2]							PRIMo 4[2]							GECDE[1]	IEDI[3]
	Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		
40.33	129.18	128.41	164.63	63.52	35.50	32.22	34.98	138.78	138.47	168.39	71.71	49.63	37.26	42.60	59	12.25

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) HRP calculated at individual body weights; 3) average bodyweights are assumed; green-red = lowest-highest value in a row

For cattle tissue and milk, the highest exposure is obtained for "other children" when FACE and PRIMo 4 are used. Regarding poultry tissue and eggs, the highest exposure is obtained for general population with TMDI and for toddlers when FACE and PRIMo are used. For fish, the highest exposure is obtained with TMDI and for "toddlers" with FACE and PRIMo. In case of honey the highest exposure is obtained with GECDE. For the combined exposure, the highest exposure is obtained for "other children" when FACE and PRIMo are used

The calculations show that in case of chronic exposure assessment, the food basket used for TMDI seems to be the most conservative model and covers all population subgroups for most foodstuffs, except eggs and milk in children (in comparison with FACE and PRIMo 4) and honey (in comparison with GECDE).

On a body weight base, the consumption figures for milk and eggs of children from the EFSA database are much higher than assumed by the TMDI. The impact of this finding will be discussed in the following sections.

Concerning the models using real consumption figures, some differences might be explained by the fact that JECFA uses summary statistics, while EFSA uses individual data. Furthermore, JECFA and JMPR use data from the whole world, whereas EFSA uses European data only. For the chronic estimates with the JMPR model, differences by using the clusters containing European data or all clusters are given in the table, were applicable. However, even the clusters containing European data sometimes contain also third country data.

In contrast to JECFA and EFSA, JMPR uses import, export and production data. As discussed in the example with real residue data, this approach leads to very low exposure estimates, probably because of low consumption figures.

Despite FACE and PRIMo 4 using the exact same consumption data, a difference is observed between both models with PRIMo 4 resulting in slightly higher estimates compared to FACE. This is due to the fact that the highest reliable percentile (HRP) of the exposure obtained with FACE is only derived up to the 95th percentile, whereas in PRIMo 4 HRP estimates are derived up to the 97.5th percentile.

5.2. Acute exposure

The consumption figures for acute exposure scenarios differ to the consumption figures used for chronic exposure estimates (5.1.). As described for the different models (3.4.1. -3.4.4.), normally acute exposure estimates are based on a high percentile consumed within one day.

Table 27: Overall acute exposure estimates for bovine (mammalian) meat and offal and milk expressed as µg/kg bw

Tissue

	TMDI[1]	FACE[2]							PRIMo 4[2]							GEADE[1]	IESTI[3]
		Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old	Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old		*
Liver	1.67	3.48	2.68	5.15	2.74	3.74	1.72	1.62	3.71	4.69	5.47	3.60	4.51	2.64	2.10	8.30	9.40
Kidney	0.83		4.54	8.47	4.76	5.64	4.35	3.83			4.76	1.72	2.09	1.59		12.90	9.40
Fat	0.83	2.39	2.38	1.87	1.52	1.05	0.97	1.00	2.39	2.60	1.96	1.78	1.34	0.97	1.01	4.80	2.03
Muscle	5.00	10.47	11.24	16.18	10.82	7.34	6.19	6.35	8.92	11.44	13.33	12.24	7.69	5.37	4.63	10.70	16.41
Tissue (total)	8.33	10.47	11.24	16.18	10.82	7.34	6.19	6.35	8.92	11.44	13.33	12.24	7.69	5.37	4.63	12.90	16.41

**IESTI gives only one value for "offal", for illustrational reasons used for liver and kidney*
only fat from EU-survey

Milk

TMDI[1]	FACE[2]							PRIMo 4[2]							GEADE[1]	IESTI[3]
	Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old	Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old		*
25.00	134.59	126.55	179.43	63.59	35.80	32.47	34.12	137.10	104.02	310.13	147.18	140.00	30.18	36.17	64	124.22

Combination of cattle (mammalian) tissue and milk

TMDI[1]	FACE[2]							PRIMo 4[2]							GEASTDE[1]	IESDI[3]
	Infants < 12 months old	Toddlers ≥ 12 months to < 36	Other children ≥ 36 months	Adolescents ≥ 10 years to	Adults ≥ 18 years to	Elderly ≥ 65 years to	Very elderly ≥ 75 years old	Infants < 12 months old	Toddlers ≥ 12 months to < 36	Other children ≥ 36 months	Adolescents ≥ 10 years to	Adults ≥ 18 years to	Elderly ≥ 65 years to	Very elderly ≥ 75 years old		**

		months old	to < 10 years old	< 18 years old	< 65 years old	< 75 years old			months old	to < 10 years old	< 18 years old	< 65 years old	< 75 years old			
33.00	134.59	126.55	179.43	63.59	35.80	32.47	34.12	137.10	104.02	310.13	147.18	140.00	30.18	36.17	64	124.22

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) calculated at individual body weights; to note: PRIMo 4 normally distinguishes between cattle and other mammalian species, however for better comparison with FACE, the values for mammalian species were used here; 3) average bodyweights are assumed; green-red = lowest-highest value in a row

Table 28 Overall acute exposure estimates for chicken (poultry) meat and offal and eggs expressed as µg/kg bw

Tissue

	TMDI[1]	FACE[2]							PRIMo 4[2]							GEADE[1]	IESTI[3]
		Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old	Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old		*
Liver	1.67	1.50	0.75	5.50	2.95	4.85	1.19	0.48	2.06	2.64	5.76	3.57	4.93	2.40	2.39	7.20	6.49
Kidney	0.17	0.00	0.00	0.00	0.00	2.30	0.00	0.00								7.20	6.49
Fat	1.50		0.75	0.88	0.91	0.66	0.25	0.34	0.24	0.84	1.12	0.91	0.78	0.47	0.41	2.30	2.90
Muscle	5.00	11.92	11.16	14.30	8.77	6.41	5.45	5.30	12.97	14.36	15.43	9.64	8.55	6.43	5.30	15.40	21.51
Tissue (total)	8.33	11.92	11.16	14.30	8.77	6.41	5.45	5.30	12.97	14.36	15.43	9.64	8.55	6.43	5.30	15.40	21.51

**IESTI gives only one value for "offal", for illustrational reasons used for liver and kidney survey from China and Canada*

Eggs

TMDI[1]	FACE[2]							PRIMo 4[2]							GEADE[1]	IESTI[3]
	Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old	Infants < 12 months old	Toddlers ≥ 12 months to < 36 months old	Other children ≥ 36 months to < 10 years old	Adolescents ≥ 10 years to < 18 years old	Adults ≥ 18 years to < 65 years old	Elderly ≥ 65 years to < 75 years old	Very elderly ≥ 75 years old		
1.67	7.54	7.05	6.41	3.80	2.72	2.79	2.43	11.53	12.95	11.65	5.33	5.91	4.56	5.22	7.30	12.41

Combination of chicken (poultry) tissue and eggs

TMDI[1]	FACE[2]	PRIMo 4[2]	GEADE[1]	IESTI[3]

	Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		
10.00	11.92	11.16	14.30	8.77	6.41	5.45	5.30	12.97	14.36	15.43	9.64	8.55	6.43	5.30	15.40	21.51

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) calculated at individual body weights; 3) average bodyweights are assumed;
green-red = lowest-highest value in a row

Table 29: Overall acute exposure estimates for fish meat expressed as µg/kg bw

TMDI[1]	**FACE[2]**							**PRIMo 4[2]**							**GEADE[1]**	**IESTI[3]**
	Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		*
5.00	8.11	11.82	10.23	9.45	6.76	5.20	4.72	11.03	11.41	11.57	7.29	7.12	6.76	4.90	27.80	31.26

**highest value of Freshwater fish (e.g. tilapia), Diadromous fish (e.g. salmon, trout) or Marine fish used*
survey from Canada

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) calculated at individual body weights; 3) average bodyweights are assumed;
green-red = lowest-highest value in a row

Table 30: Overall acute exposure estimates for honey expressed as µg/kg bw

TMDI[1]	**FACE[2]**							**PRIMo 4[2]**							**GEADE[1]**	**IESTI[3]**
	Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		*
0.33	0.83	1.43	1.76	1.13	1.18	0.82	0.81	0.90	1.74	1.76	1.25	1.67	1.32	0.83	5.50	3.64

**survey from China*

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) calculated at individual body weights; 3) average bodyweights are assumed;
green-red = lowest-highest value in a row

Table 31: Overall acute exposure estimates for cattle (incl. milk), chicken (incl. eggs), fish and honey expressed as µg/kg bw

TMDI [1]	FACE [2]							PRIMo 4 [2]							GEADE [1]	IESTI [3]
	Infants < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old	**Infants** < 12 months old	**Toddlers** ≥ 12 months to < 36 months old	**Other children** ≥ 36 months to < 10 years old	**Adolescents** ≥ 10 years to < 18 years old	**Adults** ≥ 18 years to < 65 years old	**Elderly** ≥ 65 years to < 75 years old	**Very elderly** ≥ 75 years old		*
40.33	134.59	126.55	179.43	63.59	35.80	32.47	34.12	137.10	104.02	310.13	147.18	140.00	30.18	36.17	64	124.22

1) TMDI and GECDE calculated for a standard body weight of 60 kg/person; 2) calculated at individual body weights; 3) average bodyweights are assumed; green-red = lowest-highest value in a row

For cattle tissue and milk, the highest exposure is obtained for "other children" when FACE and PRIMO are used. In case of poultry tissue and eggs, the highest exposure is obtained with IESTI and for "other children" when FACE and PRIMo are used. For fish, the highest exposure is obtained with GEADE and IESTI. For honey, the highest exposure is obtained with GEADE. Whereas for combined exposure, the highest exposure is obtained for "other children" when FACE and PRIMo are used.

In contrast to the chronic exposure estimate (5.1), TMDI seems to be by default not fit for purpose for acute exposure calculations as these scenarios normally consider only the food with the highest intake, while TMDI considers by default the whole basket. Furthermore, in the acute exposure scenario, TMDI shows lower consumption figures for most foodstuffs and therefore might not protect the consumer if an acute endpoint is relevant for the substance. GEADE and/or IESTI has the highest consumption figures for the adult population. However, for the acute estimate, it is not possible to use only European clusters, therefore the data used are from the whole world and therefore not directly comparable with the European data as used in FACE and PRIMo 4 (the country resulting in the highest exposure is named below the table).

Furthermore, JMPR and JECFA uses summary statistics, while EFSA uses individual data.

6. Comparison and evaluation of the exposure models

In the following, the approaches and concepts for dietary exposure assessment currently used by EMA (TMDI), EFSA (FACE and PRIMo), JECFA (GECDE/GEADE) and JMPR (IEDI/ IESTI) are discussed and compared with regard to the scenario assumptions, the impact of input data, and the algorithms/models used. It is intended to illustrate the main pros and cons of the individual approaches in order to derive recommendations for a harmonised method. This discussion also addresses some other, possibly critical aspects in relation to integration of the exposure estimates into the risk assessment. The methodology and conduct of risk assessments have not been systematically addressed under the Commission's current mandate, but some consideration is also given to the possible future alignment of approaches to risk assessment, particularly risk characterization.

Consumer exposure assessment is a key element of risk assessment in all regulatory frameworks examined in this report and the starting point for deriving regulatory management measures, i.e. the setting of MRLs. A harmonized exposure assessment is therefore of utmost importance for a subsequent definition of "harmonised" regulatory measures.

The typical exposure scenarios used for the assessment of residues of substances in food and discussed in this report are the so-called "acute" and "chronic" exposure, which refer to possible short- and long-term health effects of a chemical on consumers. Both scenarios and the corresponding data, tools, and models used are discussed and compared, with a focus on chronic exposure, as this is the reference scenario in most cases when defining risk management measures and setting MRLs.

6.1. Discussion of chronic exposure models

6.1.1. Some general remarks on concepts, assumptions and data used[29]

All five dietary exposure models discussed are used for regulatory approval purposes and MRL assessments for veterinary medicinal products, feed additives or pesticides. The models that are used

[29] The basic considerations presented here also apply in principle to the acute exposure scenario. Here, too, the result depends essentially on the assumptions regarding relevant residues and consumption data on which the models and the calculations are based.

in this context are currently all based on deterministic or refined deterministic approaches. Probabilistic methods are currently not used within the regulatory frameworks investigated.

Several types of data and assumptions are required to conduct the exposure assessment, and all have an impact (to a greater or lesser extent) on the results:

- Definition of the relevant residue for assessing dietary risk: The terms used in different domains to describe this residue are, for instance, "(total) residue of concern", "toxicological relevant residues", "residue for dietary risk assessment" or similar; all meaning the residue that may have undesired (toxicological) effects on the human consumer.[30]

  The definition of the residue for assessing dietary risk is the result of a hazard evaluation of a substance and its metabolites/transformation products. Consideration is given to the pharmacological/toxicological profile of the residue components, their relative potency, pharmacokinetic/toxicokinetics parameters (e.g. bioavailability) and many other factors. Although the concepts and experimental methods used are in principle comparable, they (and the underlying technical guidelines) are far from being standardised between assessment bodies. Therefore, depending on the extent and quality of data available and the consistency of the interpretation of those data (e.g., the weight attributed to certain types of evidence or the level of refinement of the hazard characterisation considered appropriate), the qualitative and quantitative assessment of the "relevant residue" can vary considerably. Differences in this assessment can lead to significantly different definitions for the respective relevant residue, which is directly (quantitatively) reflected in the final exposure estimates. [31]

- Analytical measurements are used to determine the "relevant residue" in the various food commodities at suitably specified time points (typically residue-depletion and metabolism studies).
  The residues are measured by validated analytical methods. The requirements for validation are based on guidelines in the respective regulatory context. Traditionally, radiolabelled methodology has been used to determine the totality of residues (e.g., combustion techniques) or radiometric methods (mostly) coupled with liquid chromatography/scintillation counting (HPLC/LSC) to capture and identify individual (labelled) metabolites. Increasingly, non-radiometric techniques mainly based on mass spectrometry (LC/MS and LC/MS/MS also GC/MS) are also used for identifying and measuring the relevant residues, including MS/MS-based non-targeted approaches. The performance parameters of the analytical methods are critical in order to ensure the reliability and validity of the measurements and the results obtained. Validation parameters such as selectivity, range of concentrations covered, limit of detection (LOD), limit of quantification (LOQ) (where applicable lower and upper limits of quantification (LLOQ, ULOQ)), precision and accuracy of the methods, stability of the analytes and the level down to which structural identification of metabolites is carried out[32], can potentially all have a considerable impact on the amount, and quality (e.g. level of detail) of the data available for the assessment.

- Assumption for a residue concentration in food which would be representative for the exposure scenario: The selection of the (statistically derived) concentration of the residue distribution

[30] The definitions are different at EMA/JECFA where typically the term residue of concern would be used (often based on a total residue approach) and JMPR/EFSA Primo where the term "residue for dietary risk assessment, typically based on are more refined selection of residue components, is used. For feed additives, terms such as "total residue" or "toxicological relevant residues" are used.
[31] The issue has also been discussed at JECFA/JMPR level https://www.who.int/foodsafety/areas_work/chemical-risks/SR-JECFA-JMPR.pdf and there is ongoing work to revise the OECD Guideline No. 63: Guidance document on the definition of residue (as revised in 2009)
[32] Acc. to VICH GL 46 e.g.100 µg/kg for individual metabolites (or for metabolites comprising > 10 % of the residue)

that can serve as an input for the dietary exposure model is a known source of difference between the TMDI, FACE, PRIMo 4, IEDI and GECDE approaches, which alone can significantly affect the quantitative exposure estimate (by a factor of several-fold). The different approaches are currently using either the upper tolerance limit (or MRL), a mean plus two standard deviations/highest single residue, the arithmetic mean or the median from the distribution of residue concentrations[33].

- Assumption on the amount of food consumed: The models discussed (TMDI, FACE, PRIMo 4, IEDI and GECDE) use different sources of data on food consumption including standard food baskets-based approaches, approaches using data from food balance sheets/household budget surveys and data from food consumption surveys/individual food consumption data. The approach/ source used for consumption input data can have a significant impact on the result of the exposure estimation as shown in chapters 4 and 5.

- For all models it is assumed that all foods consumed contain residues of a substance on a daily basis (i.e., assumption that all animals are treated under authorised conditions of use with animal derived food obtained at the end of the legal withdrawal periods) or that all animals ingest residues of a substance via feed at the maximum expected dietary burden (for pesticides). This basic assumption can be contrasted with data on the actual occurrence of residues obtained through monitoring and surveillance programs. For example, for pesticides such data suggest that the probability of residue occurrence and the levels of observed concentrations are much lower than currently assumed in the model assumptions used. Unfortunately, at the moment the residue control programs for veterinary medicinal products aim to detect "the illegal administration of prohibited substances and the abusive administration of approved substances" and "compliance with MRLs for residues of veterinary medicinal products" and only values above the MRLs are reported. Therefore, no representative occurrence data (including data below the respective MRLs) exist in the veterinary field at the moment. However, usage/consumption statistics for veterinary medicinal products suggest that the assumption of "all-animals-treated" represents a very pessimistic worst-case scenario. Representative monitoring and surveillance data would allow for more accurate, refined assessments of dietary exposure. Such data are, however, not yet available in pre-regulation procedures applicable to veterinary medicinal products and feed additives or pesticides. On the other hand, the use of a "conservative" assumption on the presence of residues introduces a "buffer" into the dietary exposure estimates, giving some assurance that exposure is, at least, not underestimated for any duration of exposure.

6.1.2. Specific remarks on models using food consumption survey data (FACE, PRIMo 4 and GECDE)

While 3 of the models discussed within the expert group, FACE, PRIMo 4 and GECDE, refer to the same consumption data from the Comprehensive European Food Consumption Database (Comprehensive Database), they use the consumption data in different ways:

Residue data (occurrence data) are typically measured in and reported for raw primary commodities (RPC) while the amount of food consumed also includes RPC derivatives and composite foods. To take this into account, the FACE model and PRIMo 4 currently disaggregate composite foods as consumed into RPCs, based on the information from the Comprehensive Database. In the exposure calculations, the RPC consumption data are combined with occurrence data, typically the arithmetic mean residue +

[33] Note: the baseline assumption for all exposure models investigated is that all animals of a target species would be treated and that residues remain in all the animal-derived products at the level observed in residue studies

2SD (FACE) or the arithmetic mean (PRIMo 4). The mean and the highest reliable percentile (usually the 95th percentile) of the distribution of individual exposures will subsequently be calculated separately for each dietary survey and each subpopulation class (for details see 3.4.2.1. and 3.4.3). This feature is already available in FACE and will be in PRIMo 4, which is currently under development. JECFA's GECDE model for dietary exposure assessments for European populations uses summary statistics of the surveys in the Comprehensive Database[34] (a policy for dealing with processed foods has not yet been fully developed at JECFA). For the GECDE exposure calculation, the consumption figures are combined with the median concentration from the residue distribution observed in the residue studies. The GECDE model was developed to consider high consumers as it uses the 97.5th percentile or other highest reliable percentile of the amount of chronic food consumption (consumers only) for the food commodity that is the highest contributor to dietary exposure (habitual high consumption of one category of food) plus the mean food consumption amount for the total population for all other food categories. The output is a GECDE calculated for the general population, but GECDEs may also be estimated for children and infants in case of specific toxicological concerns, or for any other population groups for which data are available (for details see 3.4.4).

The main difference between the models in terms of consumption data is that the FACE (or PRIMo 4) chronic exposure tools use (i.e., can access) food consumption data at the level of individual dietary records (by country, survey and age class), whereas GECDE uses the summary statistics derived from the individual records (as the corresponding database CIFOCOss does currently not contain the individual data). In addition, the GECDE approach does not (currently) use a conversion from composite foods to their agricultural commodity equivalents, so exposures are underestimated. This underestimation typical occurs in food types that are frequently processed into composite foods (e.g. milk and eggs). To obtain a more meaningful comparison that at least partially accounts for differences in model inputs, some exposure calculations were performed using assumptions of the FACE tool in the GECDE calculation, such as converting certain foods to raw equivalents (e.g., cheese, butter to adjusted milk equivalents) and using mean + 2SD as residue inputs. These comparisons showed relatively good agreement between the "modified" GECDE calculations and the maximum mean and dietary HRP exposure estimates for adults using the FACE tool. However, this was examined in detail only for milk (see 4.2.1). Without these adjustments, the GECDE and FACE estimates for the general population/adults may differ by a factor of up to 4. However, as mentioned above, this factor is only indicative, since no systematic study was performed.

In order to get a better understanding of the impact of different residue input values and a better comparison of the consumption data, the calculations were also run with a default residue input value of 1 mg/kg in all models. The results confirmed the obvious assumption that the use of different consumption figures is a major source of diverging exposure estimates between the models (see 5.1).

An additional quantitative difference may come from the approach used to estimate exposure from multiple species. In this case, FACE would use the consumption of mammalian or poultry tissues (i.e. animal groups), while the PRIMo 4 (for mammalian) and GECDE (for mammalian and poultry) would take the consumption figure for the respective species (e.g. bovine meat) and additional species of a group would be considered additively (e.g. bovine + goat). This means that for GECDE or PRIMo 4, the estimated dietary exposure automatically increases when exposure from additional mammalian species is added, whereas for FACE, the dietary exposure would only increase if the residues were present in the additional mammalian species at higher concentrations than in bovine meat, for example. Other

[34] For the purpose to estimate European GECDEs

pertinent differences may come from different definitions for food commodities: for example, meat (EFSA, 80% muscle and 20% fat) vs. muscle (GECDE/JECFA)[35].

Another difficulty in directly comparing the results of exposure calculations lies in certain differences between the population groups considered for exposure assessment: GECDEs are usually determined for the general population (as an average for all subgroups of the population) and only for specific subgroups (e.g. children) if specific (sub)population-specific concerns arise from the toxicological profile, whereas in the FACE/PRIMo 4 methodology exposure is calculated (by default) for all subgroups for which surveys are available, without prior matching of exposure scenarios and toxicological endpoints. These differences can be attributed to subtle differences in the approaches to risk characterisation (this cannot be discussed in detail here, but may play a role in later considerations on harmonisation of risk characterisation).

In summary, there are differences regarding the use of food definitions ("adjusted" RPCs vs. "unprocessed" RPCs[36]), the use of consumption data (animal species, age classes and individual data vs summary statistics), the input residue concentrations [median (GECDE), arithmetic mean (PRIMo 4) or arithmetic mean+2SD/high residue (FACE)] and some conceptual differences as discussed above.

Overall, there was agreement that all three models are appropriate for assessing chronic dietary exposure in the general population and specific subgroups. Compared with the GECDE approach as currently used, the FACE tool (or PRIMo 4) provides more opportunities for refined estimates based on consumption data at the level of individual consumers and in relation to a range of specific age groups. On the other hand, it was also noted that such exposure calculations based on empirical data and the conclusions derived from them may need to be updated as dietary habits change. This possibility exists, of course, although it is rather theoretical (considering that consumption habits in a population do not change in the short term). However, this does not undermine the scientific relevance of the models but rather seems to be related with the potential regulatory consequences (i.e. adaptations of the risk management) that could result from a modified exposure assessment.

6.1.3. Specific remarks on the model diet based approach (TMDI)

The TMDI approach is a simple and pragmatic way to estimate the possible exposure for consumers, based on a model daily food basket (SFB) and the assumption that residue levels are at the maximum permitted level (i.e. the MRL) in each food commodity consumed. The TMDI was used in the past by most committees, at least in the field of veterinary medicinal products. From the experience gained over many years of use as well as from calculations provided in this report, it seems that for the general population the approach is adequately protective in most cases and overly conservative for some chronic exposure scenarios.

Compared to approaches using information from food consumption surveys (i.e. FACE, PRIMo4 or GECDE), some shortcomings were identified with the TMDI/SFB model:

- The TMDI as it is currently used would only give an estimate for a 60 kg adult (a differentiation between age groups is not possible).
- For some food items, the value of the SFB may significantly underestimate the real chronic consumption at least in some subpopulations. This is particularly the case for milk, eggs, and

[35] This issue of different food classifications was already discussed by JECFA and JMPR, https://www.who.int/foodsafety/areas_work/chemical-risks/SR-JECFA-JMPR.pdf and there is ongoing discussion at Codex on a harmonisation of this issue http://www.fao.org/fao-who-codexalimentarius/sh-proxy/zh/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-730-25%252FWDs%252Frv25_09e.pdf

[36] "unprocessed RPCs" means foodstuff as obtained /produced "adjusted RPCs" including processed foods

honey, and most evident for the younger age groups (this observation is based on the data from food consumption surveys). Therefore, there is a concern regarding "overlooked" exposure risks in relation to these age groups. On the other hand, the TMDI may lead to a significant overestimation of chronic consumption and overly conservative risk characterisation in relation to consumption of edible tissues.

- The model diet assumes that all foods derived from the same tissue type (e.g. muscle) are consumed in the same amounts, irrespective of the species, and that commodities from different species are considered to be mutually exclusive (e.g. either muscle from pigs or cattle or chicken etc.) which represents an over simplification.
- The use of upper tolerance limits (i.e. MRLs) as the assumption for residues remaining in food seems to be unrealistic and overly conservative in relation to a chronic exposure scenario.
- Options to assess specific exposure scenarios are limited as there are no consumption figures other than for the four standard tissues, milk, eggs and honey and no species-specific consumption figures.
- There was consensus that in specific scenarios the TMDI might be useful as an appropriate screening tool to rapidly identify potential exposure risks (e.g. for tissues), but its limitations become particularly evident when it comes to specific age groups and in relation to consumption of milk, eggs or honey.

6.1.4. Specific remarks on the "balance sheet" based model (IEDI)

„Food balance sheet" (FBS) information on food consumption relies on the estimation of the availability of food at a country level. The balance sheets present a picture of the pattern of a country's food supply during a specified reference period. It relates to the total quantity of foodstuffs produced in a country, added to the total quantity imported minus exported amounts. The information can be obtained from a global database such as the FAOSTAT database which provides access to food and agriculture data. WHO GEMS/Food provides food consumption data from National Food Consumption Surveys (NFCS) and the GEMS/Food food consumption cluster diets allow the grouping of countries 'food balance sheets'[37]. The per capita supply of each food item available for human consumption is calculated by dividing the respective quantity by the related data on the population actually consuming it[38].

The exposure based on FBS (e.g., IEDI) is calculated for group clusters with similar consumption patterns by summing up residue intakes from food commodities which may contain residues from authorised uses. IEDIs are typically calculated per cluster and the highest one would be used in case of a global risk assessment.

The use of food balance sheet estimates has a number of limitations:

-FBS data reflect food availability for the average population rather than individual food consumption

-FBS tend to underestimate food consumption and chronic dietary exposure for high consumers as it is assumed that everyone in the population eats the food, resulting in tentatively lower mean consumption amounts

[37] https://www.who.int/data/gho/samples/food-cluster-diets
[38] https://www.fao.org/economic/the-statistics-division-ess/methodology/methodology-systems/supply-utilization-accounts-and-food-balance-sheets-background-information-for-your-better-understanding/en/

-FBS diets tend to underestimate food consumption for consumers of occasionally consumed foods (horse meat, certain offal) as it is assumed that everyone in the population eats the food

6.1.5. Specific remarks on collection and selection of occurrence values for residues

Substances that are deliberately added to food (food additives, pesticides), but also substances administered as treatment to animals, which can leave residues in food, (VMPs, feed additives)are subject to authorization/registration procedures. Therefore, data on residue concentrations (occurrence data) in food are generally available from pre-regulation residues trials. In these trials the residues are investigated under conditions of the intended use of the substance(s) or, for pesticides, in animal feeding studies investigating residues for maximum expected dietary burdens. This type of data is usually used in all exposure models investigated. The data are typically generated by sponsors/manufacturers during the pre-regulation process and relevant guidelines are available in each domain on the conduct of these studies (e.g. VICH, OECD, specific EMA/EFSA guidelines).

Regarding the guidelines, differences were noted between domains with respect to study design (e.g. sampling schedules, number of samples, individual/composite samples, sample preparation/sample analysis (including LOD/LOQ)), reporting and use of data (e.g. handling of concentrations below the LOD or LOQ). These technical factors may have an influence on the residue data generated and can thereby (theoretically) have an effect on the result of the exposure estimates, although the extent and direction of these effects is difficult to predict[39]. While there is some potential for harmonization here, it is acknowledged that the technical requirements for pre-regulation studies also depend on and are tailored to the objectives of the particular regulatory context. However, aligning technical guidance across the regulatory areas mentioned above could also have significant benefits for other reasons, as pharmacokinetics/residue and metabolism data could be (re)used, at least in part, across regulatory frameworks and for different regulatory purposes (i.e., thus avoiding repeated testing of a substance due to different regulatory requirements).

It is important to note that two types of residue definitions and data are normally used. The residue definition for monitoring/enforcement purposes (so-called marker compound) and a residue definition for consideration in the dietary exposure assessment and comparison to the HBGV in the risk characterisation process, e.g., total residues or active compound plus metabolites of toxicological concern (syn. residue of concern, syn. residue for dietary risk assessment). For the exposure estimate in the context of the risk characterisation the residue of toxicological concern would be used as the relevant residue. Where only data for the marker residues are available, these are normally corrected by suitable factors to account for the relevant residues. This approach is, in principle, used in all regulatory frameworks.

The selection of input values for residue concentrations is based on whether an acute or chronic dietary exposure assessment is required. In a chronic scenario, assuming that a consumer is exposed daily to the upper regulatory residue limits (e.g., MRLs) is very conservative. Therefore, it is reasonable to assume that over an extended period of time consumers will be exposed to varying residue concentrations that will average out over the long term and the resulting exposure most likely corresponds to a central value of the different concentration distributions in each food.

[39] Generally, the more limited the information collected on concentrations present the higher the degree of uncertainty when these observations are used to extrapolate the input value to the animal population.

6.1.6. Specific remarks on chronic exposure from "multiple uses"

When a substance is authorised in multiple domains (for multiple purposes) it is possible that residues in animal derived food are present from several uses at the same time, i.e., from veterinary medicinal products, feed additives, from pesticide use (when ingested by the animals via feed) or from biocides (used to treat the animal itself or in husbandry). While this scenario is theoretically possible, reliable empirical data on the probability, frequency and quantitative relevance of such a scenario are not available. However, it can be reasonably assumed that such a scenario can occur (at most) occasionally, but that coincidence of residue occurrence from several uses would not occur on a regular (chronic) basis.

Nevertheless, the group decided to consider a "multiple use" scenario in terms of chronic exposure and has discussed proposals, all of which are based on "worst-case" assumptions due to the paucity of (empirical) data available allowing to assess on the "true" probability of such a scenario happening.

It is in principle possible to use two different approaches related to the chronic exposure to residues in animal commodities from multiple uses:

- Highest residues from veterinary medicinal products, feed additive and pesticide
- Combined residues (sum of the all 3 uses)

Similar scenarios were investigated in a study of a FAO/WHO working group with regard to combined intake of residues of veterinary medicinal products and pesticides residues (Arcella, et al. 2019[40]). The result showed that marginal, but systematically higher residues occur through a combination of the residues from different uses. In Chapter 7 of this report, a proposal for a uniform approach is made, aiming at using an exposure scenario that is as simple and pragmatic as possible.

Note: Aggregate exposure scenarios associated with exposures from multiple pathways and routes (e.g. dietary and non-dietary/environmental sources) or cumulative exposure to multiple chemicals (e.g., multiple chemicals with a common mechanism of toxicity) "chemical mixtures", respectively, were not considered within the framework of this mandate.

6.2. Discussion of models and calculation of acute exposure

Note: The basic considerations for (chronic) exposure presented in 6.1.1 under "Some general remarks on assumptions and data used" above are in principle also valid for the acute exposure scenario. Here, too, the outcome is essentially dependent on the assumptions on relevant residues and consumption data on which the model and the calculations are based.

Acute exposure refers to specific occasions/events where a large portion of a food (e.g., edible tissue, milk, eggs, or honey) is consumed that contains high levels of residues, i.e., this is the scenario that represents "peak exposure" and it commonly considers a timeframe of one day. In such cases, an assessment based on an average daily exposure, as used for chronic dietary exposure, is not the most appropriate approach to describe the exposure risk. The "acute" exposures are compared to corresponding reference values (HBGV), which stand for possible acute health effects of a substance when ingested over a short period of time. The acute reference dose (ARfD) based on an acute Point of Departure (POD) (i.e. NOAEL or equivalent) is an internationally accepted reference value to assess acute risks. There are a number of guidelines describing the establishment of an ARfD (e.g., Solecki et al. 2005; VICH 2015, OECD. 2010, FAO/WHO. 2016.)

[40] Arcella D. et al (2019). Harmonized methodology to assess chronic dietary exposure to residues from compounds used as pesticide and veterinary drug. Crit Rev Toxicol;49(1):1-10. doi: 10.1080/10408444.2019.1578729

Acute assessments may be specifically relevant for pharmacologically active compounds used as veterinary medicinal products or feed additives (for the pharmacologically active substances assessed so far by the EMA/CVMP ~19% of ADIs were based on acute endpoints, ~37% on subacute endpoints, ~21% on subchronic endpoints and only ~23% on long-term (chronic) endpoints).[41] Substances with specific acute pharmacological/toxicological properties may also include compounds that can trigger acute hypersensitivity reactions (e.g. penicillins). On the other hand, an acute exposure assessment is only necessary if the toxicological profile suggests a relevant acute effect. An ARfD would not be established and acute exposure would not be calculated if the acute toxicity is so low that there is not a concern (i.e., the threshold or POD of the acute toxicological endpoint is so high). In other words, the assessment of acute exposure is triggered by the toxicological profile of a substance and not solely by the possibility of higher exposures in certain situations. [42]

Acute exposure estimates are typically performed for each food commodity separately, as it is considered unlikely that an individual would consume, within a meal or within 24 hours, several large portions of different commodities that contain the same residue at a high-end residue concentration. The consumption data for acute exposure scenarios used by EFSA, JECFA and JMPR are usually derived from the same dietary surveys as those used in the chronic assessment. However, the data are used differently: for the acute estimate, data for consumers only from single days are used, leading to higher consumption figures. As described for the chronic consumption figures, EFSA uses data on an individual base whereas JECFA and JMPR would use summary statistics. Additionally, PRIMo 4 uses a different level of aggregation than FACE (e.g. mammals vs bovine, goat, sheep). Furthermore, in the database of JECFA and JMPR it is, at the moment, not intended to calculate the acute exposure for the European population only. These differences can lead to different exposure estimates, even if the input value for the residue is the same, as shown in chapter 5.2.

In addition, the models currently use different residue input values (e.g., upper end of concentration range/highest reported values, high percentile/upper 95/95th percentile, observed maximum, or mean+2SD). This can lead to inconsistent acute exposure estimates, even with the same assumptions regarding food consumption. Although the concepts examined were all very similar (with the exception of the TMDI), in the interest of further harmonization, a preferred method should be agreed upon if possible. The group has developed a proposal for this, which is described in chapter 7.2.3.

6.2.1. Note regarding use of a TMDI approach in acute exposure assessments

The TMDI is traditionally considered a conservative screening tool for "worst-case" residue intake, as it is considered conservative enough to cover acute exposure to some extent. However, as shown in the calculations above (4.3 and 5.2), the TMDI does not appear to be conservative enough to cover acute exposure in every scenario, especially for individual food products or for certain subgroups of the population.

[41] The EMA does not use an acute HBGV such as the ARfD but the ADI would be based on acute endpoints where the toxicological profile suggests acute effects as the most sensitive effects

[42] The FAO/WHO has established for veterinary medicinal products and pesticides so-called "cut-off" values above which setting of an ARfD and an acute assessment would not be necessary. The JMPR has proposed a human acute toxicity threshold for pesticides of 5 mg/kg body weight, above which an ARfD would not be required. Following the same principles, a corresponding calculation was made for veterinary medicinal products. The highest MRLs/tolerances established in Codex, the EU, and the U.S. were used, as well as the 97.5th percentile of the highest consumption (consumer only, on one day) for each edible tissue. Taking into account the uncertainty in this estimate, the result was a limit of 1 mg/kg that would be appropriate for establishing an ARfD for veterinary medicinal products residues. The values should just illustrate as to when an exposure scenario for the acute effects may be needed (source http://www.who.int/foodsafety/chem/jecfa/Guidance_ARfD.pdf).

6.3. Note regarding "less-than-life-time" approach

For completeness, the so-called "less-than-lifetime" scenario will be mentioned here as an exposure scenario, which may occasionally require consideration in food safety assessments in addition to the acute and chronic assessment. A "less-than-lifetime" assessment would be triggered as a result of a specific toxicological profile of a substance and a specific exposure situation: Exposure can occur over periods longer than one day (acute) but less than a lifetime (chronic). Such exposures may be continuous or intermittent for a certain period of time during life. When assessing "chronic" risks the baseline assumption is that exposure peaks or occasional fluctuations/excursions above the "chronic" HBGV (i.e. the ADI) would be balanced out by lower intakes at other times and that the average exposure per day over the entire lifetime would determine the outcome. Certain exposure risks may, however, be underestimated if exposure over shorter periods (appreciably) exceeds the relevant ADI *and* where this ADI is based on "less -than-lifetime" health effects, as the relevant most sensitive endpoint (e.g. certain subchronic or subacute endpoints). In principle, the "less-than-lifetime" concept refers to a method to interpret and assess the risks for human health in case exposure exceeds the "chronic" HBGV. For example, in case of reproductive effects or in cases where the severity of toxicological effects underlying the ("chronic) HBGV, i.e. ADI, do not appear to progress after short periods of administration in the toxicological studies (e.g., after 2–3 months). These exposure risks and endpoints may be not adequately covered by the acute risk assessment (as the endpoint for acute hazards may be different) *and* the "averaged" chronic exposure over lifetime may underestimate this type of short-term exposure. The concept of "less-than-lifetime" exposure is a relevant concept but has not yet consistently found its way into the regulatory processes of risk assessment, or only to a limited extent (is partly used at JECFA and JMPR).

In this context, it seems worth noting that exposure models that use a range of relevant subpopulations or consumption information differentiated by age groups generate information that can be used for more accurate risk assessment in potentially vulnerable time windows of exposure. However, the group did not really discuss these issues in the context of a "true" less-than-lifetime approach, nor did it discuss the less-than-lifetime exposure concept in any depth and detail necessary to make recommendations and draw conclusions in light of the mandate. This could be explored in a follow-up investigation that would consider risk characterization methods in more detail and develop proposals for appropriate harmonization. See also the discussion under 7.2.

6.4. Note regarding possibilities to use JECFA and JMPR models

The JECFA and JMPR approaches aim at global harmonization and standard setting and therefore rely on global data on substance use, residue occurrence and consumption data. Since consumption patterns differ from country to country, as do the approved uses of substances, the results of this assessment cannot be directly applied to the specific European situation, or can only be partially applied. However, the algorithms and models used can be applied without restriction to European data, and the methods in this report have been compared (where possible) with JECFA and JMPR calculations based on EU data. Regarding consumption data, EFSA has individual data in the Comprehensive Database from the national surveys, while JECFA, for example, only has summary statistics for the same data in the CIFOCOss database. These limitations in data use, apart from differences in calculation models themselves, have somewhat affected the direct comparability of results. However, as noted above, experts agree that individual data are more accurate from a scientific perspective and should be used whenever possible.

7. Summary and recommendations

This report presents findings, conclusions and recommendations resulting from a comparison of different exposure models currently used by EMA, EFSA, JECFA and JMPR to assess residues of veterinary medicinal products (EMA, JEFCA), feed additives (EFSA, JECFA) and pesticides (EFSA, JMPR) in animal-derived food. The analysis included the major models for both short-term (acute) and long-term (chronic) exposure estimates. Other exposure concepts that are used in certain situations (e.g., "less-than-lifetime") were discussed only marginally and were not included in the comparison because they are not yet universally established in the regulatory context and were also not considered sufficiently developed to be included in a harmonized recommendation.

7.1. Lessons learned

Consumer risk assessment for residues of veterinary medicines, feed additive and pesticides are conducted in different legislative/regulatory frameworks in the EU and the methodologies used, while based on common principles and pursuing the same objectives, namely consumer protection, differ in their scientific approaches and practice. Also, at Codex Alimentarius level, exposure assessment approaches for food additives/veterinary medicinal products and pesticides differ between Codex Committees (CCRVDF, CCPR) and their respective expert committees (JECFA, JMPR).

Some of the observed differences can, of course, be attributed to certain differences in regulatory or legislative provisions and requirements (and corresponding guidelines), but to a significant extent differences were simply attributable to differences in the scientific models, scientific assumptions and types of consumption and occurrence data used. Many of these differences in approaches cannot really be explained "scientifically" but are possibly due to a historically largely independent (asynchronous) development of the scientific procedures and practices in each domain.

The expert group has examined the potential for harmonisation or alignment of procedures, with a main focus on exposure assessment methodologies for animal derived food for VMPs, feed additives and pesticides. This included the methods used at European level (EFSA/EMA) and the approaches currently used in Codex Committees for food additives/veterinary medicinal products and pesticides (JECFA/JMPR).

Exposure assessment requires data on chemical analysis of the residues in food matrices (so-called occurrence data), an estimate of daily consumption of food by consumers, and an estimate of the potential significance to human health of the residues contributing to the exposure (i.e. description of the potential chemical hazard associated with the residues to which a consumer population is exposed), and it requires a model with which to link these data. The relevance and accuracy of the exposure assessment thus depends largely on the extent and quality of the data available, and on the way in which those data are used.

The expert group has noted relevant differences between all methods and approaches currently used to gather and assess these types of data. The food consumption data used include, for instance, data of various types, such as individual food consumption data at different levels of the food chain, from raw primary commodities to processed and composite foods, data derived from food balance sheets, and hypothetical model diets.

Occurrence data are typically collected in residue trials in which the chemical is administered to the animals according to label instructions or, for pesticides, at the calculated dietary burden. However, apart from the necessary differences in the study design due to different regulatory objectives of the studies, there is a number of "avoidable" more practical/technical differences concerning sampling

schedules, types of tissues collected and data handling. Differences were also noted with respect to the analytical approaches used for identifying residue components/metabolites in animal commodities (total residues vs. individual residues), thresholds for (structurally) identifying metabolites, handling of bound/non-extractable residues, dealing with left censored data/non-detects etc.

In the following, the possibilities of alignment of approaches are discussed with respect to the use of consumption data, the choice of input data for chronic and acute exposure, and possibilities for a harmonised estimate of a combined intake from multiple sources. There was consensus that exposure estimates should, in the first instance, be calculated separately for all (sub)populations for which relevant consumption data are available to allow an optimal characterisation of the distribution of risks among different sub-populations (adults, children etc.). The way in which this exposure information is used in risk characterization depends on the hazard profile of the residues and results of the hazard assessment (e.g., types of toxicological endpoints) but also on the level of intended granularity of the assessment in relation to different population groups. Currently, there is no consistent harmonized policy, procedure and guidance on when and how, for instance, subpopulations are considered and included in risk characterization. This is an area where further discussion and effort for alignment of principles and approaches between jurisdictions would be beneficial.

7.2. Recommendations for exposure estimation

In the following sections, recommendations are made for harmonised models, assumptions, and algorithms in the exposure estimation. Recommendations concerning the implementation of these concepts in the risk assessment process are not made, but it is expected that implementation of harmonised approaches to exposure estimates will also promote certain adjustments to the concepts of risk characterisation in the different domains and have an effect on the methodology of how regulatory standards (such as MRLs) are derived.

For each element of the exposure assessment, a preferred method that can form the basis for a harmonised methodology ("preferred method") is proposed, as well as reasonable alternative options ("reasonable alternative") which, according to the group's findings, can be expected to produce comparable and acceptable results within the variability and uncertainties inherent in such an estimate.

Where recommendations are made for specific methods to be used in the future, these, of course, refer to the EU procedures in the context of the evaluation and approval of veterinary medicinal products, feed additives and pesticides. Although JECFA/JMPR methods were included in the analysis, this was more for comparison purposes and to explore possible advantages and benefits of these models.

A recommendation regarding the future use of specific "harmonized" models for FAO/WHO expert groups is, of course, outside the EU mandate. However, it would be desirable if JECFA and JMPR take into account the suggestions made here in their own harmonization efforts and with a view to the setting international standards.

7.2.1. Proposal for harmonisation in consumption data used

One of the objectives of the mandate was to identify a single reasonably accurate and acceptable model to be used in exposure assessment and to recommend it as a base model for exposure calculations in the EU and to identify the most appropriate food consumption data to be used. The currently used models are described in detail in chapter 3.4.2-3.4.4 and were considered by the expert working group.

Proposal for use of consumption data for animal derived food

Preferred source:

Consumption data based on surveys in the EFSA's "Comprehensive Database" as transformed into data on raw primary commodities (RPC) are considered as the preferred source, as it is considered the most relevant and accurate one for the European population. The data should be made available in the most detailed (disaggregated) way possible, e.g. to allow for "offal" to be differentiated in to liver and kidney.[43]

Reasonable alternatives:

CIFOCOss data: The data base contains consumption data from surveys on a global scale. Concerning data from EU member states, only "summary statistics" from EFSA's "Comprehensive Database" are available in CIFOCOss (i.e. based on the same data). Currently transformation of data into RPCs is not used, which may cause bias when compared with data from residue studies.

7.2.2. Proposal for harmonised residue (occurrence) input assumptions for acute and chronic exposure

Chronic exposure

In a chronic exposure scenario, it is recommended to preferably use the arithmetic mean of residue concentrations in relevant animal-derived food as an estimator for the daily intake:

The information on the possible residue occurrence in animal-derived food is usually obtained in (pre-authorisation) residue studies and the expected daily residue intake is derived from the distribution of residues in these samples[44]. The number of samples per time point(s) obtained in such studies is often quite small (e.g., for VMP generally less than 30 animals in total, distributed over 4 to 5 slaughter days), and in most cases no "rigorous" assumptions can be made about the "true" statistical distribution of residues at a given time point. For convenience, the assumption of a normal distribution of concentrations is therefore used as the default assumption in most cases, knowing that the actual distribution may also be asymmetric, e.g. right-skewed (or left-skewed) or even multimodal, as a result of a mixture of different distributions, which, however, would only be apparent if the whole population could be observed.[45]

For concentration data with unknown distribution of residues, i.e. where only the empirical distribution is known, the assumption of an approximate normal distribution with the arithmetic mean of the available sample as the expected value is considered a most reasonable recommendation.

However, because occurrence data are subject to multiple random errors mostly due to the combined effects of sampling error (i.e. biological variability and limited sample size) and measurement uncertainty, the arithmetic mean might lack of the adequate precision and accuracy. The associated uncertainty can be accounted for by determining a (1-α) confidence interval for the arithmetic mean (common choices are 90% or 95% confidence).

[43] This statement is based on the understanding that the consumption data in FACE and PRIMo 4 are currently prepared with different levels of detail. In principle, with a view to maximum flexibility and adaptation to different regulatory requirements, the most differentiated data basis is to be preferred

[44] a suitable time for the choice of values is, for example, the time when residue fall below the MRL, i.e. when the food can be legally placed on the market

[45] as far as is known, the distribution of residue concentrations in edible tissues in a sufficiently large sample of animals has never been described in the literature

As uncertainty extends in both directions around the mean, the “true” value can be either higher or lower than the range of measured values. Using the upper/lower boundary for the occurrence estimates, it can be assumed with probability (1-α/2) that the "true" occurrence value is below/above this value. As the confidence limit is predominately linked to the number of samples as well as the variability, it will be closer to the mean, the more robust the data are. It is recommended to always report the mean value together with the corresponding uncertainty ranges to give the risk assessor and risk manager an approximate estimate of the uncertainty interval of the occurrence values. For exposure calculations, it is justified to choose occurrence values from this range, depending on the level of uncertainty that is considered acceptable for the purpose and use of the assessment.

Typically, if a reasonably sufficient number of observations are available and the variability of the data is relatively small, the (arithmetic) mean can be taken. A further aspect to this consideration may be that the use of residue occurrence data is inherently based on the conservative assumption that all animals are treated under the approved conditions of use with food derived from animals obtained at the end of the prescribed withdrawal periods or that all animals ingest residues of a substance through their feed at the level of maximum expected dietary exposure (for pesticides).

However, depending on the quality of the data it may be necessary to use values based on the upper 90 % (or 95 %) confidence limit of the arithmetic mean for the occurrence in the exposure assessment, in particular if only few observations are available and the number of animals sacrificed in a trial cannot be increased due to ethical and economic considerations or if, for example, the occasional intake of increased (fluctuating) residues is a concern due to the specific toxicological profile (e.g. ADI based on subchronic effect or other short-term effect). This is to be decided on a case-by-case basis. In such cases, care should be taken not to underestimate by choosing the mean and the upper confidence levels should be taken.

Where pharmacokinetic data are available, i.e. data on the depletion of residues over time, suitable mean values and corresponding confidence limits may also be derived from modelling the data using e.g. regression analysis, in order to make better use of all available data.

The suitability of the median (used in some models, e.g. GECDE) as a standard estimate for chronic exposure may be questioned on the basis that the rules for finding the median tend to ignore relevant occurrence values: the median is not impacted by values at the (extreme) high end of the dataset (and also not impacted by low end values).

Also the geometric mean would not sufficiently account for "high end" values as it tends to be more sensitive to smaller numbers than larger numbers (making it relatively insensitive to high occurrence values).

The 95/95 tolerance limit, i.e. upper one-sided 95% confidence limit over the 95th percentile residue concentration, which is commonly used by EMA can be regarded as very conservative when assessing chronic exposure since use of this value assumes, unrealistically, that on each day the residues are in the range of >95% of possible residues.

Proposal for “chronic” residue input assumptions

Preferred model:

For the chronic exposure a value based on the arithmetic mean is recommended. The arithmetic mean of a limited sample comes along with uncertainty due to the randomness of the sample and the variability in the total population. This uncertainty can be described by considering a lower and upper

90% (or 95%) confidence limit of the mean[46]. All three values (mean, upper and lower confidence limit) should be calculated to obtain a range of possible occurrence data for further use in the exposure models or further risk assessment/risk management.

Reasonable alternatives:

If quality of data does not allow for use of the upper limit of the confidence interval of the arithmetic mean (e.g., data not fulfilling the basic statistical criteria), a scientifically justified alternative value may be used. This could either be the arithmetic mean and (alternative) term(s) to account for uncertainty or the arithmetic mean itself, if justified for the scenario under consideration.

Note: if the data do not allow for a quantitative (statistical) assessment of associated uncertainties, this limitation should be clearly identified to allow for an assessment of the potential impact on the overall outcome (and to manage this through a more cautious and conservative approach).

Acute exposure

For the acute exposure, it is relevant to include the most conservative residue value at the top-end of the residue distribution. It may be considered to use the upper 95 % tolerance limit (with 95% confidence) or the MRL as a "worst-case" assumption for residues present. If there are insufficient data to calculate a 95 % tolerance limit (with 95% confidence), then the maximum (highest) reported residue level from a study or the mean + 2SD could be used.

In the pesticide field it is usually assumed, that for blended commodities (e.g. milk) the mean residue value would be the reasonable input value for the acute exposure. Values at the (extreme) high (and low) end of the dataset do not seem to be of importance, because of dilution effects in bulk milk. However, this assumption may not be true for all situations in the veterinary field, as milk can be obtained directly at farm level and some products are intended to be used in the entire livestock.

Proposal for "acute" residue input assumptions

Preferred:

It is recommended to use the upper 95% tolerance limit (with 95% confidence)[47], which is mostly the same value as the MRL as a "worst-case" assumption for residues present.

Reasonable alternatives:

If there are insufficient data to calculate an upper 95% tolerance limit (with 95% confidence), then the maximum (highest) reported residue level from a study or mean + 2SD could be used.

In fields where it can reasonably be assumed that a foodstuff (e.g. milk) is always blended, mean residues can be used as input values.

[46] confidence limits = mean(X) ± k' × sd(X)
with

$$k' = \frac{t_{n-1,1-\alpha/2}}{\sqrt{n}}$$

where $t_{n-1,1-\alpha/2}$ is the (1-α/2) percentile of Student's t-distribution with n-1 degrees of freedom.

[47] tolerance limit = mean(X) + k × sd(X)
with

$$k = \frac{t_{n-1,1-\alpha}(\delta)}{\sqrt{n}}$$

where $t_{n-1,1-\alpha}(\delta)$ is the (1-α) percentile of the non-central t-distribution with n-1 degrees of freedom and non-centrality parameter $\delta = z_P \times \sqrt{n}$ (z_P the P^{th} percentile of the standard normal distribution).

7.2.3. Proposal for harmonised exposure model

The exposure modelling concepts discussed and compared in this report are all based on deterministic exposure estimates, but with varying degrees of refinement. The recommendation is based on the most refined (advanced) deterministic model(s) currently used at EFSA, EMA, JMPR or JECFA. The model inputs are derived from empirical consumption and occurrence data as outlined in the sections above.

Proposal for "chronic" exposure model

Preferred:

The preferred model should be based on i) individual-level dietary surveys (preferably using RPC values), ii) provide information on exposure in different subpopulations/age groups (e.g. infants, young children, adults), and iii) allow estimation of exposure levels at different levels of the exposure distribution (e.g. 95th percentile or other values of interest). The more refined the model, the more options there are for specific and relevant risk assessments.[48]

Reasonable alternatives:

Another suitable model is based on food consumption distribution (GECDE model), assuming consumption for one food category at a high level (e.g. 97.5th percentile consumption) and mean consumption for all other categories. It can be used to calculate exposure for the general population and population subgroups, as needed. The model uses summary statistics from the EFSA comprehensive database.

Proposal for "acute" exposure model

Preferred:

The preferred model should allow for separate estimates based on individual dietary surveys and single food commodities (preferably using RPC values). The relevant residue input value for the commodity being assessed is combined with the corresponding total consumption of the commodity on each individual day for this purpose. Higher percentile exposures (usually the 97.5th percentile) based only on days of consumption are calculated separately for each food, dietary survey and age group (e.g. infants, young children, adults).

Reasonable alternatives:

If no individual consumption data are available, summary statistics of dietary surveys could be used. The relevant residue input value is combined with a high daily consumption (97.5th percentile) of that food (meat, offal, milk, others).

7.2.4. Proposal for combining "chronic" exposure to residues from multiple uses in animal tissues

When compounds are used as pesticides, as veterinary medicinal products and/or feed additives (dual/triple-use compounds), residues may theoretically be present in animal commodities resulting from the use of the compound in all three domains (from direct use as VMP or food additive through the labelled route of application or from exposure of the animal via plant derived feed). In this case, the working group assumed that residues will be present in 100% of all animal commodities from all

[48] It should be borne in mind that all models compared here are based on deterministic models used in the regulatory field and higher tier probabilistic models are currently not included in the discussion.

uses. This is consistent with the assumption currently used for the separate assessments of veterinary medicinal products /feed additives and pesticides. The probability for this worst case to take place was however seen as very unlikely, which is inter alia evident from monitoring/surveillance data or treatment records. In the absence of accurate information on the "true" occurrence of residue from multiple uses, a pragmatic (still conservative) approach would be to use the highest mean observed residue from each species/commodity for the chronic exposure. For acute exposure this would be the highest acute exposure estimate from all three uses.

Proposal for "combining" residues from multiple uses

Preferred model:

Identify and use the highest mean observed residue per commodity/species from all uses for the chronic exposure. As the arithmetic mean of a limited sample comes along with uncertainty due to the randomness of the sample and the variability in the total population, this uncertainty can be accounted for by considering the upper 90% (or 95%) confidence limit of the mean. By doing so, it may be assumed that also subchronic endpoints are adequately covered.

For acute exposure apply the highest acute exposure estimate out of all three uses, if applicable

Reasonable alternatives:

There are currently no alternative deterministic methods. It is theoretically possible to better estimate such scenarios on the basis of probabilistic methods, but there is currently no sufficient data base or established models available for this.

Other options:

Addition of mean residues (for chronic) or highest residues (for acute) from all three uses: however, this would lead to unrealistically high estimates.

7.2.5. Proposal for harmonisation of some of technical aspects of the exposure approaches

Definition of tissues

The experts noted some differences in the classification/definition of tissues in the different models (e.g. use of a definition of meat (EFSA) as opposed to muscle (EMA/JECFA)), which can lead to different input quantities for the models. There were also some similar differences noted in the definition and use of offal tissues in the exposure estimates.

It was noted that some of these differences are due to historical rather than explicit scientific reasons. In some cases, however, these differences have a scientific basis. Whereas residue studies will investigate samples of muscle tissue and/or fat, the food consumption data used by EFSA refer to meat consumption, which may include consumption of trimmable fat. EFSA therefore uses some standard assumptions to "convert" tissue types and corresponding residue concentrations by way of calculations (e.g. residues in "meat" being a mixture of 20% fat and 80% muscle vs residues in muscle or fat). However, the group did not perform specific calculations on the quantitative impact of these differences on exposure nor did it elaborate a concrete proposal for harmonisation.

The group also noted that there is ongoing work at Codex level (CCPR, CCRVDF) on the harmonisation of definitions for edible tissues/food of animal origin for compounds with multiple uses.

Estimating exposure from multiple species

The group noted that in exposure estimates from multiple species consumption data are partly used in different ways and levels of aggregation: for example, grouping of different species (mammals) in FACE vs "cattle, sheep, goat" in PRIMo 4 (or for the JECFA models) (see 3.4.3.2.). A high-level aggregation of food consumption data (e.g. one consumption factor/input value for mammals) may on one hand simplify the exposure assessment, but on the other hand there might be situations where exposure assessment at the individual animal species is required or preferred to obtain more accurate estimates.

7.2.6. Thoughts on a harmonised use of exposure estimates in risk characterisation approaches

Risk characterization combines quantitative exposure assessments and results from hazard assessment to draw conclusions about the likelihood and magnitude of potential health effects, associated uncertainties, and options for reducing or avoiding risks. It starts with and is based on scientific data and scientific models, but also involves certain default assumptions based on expert judgment and policy choices.

It is not the intention here to go deeper into the complex mechanisms and the various aspects of decision making in risk characterization, as this would go far beyond the scope of the mandate. Only some specific aspects on the use and integration of exposure estimates into risk characterisation will be highlighted here.

Based on the review of the different approaches to exposure assessment and the comparison of the models used, the expert group unanimously concluded that both short-term and long-term exposure scenarios should be assessed in the risk characterisation.

It is of critical importance to the outcome of the risk characterisation how these exposures are used in the process. This includes not only an evaluation of the suitability of the individual exposure scenarios themselves, but also of the nature and character of the health-based guidance value (HBGV), i.e., the underlying health effects. For example, for the assessment of chronic exposures, the ADI is used as the default HBGV in all of the regulatory frameworks reviewed. The traditional basic assumption is that the ADI value, according to its definition, covers the health effects of a consumer's daily exposure throughout life and is protective across all life stages, i.e., that the average long-term exposure as presented in the estimates for the general or adult population (most life stages consist of the adult phase) would be appropriate.

However, the pattern of toxicological effects may indicate that particular life stages or subgroups may be at higher risk than the average population, and in these cases, life stage/subgroup specific risk characterisation could provide a more accurate match between the nature of the toxicological effect and the specific exposure situation (e.g., infants, children, elderly) and greatly improve the quality and relevance (i.e., safety) of the assessment. In short, the more detailed and differentiated the exposure assessment is with respect to multiple exposure scenarios, life-stages, population groups, prediction of exposure ranges, the more options will be available to the risk assessor and the more flexible, accurate, and reliable the risk characterisation can become. In the discussion, a number of considerations were made in this regard that could guide further development of approaches:

- One advantage of the FACE and PRIMo models is that detailed exposure estimates can be generated for a range of subpopulations/age groups and at different exposure levels (e.g., mean, 95th percentile) which may then be specifically and relatively precisely matched to the hazard (toxicological) profile of interest.

- The GECDE model is, in principle, also sufficiently flexible and capable of calculating exposure for specific subpopulations, life stages and high consumer groups, if required for specific toxicological reasons.

- The IEDI model is a model for estimating approximate average chronic (lifetime) exposure and refers to a general population, but is not suitable to identify specific consumption patterns and, thus not accurate and flexible enough for estimating exposure in certain subpopulations and life stages

- The TMDI model is based on a food basket for 60 kg adults and is not suitable to be used as an exposure model for risk assessment of specific subpopulations or to cover specific consumption patterns in certain subpopulations and life stages.

As noted above, exposure assessment is only one building block of risk characterization, and a uniform, valid scientific methodology for collecting, analysing, and using exposure data (the same is true for hazard data) would not guarantee a consistent outcome of risk characterization because a range of default assumptions, conventions, expert judgments (and policy choices) are applied at this step of interpreting the scientific evidence. However, input based on the best possible scientific data and the best possible scientific models can greatly increase the likelihood of consistent (harmonized) results.

8. Conclusions and Outlook

This work is based on a mandate from the EU Commission requesting scientific and technical assistance from EFSA and EMA to develop a common approach to exposure assessment methods for residues of veterinary medicines, feed additives and pesticide residues in food of animal origin. The mandate was received in July 2020.

The work was carried out by a joint EMA/EFSA working group (Enlarged Working Group on Exposure Assessment), which was established in December 2020 and included experts nominated by EFSA and EMA and, in addition, experts working for JMPR and JECFA.

The expert group has compared the methods and models used in the different domains in terms of data sets used, theoretical assumptions and calculation models, and carried out a series of comparative calculations to identify and quantify differences and the factors influencing the respective results. This work is presented and discussed in detail in chapters 1-6 of this report.

The differences between the exposure assessment methods examined could be primarily attributed to the type and use of consumption and occurrence data, but also to the calculation models and the desired level of refinement and detail of the assessments (i.e. the choice/use of methodological tier). While certain differences in the generation and handling of the data were identified, a number of differences can also be explained by a historically largely independent (i.e. asynchronous) scientific development of exposure assessment methodologies in the various domains.

Due to the complexity and multi-layered nature of the various aspects and questions to be addressed, most of the discussions took place ("intentionally") at a relatively high level of abstraction to allow for the identification and comparison of key concepts and key features of the different methodologies, rather than putting too much effort into clarification and agreement at the level of technical detail and terms.

The outcome of the work should therefore be seen as the group's agreement on the basic "building blocks" of a recommendable harmonised methodology, rather than a ready-to-use methodology, worked out to the last technical detail and directly operational in each regulatory domain. For this

reason, many downstream technical aspects and specificities were left out of the discussion for the time being.

Following this approach, a set of recommendations was developed outlining the key elements of what would constitute the "preferred methodology" (i.e. data sources and models). However, for each proposal, an alternative proposal was also developed. The guiding principle in all of this was to obtain the most realistic exposure assessment possible based on the available methodologies, i.e. to use the most specific input data and modelling assumptions that allow for a relatively high level of refinement and detail in the results, thus providing a range of options and flexibility to ensure a sufficiently specific and relevant risk characterisation.

The recommendations relate to the following aspects (see chapter 7 of this report):

- selection of consumption data
- selection of occurrence data
- selection of exposure model(s)
- exposure to residues from multiple uses
- use of commodity definitions and combined exposure from multiple species

These recommendations of the group could in principle form the "blueprint" for a future harmonised methodology. The group was also aware that if the recommendations were adopted, a number of follow-up actions would be needed to further define, elaborate and consolidate the harmonised methodology, especially at the technical level of detail, and to fit it into the respective risk assessment approaches and the legal frameworks. Some other issues related to the use of uniform definitions, terminology and the alignment of scientific guidelines, which were not considered as part of this activity, should be included in the follow-up work.

The group's recommendations focus primarily on exposure assessment as the usual first step of a risk assessment rather than the use of exposure assessment data in the subsequent steps of the risk characterisation. Although some aspects of the risk characterisation were discussed, no recommendations were developed under the current mandate.

As a starting point, the group agreed to include in the comparison only those exposure assessment methods that are (currently) actually used in the regulatory areas for residues of veterinary medicinal products, feed additives and pesticides. As mentioned above, all these methods are based on traditional deterministic approaches, using varying degrees of refinement. Agreement on the "best possible" existing methodology or on a reasonable combination of the "best possible components" of existing methods and models were considered an important step towards harmonisation.

However, this does not mean that possibilities for further scientific optimisation and meaningful extension of the methods or integration of further tools into the existing approaches were not discussed, i.e. the perspectives on how a "harmonised" methodology could be further developed and refined to answer additional questions related to exposure assessments in the future. Here, the group has made some initial considerations, which are by no means to be regarded as comprehensive or conclusive. None of these aspects or options are currently integrated into existing standard methodologies, so these suggestions should be seen solely in terms of future developments:

- Combined exposure assessment: The harmonised methodology for tissues could be extended to allow for assessment of exposure to substances with multiple uses, i.e. combined assessments of chronic dietary exposure from animal plus plant derived foods, and in a subsequent step it might be considered

to also integrate cumulative combined exposure (i.e. multiple sources) to substances belonging to groups with a common mechanism of toxicity.

- Use of monitoring data: The exposure estimates currently conducted are based on residue data from pre-authorisation studies conducted under the intended conditions of use. The assumptions underlying the study design are intentionally conservative, and the results may not accurately reflect the "real-life" residues in food as they are available on the market[49]. Data from monitoring and surveillance programs (post-market) may be more appropriate here, as they provide information on levels and occurrence frequencies of residues in food as they are actually ingested by consumers. However, monitoring data are often based on targeted sampling for enforcement purposes (to demonstrate compliance/non-compliance with legal uses) and are therefore often not sufficiently representative for the background exposure. Therefore, it would be desirable to have truly representative data available based on samples from a representative random sampling design, ideally using modern analytical methods able to detect a broad range of residue components (i.e., including relevant metabolites). Where such data are available, it may be appropriate to revisit exposure estimates at appropriate times after approval to refine the original exposure estimate.

- Consideration of ADME/pharmaco-/toxicokinetic data: Current exposure assessments only address external exposure (via oral intake), while options that consider internal (systemic) exposure, i.e. the actual amount of substance released from food matrix and absorbed/acting in the human body, which would allow the best possible comparison with toxicological effects in the context of risk characterisations, are usually not considered. Existing toxicokinetic information, in particular on the (relative) bioavailability/bioaccessibilty of residues from the food matrix, could be included in a harmonised assessment approach, which could lead to a more realistic assessment in many cases.[50]

- Consideration of food processing: Most food is consumed in processed form (e.g. cooking/baking, pasteurisation, also ageing), which not only affects the concentrations found, but in part also the qualitative composition of the residues, i.e. the type of residues (incl. de-toxification as well as toxification reactions). The residues formed or possibly changed under these conditions are not or not adequately taken into account in the usual exposure estimates which are typically based on measurements in the raw animal derived commodities. Here, too, consideration could be given to how such information could be integrated into exposure estimates to derive more accurate and relevant estimates.

-Less-than-lifetime approaches: The models examined refer to acute (short-term) and chronic (long-term) exposures while other possible scenarios commonly referred to such as "less than lifetime " were excluded from the comparisons, mainly because these methods were not consistently used or considered as not being sufficiently established in the regulatory areas examined. However, in certain cases, based on a specific toxicological profile of a substance, it may be appropriate to consider scenarios based on intermittent, fluctuating and peak exposures that are not consistent with chronic exposure and are also not sufficiently covered by the acute exposure estimates. In such cases, it may

[49] For example, in the studies with veterinary medicinal products, animals are treated at the intended maximum dose/duration and food is obtained at the earliest possible time of legally possible food production (e.g., after the expiration of the withdrawal periods), whereas in practice much longer withdrawal periods usually occur (ii) also the default assumption regarding the frequency of occurrence of residues is probably too conservative (it is based on the assumption that all animals are treated and all samples contain residues, which is not consistent with available sales/consumption data). However, in the absence of reliable monitoring data, this is currently the only valid assumption we can make regarding the frequency of occurrence of residues.

[50] The term "relative" refers to a comparison of "bioavailability/bioaccessibility" of residues of a substance in food matrix compared to the formulation of the substance used in the corresponding study to quantify the toxicological effect. The default assumption is that both parameters would be identical ("bioequivalent") which is in many cases an overly conservative assumption (note: this approach would normally not be applicable in case of sensitive local effects, e.g. in the GI tract)

be appropriate to assess exposure separately using an LLT approach complementary to acute/chronic exposure and to include this information in the risk characterisation.

- Use of probabilistic methodologies: Increasingly, probabilistic methods (e.g. Monte Carlo methods) are being used to generate and analyse exposure distributions. Probabilistic and deterministic approaches, as currently used for regulatory processes, do not necessarily produce different estimates of dietary exposure for a population if enough iterations are performed, but probabilistic methods can provide better information on the variability of dietary exposure estimates as they consider all available data, i.e. the full range of values and variability for each parameter. The possibility of using such techniques when data requirements are met should be further pursued and explored.

A change in the exposure assessment methodology may have a direct impact on the outcome of the risk assessment and consequently on risk management, which is closely linked to the outcome of the risk characterisation (e.g. the setting of numerical MRLs or other risk management measures). The group discussed risk management issues only in passing, but it was recognised that the impact on risk management may be particularly relevant when exposure estimates in a regulatory area differ significantly from previous assumptions due to the introduction of new methodologies (e.g. moving from a broader to a more specific methodology) or when new approaches are introduced (e.g. acute exposure assessment). However, a more detailed assessment of the scientific and legal/administrative implications can only be made once the harmonised methodologies are sufficiently clearly defined and implemented in the respective areas. Further, it is recognised that with any agreed change in approach it will be necessary to introduce sufficiently long transitional phases in order to make the necessary adjustments.

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10. Abbreviations

(The precise definitions of the terms below may vary in different sectoral legislation and guidelines and the reader is advised to consult the relevant texts for further details.)

ADI	Acceptable Daily Intake
ARfD	Acute Reference Dose
AUC	area under the curve
BMDL	Benchmark Dose Level
CCPR	Codex Committee on Pesticide Residues
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Foods
CIFOCOss	FAO/WHO Chronic Individual Food Consumption – summary statistics
CVMP	Committee for Medicinal Products for Veterinary Use
EC	European Commission
EFSA	European Food Safety Authority
ECHA	European Chemicals Agency
EHC 240	Environmental Health Criteria 240
EMA	European Medicines Agency
EU	European Union

FACE	Feed additives consumer exposure
FAO	Food and Agriculture Organization
FBS	Food balance sheet
FEEDAP	Panel on Additives and Products or Substances used in Animal Feed
FoodEx	Multipurpose food classification and description system developed by EFSA
GC	Gas chromatography
GEADE	Global Estimate of Acute Dietary Exposure
GECDE	Global Estimate of Chronic Dietary Exposure
GEMS	Global Environment Monitoring System
GL	Guideline
HBGV	Health Based Guidance Value
HPLC	high performance liquid chromatography
HR	Highest Residue
HRP	Highest Reliable Percentile
IEDI	International Estimated Daily Intake
IESTI	International Estimated Short-Term Intake
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LC	Liquid chromatography
LOD	Limit of Detection
LOQ	Limit of Quantification
LLOQ	Lowe Limit of Quantification
LSC	Liquid Scintillation Counting
LTL	Less than lifetime exposure
MR	Marker Residue
MR:TR	Ratio Marker Residue : Total Residue Ratio
MRL	Maximum Residue Limit/Level
MS	Mass spectrometry
NFCS	National Food Consumption Surveys
NOAEL	No Observed Adverse Effect Level

NOEC	No Observed Effect Concentration
OECD	Organisation for Economic Co-operation and Development
PoD	Point of Departure
PRIMo	Pesticide Residue Intake Model
RAC	Raw Agricultural Commodity
RoC	Residue of Health Concern
RPC	Raw Primary Commodity
RPCD	Raw Primary Commodity derivatives
SD	Standard deviation
SFB	Standard Food Basket
TMDI	Theoretical Maximum Daily Intake
TPoD	Critical time point for risk characterisation
TR	Total Residue
ULOQ	Upper Limit of Quantification
UTL	Upper95 % tolerance level with 95 % confidence
VICH	Veterinary International Conference on Harmonization
VMP	Veterinary Medicinal Product
WHO	World Health Organisation

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