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Report of EuroMix First Workshop on International Harmonisation on the Risk Assessment of Combined Exposures to Chemicals

20 -21 October 2016, Celia Hensman Suite, W12 Conferences, Imperial College London, Hammersmith Campus, London W12 0HS

Background

EUROMIX organised the first of a series of workshops on the international harmonisation of the risk assessment of combined exposures to chemicals from 20-21 October, 2016 at Imperial College London, UK. The aim of these workshops is to explore options and potential limitations in the international acceptance of approaches to the assessment of combined exposures to chemicals. This has obvious implications for those commodities where Maximum Residue Limits (MRLs) have to be established for residues, in that if very different approaches were to be used for combined risk assessment, the acceptability of MRLs could vary markedly. This first workshop focused on the scientific issues involved and identified those topics of greatest priority for consideration at future workshops in this series.

The workshop took place over 1.5 days, from 14:00 on day 1 until around 16:00 on day 2. The programme of the workshop is provided in the Annex. Participants were selected from representative geographical regions and organisations, with participation from Europe, North and South America, Australasia and North Africa. The following individuals attended the workshop:

Name	Country/Region	Organisation
Luc Mohimont	Europe	EFSA
Eeva Leinala (Day 2 only)	International	OECD
Vittorio Fattori	International	FAO
Cecilia Tan	USA	EPA
Yasunobu Aoki	Japan	National Institute for Environmental Studies
Matthew O'Mullane	Australia	APVMA
Mohammed El Azzouzi	North Africa	University of Rabat
Andrew Worth	Europe	JRC
Bette Meek	Canada	University of Ottawa
Angelo Moretto	Italy	University if Milan
Jacob van Klaveren	The Netherlands	RIVM
Eloisa Dutra Caldas	Brazil	University of Brasilia
Roland Solecki	Germany	BfR
Alan Boobis	UK	Imperial College London

The meeting room was arranged in board room style. The meeting was chaired overall by Alan Boobis. Each topic on the agenda started with a short introduction by a designated participant, followed by a round table discussion during which existing areas of harmonisation were identified

and those where further work would be needed before harmonisation would be possible were agreed. The intention at the first meeting was not necessarily to resolve outstanding issues but list and prioritise these for further discussion at a later date.

The meeting started with participants introducing themselves, which was followed by a brief description of the EU funded EuroMix project (grant agreement number 633172) by Jacob van Klaveren. The key focus of EuroMix is developing methods and approaches for mixture toxicology that will help inform risk management in Europe, and elsewhere. This will be achieved by proof-of-principle studies of a tiered approach to assessing the risk from combined exposures and a test strategy to confirm or to refine the assumptions made in current cumulative risk assessment proposals or practices in Europe and elsewhere. An important aspect of this is international harmonisation, to the extent possible, of the approaches proposed.

One of EuroMix's deliverables is a survey of the legal requirements for cumulative risk assessment in different regions and countries. An advanced draft of the report is now available. It was agreed that it would be very helpful for this to be circulated to participants and ask for feedback, particularly from those countries not well described at present.

Problem formulation

Key messages

- Problem formulation by risk managers, in dialogues with risk assessors, is critical to success
- A tiered approach using existing tools enables pragmatic decisions
- Terminology for cumulative risk assessment should be harmonised to achieve a shared global understanding

The first topic addressed at the workshop was **problem formulation**, introduced by Bette Meek. From an international perspective, the key question is what is the purpose of assessing the risks from combined exposure to chemicals? Is the objective to harmonise methodology, the approach to setting MRLs, or some form of global risk assessment of real world exposures?

In the context of international harmonisation, it was agreed that in the short term, harmonisation might be possible for pesticides, due to the relatively limited number of chemicals in this sector, but that for other chemicals such as contaminants, more work would be needed before harmonisation is likely to be achievable.

In general, problem formulation is not well developed for the assessment of combined exposures to chemicals. It is often not well articulated, leading to lack of transparency. Elements in problem formulation should include the nature of the chemical sector, the regulatory context (legislative and policy considerations), the objective of the assessment, the timescale within which the assessment was required and the resources available, and the level of uncertainty that would be acceptable. It was agreed that clarity of problem formulation is critical.

Of the two major exposure scenarios (for authorised compounds such as pesticides), actual (real world) exposure (based on specific measurements of the compounds in question) and that for MRL setting ('worst case', based on conservative assumptions), harmonisation would be easier to achieve for the approach to the latter, though it should be possible to harmonise at least the methodology used for the former as well.

A key component in problem formulation is agreement on how chemicals should be grouped for assessment (cumulative assessment groups, CAGs). Should this be based on a common phenotypic

effect or MOA (this was discussed in more detail later in the workshop – see below). Information on both hazard and on exposure would be necessary, although the weight given to them will vary with the chemical sector. For new pesticides, particularly when considered authorisation, most information available is on hazard and a typical average or high end consumer is used to estimate potential exposure. However, when considering combined exposure, for example when a new pesticide shares a similar adverse outcome with several pesticides already on the market, sufficient exposure data are available in Europe on the other pesticides in the group, but might be lacking in other parts of the world. In contrast, when assessing possible risks from exposure to commodity chemicals, particularly in the form of contaminants in food, often more information is available on exposure although this varies considerable among chemical classes and monitoring practices. For chemicals migrating from food packaging materials very little data exist, whereas levels of dioxins and PCBs are well monitored because of EU regulation.

The importance of tiered approaches was emphasised, only doing what is necessary to address the problem, but this varies with the chemical sector (problem formulation). The WHO Framework for assessing combined exposures to multiple chemicals was a good starting point for this purpose[1]. However, this will require that the level of uncertainty is specified and that the uncertainty associated with the various tiers can be determined. This should then be linked to regulatory consideration of what is an acceptable margin of exposure and generally this is lacking in the problem formulation. Lower tiers are associated with higher uncertainties and hence require larger margins of exposure compared to higher tier assessments, where more data are available or refined modelling approaches can be utilised. It is necessary to determine where the best options are for refinement of the groupings, and should this be based on hazard or on exposure. In practice, this will be determined by both scientific and by policy considerations.

Problem formulation should stipulate the degree of discrimination required, i.e. what level of uncertainty is acceptable and hence what margin of exposure is acceptable as a threshold for regulatory consideration at each tier. This is a risk management issue, but is often not stated explicitly. With the move to probabilistic approaches, particularly for exposure (see discussion below), agreement will be needed on which percentile (or percentiles) should be assessed within each tier, for the distributions used (e.g. population exposure level, commodity consumption, incidence of toxicological effect).

The value of mapping the risk assessment tools developed by IPCS against the various tiers for assessment of combined exposures was emphasised.

There are issues with the terminology used in cumulative risk assessment, which is still not harmonised.

Exposure considerations

Key messages

- Problem formulation and available risk management options shape exposure considerations
- Both toxicokinetics and toxicodynamics need to be taken into account
- Chemicals should be grouped based on relevant use patterns and biological characteristics

The second and third sessions, introduced by Alan Boobis were discussed together. These were on: what is the **definition of an exposure combination of concern**, i.e. what is the chemical domain of

[1] Meek ME, Boobis AR, Crofton KM, Heinemeyer G, Raaij MV and Vickers C (2011). Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework. Regul Toxicol Pharmacol 60: S1-S14.

concern taking account of “legislative/regulatory silos” and **what is meant by co-exposure** (i.e. how should toxicokinetic and toxicodynamic considerations be taken into account).

There was general recognition that humans are exposed to a wide variety of chemicals from many categories of product, by many routes. Exposure levels vary markedly. In general, different categories of chemical are regulated under different legislation and often by different departments/agencies with little or no interaction.

The scenario determining the exposure combination of concern should be identified in problem formulation. Is the objective of the assessment limit setting – where issues of product approval and permitted conditions of use are factors, or is it determination of the risk of the population to actual exposures – where consideration needs to be given to existing scenarios and to the change that would result from the introduction of a new product. An important issues is what risk management options are available and feasible.

In considering co-exposure, exposure to different chemicals may occur simultaneously in time and space (e.g. pre-formed mixtures), separated by time, separated by space or separated by both. One possible definition of co-exposure would be chemical exposure in space and time such that there is simultaneous systemic exposure to, or simultaneous effects of, more than one chemical. This would require consideration not only of toxicokinetics but also of the persistence and reversibility of the toxicodynamic response.

Examples are known of chemical combinations where, for any combined effect, exposure has to be at the same time and space due to rapid elimination and reversibility; where there can be separation of some time or space between exposure to the different chemicals due to slow elimination and/or slow reversibility; or where there can be a considerable separation between exposures (months or years), for example cancer initiation and promotion. This has implications for the scope of a combined assessment and is therefore critically dependent on problem formulation – the objective of the assessment and the options that would be available. It will also impact on how assessment groups are constructed. For example, the chemical grouping that would need to be considered for possible initiation/promotion interactions would be very different from that needed to consider acute additive effects from simultaneous exposure.

How should the toxicokinetic and toxicodynamic characteristics of chemicals in an assessment group be assessed and taken into account when exposure is separated in time and/or space? In the case of toxicokinetics, information will often be available (or can be predicted) on persistence, e.g. half-life. For toxicodynamics, it will be important to consider the nature of the effect, for example the MOA, reversibility, role of adaptation and repair, indirect effects (e.g. cardiac toxicity influencing renal function). It will also be necessary to consider potential windows of susceptibility, for example during early development.

Information on the use profile of chemicals will be of value in assessing the likelihood of co-exposure. Depending on the scope of the assessment, if this becomes very broad, agreement will be needed on default assumptions regarding co-exposure. Methods are being developed to determine which real world combinations of chemicals co-occur in food, using probabilistic approaches (see below).

For pesticide residues and residues of veterinary drugs, levels in food are generally very low however for other chemicals this is not always the case. For these, regional use profiles would be of value, for example for food additives, although this information is often not available in some parts of the world. Use of common methodology to obtain and evaluate such data would be beneficial.

Biomonitoring data is invaluable in determining real-world co-exposures, as it provides direct information on the nature and levels of systemic co-exposure occurring in individuals and it takes into account multiple routes of exposure (food intake, inhalation, dermal contact).

Advances in computational biology will result in the increasing use of modelling to predict the effects of combined exposures. This brings with it a number of additional issues with respect to any international harmonisation, but this aspect was not discussed further at the first workshop.

Formation of cumulative assessment groups requires some biological basis for grouping. However, prior to considering the biological effects of chemicals, an alternative would be to consider likelihood of co-exposure and the levels of exposure occurring. Most authorities group on hazard first and then consider exposure, but this is for specific chemical sectors, where there is a limited number of chemicals in scope (e.g. pesticides). Chemical groups based on biology could be assessed using a tiered approach, taking account of potency, MOA and exposure.

Between the two options, group by biology, followed by consideration of exposure and group by co-exposure, followed by consideration of biology, it is likely that the choice will depend on problem formulation. Harmonisation on this should be possible. For example, in assessing pesticides it could be agreed that the first approach should be adopted.

Cumulative assessment groups

Key messages

- There is a need to harmonise how chemicals are combined into assessment groups
- The rationale for an assessment group needs to be clearly defined, whatever its basis
- While synergy is highly unlikely, guidance should be developed to help consider it as needed
- The use of data generated using non-animal methods will need careful integration into the entire weight-of-evidence

The second day started with a session on **how should chemicals be combined into assessment groups**, introduced by Angelo Moretto. This is an area where there is currently little international harmonisation. Amongst the key issues that need resolution are whether an inclusion approach (as used by US OPP) or an exclusion approach (as proposed by EFSA's Pesticides Unit) should be employed and how information on MOA/AOP should be used to inform the assessment of combined exposure to chemicals. Additional areas where there could be an improvement in consistency across authorities are: the information used as the basis of grouping chemicals (e.g. chemistry, function/target, common phenotypic effect, common MOA/AOP, some combination of these), common understanding on what is meant by a shared mode of action, the minimum information required to include or exclude a shared mode of action and related uncertainty, and whether the relative potency between the common and the critical effect should be taken into account in some way. In addition, there is the question of how rare but possible synergy (or inhibitory interactions) should be addressed. Finally, agreement is needed on what the default assumptions (e.g. dose-addition or response addition, when the possibility of synergy needs to be considered) should be regarding combined action.

It was noted that assessment groups based on common target organ (e.g. liver) or even phenotypic effect (e.g. hepatic steatosis) can lead to large groupings, even for chemical sectors with less than 1000 members in total, such as pesticides. An appreciable number of compounds belong to more than one CAG, based on phenotypic effect, but some of these effects form part of a toxicological continuum so should not be treated independently. Given that the focus of EuroMix and many other initiatives is the use of non-animal methods for regulatory toxicology, there will need to be agreement on how these methods can be used to help in grouping of chemicals based on AOPs.

What type and how much information would be needed? Perhaps of equal importance to demonstrating that compounds share the same AOP, it will be important than non-animal methods can be used to exclude involvement in a shared AOP. It will be necessary to determine the confidence in such a conclusion.

EFSA will conduct a cumulative risk assessment for two of its assessment groups (thyroid and neurotoxicity) in Q3-Q4, 2017, using monitoring data to inform the exposure assessment. In the meantime, the assessment groups based on the other target organs will be developed one by one. When all assessments groups have been established and an impact assessment completed application in MRL setting will commence. EFSA have indicated that when relevant information on MOA is available this will be taken into account in cumulative risk assessment. It is likely that EFSA will identify options or make recommendations for research to refine its CAGs before their use in a regulatory context. In this respect, EFSA and DG SANTE are working in close cooperation to determine the fitness-for-purpose of the methodology developed for the regulation of pesticides.

Some authorities such as US EPA OPP have used chemical structure as one of the criteria for grouping chemicals for cumulative risk assessment. However, use of such information is nuanced and not as transparent as it might be. Compounds with the same structure may be excluded from a group but the reasons for this (e.g. because exposure is negligible) are not always obvious from the assessment report

Adoption of non-animal methods will necessitate consideration of the possible role of metabolism in the cumulative effects of chemicals. The parent compound may be converted to a metabolite in vivo, e.g. in the rat or human, which is not produced in the non-animal models used. As this metabolite might share an MOA/AOP with an assessment group, separate evaluation of such a possibility will be needed. Metabolic prediction software can be used to assess the potential formation of reactive metabolites and though perhaps not as reliably, the potential formation of stable metabolites. An alternative in the latter case is to test metabolites identified in plant or target species using non-animal methods, to assess whether they share AOPs with other chemicals.

EuroMix is developing novel approaches and methodology for combined exposure assessment (see below). With increasing reliance on non-animal methods, quantitative exposure assessment will assume critical importance. There is a need to extrapolate from in vitro findings to the in vivo situation. Chemicals may activate key events in vitro but produce no effect in vivo, because the necessary concentration for the effect is not achieved at the active site. Hence physiologically-based pharmacokinetic modelling will play a key role as will consideration of the active site concentrations attained in individuals on exposure to the chemicals in an assessment group.

There is little international agreement on whether or how to take potency for the common effect into account in developing or refining assessment groups. One possibility is to compare the potency for the common effect amongst members of a CAG. Those compounds with a very low potency (e.g. as judged using the RISK21 methodology[2]) could then be considered for exclusion from the CAG in order to prioritise potential risk management focus on those compounds of higher concern. The need for such an approach will depend, in part, on the total number of chemicals to be addressed in the assessment. If any compound exceeds its respective health based guidance value (ARfD, ADI, etc), it would be logical to exclude it from consideration of the risk from the combined effects of this CAG, until risk management measures have been taken to address concerns about this compound. The potency for the common effect could also be compared with that for the critical effect (i.e. the effect that drives the establishment of health based guidance values) for the same chemical. Where

[2] Embry MR, Bachman AN, Bell DR, Boobis AR, Cohen SM, Dellarco M, Dewhurst IC, Doerrer NG, Hines RN, Moretto A, Pastoor TP, Phillips RD, Rowlands JC, Tanir JY, Wolf DC and Doe JE (2014). Risk assessment in the 21st century: roadmap and matrix. Crit Rev Toxicol 44, Suppl 3:6-16

the difference in potency for the two effects is very large, controlling exposure for the critical effect would ensure that the common effect from that chemical would be at a very low level. This is an option that might be considered in particular when dealing with combined exposure to a large number of environmental contaminants. Whilst the view was expressed by some that compounds should not be removed from a CAG on the basis of their relative risk, there may still be scope to explore conservative defaults (determined by database analysis). Decisions on whether or not to use any of these approaches would be the responsibility of risk managers, in discussion with risk assessors.

It was noted that determining the POD for a common effect, if is not the critical effect for that chemical, would take time and effort as intermediate effects are not subject to the same scrutiny and peer review as is the critical effect when conducting chemical risk assessment. It was noted that in the case of pesticides, EFSA was already preparing a list of common effects and their NOAELs for each member of its CAGs.

There was general agreement that whatever the basis used for grouping chemicals, this should be transparent and explicit, which has not always been the case. It should be clearly stated in the problem formulation.

There is appreciable variation in the choice of POD (e.g. BMDx, BMDLx, NOAEL) for cumulative risk assessment. There was agreement that as a minimum a consistent POD should be used for members of a CAG. However, there was no conclusion as to which POD should be used, though there is a scientific preference for the use of the BMD approach. Choice of POD will also impact on calculation of relative potency factors, as will the member of the CAG selected for this purpose (index compound). In addition, there is a lack of consistency in the criteria used for index compound selection, although it is generally preferred that this is a well-studied compound, in order to minimise the uncertainty in the hazard characterisation.

There is currently no consistent method for assessing the potential for chemicals in an assessment group to act synergistically. However, most authorities (e.g. EFSA, USA EPA) have concluded, based on scientific review of the available information, that this is not an issue of concern at human relevant exposures to dietary residues. The possibility of synergy should be considered on a case-by-case basis, but consistent guidance for how this might be done is lacking.

For chemicals with internationally accepted limit values, such a pesticides, there is a need for harmonisation of the approaches used to establish assessment groups.

The European Commission is currently discussing how to apply cumulative risk assessment methodology for pesticide MRL setting.

Exposure assessment

Key messages

- Refinements in exposure assessments are ongoing, with a shift in focus to probabilistic methods, and in particular to individual co-exposures
- Harmonisation of probabilistic exposure assessments will compliment efforts to harmonise how chemicals are combined into assessment groups.

The last topic addressed was **exposure assessment**, introduced by Jacob van Klaveren. What methodology should be used and what assumptions are made?

Currently, a deterministic approach is used for exposure assessment of individual pesticides in Europe, using the PRIMo model. This model is derived from 10 diets with uncertain consumption data. Information from 52 diets is now available within the EFSA data warehouse, which can be used fully probabilistically via web-based interfaces with calculation times of only a few hours, but it is not yet being used in pesticide risk assessment. Deterministic approaches such as PRIMo have a number of significant limitations, particularly for cumulative exposure assessment. However, until recently it was not possible to change the approach used in Europe within the regulatory context, for several reasons including reproducibility of the modelling approach.

The US EPA developed probabilistic approaches some time ago and has been applying them routinely for cumulative risk assessment of pesticides. In Europe, the Acropolis project developed the MCRA tool for this purpose, and this is now at the stage for application in cumulative risk assessment. In addition, EFSA has published guidance on the use of probabilistic methodology for modelling dietary exposure to pesticide residues.

RIVM, in collaboration with EFSA, have now used the MCRA tool to assess cumulative exposure to the EFSA CAGs for neurotoxicity and thyroid effects, in 10 populations of consumers (similar to the diets upon which PRIMo is based). Using the substantial computer power available to RIVM, which can be uprated such that all 52 European diets can be included, the computations took only 6 h.

Amongst gaps identified in conducting such assessments were the lack of some processing factors, absence of data on real agricultural use, and a clear definition of what is meant by co-exposure.

MCRA can be combined with the IPRA (Integrated Probabilistic Risk Assessment) tool developed in the Netherlands to provide an integrated probabilistic assessment of cumulative risk, based on the distribution of MOEs (margins of exposure).

There are a number of approaches and assumptions that can be used in probabilistic assessments. There is little or no harmonisation at present, as there has been no pressing need. However, to compliment harmonisation efforts for the hazard assessment of combined exposures, consideration will need to be given of what needs to be harmonised in probabilistic exposure assessment and how this might be achieved. Currently, DG SANTE is working together with the European Member States on harmonising some of these issues and they will use MCRA for this. In addition to the probabilistic method used, harmonisation of reporting will be important as will the structure of input data, e.g. consumption, to enable inter-regional comparisons and data-sharing. It was agreed that, for implementation on a global scale, there first needs to be recognition and harmonisation of the use of probabilistic modelling, followed then by software harmonisation. The use of probabilistic modelling was explored by the Codex Alimentarius in the period 2000-2005, but at that time consumption data were lacking, underlying assumptions and formats were not fully understood and suitable web-based models were not available. In a number of countries outside Europe, MCRA and other software packages have been explored to generate probabilistic results at the national level (e.g. China, Brazil). Furthermore, the use of probabilistic modelling has been explored by a number of stakeholders. The first probabilistic results were generated by NGOs in the US and in Europe twenty years ago. MCRA and/or other probabilistic software can be used to explore the issues that need to be harmonised in the EuroMix harmonisation workshops.

EuroMix will define templates for data input and links to other web-services, and will provide a computing platform for probabilistic exposure assessment, openly accessible to all stakeholders. Work is ongoing to input data on chemicals, in addition to pesticides, such as food additives, dioxins and PCBs, heavy metals and BPA from the EuroMix partners. These data are similar to those sent to

EFSA by the Member States and stored in the EFSA data warehouse. The preferred option is to work closely with EFSA on data quality and further refinement of the web-services and model platform infrastructure.

As part of the EuroMix project, a proof-of-principle study on 140 subjects will be performed in Norway. Information will be collected on exposure including the diet, biomarkers of exposure and of effect. There are links with other major ongoing exposure projects - EU HBM4ME and the Human Exposome. This study will test the predictions of the various EuroMix models for combined exposure via multiple exposure routes. .

It was noted that the mixture selection functionality in MCRA is a useful addition to probabilistic modelling and helpful in selecting the chemicals for the experimental studies to be conducted within EuroMix. Generally, this helps in setting priorities for testing based on exposure considerations. This might underpin an exposure driven test strategy and would form the starting point to calculate the likelihood of co-exposure. The MCR (Maxium Cumulative Ratio) approach has been included, but use of this approach for human health risk assessment has not yet been explored. This will require further discussion (see above).

Conclusions and next steps

The meeting closed with a brief summary of **conclusions and next steps**. It was agreed that harmonisation of the approach used in assessing the risk from combined exposures to chemicals was highly desirable and in some areas such as pesticides it was essential, to ensure the safe and effective continuation of international trade in food commodities. A number of key issues were identified where harmonisation has yet to be achieved, such as the scope of cumulative risk assessments (which “silos”), the basis for grouping chemicals into assessment groups, and how information on modes of action/adverse outcome pathways would be taken into account in such assessments. These topics will be discussed in more detail at later workshops in this series. The next workshop will include risk managers and will focus on impending and future legislation and how and when the approaches and methods developed by EuroMix can contribute.

It was agreed that the review of relevant legislation prepared as deliverable 9.1 should be circulated to participants as soon as possible, to check on accuracy and to fill any gaps.

Annex

EUROMIX First workshop on international harmonisation on the risk assessment of combined exposures to chemicals

Celia Hensman Suite, W12 Conferences, Imperial College London, Hammersmith Campus, Artillery Lane, 150 Du Cane Road, London W12 0HS

20 -21 October 2016

Program

The designated lead will provide a brief introduction to each topic, followed by discussion on common approaches, identification of gaps and possible ways forward

Day 1

14:00 – 15:00: Problem formulation: what is the objective of risk assessment of combined exposure from an international perspective (e.g. harmonisation of methodology, harmonisation of approach to setting MRLs) (Lead: Dr Bette Meek)

15:00 – 16:00: Definition of exposure combination of concern – which chemicals ("legislative/regulatory silos") (Lead: Prof Alan R Boobis)

16:00-16:30: Break

16:30 – 17:30: What is meant by co-exposure (toxicokinetic and toxicodynamic considerations) (Lead: Prof Alan R Boobis)

Day 2

How should chemicals be combined into assessment groups? (Lead: Prof Angelo Moretto)

09:00 – 10:00: Inclusion versus exclusion approach? Assumptions re additivity? Bases for grouping (e.g. chemistry, common effect, common MOA/AOP, function/target)

10:00-10:30: Break

10:30 – 11:30: Use of information on mode of action/AOP (what is meant by common mode of action)? Minimum information to include or exclude common mode of action?

11:30 – 12:30: Potency considerations: common versus critical effect

12:30 – 13:30: Lunch

13:30 – 14:30: How should possible synergy be addressed?

14:30-15:30: Exposure assessment methodology and assumptions? (Lead: Dr Jacob van Klaveren)

15:30-16:00: Break

16:00-17:00: Conclusions and next steps