Animal NOAELS: does adding human data help?

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AIMS

The overall aim of the project (LRIB10-ICL) is to provide a systematic and quantifiable comparison of NOAELs identified from animal studies with those from human studies for a range of chemicals, and to develop robust evidence synthesis (meta-analytical) methodology combining all available information for identification of an integrated NOAEL.

PROGRESS to October 2012

The project commenced in January 2012 and is due to be completed in November 2013. It comprises 5 Work Packages (WPs) described in more detail below. WPs 1 & 2 have been completed and reports are available. Wp3 is in progress, and WPs 4 & 5 have yet to commence.

WP1

Objective: Identification and listing of chemical agents for which substantial animal and human data are available.

WP1 consists of a systematically-conducted review of available published and other sources to identify chemical agents for which human data are available for exposure limit setting purposes.

Methods

The aim of the approach was to follow the principles of systematic reviewing (CRD, 2009) as far as possible in this context, in order to provide a summary of relevant examples to date through a review process which is transparent and reproducible and may easily be updated or extended. Some key papers (principally the earlier systematic review by Persad and Cooper (2008)), suggestions for about 30 suitable chemicals from CEFIC and databases of reviews and toxicological risk assessments were identified by members of the project team from their previous experience in the field, supplemented by input canvassed from scientists at the UK FSA and the ECETOC Scientific Committee.

Open internet resources, such as web-published authoritative reviews, assessments and databases were searched systematically to identify chemicals for which human and animal data exist. The IRIS and ATSDR databases provided the initial large list of chemicals; the other sources provided additional information on these and additional chemicals.

Results

More than 180 substances were so identified. Details are available in the report on WP1.

Conclusions

Sufficient data are available to allow the comparison of NOAELs based on human or on animal data alone to continue.

WP2

Objective: Description of available animal and human data including study design, size, route and form of exposure and health endpoints; Quality of the information and suitability for identification of NOAELs will be evaluated.

Methods and Results

A purposive sample of 20 was chosen from the list of 180 substances identified in WP1, to include substances in several categories (e.g. metals, solvents, pesticides, other) for which appropriate human (and animal) data were likely to be available, and to cover a range of adverse health effects. The substances chosen were: acetone, antimony, captan, carbon tetrachoride, chlorpyrifos, chromium, endosulfan, endrin, iodine, mercury, methanol, nickel, paraquat, parathion, selenium, silver, toluene, trichloroethylene, vanadium, xylene. Summaries of the extensive data sets reviewed are available in the report on WP2.

WP3

Objective: For substances with good quality data, categorised by class of substance and endpoint, comparison of the NOAELs identified from human data and animal data in relation to the nature and quality of the data, the derivation methods and the relevance to the most common human route and form of exposure; investigation of factors affecting the relationship between animal and human NOAELS, using regression modelling and other methods

Methods

Following Lavelle et al (2012)'s framework for good practice, we are developing Dourson et al (2001)'s approach, initially in a pilot sample of 5 substances (acetone, chlorpyrifos , paraquat, mercury, TCE) drawn from the WP2 sample. Other possible candidates include Cd, Me-Hg, Pb, n-Butylacetate, N,N-DMF, EG, and n-hexane.

Results to date

As well as seeking to compare NOAELs based only on animal data with those based only on human data, comparison of reference doses (RfDs) on, say, human data with (surrogate) RfDs calculated using just animal data should also be informative. An example of the data available as the basis for comparisons is provided for acetone in the table below:

Agency/date	Route/duration	Reference value	PoD	Species/Endpoint
ATSDR (1994)	Inhalation Acute MRL	26 ppm	237 ppm LOAEL	Human (volunteer) Neuro: neurobehavioural effects
ATSDR (1994)	Inhalation Interm^{te}/chronic MRL	13 ppm	1250 ppm LOAEL	Human (volunteer) Neuro: neurobehavioural effects
ATSDR (1994)	Oral Intermediate MRL	2 mg/kg/day	200 mg/kg/day NOAEL	Animal Systemic (haemato): macrocytic anaemia
IRIS/EPA (2003)	Oral RfD	0.9 mg/kg/day	900 mg/kg/day	Animal Systemic (renal): mild nephropathy
WHO – IPCS/ INCHEM (1998)	Oral Guidance value	9 mg/kg/day	900 mg/kg/day	Animal Systemic: parameters including organ weights

WP4

Objective: Building on available cross-design evidence synthesis methods, development of meta-analysis techniques for combining human and animal data to derive dose-response curves (and thresholds if they exist). Application to selected examples; comparison of added value of combining animal and human data with use of either alone.

Suitable case studies for WP4 will be identified in the course of carrying out WP3. Synthesis methods will include those based on the method of Jones et al (2009).

WP5

Objective: Development of recommendations for evaluation of future substances and for design of future studies.

This final work package will build on the experience gained in WP1-4.

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