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# Society of Toxicologic Pathology Position Paper

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TOXICOLOGIC PATHOLOGY, vol 31, no 2, pp 252–253, 2003  
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DOI: 10.1080/01926230390183751

## Recommended Tissue List for Histopathologic Examination in Repeat-Dose Toxicity and Carcinogenicity Studies: A Proposal of the Society of Toxicologic Pathology (STP)

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### ABSTRACT

The Executive Committee of the Society of Toxicologic Pathology (STP) appointed an ad hoc task force to devise and recommend a standard list of tissues to be evaluated histopathologically in repeat-dose toxicity and carcinogenicity studies that are used to support the registration of new pharmaceutical products. The recommended tissue list is intended to be a minimum core list that can be used for all types of repeat-dose toxicity and carcinogenicity studies, regardless of route of administration, species or strain of mammalian laboratory animal, duration, or class of drug to be tested. The resulting recommendations of the task force, presented here, were subsequently reviewed by the STP membership and endorsed by the STP Executive Committee.

*Keywords.* Animals; carcinogenicity; histopathology; organs; regulations; repeat-dose; tissues; toxicity.

### INTRODUCTION

At a meeting of the Pharmaceutical Research and Manufacturers of America in August 1999, representatives of the Center for Drug Evaluation and Research of the U.S. Food and Drug Administration recommended that the pharmaceutical industry propose a standard tissue list for histopathologic examination in repeat-dose toxicity and carcinogenicity studies. In response to this recommendation, the Society of Toxicologic Pathology (STP) convened an ad hoc task force to compile a core list of tissues that should be examined histopathologically in repeat-dose toxicity and carcinogenicity studies that will support the registration of new pharmaceutical products. This document presents the recommendations of the task force, which have been subsequently reviewed by the STP membership and endorsed by the Executive Committee of the STP.

Although there are currently no FDA guidelines for tissues to be examined histopathologically, Japan and the European community have published standard lists of tissues for repeat-dose toxicity and carcinogenicity studies. In developing the proposed tissue list, the STP task force referred to the guidelines of the Committee for Proprietary Medicinal Products (CPMP [European guidelines]) (1, 2), the Japanese

Ministry of Health and Welfare (3), and the National Cancer Institute/National Toxicology Program (NCI/NTP) (4). Also considered during the development of the tissue list was the “Guidelines for the Common Technical Document (CTD),” which has been developed by the International Conference on Harmonization (ICH). The draft ICH guidelines contained a requirement to indicate whether or not the histopathologic examination for repeat-dose toxicity and carcinogenicity studies meets the Japanese and/or CPMP guidelines. (This requirement was not included in the adopted version of November 9, 2000.) Regulations of the U.S. Environmental Protection Agency (EPA) (5) and other regulations concerning nonpharmaceutical chemical entities were also considered in the drafting of this proposal, but not as heavily as pharmaceutical regulatory guidelines. Finally and most importantly, the STP task force attempted to base its recommendations on sound scientific principles, knowledge of current pharmaceutical industry practice, and concern for human safety.

### RECOMMENDATIONS

The STP Tissue List Task Force proposed a core (minimally acceptable) list of tissues to be examined histologically for all repeat-dose GLP toxicity studies of 2 weeks/1 month to 1 year in duration and carcinogenicity studies regardless of route of administration (Table 1). Other tissues specific to the route of administration and target tissues associated with

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TABLE 1.—STP-recommended core list of tissues to be examined histopathologically in repeat-dose toxicity and carcinogenicity studies (for all species, where applicable).<sup>a</sup>

Adrenal gland	Pancreas
Aorta	Parathyroid gland
Bone with bone marrow <sup>b</sup>	Peripheral nerve
Brain	Pituitary
Cecum	Prostate
Colon	Salivary gland
Duodenum	Seminal vesicle
Epididymis	Skeletal muscle
Esophagus	Skin
Eye	Spinal cord
Gallbladder	Spleen
Harderian gland	Stomach
Heart	Testis
Ileum	Thymus
Jejunum	Thyroid gland
Kidney	Trachea
Liver	Urinary bladder
Lung	Uterus
Lymph node(s)	Vagina
Mammary gland <sup>c</sup>	Other organs or tissues with gross lesions
Ovary	Tissue masses

<sup>a</sup>This tissue list is intended to be a minimum core list that can be used for all types of repeat-dose toxicity and carcinogenicity studies, regardless of route of administration, species or strain of mammalian laboratory animal, duration of study, or class of drug to be tested. It is recommended that the route of administration be considered at the time of study design and that tissues relevant to the route of administration be added to this core list. For example, the addition of nasal cavity and turbinates, larynx, and tracheobronchial lymph nodes may be considered for inclusion in the tissue list for nasal inhalation studies. Likewise, depending upon the species or strain of laboratory animal, the addition of organs or tissues unique to or characteristic of that species or strain may be selected, as appropriate. It is also recommended that additional tissues that are known to be targets of the test article or those of its class be added to this core tissue list.

<sup>b</sup>For nonrodents, either rib or sternum. For rodents, femur including articular cartilage.

<sup>c</sup>Females only.

particular classes of compounds were not included in this core list, but should be added to the core list, as necessary.

## DISCUSSION

The intention behind STP tissue-list recommendation was not to make it inclusive of all organs and tissues, or even to include all organs and tissues recommended by the United States (EPA), Japan, or the European regulatory agencies. Ideally, when making an assessment of toxicologic or carcinogenic potential, it would be desirable to detect every pathologic lesion in all test animals. However, that would require the examination of every cell in the body of every study animal. Clearly, that is not possible with current technology. Instead, the pathologist and regulatory agencies must rely on a representative sampling of tissues to maximize resources, yet ensure safety. These tissues in STP's recommended list were selected to optimize the effort expended by pathologists and pharmaceutical companies on safety-assessment studies. Several tissues recommended by one or more regulatory agencies, including optic nerve, oviduct, ureter, nasal cavity, Zymbal's gland, clitoral/preputial gland, diaphragm, extraorbital lacrimal gland, rectum, three different salivary glands, larynx, pharynx, coagulating gland, and tongue, were not included. Reasons to exclude tissues from the STP-recommended tissue list included:

1. Morphologic evidence of toxicity and/or carcinogenicity rarely occurs in some tissues (optic nerve, nasal cavity, diaphragm, multiple salivary glands, etc.).
2. Other tissues on the STP-recommended list adequately screen for toxicologic or carcinogenic responses to chemicals in a specific organ system. For example, the accessory male reproductive organs are adequately represented by prostate and seminal vesicle; so, routine examination of the coagulating gland would add little value. One salivary gland, rather than three distinct glands, is sufficient to screen for salivary gland toxicity. This reasoning also applies to other excluded organs: diaphragm, oviduct, pharynx, rectum, tongue, and optic nerve.
3. Toxicity and carcinogenicity in some tissues often are accompanied by gross lesions or clinical observations. In these cases, gross or clinical evidence of toxicity would trigger histopathologic examination of suspected target organs, and routine examination would not be required (e.g., clitoral/preputial gland, pharynx, oviduct, and tongue).
4. Certain tissues found in laboratory animals, including Zymbal's gland, extraorbital lacrimal glands, and clitoral/preputial glands, do not have human counterparts; therefore, toxicologic or carcinogenic responses in these tissues have questionable relevance to human safety.

The STP tissue list is intended to be a minimum core list for microscopic evaluation that can be used for all types of repeat-dose toxicity and carcinogenicity studies, regardless of route of administration, species or strain of mammalian laboratory animal, duration of study, or class of drug to be tested. It is recommended that the route of administration be considered at the time of study design and that tissues relevant to the route of administration be added to this core list. For example, the addition of nasal cavity and turbinates, larynx, and tracheobronchial lymph nodes may be considered for inclusion in the tissue list for nasal inhalation studies. Likewise, depending upon the species or strain of laboratory animal, the addition of organs or tissues unique to or characteristic of that species or strain may be selected, as appropriate. It is also recommended that additional tissues that are known or suspected to be targets of the test article or those of its class be added to this core tissue list.

## REFERENCES

1. Committee for Proprietary Medicinal Products (1999). Note for guidance on repeat dose toxicity testing; Appendix A.
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