LRI RfP

Title: A comparison between NOAELs from animal data with those from human data

Project code number: LRI-B10

Occupational and environmental exposure limits are set either on animal data or on human data. Both types of data have their intrinsic properties. Human data are mostly observational with the potential for confounding and bias. Results from animal testing must be extrapolated to humans and their relevance is not always clear. There is quite some uncertainty involved in extrapolating the results from animal studies to humans and a number of default Assessment Factors are applied in this process. There is no systematic evidence available to underpin the magnitude of these Assessment Factors and it is not clear whether they are too conservative, or not conservative enough. Although for specific agents comparisons have been made, a more systematic and generic analyses have so far not been made other than an analysis of a limited number of occupational exposure limits (Fairhurst 1995). To date it is not clear whether NOAELs observed in animal studies are predictive for NOAELs in humans. Are animal data over or underestimating health risks for humans or are they reliable predictors? The objective of this RfP is to carry out a systematic comparison made between NOAEL from animal studies and those from human observations.

For a substantial number of chemicals animal data as well as human data are available and by making a systematic comparison the predictive value in terms of NOAEL can be assessed. This information can be very helpful in instances where only animal data are available and where it is unlikely that positive human data (including the NOEAL) will ever be collected. The type of animal and strain should be taken into consideration. Furthermore analyses should be made to evaluate if there are differences in predictive value for specific dosing routes, groups of effects (e.g. acute-chronic, direct-systemic) and classes of substances. The chemicals selected should mainly consist of agents relevant to the chemical industry although it can be considered to include some pharmaceuticals and nutrients to expand the database. In the project a list of substances must be compiled, for which animal data as well as human data are available. Such a list can be made by reviewing the documents prepared by regulatory agencies to derive exposure standards, for example for the working environment and by consulting a group of experts in the field and searching literature databases. Other sources such as ECETOC reports, REACH dossiers and NIOSH studies on organic solvents and organophosphates are recommended. Next, the key good quality human studies and animal studies (based on predetermined sets of quality criteria) must be identified and

systematically abstracted with respect to the NOAEL data. An efficient approach would be to start with compiling a list of substances for which there are human NOAEL data available. At this point it is not certain that there are enough substances for which human data are available to estimate the NOAEL. Therefore the project has been divided in two phases: The first phase is to compile a list of substances for which human data are available. If the investigators can demonstrate that for a sufficient number of substances human data of good quality are available the second phase of the project can be started. It is recommended that the investigators describe in their proposal how they will address negative human data and the human relevance of animal data.

Deliverables:

1. A list of substances for which adequate human NOAEL data and animal data are available.
2. For each of the substances a description of the NOAELs for human data and animal data, including the references
3. A comparison between the NOAELs from human data and animal data, divided into a number of substance classes and endpoint classes.
4. Preparation and submission of one or several manuscripts in peer reviewed journals

Proposed budget: 135,000 Euro (20,000 Euro for phase 1 and 115,000 Euro for phase 2
Time frame: 2 year