

Note 4: If samples are taken from main study animals it should be considered whether samples should be taken from *all* the dosed animals and the controls in order to treat all animals on the study in the same way, or whether samples should be taken from representative subgroups of the same size.

Note 5: In this context, a "no-toxic-effect dose level" (deemed to be the same as "no-observed-adverse-effect dose level") is defined as a dose level at which some pharmacological response may be observed, but at which no adverse effect is found.

Note 6: In these circumstances it should be established that absorption is the rate limiting step and that limitations in exposure to the administered substance are not due to an increased clearance.

Note 7: The limits placed on acceptable volumes which can be administered orally to animals may constrain the dose levels achievable for comparatively non-toxic compounds administered as solutions or suspensions.

Note 8: It is often considered unnecessary to assay samples from control groups. Samples may be collected and then assayed if it is deemed that this may help in the interpretation of the toxicity findings, or in the validation of the assay method.

Note 9: Measurement of metabolite concentrations may be especially important when documentation of exposure to human metabolite(s) is needed in the nonclinical toxicity studies in order to demonstrate adequate toxicity testing of these metabolites.

Note 10: It is recognised that measurement of metabolite(s) as a part of toxicokinetic evaluation serves only to assess exposure and cannot account for possible reactive intermediate metabolites.

Note 11: Treatment regimen encompasses dosage, formulation, route of administration, and dosing frequency.

Note 12: The first repeat dose study incorporating toxicokinetic data for each species is normally of 14 day's duration or longer.

Note 13: Additional studies may be required in order to compare exposure to the compound administered in diet and by gavage or by routes different from the intended clinical route.

Note 14: It should be noted that while it is important to consider the transfer of substances entering the embryo-fetal compartment, fetal exposure is the parameter which is most often assessed in practice in separate studies and expressed as "placental transfer."

6. References (other ICH Guidance)

1. Code SIC "Carcinogenicity: Guidance for Dose Selection Dose Selection for Carcinogenicity Studies of Therapeutics."
2. Code S5A "Detection of Toxicity to Reproduction for Medicinal Products."

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William B. Schultz,

Deputy Commissioner for Policy.

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