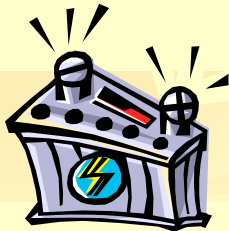


ILSI and ICH Battery Maintenance:
Increased Voltage



or

Hazard Identification Short Circuit?



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The current situation

- *The number of in vitro mammalian positive genotoxicity findings is concerning*
 - *We don't know how to interpret these results*
 - *Additional follow-up is required*
- *This has led to a search for new approaches to safety assessment*
- *New technologies are being harnessed to address the issue of safety assessment of regulated products*
- *Caveat: There is no gold standard against which to develop or assess new technologies (rodent carcinogenicity bioassay may not reflect human risk)*

Ongoing approaches to address the problems

- FDA/CDER Weight of Evidence (WOE) guidance (2006)
- ICH S2 revision
- ILSI workshops on *Relevance and Follow-up of Positive Results in in vitro Genetic Toxicity Testing (IVGT)*
- *IWGT workshops on improving current tests*
- *ILSI workshops on genomic approaches*

Current ICH test battery

- Bacterial mutagenesis assay (OECD 471)

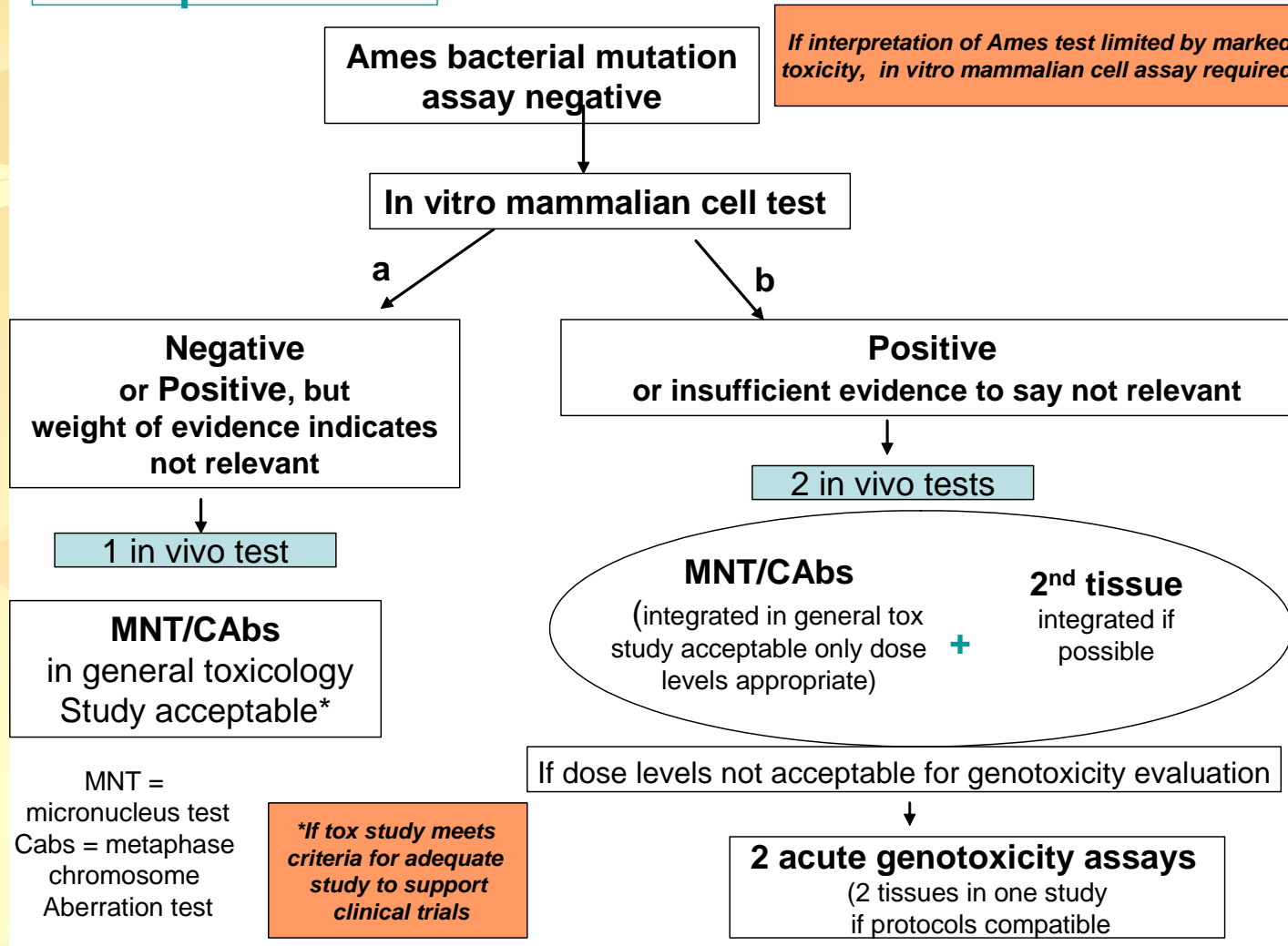
In vitro mammalian assay

- Mouse Lymphoma Assay (MLA) (OECD 476/CFSAN Redbook) OR
- Chromosomal Aberration assay (CA) (OECD 473)
- Short term in vivo assay: rodent bone marrow micronucleus (OECD 474) or bone marrow CA assay (OECD 475)
- *Note: all 3 tests are done in parallel*

Draft new ICH test battery options*

*drafts subject to change

Option 1



Draft new ICH test battery options*

*drafts subject to change

Option 2

If interpretation of Ames test limited by marked toxicity, in vitro mammalian cell assay required

Ames bacterial mutation assay negative

Choice of second in vivo endpoint/tissue depends on knowledge of ADME etc



If dose levels not acceptable for genotoxicity evaluation

In vitro mammalian cell test; follow option 1

or

2 acute genotoxicity assays
(2 endpoints in one study if protocols compatible)

Concerns over the current ICH S2 revision

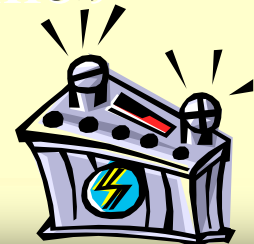
- Option 2 eliminates the mammalian *in vitro* assays entirely
 - This affects the potential of hazard id
 - In some contexts, there is inherent value in identifying genotoxins apart from their role as a surrogate for carcinogenicity
 - We are losing information
- The two test battery options are unequal, complex and liable to be confusing to FDA reviewers and to industry alike
 - *Testing is no longer parallel, but sequential, requiring extra decisions*
 - *How to select option 1 or option 2*
 - *How to select the in vivo assay*
 - *How to integrate the genotoxicity studies with ongoing toxicology studies (e.g. when is the dosimetry acceptable?)*

Concerns over the current ICH S2 revision

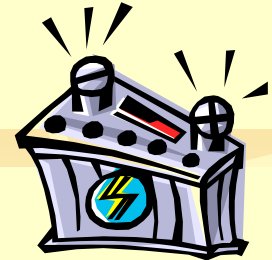
- The new test Option 2 adds *in vivo* assays for which there is
 - *Lack of a harmonized, defined protocol*
 - *Lack of validation experience with the assay integrated into ongoing toxicology studies*
- It relies increasingly on animal tests and may be untenable in the long run, due to efforts to minimize or eliminate animal testing

Concerns over the current ICH S2 revision: *Hazard identification (safety) short circuit?*

- Option 2 eliminates the *in vitro* mammalian assays, which identify the broadest set of genotoxic agents
- The top concentrations for *in vitro* tests in Option 1 have been lowered by 10-fold
- Cytotoxicity limits have also been altered, resulting in lower test concentrations
- For many products, *in vitro* genotoxicity testing is the only set of tests performed for cancer risk assessment (some drugs, most food contact substances, most medical devices)



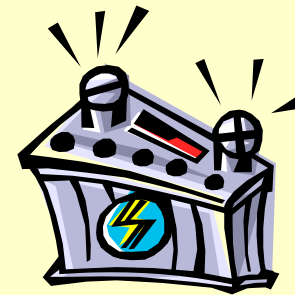
Concerns over the current ICH S2 revision: *Regulatory short circuit?*



- Debates between FDA and industry over
 - Which test option (when?) Which in vivo assay (when?)
 - *Leading to an iterative and slowed review process*
- Dis-harmony among FDA centers over the genotoxicity test battery, now harmonized among
 - ICH S2B (drugs)
 - CFSAN Redbook (food additives)
 - ISO-10993-3 genotoxicity standard (medical devices)
 - VICH (veterinary products and food animals)

Concerns over the current ICH S2 revision: *Regulatory short circuit?*

- Dis-harmony among world-wide efforts to decrease animal testing for safety assessment
 - European REACH
 - ICVAAM, ECVAM, JACVAM
 - FDA
- Short-circuits efforts to improve the *in vitro* assays
 - ILSI approaches on *in vitro/in vivo* extrapolations (quantitative group)
 - ILSI approaches on follow-up testing
 - IWGT efforts to improve the standards for testing and data interpretation



ILSI approaches: *Increased voltage?*

- Survey, critique and discussion of available genotoxicity tests and their optimal use
- Survey and attempted integration of new tests and new technologies
- Decision-tree for follow-up to positive *in vitro* mammalian test results
- Quantitative analysis of *in vitro/in vivo* correlations for improved value in risk assessment (*in vitro* to animal; animal to human extrapolations)



ICH and ILSI: on different paths

Can these be re-directed/harmonized?

- The goals seem to be similar: improved genotoxicity testing for human risk
- But the paths seem quite divergent

Can we work together to find a common path?

Thinking outside the box

- *Can we integrate new technologies that allow direct measurement of genotoxicity in humans?*
 - *E.g. monitoring during human clinical trials*
 - *Measurement of constitutional, i.e. germ cell mutations, in genes likely to be monitored in populations (e.g. CYP genes affecting metabolism)*
 - *Long-term monitoring of cancer development*
- *Can we find ways around the objections to clinical trial monitoring involving product liability?*