

## International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) progress to date and future plans

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**Abstract:** The INHAND Proposal (International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice) has been operational since 2005. A Global Editorial Steering Committee (GESC) manages the overall objectives of the project and the development of harmonized terminology for each organ system is the responsibility of the Organ Working Groups (OWG), drawing upon experts from North America, Europe and Japan. Great progress has been made with 9 systems published to date – Respiratory, Hepatobiliary, Urinary, Central/Peripheral Nervous Systems, Male Reproductive and Mammary, Zymbals, Clitoral and Preputial Glands in *Toxicologic Pathology* and the Integument and Soft Tissue and Female Reproductive System in the *Journal of Toxicologic Pathology* as supplements and on a web site – [www.goreni.org](http://www.goreni.org). INHAND nomenclature guides offer diagnostic criteria and guidelines for recording lesions observed in rodent toxicity and carcinogenicity studies. The guides provide representative photo-micrographs of morphologic changes, information regarding pathogenesis, and key references. During 2012, INHAND GESC representatives attended meetings with representatives of the FDA Center for Drug Evaluation and Research (CDER), Clinical Data Interchange Standards Consortium (CDISC), and the National Cancer Institute (NCI) Enterprise Vocabulary Services (EVS) to begin incorporation of INHAND terminology as preferred terminology for SEND (Standard for Exchange of Nonclinical Data) submissions to the FDA. The interest in utilizing the INHAND nomenclature, based on input from industry and government toxicologists as well as information technology specialists, suggests that there will be wide acceptance of this nomenclature. The purpose of this publication is to provide an update on the progress of INHAND. (DOI: 10.1293/tox.2014-0049; J Toxicol Pathol 2015; 28: 51–53)

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Standardization of microscopic pathology nomenclature and diagnostic criteria, especially for rats and mice, has been under discussion for many years by pathologists in the profession of toxicologic pathology. In 2005, the So-

ciety of Toxicologic Pathology (STP) and European Society of Toxicologic Pathology (ESTP), along with Registry of Industrial Toxicology Animal-data (RITA), established a collaborative process to review, update, and harmonize existing nomenclature documents and databases. The British Society of Toxicologic Pathology (BSTP) and the Japanese Society of Toxicologic Pathology (JSTP) joined the project in 2006, making this a genuinely global initiative. The result of these discussions was the INHAND Proposal (International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice). A Global Editorial Steering Committee (GESC) manages the overall objec-

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tives of the project, and Working Groups (WG) formulate the terminology proposals for each organ system<sup>1</sup>. Both the GESC and the WGs are composed of experts from the North American, British and European and Japanese Societies of Toxicologic Pathology.

Noteworthy headway has been made with nine systems to date. Rodent Respiratory, Hepatobiliary, Urinary, Central/Peripheral Nervous Systems, Male Reproductive and Mammary, Zymbal's, Clitoral and Preputial Glands have been published in *Toxicologic Pathology*, official journal of the STP and the BSTP. The Integument and Soft Tissue Systems and Female Reproductive System have been published in the *Journal of Toxicologic Pathology*, official journal of the JSTP. These manuscripts can be found as supplements in the respective journals and on the goRENI (global online Registry Nomenclature Information) System) web site – [www.goreni.org](http://www.goreni.org) - with member access for scientists working in the field of toxicologic pathology, members of any society of toxicologic pathology or of a regulatory agency. INHAND guides provide diagnostic criteria and guidelines and preferred terminology for recording lesions observed in rodent toxicity and carcinogenicity studies. The guides also provide illustrative photo-micrographs of lesions and information regarding pathogenesis, along with germane references. The goRENI web site also provides convenient, online, interactive access to the diagnostic criteria and images for each individual diagnosis that many pathologists find useful and refer to while conducting their microscopic evaluations.

INHAND and GESC will continue current OWGs until publication of all systems is complete. The remaining rodent systems include Digestive, Cardiovascular, Skeletal, Endocrine, Special Senses and Lymphoid/Hematopoietic. In order to establish the format and style that would be suitable for the content of these nomenclature guides, the STP supported the publication of the first several systems in *Toxicologic Pathology*. Working closely with scientific and technical colleagues from *Toxicologic Pathology*, the editorial and scientific staff of the *Journal of Toxicologic Pathology* adapted the publication style to their journal, so that the appearance of all INHAND supplements will remain uniform, regardless of the journal in which they are published. As new organ systems become available for publication, the GESC will coordinate with the editorial staff of *Toxicologic Pathology* and the *Journal of Toxicologic Pathology* to ensure equitable distribution of supplement publications and in the most effective and cost-efficient manner. Whether systems will be published separately or bundled together will depend largely on the size of the documents.

### Non-Rodent Terminology

In addition to terminology for rodents, a new directive for separate committees to develop species-specific terminology has been established under GESC – dog, monkey, rabbit and minipig. Committees are reviewing the rodent nomenclature as the starting point and then providing a

manuscript on terminology that is in common use in each species, terminology that is unique for each species as well as rodent terminology not appropriate for use in non-rodent species. This information would be posted on goRENI. Publication as an article or supplement will be determined on a case-by-case basis.

### Relationship between INHAND and SEND

During 2012, INHAND GESC representatives attended meetings with representatives of the FDA Center for Drug Evaluation and Research (CDER), Clinical Data Interchange Standards Consortium (CDISC), and the National Cancer Institute (NCI) Enterprise Vocabulary Services (EVS) to initiate integration of INHAND terminology as the preferred terminology for SEND (Standard for Exchange of Nonclinical Data). SEND is a formal mechanism for submitting data from non-clinical studies to the FDA electronically and in a standardized format. INHAND GESC assists the SEND Controlled Terminology (CT) committee in providing definitions for base processes and modifiers associated with the INHAND published terminology. INHAND ad hoc members of the SEND CT committee will participate in this endeavor and take issues to the full GESC and/or appropriate OWG for resolution. The GESC may also call on experts in the field to assist in any aspect of their role as a 'Scientific Advisory Board'. The interest in utilizing the INHAND nomenclature, based on input from industry and government toxicologists as well as information technology specialists, signifies the potential for wide acceptance of this nomenclature<sup>2</sup>.

GESC will become a permanent standing committee of the various Societies of Toxicologic Pathology with a defined appointment and term of members and establishment of several new roles, due to the expectation for ongoing interactions with the SEND project and future needs to serve in an advisory role. GESC will act as a clearinghouse for comments and requests for updates to the INHAND terminology from the SEND CT committee as well as from the memberships of each Society.

### INHAND as an Ongoing Process

Although the published INHAND nomenclature for each organ system is expected to be very comprehensive, it is recognized that additional lesions may need to be included, omissions rectified or inaccuracies corrected as they become apparent. To address this, a formal change control process was implemented in 2013 and is available on [www.goreni.org](http://www.goreni.org) and each Society website. Society members are encouraged to submit suggestions for changes to the nomenclature systems and provide justifications for such changes through this mechanism. GESC will continue to interface with goRENI and editorial staff at the journals so that the basic structure for future publications is maintained.

The GESC and STP, BSTP, ESTP and JSTP leadership greatly appreciate the efforts of all of those serving on the

OWGs and the newly-formed non-rodent working groups, and look forward to working with the global toxicologic pathology community as additional systems are drafted, reviewed, and completed. The international scope and review of the INHAND documents will provide a strong framework for use by pathologists and regulatory agencies that are engaged in the safety assessment of drugs, biologics, and chemicals.

## References

1. Vahle J, Bradley A, Harada T, Herbert R, Kaufmann W, Kellner R, Mann P, Pyrah I, Rittinghausen S, and Tanaka T. The international nomenclature project: an update. *Toxicol Pathol.* **37**: 694–697. 2009. [[Medline](#)] [[CrossRef](#)]
2. Keenan CM, and Goodman DG. Regulatory Forum Commentary: Through the Looking Glass-SENDing the Pathology Data We Have INHAND. *Toxicol Pathol.* **42**: 807–810. 2013. [[Medline](#)] [[CrossRef](#)]