– DRAFT Proposal –

INHAND

International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice

This document describes the view of the European Society of Toxicologic Pathology, ESTP, and the RITA group, Registry of Industrial Toxicology Animal-data, regarding the above mentioned project. It was compiled by

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Current document status: draft proposal, **November 21, 2005**

Remark: please keep in mind that the authors of this document are not native English speakers and that therefore the wording may not always be correct and perfect.

1 Introduction

ESTP and RITA have discussed the initiative "Revision of Standardized Nomenclature for Lesions in the Rat and Mouse" proposed by the Scientific Regulatory Policy Committee (SRPC) of the American Society of Toxicologic Pathology STP and came to the following conclusions:

- the initiative is highly appreciated and will be supported by ESTP and RITA
- it is a very challenging approach, in particular, the incorporation of the non-proliferative lesions
- the request of SRPC regarding a close co-operation with RITA for the nomenclature and diagnostic criteria of proliferative lesions is gratefully acknowledged and RITA is willing to co-operate and to share the expertise gathered during the 17-years existence of the RITA project
- the envisioned international approach based on the inclusion of knowledge and experts of other societies of toxicologic pathology, like ESTP, BSTP, SFTP, JSTP, etc. (just to name a few), comes at the right time

Driven by the (technical) background of the RITA data base, practical necessities of using pathology data entry systems during daily work and the long-term experience with the WebRENI system[*)], ESTP and RITA have jointly developed an organizational and technical concept, which is described in more detail in this document. The figure on the next page presents a schematic overview of the organizational process and more details (sometimes of technical nature) follow in the subsequent chapters.

ESTP and RITA are aware that two organ system groups (for the immune and respiratory system) have already started their work, however, it should currently not be too late for those colleagues to also follow the procedures outlined below.

[*)] WebRENI is the Web-based and extended version of the publications "International Classification of Rodent Tumors". Part 1, The Rat, was published in a series of 10 fascicles between 1992 and 1997 by WHO/IARC, Part 2, The Mouse, was published 2001 by Springer under the auspices of WHO/IARC.

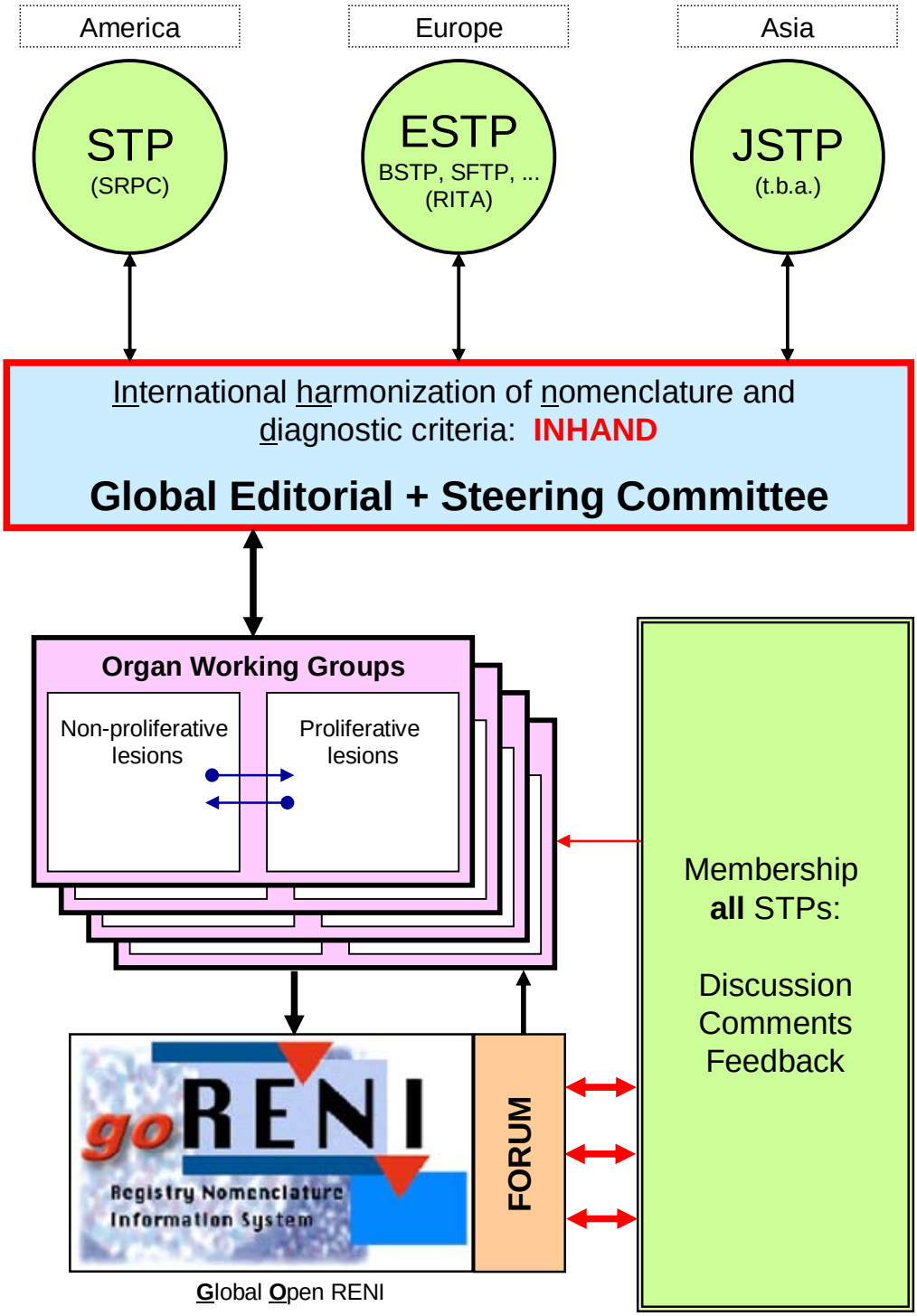

Figure 1: schematic overview of the organizational process

2 Name of the initiative / project

The goal of the joint global initiative is the "International harmonization of nomenclature and diagnostic criteria" and we feel that this should be demonstrated by a **name**, which is easy to remember, easy to speak and easy to associate with a "common" term. Our proposal is to simply take some of the first characters of the overall title and to form from this the word

INHAND

(as shown above by underlining).

3 The Global Editorial and Steering Committee

From the European point of view, we need to have a committee, which is in charge to overlook and "drive" the complete process of establishing the "International harmonization of nomenclature and diagnostic criteria".

3.1 Name

As a name/title for such a committee, we propose

Global Editorial and Steering Committee (GESC)

This name should express

- the overall "**global**" approach of the project
- the **scientific** competence of the committee (important, when decisions regarding the finalization of manuscripts and/or publications have to be taken)
- the **coordinating** competence regarding the establishment of a harmonized structure in terms of nomenclature ("terminology") and of the layout and structure of the manuscripts, which must be comparable across organ systems

Furthermore, a name is proposed, which should not stay in any conflict with names of already existing committees, like "Executive Committees" of the different societies of toxicologic pathology or "Editorial Boards" of the journals, associated with the societies.

3.2 Establishment and size of the GESC

The "Global Editorial and Steering Committee" should consist of 9 to 12 individuals who represent the major societies of toxicologic pathology in America, Europe, and Asia, as shown in the chart. The members are nominated and elected by either the Executive Committees of the related societies or by existing sub-committees (e.g., the SRPC in the US).

An equal representation of the "world regions" America, Europe, and Asia needs to be reached. However, in Europe we currently have besides the European Organization ESTP, also well established national organizations, like the BSTP or the SFTP, who should also have the chance to participate and to be represented in the "Global Editorial and Steering Committee". A similar situation may also exist in Asia.

3.3 Duties of the GESC

Initial tasks (please note the sequence):

1. Discuss and finally agree on a proposed systematized terminology / nomenclature for non-proliferative and proliferative lesions in rats and mice (see Appendix 1 and chapter 5.2).
2. Agree on a common format for the presentation and structure of "manuscripts" (see Appendix 2).
3. Establish organ working groups and propose members (see chapter 4).
4. Discuss the proposed terminology with the organ working groups, in particular, for non-proliferative lesions.
5. Involve the executive committees of all "Societies of Toxicologic Pathology" and get approval for the proposed systematic terminology and the manuscript format.
6. Get the organ working groups "working".

Further tasks:

- Discuss the possibility of sponsorship (for initial ideas see chapter 6).
- Find an agreement on publications.
- Review final draft versions of the manuscripts on formal aspects.
- (probably more topics need to be added here)

4 Organ Working Groups

Definitions:

- For each organ system an "Organ Working Group" needs to be established. Larger organ systems may be split into separate working groups.
- Each organ working group has a chair.
- In order to minimize species differences, the same working group should be responsible for rat and mouse manuscripts and the manuscripts should be established/revised at the same time.
- Each working group may be divided into sub-groups, which are responsible for non-proliferative lesions and proliferative lesions, respectively.
- Each sub-group has one responsible compiler, who can "moderate" the *go*RENI forum (see chapter 5.3) and who is the contact to Fraunhofer ITEM for submitting a new/revised version of a manuscript.
- For manuscripts on proliferative lesions, the responsible compiler should be a member of the RITA group. RITA has already identified compilers for all manuscripts (rats and mice).

Duties of the Working Group Chair

- Organizes the group
- Conducts business, preferably by teleconference and e-mail
- Assigns tasks to members, e.g., responsibilities for specific organs
- Coordinates the flow of information between the sub-groups for non-proliferative and proliferative lesions
- Takes care for time lines

Duties of a Working Group

- Drafts document describing proliferative and non-proliferative lesions for rat and mouse for the specific organ system according to the proposed structure (see Appendix 2).
- Members provide images in order to illustrate all lesions if feasible.
- Provides final draft within approx. 1 year.

Basic documents for Organ Working Groups

- For proliferative lesions (see also chapter 5.2):
  Once a compiler/organ working group has been established the responsible compiler gets a **word file** with the currently existing published diagnostic criteria of the rat and mouse lesions for the related organs. This should be used as the basis for discussion within the compiler/organ working group. In a number of cases, such documents include already revisions, which have been made after publication by RITA members and/or the RITA panel.
- For non-proliferative lesions:
  The either published or discussed drafts of the STP (see Appendix 3) should be used as a starting point.

5 "*go*RENI"

WebRENI is in existence since many years and contains the published diagnostic criteria of proliferative lesions in rats and mice. Access to WebRENI is limited to RITA members and to individuals who have bought the Springer book "International classification of rodent tumors: The mouse". RITA members have access to additional information and images, which are important for the data base. This should not be changed during the development period of INHAND.

It is therefore necessary to establish a "2nd WebRENI" to be used for the discussion process. This system will be named

go*RENI** for "g***lobal ***o***pen **RENI**"

The structure of *go*RENI will be identical to WebRENI, however, with 2 important extensions:

- it includes the nomenclature and diagnostic criteria for non-proliferative lesions
- it includes an integrated discussion **Forum**

Overall goal:

- *go*RENI should be **open** to all colleagues, working in the field of toxicologic pathology, who are members of any society of toxicologic pathology or of a regulatory agency!

5.1 Access to *go*RENI

*go*RENI will make use of the same User data base as WebRENI, which means that

- only registered users have access
- a login with user name and password is always required

Access will be provided to:

- Members of all Societies of Toxicologic Pathology (e.g., STP, ESTP, BSTP, SFPT, JSTP, ...).
  Requirement: each Society sends an Excel file with the relevant user data [structure will be announced] and decides whether all members or only selected members should have access.
- Members of regulatory agencies:
  they can either be "nominated" by a Society of Toxicologic Pathology or they send in their individual request for an account.
- RITA members (usually also members of a ToxPath Society).

Such a "controlled access" will make sure that the platform is used only by qualified (toxicologic) pathologists, which is particularly important for discussions within the Forum (see chapter 5.3).

5.2 Initial content of *go*RENI

*go*RENI will not come as an empty system.

Terminology / lexicon:

For proliferative rat lesions, the mutually agreed "Harmonized Rat Nomenclature" (see http://reni.item.fraunhofer.de/reni/rat_nomenclature/index.htm and http://www.toxpath.org/nomen/index.htm) will be implemented. The terminology for proliferative lesions in the mouse will be adapted to that of the rat (necessary only for a few lesions). For non-proliferative lesions, a proposal for a terminology will be implemented, which is currently "under construction" at Fraunhofer ITEM and which is based on the NTP TDMS system (http://hazel.niehs.nih.gov/user_spt/pct_terms.htm) and on STP documents and drafts as far as they are available to the authors (see the list in Appendix 3).

Diagnostic criteria / manuscripts:

- **Proliferative lesions, published manuscripts:**
  - Text of all published manuscripts (in some cases with updates which have been already made after publication by the current RITA compilers and/or the RITA Panel and which can be identified by a different color).
  - Additional references (added after publication).
  - Images: rat: all, mouse: initially, only thumbnails of published images until legal (copyright) issues have been clarified. The responsible compiler (as a RITA member) has access to the published images as well as to the RITA images.

- **Proliferative lesions, new manuscripts:**
  - Some manuscripts have been established by RITA members after the publication. They are also included with the (draft) diagnostic criteria and images.

- **Non-proliferative lesions:**
  - Probably, we will start with blank pages, where only the header (organ and suggested lesion name) is listed.

The RENI Forum will be available on all pages!

5.3 The *go*RENI Forum

In order to allow (and to stimulate) a discussion among all *go*RENI users, each manuscript page will include a "Discussion Forum":

- Comments, ideas for improvements, etc. can easily be posted (and discussed) here.
- There are no anonymous postings possible: due to required login, each user is identified.
- The responsible compiler should be the "moderator" of the related forum, which means that he/she can edit and/or delete entries (e.g., when ideas have been incorporated into a new version of the manuscript).
- In addition to the "manuscript level", postings are also possible on the related "organ level" and "organ system level": This should, however, be used only for general remarks, covering more than one lesion in order to avoid multiple postings on the same topic.
- An "alert" list (accessible from the *go*RENI home page) will show available postings, sorted by date and time (newest on top).

6 Costs and Support

The establishment of *go*RENI and in particular the continuous update of the *go*RENI Web site with new and/or revised manuscripts and images will of course need manpower and money. The vision of ESTP and RITA is **not** to raise these costs from the membership of the different ToxPath societies! Instead, a proposal is currently under discussion within ESTP and RITA, to get the necessary funds from "sponsors", who might be interested to be named in conjunction with this initiative (e.g., with logos on the Web site). Possible "targets" could be publishers of scientific journals and books, animal breeders, vendors of microscopes, image analysis systems or image scanning systems, etc. (i.e., in principle those companies who also show up as exhibitors at the annual meetings of the ToxPath societies). Sponsorship from the participating societies itself, i.e., the organizations and not the members, would also show a positive signal.

An important issue (which needs to be discussed in the GESC) is, to select as sponsors clearly only such companies, whose products do not create any "conflict of interest" with the envisaged goal of our initiative (perhaps vendors of pathology data acquisition systems - to be discussed) ! Such companies (like PDS, Instem, Xybion, etc.) should have in principal a vital interest of participation, however, they may have their established glossaries and the question is, are they willing to change it.

Support and maintenance for the *go*RENI system will be provided by the same team at Fraunhofer ITEM, which is also in charge to maintain the RITA data base and WebRENI.

Appendix 1:
Nomenclature / Terminology

General

- Language: US English should be used.
- The terminology should allow an easy use and an easy implementation into pathology data acquisition systems and should therefore be as systematic as possible, i.e. "computer ready". Functions will be available to download the terminology as Excel files.
- The terminology should be identical for the two involved species rat and mouse (as far as possible).

Lesion names

Names of lesions should be "constructed" by using a systematic approach and by allowing **two variants**. "Systematic" in this context means that similar lesions should always have the same name across organs or organ systems. Two variants seem to be necessary in order to

(a) fulfill requirements for an implementation into pathology data acquisition systems or data bases, and to

(b) allow the use of the more commonly used "speaking form".

Variant A:

The *type of the lesion* (e.g., tumor, adenoma, carcinoma, hyperplasia, inflammation, mineralization, etc.) is always the first word, which can be followed by further descriptive terms (like "C-cell", "hepatocellular", etc.). Terms are separated from each other by a comma.

Benefit: lesions of the same or similar biological behavior are listed together when viewing a sorted list.

Variant B:

The ordering of words is changed by placing the descriptive component first.

Benefit: lesions of the same cell type or morphological pattern are listed together when viewing a sorted list.

In any case, so-called "**preferred terms**" should be established! Any number of synonymous terms can be mentioned in the manuscript under the heading "Synonyms".

Examples:

Variant A	Variant B
Adenoma, C-cell	C-cell adenoma
Carcinoma, C-cell	C-cell carcinoma
Hemangiopericytoma, benign	Benign hemangiopericytoma
Mesothelioma, atriocaval, benign	Benign atriocaval mesothelioma
Tumor, neuroendocrine cell, malignant	Malignant neuroendocrine cell tumor
Hyperplasia, epithelial	Epithelial hyperplasia
Metaplasia, squamous cell	Squamous cell metaplasia

*go*RENI will provide **both** variants of presenting lesion names: via a configuration menu, the user decides which variant he/she wants to see.

Biological behavior of the lesion

Each lesion needs to be clearly classified in terms of its biological behavior according to the following possibilities:

M: malignant tumor [systemic (malignant) tumors are included]

B: benign tumor [polyps are included]

H: pre-neoplastic lesion (usually hyperplasia or metaplasia)

N: non-proliferative and non-preneoplastic proliferative lesion

Organ names

Names or organs should be given always in singular, also for paired organs. The lexicon contains the information whether an organ exists paired, but it is not mentioned in the name.

Lesion - organ relations

The fact that a particular lesion can occur in (one or more) particular organ(s) is defined and described by a "manuscript" (see below). If a lesion can be diagnosed practically in all organs, the location should be defined as

- Soft tissue
- Skeletal system
- Peripheral nervous system
- Vascular system
- Generally used preferred terms

Systemic lesions of the hematopoietic / lymphoreticular system are named under the location "hematopoietic tissue" or "mononuclear phagocytic tissue".

The above described and recommended systematic approach has been successfully used within the RITA data base (for proliferative lesions), now for about 17 years. An extension to the terminology for non-proliferative lesions in a similar way should be possible.

Appendix 2:
Definition and Structure of a "Manuscript"

A manuscript describes the diagnostic criteria for **one** lesion in **one** species, which may occur in one or more than one organ. If the diagnostic criteria are identical for both species, a copy will be stored in *go*RENI; images and literature references should be species-specific.

A manuscript consists of the following chapters / "entities":

Lesion name [mandatory]

The preferred term for the lesion - see above.

Biological behavior [mandatory]

Is part of the lesion - see above.

Organ name(s) [mandatory]

One or more organs can be mentioned here - see above.

Sub-topographies [optional, non-proliferative lesions only]

Possible sub-topographies for a diagnosis, like zona fasciculata, zona glomerulosa, zona reticularis in the adrenal gland.

Synonyms [optional]

Any list of names used (in literature) synonymous for this lesion.

Modifier [optional]

List of modifiers, which can be used to sub-classify a lesion (e.g., according to a specific growth pattern or a distinct cell type). Criteria for using a modifier should be given in the chapter "Diagnostic Features" under sub-headings.

Histogenesis [mandatory for proliferative lesions]

This section mentions the tissue from which the lesion originates.

Macroscopic Diagnostic Features [optional]

Typical macroscopic features of the lesion. Does not exist in WebRENI so far. Should be separated for

- naturally occurring lesions
- induced lesions

Microscopic Diagnostic Features [mandatory]

Bulleted list of essential diagnostic criteria to be used for a specific finding, including staining characteristics, size criteria or growth patterns. Should be separated for

- naturally occurring lesions
- induced lesions

Differential Diagnoses [mandatory for proliferative lesions]

List of lesions with similarities to the currently described one together with their main criteria for the differentiation (only "striking diagnostic criteria" need to be listed).

Comment [optional]

Any additional information regarding the description of the lesion which is not necessarily relevant for making a diagnosis. In contrast to WebRENI, this chapter should be structured by sub-headings, like

- Frequency of the lesion

  Usual occurrence of this lesion in control animals (separated by sex), given as "extreme rare", "rare", "frequent". Remarks on the age-related occurrence should be included also.

- Induced lesions

  Further comment on the induction of this lesion, e.g. by naming substance classes.

- Regulatory issues/remarks

  Any remarks regarding regulatory guidelines which need to be considered in certain studies when diagnosing this lesion.

Special Techniques for Diagnostics [optional]

Methods and markers can be described here, which can be used to help to establish a more precise diagnosis (does not exist in WebRENI so far). Categories:

- Special stains, histochemistry
- Immunohistochemistry
- Electron microscopy
- In Situ-Hybridization
- Other special diagnostic methods

Clinical Findings [optional]

Does not exist in WebRENI so far.

Clinical Pathology [optional]

Parameters measured in blood, urine, etc. Does not exist in WebRENI so far.

References

Literature should not be older than 10 to 15 years, except fundamental and important papers. The citation format should be identical to the existing manuscripts. If abstracts in PubMed are available, links will be included.

Images

Categories:

- gross lesions (naturally occurring lesions / induced lesions)
- micro photographs (naturally occurring lesions / induced lesions)

Preferable data in the legend:

- Organ, lesion, modifier
- Spontaneous vs. induced (by ...[type of compound])
- Strain (breeder), sex, age, animal status
- further description ...

Trimming

Links to the trimming guides will be automatically inserted by the software (see http://reni.item.fraunhofer.de/reni/trimming).

Appendix 3:
STP documents on non-proliferative lesions

- Bertram TA, Markovits JE, Juliana MM: Nonproliferative lesions of the alimentary canal in rats. Final proposal, October 1994
- Detilleux PG, Gruebbel MM, Botts S, et al.: Nonproliferative changes of the liver, exocrine pancreas, and salivary glands of the rat. Final proposal, June 1997
- Ernst H, Miller RA, Monticello TM, et al.: Nonproliferative lesions of the respiratory tract in mice. No date given.
- Frith CH, Botts S, Jokinen MP, et al.: Nonproliferative lesions of the endocrine system in rats. In: Guides for Toxicologic Pathology. STP/ARP/AFIP, Washington, D.C.
- Frith CH, Ward JM, Chandra M, et al.: Nonproliferative lesions of the hemopoietic system in rats. In: Guides for Toxicologic Pathology. STP/ARP/AFIP, Washington D.C.
- Greave P, Carlton WW, Courtney CL, et al.: Non-proliferative and proliferative lesions of soft tissue and skeletal muscle in mice. Final proposal, September 16, 1997
- Greaves P, Seely JC: Non-proliferative lesions of soft tissues and skeletal muscle in rats. Final proposal, 12 October 1994
- Hard GC, Alden CL, Bruner RH, et al.: Nonproliferative lesions of the kidney and lower urinary tract in the rat. No date given.
- Long PH, Ernst H, JR Leininger, JR, et al.: Proliferative and nonproliferative lesions of bone, cartilage, tooth, and synovium in mice. No date given.
- Long PH, Leininger JR, Ernst H: Non-proliferative lesions of bone, cartilage, tooth, and synovium in rats. Guides for Toxicologic Pathology, STP/ARP/AFIP, Washington, 1996
- McMartin DN, O'Donoghue JL, Morrissey R, et al.: The Society of Toxicologic Pathologists standard nomenclature of nonproliferative changes in the nervous system of rats. Initial proposal, June 1994
- Morris CF, Mann PC, Gibson GW: Standardized system of nomenclature and diagnostic criteria. Non-proliferative lesions of the rat: Integumentary system. Final proposal, May 1994
- Ruben Z, Arceo RJ, Bishop SP, et al.: Nonproliferative lesions of the heart and vasculature in rats. Final draft, S.O.T.P. Meeting, San Diego, CA, June 1995
- Wosu NJ, McConnell RF, Valerio M, et al.: Nonproliferative lesions of the genital system in female rats. Final draft, June 1995
- Wosu NJ, McConnell RF, Valerio M, et al.: Nonproliferative lesions of the genital system in male rats. Final draft, June 1995

Appendix 4:
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