

Thoughts of hope and reality concerning humane endpoints

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Disclaimer:

This presentation is limited to a discussion of humane endpoints in the context of regulatory risk assessments.

Once there was an initiative to develop a document on humane endpoints...

OECD Guidance Document on Humane Endpoints

- History of the Document (1):
 - December 1994: establishment of an *ad hoc* Working Group (Germany, Netherlands, UK, USA);
 - February 1995: first meeting of the Working Group to discuss scope of work;
 - 1995: first draft produced by Prof. Morton;
 - January 1996: second meeting of the Working Group to discuss 1st draft of the document;
 - 1996: revision of the draft version based on comments;

OECD Guidance Document on Humane Endpoints

- History of the Document (2):
 - October 1998: expert review of the 2nd draft in all Member countries;
 - November 1998: Nominated Expert Meeting, Zeist, The Netherlands;
 - January- March 1999: revision of various chapters by Nominated Expert subgroups;
 - August 1999: second expert review (3rd draft) in all Member countries;
 - November 2000: publication of final document.



Guidance Document on the Recognition, Assessment,
and Use of Clinical Signs as Humane Endpoints for
Experimental Animals Used in Safety Evaluation

Observation:

It took 6 years of intense scientific discussions to agree on clinical signs of severe pain and distress ...

OECD Guidance Document on Humane Endpoints

Humane Endpoints: the earliest indicators in an animal experiment of impending death or severe pain, distress, or suffering. Once identified, this condition can be minimized or eliminated, either by humanely killing the animal or by termination of exposure and possible therapy, thus allowing the animal to recover.

Clinical signs and conditions where humane killing may be appropriate:

- prolonged or irreversible inability to eat or drink,
- disease or conditions indicating severe pain, distress or suffering,
- rapid or continuing weight loss,
- severe or continuing respiratory distress,
- generalized decrease in grooming and abnormal appearance over an extended time period,
- frank bleeding,
- evidence of microbial infections or other diseases.

Two concepts of humane endpoints:

- Indicators of existing severe pain, distress, suffering, and impending death (the damage is done).
- Indicators signaling that severe pain, distress, suffering, and possibly death may occur at a later stage if no action is taken (the damage may be avoided).

Indicators confirming existing severe pain, distress, suffering, and/or impending death:

Reduce the suffering by:

- *killing the animal humanely;*
- *Termination of exposure;*
- *Therapy to allow recovery.*

▶▶ Take the animal out of the experiment

Implications of removing animals from the experiment (1):

- For all tests: death is a highly definitive endpoint and the most adverse observation;
- For acute toxicity tests: the animal counts as death resulting from treatment: valid endpoint;
- For repeated exposure tests: more than 10-20% mortality invalidates the test results for that treatment group;
- For life-span studies: life-span is an important endpoint and humane killing is often not considered an option (bad practice!)

Implications of removing animals from the experiment (2):

The decision is a balance of ethical and economical arguments and not so much a scientific challenge.

Implications of removing animals from the experiment (3):

Tendency for the ethical arguments to prevail:

- International test guidelines start to include: “animals showing continuous severe pain or distress should be humanely killed without delay”
- It is essential that all clinical signs and conditions indicative of severe pain are carefully recorded;
- Let’s not (yet) talk about validation (reliability).

Time to move on and look at prediction of pain and distress, rather than to stop short at confirming existing pain and distress.

Indicators signaling that severe pain, distress, suffering, and possibly death may occur at a later stage if no action is taken.

The prediction of suffering, pain, distress, and possibly death requires that the concepts (mechanisms, physiology) of pain, distress, suffering are well defined and “measurable”.

▶ ▶ research need

Indicators signaling that severe pain, distress, suffering, and possibly death may occur at a later stage if no action is taken.

It also requires a good understanding of underlying toxicological phenomena resulting from the test conditions and causing the pain and suffering;

▶ ▶ research need.

Indicators signaling that severe pain, distress, suffering, and possibly death may occur at a later stage if no action is taken.

The endpoints should be quantitative and proven to correlate well with pain, distress, suffering.

▶ ▶ in other words: proper validation!

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INTERNATIONAL ACCEPTANCE OF NEW OR UPDATED TEST METHODS
FOR HAZARD ASSESSMENT

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Validation should be a flexible process allowing various approaches rather than a rigid, academic exercise bound by plenty rules and procedures.

Indicators predicting future pain and distress (1):

Assuming these indicators are available, and predict future pain, what would be the next step?

- *Kill the animal?*
- *Therapy?*
- *Stop, or lower the level of exposure to test substance?*

Indicators predicting future pain and distress (2):

Kill the animal?

- death is the most adverse effect;*
- the animal is no longer available for observations;*
- developing reliable indicators for future death is likely to be extremely difficult and hard to validate.*

▶ ▶ probably not the best solution

Indicators predicting future pain and distress (3):

Therapy?

–therapy would mask or cure toxicity induced by the treatment, interferes with normal body functions and invalidates the test results.

▶ ▶ probably not a good solution either

Indicators predicting future pain and distress (4):

Stop, or lower the level of exposure to test substance?

- lowering exposure levels would still produce valuable test results, although far more difficult to interpret*
- ending the exposure would result in less valuable but still to some extent useable results.*
- ▶ ▶ probably the preferred option

Conclusions and recommendations (1):

- Indicators of existing severe pain and suffering could and should be measured and recorded in all experiments;
- Correlations between these indicators and spontaneous mortality should be reported and accumulated over studies as a means to establish a more complete set of these indicators;
- The validation is could be based on real test data and observed correlations.

Conclusions and recommendations (2):

- Research is needed to enable defining and quantifying pain and suffering;
 - From subjective to objective observations;
 - Allowing potency measurements (pain gradients);
 - Linking to physiological phenomena.

Conclusions and recommendations (3):

- More sophisticated concepts of hazard identification and characterization are needed when introducing indicators predicting future pain, suffering and/or death.
 - Extrapolation of variable exposure regimens;
 - Extrapolation of early observations and their presumed progression if treatment regimen had not been reconsidered.

Thank you for your attention.