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Assessment of Hyperplastic Lesions in Rodent Carcinogenicity Studies

The contribution of hyperplastic lesions in two-year rodent carcinogenicity studies to human hazard identification and risk assessment is a complex issue. Although hyperplasia is a common, spontaneous age-related change in many tissues, it can also be part of other pathologic conditions that in some cases represent a morphologic/biologic continuum leading to neoplasia, and therefore may be considered part of the “the weight of evidence” for carcinogenicity assessment (3, 4, 5). This paper provides a general perspective for toxicologists, pathologists, and other scientists involved in carcinogenicity hazard identification and risk assessment.

There currently are no regulatory guidelines that discuss the relationship of non-neoplastic proliferative changes (i.e., regenerative hyperplasia, atypical hyperplasia, physiologic hyperplasia, etc.) to neoplastic processes in rodent carcinogenicity studies; however, some useful generalizations for interpreting hyperplastic lesions can be made. First and foremost, hyperplasia must be viewed within the context of the study. Factors that may contribute to an accurate assessment of the relevance of hyperplasia to coexisting neoplastic processes include a common cell of origin for hyperplastic and neoplastic processes, the presence or absence of a morphological continuum between hyperplasia and neoplasia within the study, histologic similarities of hyperplastic and neoplastic lesions, the incidence and severity of spontaneous chronic diseases that may influence development of hyperplastic and neoplastic lesions, incidences of hyperplasia and neoplasia, and other evidence for treatment-related toxicity. Furthermore, hyperplasia has different implications depending on the specific type(s) of morphologic changes (diffuse or focal, with or without cellular atypia), the biochemical mechanisms stimulating cellular proliferation, concurrent lesions, the organ/tissue sites involved, and the presence or absence of other neoplastic findings in the tissue with hyperplasia.

The pathologist evaluating the study must determine whether nonneoplastic lesions are relevant to assessment of hyperplastic and neoplastic responses based on morphologic similarities, mechanistic data, and scientific knowledge. Information regarding the specific compound or class of compound in question, including expected pharmacologic effects and mechanisms of action, mutagenicity, chemical groups known to be associated with carcinogenicity, and characteristics of absorption, distribution, metabolism, and excretion should be considered. Data from other nonclinical studies with the same or a related compound may add to the weight of evidence. Obviously, consistent diagnostic terminology must be used to distinguish hyperplastic lesions relevant to carcino-

genicity assessment. In this regard, it is noteworthy that there may be multiple terms currently in use that can be applied to hyperplastic lesions. Use of standardized nomenclature such as that endorsed by the Society of Toxicologic Pathology (1) and clear, cogent communication of the findings and their interpretations are essential to appropriate interpretation.

It is important to determine if hyperplastic lesions are a direct effect of compound action, or alternatively are secondary to a primary degenerative, necrotic or apoptotic event leading to a reparative (regenerative) hyperplasia. Focal hyperplasia that appears morphologically similar to neoplasia in the same tissue without evidence of concurrent toxicity or tissue injury may be considered more indicative of a potential direct treatment-related neoplastic response. Hyperplasia and cancer in tissue with an inciting factor such as inflammation or degeneration/regeneration induced by the test agent may suggest that the carcinogenic process is secondary to chronic tissue injury. If hyperplasia can be clearly associated with tissue toxicity, then one can assume that exposures insufficient to cause the inflammation or degenerative/regenerative changes are unlikely to cause cancer. Even if the hyperplastic precursor lesions (whether in the same study or in earlier shorter term studies) are considered to be a primary effect of the test article, there are different implications depending on the type of change (i.e., diffuse or focal, with or without cellular atypia or dysplasia), the biochemical mechanism(s) stimulating cellular proliferation, associated concurrent lesions, the tissue involved, and the type of related neoplastic findings. For example, a chemical producing a marginal increase in transitional cell papilloma or carcinoma of urinary bladder at the high dose in a 2-year bioassay in rats, but also with multiple foci of transitional cell hyperplasia with cellular atypia in the high and mid dose groups, may have greater risk for carcinogenicity than a chemical with only a marginal increase in transitional cell neoplasms at the high dose. Thus, the appropriate perspective of pathologic changes is critical in assessing and communicating the risk.

The role of hyperplastic lesions in the assessment of carcinogenicity should be interpreted very carefully since our understanding of the causes and progression of many chemically-induced neoplastic processes is limited. Although it is common to analyze incidences of benign and malignant neoplasms separately, the incidences of benign and malignant neoplasms arising from the same cell type are usually also combined for statistical analyses (2, 3). This is logical, since many benign and malignant neoplasms generally are considered irreversible with the potential for

TABLE 1.—Recommended qualitative use of hyperplasia incidence data in evaluating tumorigenic responses in rodents.

Relevant hyperplastic lesions	Benign neoplasms	Malignant neoplasms	Benign and malignant neoplasms combined	Interpretation
Increased	Increased or equivocal effect	No effect	No effect or equivocal effect	Relevant hyperplastic responses contribute to weight of evidence of neoplastic effect
Increased	No effect	Increased or equivocal effect	No effect or equivocal effect	
Increased	Equivocal effect	Equivocal effect	Increased	No neoplastic effect Lack of hyperplastic response suggests equivocal results may not be related to treatment
Increased	Increased	Increased	Increased	
Increased	No effect	No effect	No effect	
No effect	Equivocal effect	No effect	No effect	
No effect	No effect	Equivocal effect	No effect	
No effect	No effect	No effect	Equivocal effect	

Note: The pathologist must determine which hyperplastic lesions are relevant to assessment of carcinogenicity in rodents, and only those relevant lesions should be considered in this assessment.

biological/morphological progression (3, 5). However, unlike benign and malignant neoplasms, hyperplastic lesions may not progress to neoplasia and may be reversible (3). Although some morphologic and biochemical criteria may suggest the potential for a hyperplastic lesion to progress to neoplasia, it is often not possible to distinguish hyperplastic lesions that are self limiting from those that can potentially progress to neoplasia using standard bioassays lacking animals in recovery groups. For example, in chronic progressive nephropathy in rats, regenerative tubular hyperplasia with small basophilic cells is not usually relevant to renal tubular neoplasia, while atypical tubular hyperplasia generally is considered a pre-neoplastic lesion. Only hyperplastic lesions considered relevant to the assessment by the pathologist should contribute to the evaluation of carcinogenic potential. The occurrence of hyperplasia without a concurrent neoplastic response of the same cellular origin should not be interpreted as evidence that a neoplastic response will occur. Although a specific hyperplastic response may, in some instances, suggest the potential for the future progression to neoplasia, the appearance of neoplasms is the only conclusive evidence of a carcinogenic response. In those cases in which hyperplastic lesions are believed to be relevant for assessment of carcinogenicity, qualitative evaluation of hyperplastic lesions is more appropriate than statistical analysis. It is not appropriate to combine hyperplastic and neoplastic lesions for statistical analysis. Table 1 illustrates some general concepts guiding the qualitative use of incidence data for hyperplastic lesions considered relevant to carcinogenicity hazard identification, recognizing that the pathologist must use professional scientific judgment to identify and describe those hyperplastic lesions that should be considered in a weight-of-evidence approach.

In summary, exposure to chemicals may result in a spectrum of proliferative changes ranging from hyperplasia to neoplasia. Accurate assessment of hyperplastic changes as they relate to neoplasia is critical to the appropriate determination of carcinogenic hazard in the test species and ultimately for determining potential human risk. The association of hyperplasia with neoplastic changes must be done with careful consideration of the multiple factors that impact such a correlation. It is essential to understand the underlying causes of hyperplastic changes, at least to the extent possible, since the interpretation is always based on weight of evidence that varies among individual studies. The potential significance of hyperplastic changes must be addressed clearly in the pathology narrative to ensure accurate communication of the context and significance of these changes.

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