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### Assessing the Quality and Making Appropriate Use of Historical Negative Control Data: A Report of the International Workshop on Genotoxicity Testing (IWGT)

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Historical negative control data (HCD) have played an increasingly important role in interpreting the results of genotoxicity tests. Indeed, "Criterion C" can be found in most Organisation for Economic Co-operation and Development (OECD) *in vivo* genetic toxicology Test Guidelines, and involves comparing responses produced by exposure to test substances with the distribution of HCD. Because of the potential for inconsistency in how HCD are acquired, maintained, described, and used to interpret genotoxicity testing results, a workgroup of the International Workshops for Genotoxicity Testing was convened to provide recommendations on this crucial topic. The Workgroup used example data sets from four *in vivo* tests, the Pig-a gene mutation assay, the erythrocyte-based micronucleus test, the transgenic rodent gene mutation assay, and the *in vivo* alkaline comet assay to illustrate how the quality of HCD can be evaluated. In addition, recommendations are offered on appropriate methods for evaluating HCD distributions.

Recommendations of the Workgroup are:

1. When concurrent negative control data fulfill study acceptability criteria, they represent the most important comparator for judging whether a particular test substance induced a genotoxic effect.

2. HCD can provide useful context for interpreting study results, but this requires supporting evidence that i) HCD were generated appropriately, and ii) their quality has been assessed and deemed sufficiently high for this purpose.
3. HCD should be visualized before any study comparisons take place; graph(s) that show the degree to which HCD are stable over time are particularly useful.
4. Qualitative and semi-quantitative assessments of HCD should also be supplemented with quantitative evaluations. Key factors in the assessment of HCD include: i) the stability of HCD over time, and ii) the degree to which inter-study variation explains the total variability observed.
5. When animal-to-animal variation is the predominant source of variability, the relationship between responses in the study and an HCD-derived interval or upper bounds value (i.e., OECD Criterion C) can be used with a strong degree of confidence in contextualizing a particular study's results.
6. When inter-study variation is the major source of variability, comparisons between study data and the HCD bounds are less useful, and consequentially, less emphasis should be placed on using HCD to contextualize a particular study's results.

**Keywords:**

Historical control data (HCD), Genetic toxicology, Organisation for Economic Co-operation and Development (OECD), Data interpretation, Statistics.