- For risk assessment, the distinction between benign and malignant generally is not of great importance, with exception of rare cases, when a substance only increases the aggressiveness of tumors.

The following proliferative lesions can generally be combined in life-time bioassays (203):

- Neoplasms in the respiratory tract or in the peripheral lung, but generally not from both locations together
- Squamous cell neoplasia of the upper alimentary tract including forestomach
- Epithelial neoplasm of the small intestine or the large intestine and—depending on the type of proliferative lesions—also of small and large intestine combined
- Smooth muscle neoplasia body-wide with exception of those of the GI tract and reproductive tract, which must be evaluated separately

The types of proliferative lesions which can be combined have often to be determined on a case-by-case basis (204).

6. INVESTIGATION OF UNCLEAR PATHOLOGICAL FINDINGS

6.1. Additional Investigations of Available Samples

If unclear histopathological findings are detected, additional investigations might be warranted (205). They can sometimes be performed on samples already available from the study in question, or from previously conducted toxicity studies (206). Examples for possible investigations include:

- *Blood samples for hormones* (207,208), particularly for findings in endocrine organs. As already mentioned, hormone levels provide important insights into the trophic effect on a particular endocrine regulated organ. Increased or decreased stimulation of an organ is associated with hypertrophy/hyperplasia or—conversely—atrophy of the organ in question. Hyperplasia is often associated with tumor formation in that particular organ in life-time rodent bioassays.
- *Blood or tissue samples for gene or mRNA expression or for marker proteins* or protein patterns by proteomics (209). Such investigations have become fashionable in the past few years. However, the future will have to show to what extent they are actually useful.
- *Tissue samples for investigations by EM or by immunohistochemical methods*. Applications include identification of the proliferative cell type (16,210), measurement of cell proliferation (by PCNA) (57,211) or apoptosis (212). Even with formalin-fixed tissue, EM investigation may show important subcellular details which help