Literature review on aggregate exposure methodologies

In the past, exposure assessments focussed on exposure to single substances and by single routes. In the nineties, aggregate exposure assessment began to receive more attention and instruments to enable these assessments started to develop. The development of regulatory frameworks requiring aggregation of exposure for e.g. pesticides supported this development. However, in some areas such as contaminated site assessment, aggregate exposure assessment has long been the routine approach for screening risk assessments.

This literature review provides a summary of regulatory, policy and scientific documents that address the issue of aggregate exposure. The focus of the review is on the rationale, background and processes for aggregate exposure. In addition the review in chapter 2 focuses on the models and techniques.

1.1 Aggregate exposure following the US Food Quality Protection Act

In 1996 the Food Quality Protection Act (FQPA) was published in the United States. This act introduced the concept of safety of pesticides as “reasonable certainty that no harm will result

from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information". The publication of this FQPA raised a number of science policy issues, which resulted in the development of General Principles for Aggregate Exposure and Risk Assessment (US-EPA, 2001). The same legislation was one of the triggers for the ILSI Risk Science Institute to organize a workshop on aggregate exposure (ILSI, 1998) . Within this framework, a series of models were developed.

1.1.1 ILSI Aggregate exposure workshop report

The objective of the workshop was to: evaluate the methodologies currently available for aggregate exposure assessment, with emphasis on the practical scientific issues and data requirements for pesticides. For purposes of the workshop, a definition of aggregate exposure assessment (which is still one of the basic definitions used today) was formulated as: a process for developing an estimate of the extent of exposure of a defined population to a given chemical by all relevant routes and from all relevant sources.

The workshop strongly endorsed the use of distributional analysis and probabilistic methods in estimating and characterizing pesticide exposures from all sources. The concept that the modelling of exposures should begin with the estimation of exposures for an individual on a given day (calendar-based models) and build to population distributions using Monte-Carlo-type simulation techniques also was generally accepted. Default models that use single values for input parameters and that generate point estimates as output are designed to produce conservative, high-end estimates of exposure. Most were developed as screening tools to identify chemicals that may warrant further considerations and scrutiny in exposure assessments. Despite their conservative predictions of exposure there was some support for the use of these models as first tier screening tools, simply to reduce the number of pesticides requiring more careful evaluation.

1.1.2 US-EPA General Principles for Aggregate Exposure and Risk Assessment

In response to the FQPA mandates to consider aggregate exposure, the Office of Pesticide Programs (OPP) issued a guidance document on aggregate exposure. The guidance explicitly stated the preference for a distributional analysis. The guidance document provided a framework for aggregate exposure and risk assessment and started from the basic idea that exposures should be based on an individual in the population and then on assessing exposure to the (sub)population as a whole.

The guidance document provides a framework consisting of ten steps that should be considered (not necessarily taken) when conducting an aggregate exposure assessment. The framework is shown in Figure 1 . The two initial steps, which are the identification of toxicological parameters and the identification of potential exposure scenarios for each pathway are more or less parallel steps in the process.

The *toxicological step* requires the identification of critical toxicological endpoints and their associated parameters such as dose, duration and route. If toxicological endpoints are the same, toxicological effects that occur at different dose levels via different routes of exposure should be combined. If not, more than one aggregate exposure assessment – one for each critical endpoint – could be performed.

The *potential exposure scenario step* requires all relevant pathways [1] to be identified as well as the corresponding exposure scenarios
[2]
(including duration and route). By using bounding estimates, exposure scenarios that can be excluded from the refined assessment because of negligible contribution, can be identified.

The guidance document considers focussing the aggregate exposure and risk assessment by limiting the number of potential exposure scenarios an essential step in the process. This scoping exercise should be done by conducting a bounding estimate on all exposure scenarios.

Some guidance criteria are provided for scoping exercises. The fist step should be to evaluate the relative contribution of routes and pathways. If a pathway would contribute < 1% of the total PAD [3] in the most refined assessment performed, then such use should not be included in a quantitative refined scenario. The same applies if an exposure scenario contributes less than 0.1 % of the PAD. In this way, no more than 10 % of the PAD should be excluded and this

should be the case for all identifiable subgroups that are potentially exposed. Similarly, if specific uses provide a negligible contribution or the toxicity by a particular route is low, uses or routes could be eliminated from the final assessment. The identification of negligible scenarios, pathways, uses or routes can be done by providing a bounding exposure estimate (using a combination of conservative assumptions for exposure parameters).

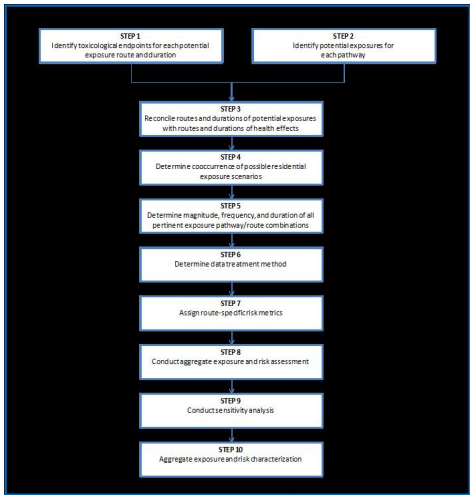

Figure 1 : Ten steps in aggregate exposure assessment (based on (US-EPA, 2001))

In *step 3* the routes and duration of exposure are matched with the routes and durations of the health effects. An aggregate risk

assessment should only be conducted on the matches. *Step 4* should then assure that a logical combination of exposure scenarios is made based on potential co-occurrence of exposures.

In the next steps, the quantification of exposure is worked out in further detail by determination the magnitude, frequency and duration of exposure for all pertinent exposure combinations, including temporal and spatial issues (*step 5*); and by choosing between probabilistic or deterministic techniques for input data (*step 6*).

A key issue in aggregate risk assessment is the choice of the appropriate risk metric *(Step 7*). Depending on the policy context or the data available, different approaches can be followed. The guidance illustrates the use of the Total MOE (Margin of Exposure) if a common uncertainty factor exists; and the ARI (Aggregate Risk Index) if dissimilar uncertainty factors over routes exist.

The final steps are then the quantification of the aggregate exposure and risk (*step 8*), the sensitivity analysis (*step 9*) to characterize risk drivers, and the final risk characterization (*step 10*), which is the integration and evaluation of the previous steps

1.1.3 Models related to US-EPA's aggregate exposure of pesticides

A list of models is published on the US-EPA's pesticide assessment website. With regard to human exposure, following models are listed, some of which are discussed in chapter 2 (http:/ /www.epa.gov/pesticides/science/models_db.htm
):

· SWIMODEL: screening tool for conducting exposure assessment of pesticides found in indoor swimming pools and spas (http://www.epa.gov/oppad001/swimodel.htm)

· DEEM (Dietary Exposure Evaluation Model): provides dietary probabilistic assessments of dietary pesticide exposure
(http://www.exponent.com/probabilistic_risk_assessment/#tab_overview).

· CALENDEX: evaluates aggregated exposure that appropriately incorporates the probability of simultaneous exposures across multiple pathways.
(http://www.exponent.com/probabilistic_risk_assessment/#tab_overview)

· CARES (Cumulative and Aggregate Risk Evaluation System):
(http://www.ilsi.org/researchfoundation/pages/cares.aspx)

· LifeLineTM Version 2.0: allows the user to investigate exposure to pesticide residues in diet, tap water, and in residential environments.

· LifeLineTM Version 4.3: is used to assess dietary, aggregate and cumulative risks of

pesticides. Version 4.3 is 50% faster than the prior version of LifeLine and includes new features in virtually every portion of the model. (http://www.thelifelinegroup.org/lifeline/index.htm , more recent version available)

· REx (Residential Exposure Assessment) (note: model not found)

· SHEDS (Stochastic Human Exposure and Dose Simulation Model): is a physically-based stochastic model developed to quantify exposure and dose of humans to multimedia, multipathway pollutants. (http://www.epa.gov/heasd/products/sheds_multimedia/sheds_mm.html)

· PBPK (note: model not found – probably ERDEM) (http://www.epa.gov/heasd/products/erdem/erdem.html)

In 2003, Health Canada as well published its General Principles for aggregate exposure and risk assessment (Health Canada, 2003). The Canadian guidance is in essence a copy of the US-EPA guidance (with replacement of certain concepts and terminology by the corresponding Canadian ones).

1.2 Aggregate exposure following the EU REACH regulation

REACH is the Regulation for Registration, Evaluation, Authorisation and Restriction of Chemicals (EC N° 1907/2006). It entered into force on 1st June 2007 and was designed to streamline and improve the former legislative framework for chemicals of the European Union (EU). Part of this regulation concern the Chemical Safety Assessment (CSA), which has to be done for all substances manufactured and imported in quantities ≥ 10 tonnes/year to determine

and demonstrate the safe use of a substance. The first step of the CSA is to determine whether the chemical is to be classified as dangerous or as a PBT or vPvB substance. In these cases an exposure assessment and risk characterization is required. Exposure scenarios are used to assess the exposure to chemicals of humans and the environment and to identify the appropriate risk management measures. The Chemical Safety Assessment distinguishes between exposure of workers, consumers who use products containing the chemical of interest and environmental exposure of the general population. Guidance documents as well as models are available to perform the exposure and risk assessment. The risk assessment may be an iterative process (Guidance on chemical safety assessment), if first assessments show unacceptable risk:

- Hazard information can be revised or generated taking the legal obligations on information requirements into account.
- Exposure information can be collected from the supply chain or it can be decided to generate new exposure data on a voluntary basis (e.g., measurements at sites or in the environment) or higher tier models can be applied.
- Or both types of information may be revised.

The guidance document (Guidance on chemical safety assessment, part D – version 1.1) clearly distinguishes a tier 1 (screening, conservative) approach from the higher tiers and provides guidance and potential models for the various tiers.

1.2.1 Guidance for aggregating exposure

Details on aggregating exposure are provided in the guidance document on chemical safety assessment, part D (risk characterization).

The (semi)-quantitative risk characterization is carried out by comparing the estimated exposure for relevant exposure scenarios with the critical DN(M)EL [1] for the leading health effect. This is done separately for each relevant combination of exposure pattern. With regard to time-frame, a distinction is made between long-term and acute exposure/health effects.

The guidance document provides a separate chapter for combined exposures, which covers both aggregate and cumulative exposure. The terms aggregate and cumulative exposure are not used as such.

“In situations where the same person is potentially exposed to the same substance in the same setting via different routes of entry into the body or from different products containing the same substance, exposure scenarios reflecting these concomitant exposures should be assessed in the exposure estimation. These scenarios – typically related to workplaces and aggregated exposure for consumers – need specific attention in the risk characterisation step.

In addition, humans are exposed at work, from consumer products and via environmental exposures. It should be considered in which cases it is relevant to make risk characterisation for such scenarios, representing exposure from all sources. Typically it is most relevant to combine consumer exposures with indirect exposure of humans via the environment.” (source: Echa, 2008: Guidance on information requirements and chemical safety assessment Part E: Risk Characterisation, page 27)

The guidance states that concurrent exposure via various routes of exposure needs to be accounted for when characterizing overall systemic health risks. It is recommended to perform human health risks in a two-step procedure. In the first step, route-specific risks (by comparing exposure levels with DNELs per route) should be dealt with separately. Risk management should focus on the route with the highest risk characterization ratio (RCR [2]). Once all route-specific health risks are controlled, the remaining health consequences due to concurrent exposure via the various routes have to be considered. This is done by summing up the RCR values for the various routes (oral, dermal, inhalation: RCR (for simultaneous exposure via three routes) = RCR (oral) + RCR (dermal) + RCR (inhalation)). Separate calculations are performed for the different populations (workers and the general public).

“In some cases, substances may have toxicity data showing similar target organs for all routes

of exposure, and the formula above should, of course, be used. If the data shows different main target organs or target effects (for which the DNELs are based on; e.g., liver for one route and kidney for the second), but that the overall toxicity profile contains the same organs (liver and kidney being affected by both routes), the recommended formula might not fully represent the true situation. However, it is recommended to use the unmodified formula as a default, conservative approach even in case of differing main route-specific organ toxicity, but to additionally express the corresponding uncertainty in a qualitative manner.”.” (source: Echa, 2008: Guidance on information requirements and chemical safety assessment Part E: Risk Characterisation, page 28)

Additionally, the potential need to assess combined exposure [3] (i.e. exposure from different uses of a substance) is recognized. Combined exposure of substances with consumer use and potential contamination in food items may need to be assessed. Worker exposure normally greatly exceeds all other exposures and thus need not to be combined with consumer or exposure via the environment.

The consumer guidance (ECHA, 2008a) explicitly indicates that if exposure occurs through multiple routes or through presence in multiple consumer products, this should be accounted for in the risk assessment by combining the exposures (normally separately for acute and long-term exposure).

1.2.2 Other developments related to aggregate exposure

In 2006, RIVM published a report on comparison of consumer exposure models as part of improvements to of the ConsExpo model (Park, M. V. D. Z. et al., 2007). The ConsExpo model was developed under the EU legislation on new and existing substances, which has been replaced by the REACH regulation. At that moment (and until now), the ConsExpo model is not designed for aggregate exposure assessment, but the need to incorporate this feature was recognized. RIVM worked further on this issue, by evaluating some models for aggregate exposure assessment (with focus on environmental exposure, exposure to pesticides and consumer exposure) for the French Agency AFFSET. From this an initial method for aggregate exposure assessment of

substances in consumer products was formulated
(Delmaar, J. E., Engelen, J. G. M. v., 2006)
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The authors proposed a tiered approach, which is steered by the scope and purpose of the assessment, consisting of 3 tiers:

Tier 1: screening level assessment;

Tier 2: detailed population assessment in which only chronic exposure endpoints are to be considered;

Tier 3: detailed assessment of the population exposure on a day-by-day basis, including assessment of acute (daily averaged) exposures.

In *tier 1* the exposure is assessed using conservative assumptions. Because of aggregation, consistency of the exposure profile needs to be maintained. Thus different subpopulations with different exposure profiles may be defined. The assessment is based on a representative person by subpopulation.

In *tier 2* the focus is on long-term exposure (yearly average), but with replacement of the hypothetical individual by the entire (sub)population, making use of distributions on exposure determinants.

In *tier 3* short-term exposures are accounted for which requires the exposure estimate to be on, for example, a day-by-day basis and to explicitly consider correlations between exposure events and history of exposure events.

RIVM then further evaluated the possibilities and limitations of aggregate exposure assessment by running a series of case studies (Wolterink, G. et al., 2009). Case studies involved exposure to triclosan and permethrin as synthetic substances and carvone and calcium as natural substances.

1.2.3 Models related to EU REACH exposure assessment (Guidance on chemical safety assessment, part D)

A series of models has been developed or can be used to fulfill the requirements of the EU REACH exposure assessment.

The guidance document (ECHA, 2008a) provides algorithms for tier 1 consumer exposure assessment. Exposure is calculated as a daily average. For higher tiers, reference is made to the ConsExpo model and the E-Fast model. The draft revision of the guidance document (ECHA, 2009)
discusses the ECETOC TRA and ConsExpo Tier 1 model. Higher tier consumer models are mentioned as well.

Environmental exposure and risk assessment within REACH can be done with the EUSES model or with the TGD Excel sheet, both are suitable for Tier 1 and higher tiers (ECHA, 2008b). The TGD Excel tool is incorporated in the combined consumer/environment ECETOC TRA tool. A new model (CHESAR), incorporating the EUSES model, is under development. A list of higher tier environmental models (focusing on transfer and dispersion) is given in the guidance (ECHA, 2008b, ECHA, 2010)
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AISE, the International Association for Soaps, Detergents and Maintenance Products further

developed the tiered approach for their products. For first tier assessment, the TRA model is recommended; a refinement to tier 1 is provided with refined exposure parameters and emission factors (so-called tier 1.5). As a final option, after higher tier models, the use of measurements could be considered.

1.3 WHO Harmonization Project

Within the framework of the WHO Harmonization Project, a workshop on aggregate/cumulative risk assessment was organized in March 2007 (IPCS, 2007). However, the focus of the workshop and the framework document that will result from it is only concerned with cumulative exposure. Elements of aggregate exposure were only addressed in relation to cumulative exposure. However, the participants of the workshop recognized that aggregate exposure should be the subject of further work by IPCS.

1.4 Aggregate exposure in contaminated sites assessment

Aggregate exposure has long been common practice in human health risk assessment at contaminated sites (Ferguson, C. et al., 1998), as exposure to contaminants in soil results from their transfer to contacting compartments (soil, dust, air, food). However, the tools used for exposure assessment are generally only available at a screening level and aggregation of exposure and risks is often done in a basic way. Aggregation is often limited to the soil source, although some authorities require account to be taken of overall population exposure from other sources.

1.5 Summary

Two main regulatory frameworks, the Food Quality Protection Act in the US and the REACH Directive in the EU, have initiated the development of guidance on aggregate exposure assessment and use some definitions or make a divison into tiers. The description of the possible tiers is different however in the existing methodological reports, but broadly define a screening stage, a qualification/quantification of population sub-group exposure using the available (default) data and a full and refined exposure assessment across the sources, pathways and routes with a non-negligible contribution to the aggregate exposure. We use this insight to develop our rationale for a tiered approach.

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[1] DNEL: Derived No Effect Level; DMEL: Derived Minimal Effect Level

[2] RCR (Risk Characterisation Ratio): ratio of exposure level to DNEL or DMEL

[3] Note that the notion of combined exposure is somewhat different in different documents

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[1] Pathway: the physical course a chemical or pollutant takes from the source to the organism exposed

[2] Exposure scenario: a combination of facts, assumptions, and inferences that define a

discrete situation or activity where potential exposures may occur

[3] PAD (Population Adjusted Dose): the reference dose adjusted by the FQPA safety factor