APPENDIX C: GLOSSARY[1]

Accuracy: (a) The closeness of agreement between a test method result and an accepted reference value. (b) The proportion of correct outcomes of a test method. It is a measure of test method performance and one aspect of "relevance". The term is often used interchangeably with "concordance" (see also "two-by-two" table). Accuracy is highly dependent on the prevalence of positives in the population being examined.

Adjunct test: A test that provides information that adds to or helps interpret the results of other tests and provides information useful for the risk assessment process.

Assay: The experimental system used. Often used interchangeably with "test" and "test method".

Coded chemicals: Chemicals labeled by code rather than name so that they can be tested and evaluated without knowledge of their identity or anticipation of test results. Coded chemicals are used to avoid intentional or unintentional bias when evaluating laboratory or test method performance.

Concordance: The proportion of all chemicals tested that are correctly classified as positive or negative. It is a measure of test method performance and one aspect of "relevance". The term is often used interchangeably with "accuracy" (see also "two-by-two" table). Concordance is highly dependent on the prevalence of positives in the population being examined.

Dose-response assessment: That part of risk assessment associated with evaluating the relationship between the dose of an agent administered or received and the incidence or severity of an adverse health or ecological effect.

Endpoint: The biological or chemical process, response, or effect assessed by a test method.

Essential test method components: Structural, functional, and procedural elements of a validated test method that should be included in the protocol of a mechanistically and functionally similar proposed test method. These components include unique characteristics of the test method, critical procedural details, and quality control measures. Adherence to essential test method components is necessary when the acceptability of a proposed test method is being evaluated based on performance standards derived from a mechanistically and functionally similar validated test method. [Note: Previously referred to as "minimum procedural standards" (6).]

False positive: A substance incorrectly identified as positive by a test method.

False positive rate: The proportion of all negative substances that are falsely identified by a test method as positive (see "two-by-two" table). It is one indicator of test method accuracy.

False negative: A substance incorrectly identified as negative by a test method.

False negative rate: The proportion of all positive substances falsely identified by a test method as negative (see "two-by-two" table). It is one indicator of test method accuracy.

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[1]NIEHS. 1997. Validation and regulatory acceptance of toxicological methods: A report of the *ad hoc* Interagency Coordinating Committee on the Validation of Alternative Methods. NIH Publication No. 97-3981. NIEHS, Research Triangle Park, NC.

Good Laboratory Practices (GLPs): Regulations promulgated by the U.S. Food and Drug Administration (FDA), and the U.S. Environmental Protection Agency (EPA), and principles and procedures adopted by the Organisation for Economic Co-operation and Development (OECD) and Japanese authorities that describe record keeping and quality assurance procedures for laboratory records that will be the basis for data submissions to national regulatory agencies.

Hazard: The potential for an adverse health or ecological effect. A hazard potential results only if an exposure occurs that leads to the possibility of an adverse effect being manifested.

Interlaboratory reproducibility: A measure of whether different qualified laboratories using the same protocol and test chemicals can produce qualitatively and quantitatively similar results. Interlaboratory reproducibility is determined during the prevalidation and validation processes and indicates the extent to which a test method can be transferred successfully among laboratories.

Intralaboratory repeatability: The closeness of agreement between test results obtained within a single laboratory when the procedure is performed on the same substance under identical conditions within a given time period.

Intralaboratory reproducibility: The first stage of validation; a determination of whether qualified people within the same laboratory can successfully replicate results using a specific test protocol at different times.

Mechanistically based methods: Methods that provide a direct relationship between the biological effects observed and the biological effects of interest.

Performance: The accuracy and reliability characteristics of a test method (see "accuracy", "reliability").

Performance standards: Standards, based on a validated test method, that provide a basis for evaluating the comparability of a proposed test method that is mechanistically and functionally similar. Included are (1) essential test method components; (2) a minimum list of reference chemicals selected from among the chemicals used to demonstrate the acceptable performance of the validated test method; and (3) the comparable levels of accuracy and reliability, based on what was obtained for the validated test method, that the proposed test method should demonstrate when evaluated using the minimum list of reference chemicals.

Prediction model: A formula or algorithm used to convert the results obtained using a test method into a prediction of the toxic effect of interest. A prediction model contains four elements: (1) a definition of the specific purpose(s) for which the test method is to be used, (2) specifications of all possible results that may be obtained, (3) an algorithm that converts each study result into a prediction of the toxic effect of interest, and (4) specifications as to the accuracy of the prediction.

Predictivity (negative): The proportion of correct negative responses among substances testing negative by a test method (see "two-by-two" table). It is one indicator of test method accuracy. Negative predictivity is a function of the sensitivity of the test method and the prevalence of negatives among the substances tested.

Predictivity (positive): The proportion of correct positive responses among materials testing positive by a test method (see "two-by-two" table). It is one indicator of test method accuracy.

Positive predictivity is a function of the sensitivity of the test method and the prevalence of positives among the substances tested.

Prevalence: The proportion of positive or negative substances in the population of substances tested (see "two-by-two" table).

Prevalidation: The process during which a standardized test method protocol is developed and evaluated for use in validation studies. Based on the outcome of those studies, the test method protocol may be modified or optimized to increase intra- and/or inter-laboratory reproducibility for use in further validation studies.

Proprietary test method: A test method for which manufacture and distribution is restricted by patents, copyrights, trademarks, etc.

Protocol: The precise step-by-step description of a test method, including the listing of all necessary reagents and all criteria and procedures for generating and evaluating test data.

Quality assurance: A management process by which adherence to laboratory testing standards, requirements, and record keeping procedures is assessed independently by individuals other than those performing the testing.

Reduction alternative: A new or modified test method that reduces the number of animals required.

Reference chemicals: Chemicals selected for use during the research, development, prevalidation, and validation of a proposed test method because their response in the *in vivo* reference test method or the species of interest is known (see "reference test method"). Reference chemicals should represent the classes of chemicals for which the proposed test method is expected to be used and cover the range of expected responses (negative, weak to strong positive). Different sets of reference chemicals are likely to be required for the various stages of validation.

After a proposed test method has been recommended or accepted as valid for its intended purpose (i.e., has been recommended as a validated test method to Federal agencies), a representative subset of chemicals used during the validation process may be selected to validate a mechanistically and functionally similar test method. To the extent possible, this subset of reference chemicals should:

- Be representative of the range of responses that the validated test method is capable of measuring or predicting
- Have produced consistent results in the validated test method and in the reference test method and/or the species of interest
- Reflect the accuracy of the validated test method
- Have well-defined chemical structures
- Be readily available
- Not be associated with excessive hazard or prohibitive disposal costs

This list of reference chemicals would represent the minimum number of chemicals that should be used to evaluate the performance of a proposed, mechanistically and functionally similar test method with established performance standards. If any of the recommended chemicals are unavailable, other chemicals for which adequate reference data are available could be substituted. If desired, additional chemicals representing other chemical or product classes and for which adequate reference data are available can be used to more comprehensively evaluate the accuracy of the proposed test method.

Reference species: The species used in the reference (or traditional) test method to which a new or modified test is being compared. This may be the target species when it is also the species of interest, or it may be a surrogate species when it is not possible to perform testing on the target species.

Reference test method: The accepted *in vivo* test method used for regulatory purposes to evaluate the potential of a test substance to be hazardous to the species of interest.

Refinement alternative: A new or modified test method that refines procedures to lessen or eliminate pain or distress in animals or enhances animal well-being.

Relevance: The extent to which a test method correctly predicts or measures the biological effect of interest in humans or another species of interest. Relevance incorporates consideration of the "accuracy" or "concordance" of a test method.

Reliability: A measure of the degree to which a test method can be performed reproducibly within and among laboratories over time. It is assessed by calculating intra- and inter-laboratory reproducibility and intralaboratory repeatability.

Replacement alternative: A new or modified test method that replaces animals with nonanimal systems or one animal species with a phylogenetically lower one (e.g., a mammal with an invertebrate).

Reproducibility: The consistency of individual test results obtained in a single laboratory (intralaboratory reproducibility) or in different laboratories (interlaboratory reproducibility) using the same protocol and test samples (see intra- and interlaboratory reproducibility).

Risk: The probability or degree of concern that exposure to an agent will cause an adverse effect in the species of interest.

Screen/screening test: A rapid, simple test conducted for the purposes of a general classification of substances according to general categories of hazard. The results of a screen generally are used for preliminary decision making and to set priorities for more definitive tests. A screening test may have a truncated response range (e.g., be able to reliably identify active chemicals but not inactive chemicals).

Sensitivity: The proportion of all positive chemicals that are classified correctly as positive in a test method. It is a measure of test method accuracy (see "two-by-two" table).

Specificity: The proportion of all negative chemicals that are classified correctly as negative in a test method. It is a measure of test method accuracy (see "two-by-two" table).

Standard operating procedures (SOPs): Formal, written procedures that describe how specific laboratory operations are to be performed. These are required by GLP guidelines.

Substitute method: A new or modified test method proposed for use in lieu of a currently used test method, regardless of whether that test method is for a definitive, screening, or adjunct purpose.

Test: The experimental system used; used interchangeably with "test method" and "assay".

Test method: A process or procedure used to obtain information on the characteristics of a substance or agent. Toxicological test methods generate information regarding the ability of a substance or agent to produce a specified biological effect under specified conditions. Used interchangeably with "test" and "assay". See also "validated test method" and "reference test method".

Test method nomination: Test methods proposed to ICCVAM for review and evaluation for which a complete test method submission is not available. Four examples are (1) test methods for which adequate validation studies presumably have been completed but lack a complete submission package; (2) test methods that appear promising based on limited prevalidation or validation data and are proposed for additional validation studies; (3) test methods that have been developed and are proposed for prevalidation or validation studies; and (4) test methods that are recommended for a workshop or other activity.

Test method nominator: The organization or individual that submits a test method nomination to ICCVAM for consideration.

Test method sponsor: The organization or individual that puts forward a test method submission to ICCVAM for consideration.

Test method submission: A test method proposed to ICCVAM for consideration for which adequate validation studies have been completed to characterize the usefulness and limitations of the test method for a specific proposed regulatory testing requirement or application, and adequate documentation of the scientific validity has been prepared in accordance with ICCVAM test method submission guidelines.

Transferability: The ability of a test method or procedure to be accurately and reliably performed in different, competent laboratories.

Two-by-two table: The two-by-two table can be used for calculating accuracy (concordance) ([a+d]/[a+b+c+d]), negative predictivity (d/[c+d]), positive predictivity (a/[a+b]), prevalence ([a+c]/[a+b+c+d]), sensitivity (a/[a+c]), specificity (d/[b+d]), false positive rate (b/[b+d]), and false negative rate (c/[a+c]).

		New Test Outcome		
		Positive	Negative	Total
Reference Test Classification	Positive	A	c	a+c
	Negative	B	d	b+d
	Total	a+b	c+d	a+b+c+d

Validated test method: An accepted test method for which validation studies have been completed to determine the accuracy and reliability of this method for a specific proposed use.

Validation: The process by which the reliability and accuracy of a procedure are established for a specific purpose.