

The IPCS Conceptual Framework for Cancer Risk Assessment

Framework Guidelines: Suggested Section Headings

1. Introduction

This section describes the cancer endpoint or endpoints that have been observed and identifies which of these is addressed in the analysis. (The nature of the framework is such that only one mode of action is analysed at a time; hence, for example, tumour types associated with a different mode of action, even if recorded in the same animals, will require separate framework analyses). However, where different tumours are induced by related mode of action, they are best addressed in a single analysis. It should also be noted that some modes of action will involve multiple contributing components.

2. Postulated mode of action (theory of the case)

This section comprises a brief description of the sequence of events on the path to cancer for the postulated mode of action of the test substance. This explanation of the sequence of events leads into the next section which identifies the events considered “key” (*i.e.* measurable) given the data base available for the analysis.

3. Key events

This section briefly describes the “key events” — *i.e.* measurable events that are critical to the induction of tumours as hypothesised in the postulated mode of action. To support an association, a body of experiments needs to define and measure an event consistently. Pertinent observations: *e.g.* tumour response and key events in same cell type, sites of action logically relate to event(s), increased cell growth, specific biochemical events, organ weight, histology, proliferation assays, hormone or other protein perturbations, receptor-ligand changes, DNA or chromosome effects, and cell cycle effects. For example, key events for tumours hypothesised to be associated with prolonged regenerative proliferation might be cytotoxicity as measured histopathologically and an increase in labelling index. As another example, key events for induction of urinary bladder tumours hypothesised to be due to formation of bladder stones composed primarily of calcium phosphate might include elevated urinary calcium, phosphate and pH and formation of bladder stones followed by irritation and regenerative hyperplasia of the urothelium.

4. Dose–response relationship

This section should detail the observed dose–response relationships and discuss whether the dose–response for the key events parallels the dose–response relationship for tumours. Ideally, one should be able to correlate increases in incidence of a key event with increases in incidence or severity (*e.g.* lesion progression) of other key events occurring later in the process, and with the ultimate tumour incidence. Comparative tabular presentation of incidence of key events and tumours is often helpful in examining dose–response.

5. Temporal association

This section should detail the observed temporal relationships or sequence of events and discuss whether the key events precede the tumour response. One should see the key events before tumour appearance; this is essential in deciding whether the data support the postulated mode of action. Observations of key events at the same time as the tumours (*e.g.* at the end of a bioassay) do not contribute to temporal association,

but can contribute to analysis in the next section. Most often, complete data sets to address the criterion of temporality are not available.

6. Strength, consistency and specificity of association of tumour response with key events

This section should discuss the weight of evidence linking the key events, precursor lesions and the tumour response. Stop/recovery studies showing absence or reduction of subsequent events or tumour when a key event is blocked or diminished are particularly important tests of the association. Consistent observations in a number of such studies with differing experimental designs, increases that support since different designs may reduce unknown biases or confounding. Consistency, which addresses repeatability of key events in the postulated mode of action for cancer in different studies is distinguished from coherence, however, which addresses relation of the postulated mode of action with observations in the broader database (see point 7). Pertinent observations are, *e.g.*, tumour response and key events in same cell type, sites of action logically relate to event(s), initiation–promotion studies, and stop/recovery studies.

7. Biological plausibility and coherence

The postulated mode of action and the events that are part of it need to be based on current understanding of the biology of cancer to be accepted, though the extent to which biological plausibility as a criterion against which weight of evidence is assessed is necessarily limited, due to considerable gaps in our knowledge in this regard. One should consider whether the mode of action is consistent with what is known about carcinogenesis in general (biological plausibility) and in relation to what is also known for the substance specifically (coherence). For the former, likeness of the case to others for structural analogues may be informative (*i.e.* structure–activity analysis). Additionally, this section should consider whether the database on the agent is internally consistent in supporting the purported mode of action, including that for relevant non-cancer toxicities. Some modes of action can be anticipated to evoke effects other than cancer, *e.g.* reproductive effects of certain hormonal disturbances that are carcinogenic. Moreover, some modes of action are consistent with observed lack of genotoxicity. Coherence, which addresses relation of the postulated mode of action with observations in the broader database — for example, association of mode of action for tumours with that for other endpoints — needs to be distinguished from consistency (addressed in Point 6 above) which addresses repeatability of key events in the postulated mode of action for cancer in different studies.

8. Other modes of action

This section discusses alternative modes of action that logically present themselves in the case. If alternative modes of action are supported, they need their own framework analysis. These should be distinguished from additional components of a single mode of action which likely contribute to the observed effect, since these would be addressed in the analysis of the principal mode of action.

9. Assessment of postulated mode of action

This section should include a clear statement of the outcome with an indication of the level of confidence in the postulated mode of action — *e.g.* high, moderate or low.

10. Uncertainties, Inconsistencies, and Data Gaps

Uncertainties should include those related to both the biology of tumour development and those for the database on the compound of interest. Inconsistencies should be flagged and data gaps identified. For the identified data gaps, there should be some indication of whether they are critical as support for the postulated mode of action or simply serve to increase confidence therein.