Joint EFSA / EBTC Colloquium

Briefing notes DG4: Using multiple endpoints and multiple studies for dose-response modelling: quantitative approaches

1. Background

Evidence integration, in the context of dose-response modelling when estimating reference points (RP) or point of departures (PoD) using benchmark dose modelling (EFSA, 2017), is the process of combining information on the hazard of interest coming from a) multiple endpoints observed in a single study as well as b) one or multiple endpoints of several studies. When modelling the data for estimation, information characteristics need to be carefully considered accounting for different aspects such as study design, endpoints measured, dependences, etc. Current practices of setting RPs/PoDs, often circumvent integration by focussing on the most critical study and the critical endpoint.

Advances statistical models allow incorporating several endpoints from a single study, among other by multivariate approaches, to derive values such as RP and PoD. Other simplified methods such as the analysis of each individual endpoint studied could also incorporate evidence provided within streams in a more ad-hoc fashion, but not necessarily implying a loss of efficiency and precision. Bayesian models provide the framework to incorporate uncertainties and variabilities not only among endpoints, but also among studies. In this context also model uncertainty plays an important role, which can be addressed by model averaging techniques that can out-perform any single model in terms of coverage of interval estimates of the parameters of interest.

2. Objective

As a follow up of lectures 5 to 7, the objective of this group is to discuss quantitative approaches to combining evidence within a study, considering information on several endpoints measured as well methods that could be expanded to incorporate information from multiple studies on the same hazard.

The discussion will focus on:

- Current practices when defining health based guidance values based on dose-response models: pros and cons;
- Available knowledge and methods to incorporate several endpoints within a study when modelling dose-response data: multivariate models or other statistical technique;
- Incorporating variability and uncertainties coming from different studies in dose response modelling that include several endpoints: Bayesian methods or other modelling frameworks;
- Recommendations for future developments in the field.

3. Bibliography

EFSA Scientific Committee, Hardy A, Benford D, Halldorsson T, Jeger MJ,Knutsen KH, More S, Mortensen A, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Silano V,Solecki R, Turck D, Aerts M, Bodin L, Davis A, Edler L, Gundert-Remy U, Sand S, Slob W, Bottex B,Abrahantes JC, Marques DC, Kass G and Schlatter JR, 2017. Update: Guidance on the use of the benchmark dose approach in risk assessment. EFSA Journal 2017;15(1):4658, 41 pp. doi:10.2903/j.efsa.2017.4658

DG4	Using multiple endpoints and multiple studies for dose-response modelling: quantitative approaches
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Follow-up of lectures 6 and 7	Combining evidence on multiple endpoints in dose-response assessments: multivariate models Wout Slob, National Institute for Public Health and the Environment (RIVM), Ministry of Health, Welfare and Sport, The Netherlands Other quantitative methods for combining multiple studies and endpoints Matthew Wheeler, The National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention (CDC), USA
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