

## 2. TECHNICAL POST-MORTEM PROCEDURES

### 2.1. Introduction

This section provides a general description of routine techniques. The procedures need to be adapted depending on the study type. The main determinants for tissue sampling, processing, and histopathological investigations follow:

**Study duration:** For *acute* studies histopathological investigations are limited to unclear macroscopic findings, because histopathological findings are generally unspecific (e.g., necrosis and edema) and reflect acute intoxication with failure of various organs. For *subacute/subchronic* (1–3 months) and *chronic* (6–9 months) toxicity studies, extensive histopathological investigations are carried out according to regulatory requirements, as described in Chapter 10. This also applies to *life-time bioassays*, which include additional organs generally not sampled in studies of shorter duration (e.g., lachrymal gland) and additional samples (e.g., additional liver sections).

**Route of application:** The application site has to be sampled and evaluated carefully. Examples include skin (dermal application), muscle (intramuscular application), subcutaneous tissue (subcutaneous application), vein (intravenous application) (32), nasal cavity (inhalation studies by nasal application) or implantation site (implantation e.g., of chips etc.) (33).

**Type of tested compound, device, etc.:** In addition to conventional chemical entities, newer types of test material include skin equivalents (34), humanized monoclonal antibodies (mAb) (35), synthetic oligonucleotides (36), gene therapy (37), and other biotechnology products (38,39).

**Species:** Organ/tissue sampling procedures are significantly influenced by the size of the animal and its organs. While cross sections of the whole left and right liver lobe are taken for rodents, samples, which are much smaller than the whole organ, are preserved from different liver lobes of dogs.

**Purpose of investigation:** While for a standard toxicity study the procedures are regulated mostly according to ICH guidelines (Chapter 10), the investigator running a mechanistic study for elucidation of unclear findings in a previous study is free to concentrate on the most important parameters and organs/tissues.

The awareness that immunotoxicity can be an issue has significantly increased over the more recent years and requires careful pathological investigation of the hemo-lympho-reticular system, at times complemented by functional tests (40–42).

### 2.2. Necropsy

All animals in a toxicity study or life-time bioassay are subjected to a postmortem necropsy. After euthanasia, the animal is generally exsanguinated. Consistent