

The concept of Evidence-Based Toxicology

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Evidence-based-medicine (EBM) has been a revolution in clinical medicine over the last three decades, showing the advantage of objective, critical and systematic reviews of current practices as well as formal meta-analysis of data and central deposits of current best evidence for a given medical problem. Toxicology might benefit from a similar rigorous review of traditional approaches and the development of meta-analysis tools as well a central quality-controlled information portal. Already in 1993 Neugebauer and Holaday in their book "Handbook of mediators of septic shock" showed that EBM methods can be applied to animal studies and *in vitro* work. With Sebastian Hoffmann and his thesis "Evidence-based *in vitro* toxicology" in 2005 we developed initial concepts of an evidence-based toxicology (EBT).

EBM was born from the need to somehow handle the flood of information in medicine and to sort the available evidence in an objective manner, which includes traditional approaches and new scientific developments of variable quality. More than half a million papers included in MedLine per year of an estimated more than 2 million in medicine every year address questions relevant to the life sciences and therapy. For example, entering the search term "toxicology" for the time period since 2003 results in 28,500 article hits in PubMed, a database not even covering all relevant publications in the biomedical field. Instead of expecting individuals to determine what is the best evidence for a specific question or approach at a given time-point, high-quality reviews available at a central deposit should represent a primary resource of information. This requires agreed quality standards, so that the individual physician can rely on the information received. This is the key difference between evidence-based and traditional ("narrative") reviews: most reviews represent a story told by (knowledgeable) authors who present their personal views on their topic of interest. They tend to select their own papers and those that fit the story line of their review. The systematic review proceeds differently: The sources and a search strategy, i.e. which decides which papers shall be considered and which not, are defined upfront. Before collecting the actual articles, the procedure for information analysis is defined. Ideally, these search and analysis strategies are peer-reviewed to safeguard objective and efficient processes. The analysis of the collected evidence requires weighing the quality of individual pieces of evidence and summarising these as objectively as possible. The latter often involves meta-analysis, i.e. statistical approaches to combine results from different studies.

Obviously, toxicology has a similar problem of information flooding and coexistence of traditional and modern methodologies, as well as various biases. It is most difficult to find and summarise the relevant information for any given major question. This has been nicely illustrated by Christina Ruden (2001): She showed the divergence in judgment and limitations of analysis for 29 cancer risk assessments carried out for trichloroethylene – 4 assessments concluded that the substance is carcinogenic, 6 said it is not and 19 were equivocal. The main reason for this divergence was a selection bias in the materials considered, i.e. an average reference coverage of only 18%, an average citation coverage of most relevant studies of 80%, as well as an interpretation difference of most relevant studies in 27%, and the lack of study/data quality assessment not documented in 65% of the assessments.

The similarities between the problems of toxicology and clinical medicine, and especially the similarities between making a diagnosis in medicine and deciding on whether a substance is hazardous (Hoffmann and Hartung, 2005), prompted us to think about whether EBM tools could be suitable for toxicology (Hoffmann and Hartung, 2005).

A major step toward the formation of an EBT movement was the first International Forum toward an Evidence-based Toxicology in 2007 (www.ebtox.org). The Forum formulated a

declaration and ten defining characteristics of EBT, but not a consensus definition yet. Proceedings are now available. The first major development of EBT was the ToxR-Tool to systematically assign quality scores to existing in vivo and in vitro studies (Schneider et al. 2009), which can be downloaded from the ECVAM website. Such evaluation is critical for any meta-analysis but also for programs like REACH using existing information for notifications.

With the creation of the first chair for EBT at Johns Hopkins in 2009, the EBT idea has been institutionalized for the first time in a major academic institution. It is hoped to become a starting point for further developments of an EBT movement.

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