

# Masterstudiengang TOXIKOLOGIE

## *Kolloquium Toxikologie*

**„Präklinische Untersuchungsstrategien in  
der Europäischen Arzneimittelzulassung“**

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# Arzneimittelzulassung

- Gesetze (Europa, national)
- Technische Anweisungen (Antragsformate)
- „Guidelines“ (Durchführung von Prüfungen)
  - Akute Toxizität
  - Chronische Toxizität
  - etc.
  - „Guidelines“ (Schwangerschaft)
  - „Guidelines“ (klinische Prüfung)
- „Scientific Rational“ (Strategie)

# Arzneimittelgesetzgebung

- The *testing Council Directive 75/318/EEC* (20-05-1975 as amended):  
Introduction of „*Standards and protocols*“ for the performance of tests and trials: protection of public health *and* facilitation of „Free movement of goods“ within the EU
- Adoption of „*Uniform rules*“ applicable to tests and trials *and their assessment* will provide same chances for all companies

# Arzneimittelgesetzgebung

- ***Nota bene:***  
The relevant EU Legislation is now set out in Directive 2001/83/EC as amended by Commission Directive 2003/63/EC, thus incorporating the updated ANNEX I (previously Annex I to Directive 75/318/EC) on the „*Testing of medicinal products*“ (as set forth in Art. 8(§)(i) of this Directive):
- ***Q, S, E Standards and Protocols in respect of the testing of medicinal products for humans***

# Technische Anweisungen

- Notice to Applicants
- Notice to Marketing Authorisation Holders
- Common Technical Document (CTD)
- eCTD

# Guidelines

- <http://www.emea.europa.eu/htms/human/ich/ichsafety.htm>
- <http://www.emea.europa.eu/htms/human/ich/ichmulti.htm>
- <http://www.emea.europa.eu/htms/human/humanguidelines/nonclinical.htm>

# Untersuchungsstrategien

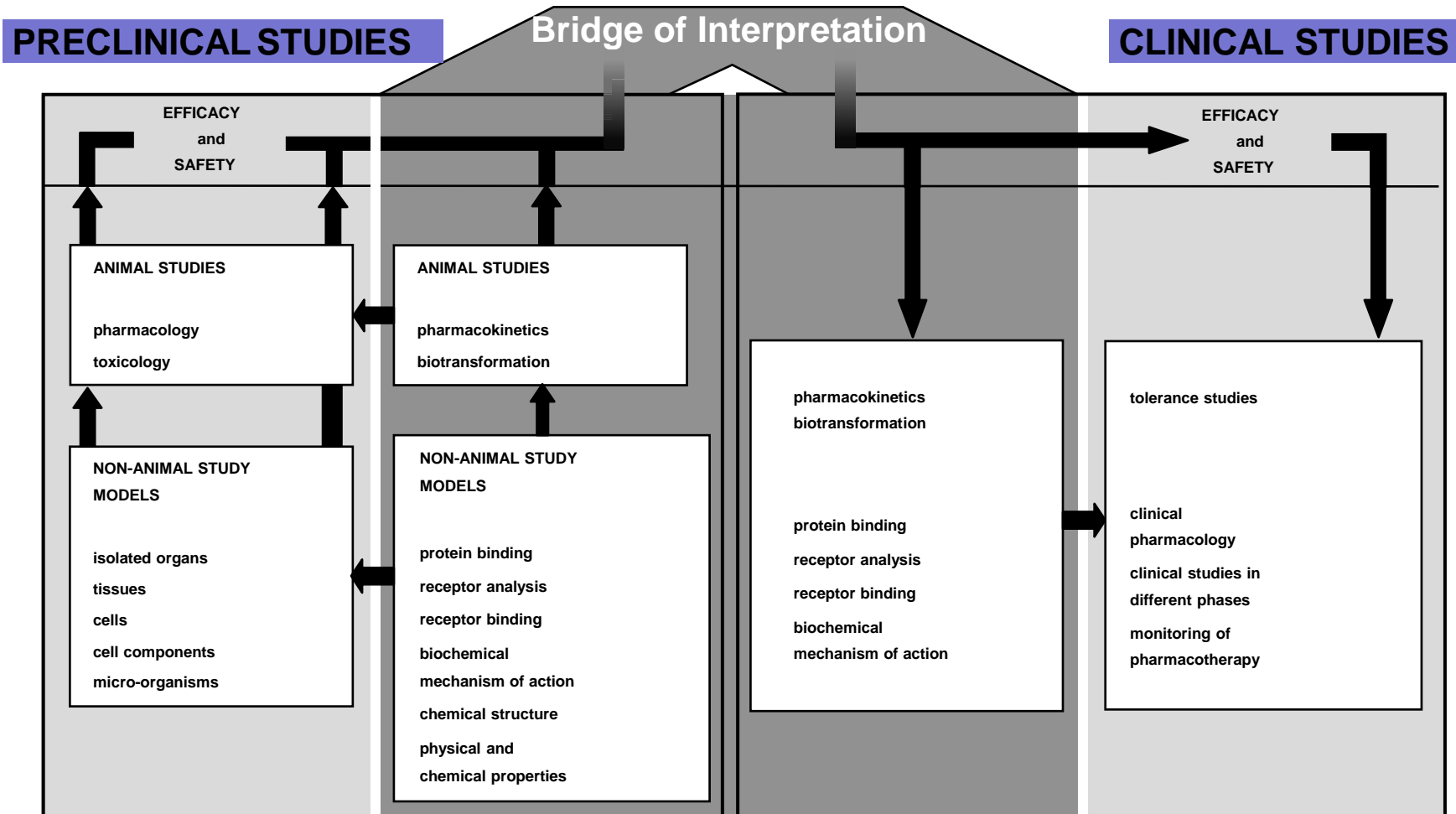
- Von der präklinischen „l'art pour l'art“ zur Koppelung an die klinische Zweckbestimmung des Arzneimittels
  - Anforderungen für die Klinische Prüfung
  - Anforderungen für die Marktzulassung
  - Problemlösungen
  - Spezielle Populationen und Situationen

# Anforderungen und -möglichkeiten

- Safety Pharmacology
- Toxicokinetic and Pharmacokinetic Studies
- Acute Toxicity Studies
- Repeated Dose Toxicity Studies
  - Clinical development studies
  - Marketing Authorisation studies
- Studies Supporting the Estimation of the First Dose in Human
- Studies Supporting Exploratory Clinical Studies
  - Microdose studies
  - Single dose studies up to sub-therapeutic / intended therapeutic range
  - Multiple dose studies
- Local Tolerance Studies
- Genotoxicity Studies
- Carcinogenicity Studies
- Reproduction Toxicity Studies
  - Men
  - Women not/ of child-bearing potential, pregnant women
- Paediatric populations
- Other Toxicity Studies, Immunotoxicity, Phototoxicity, Abuse Liability
- Fixed combinations



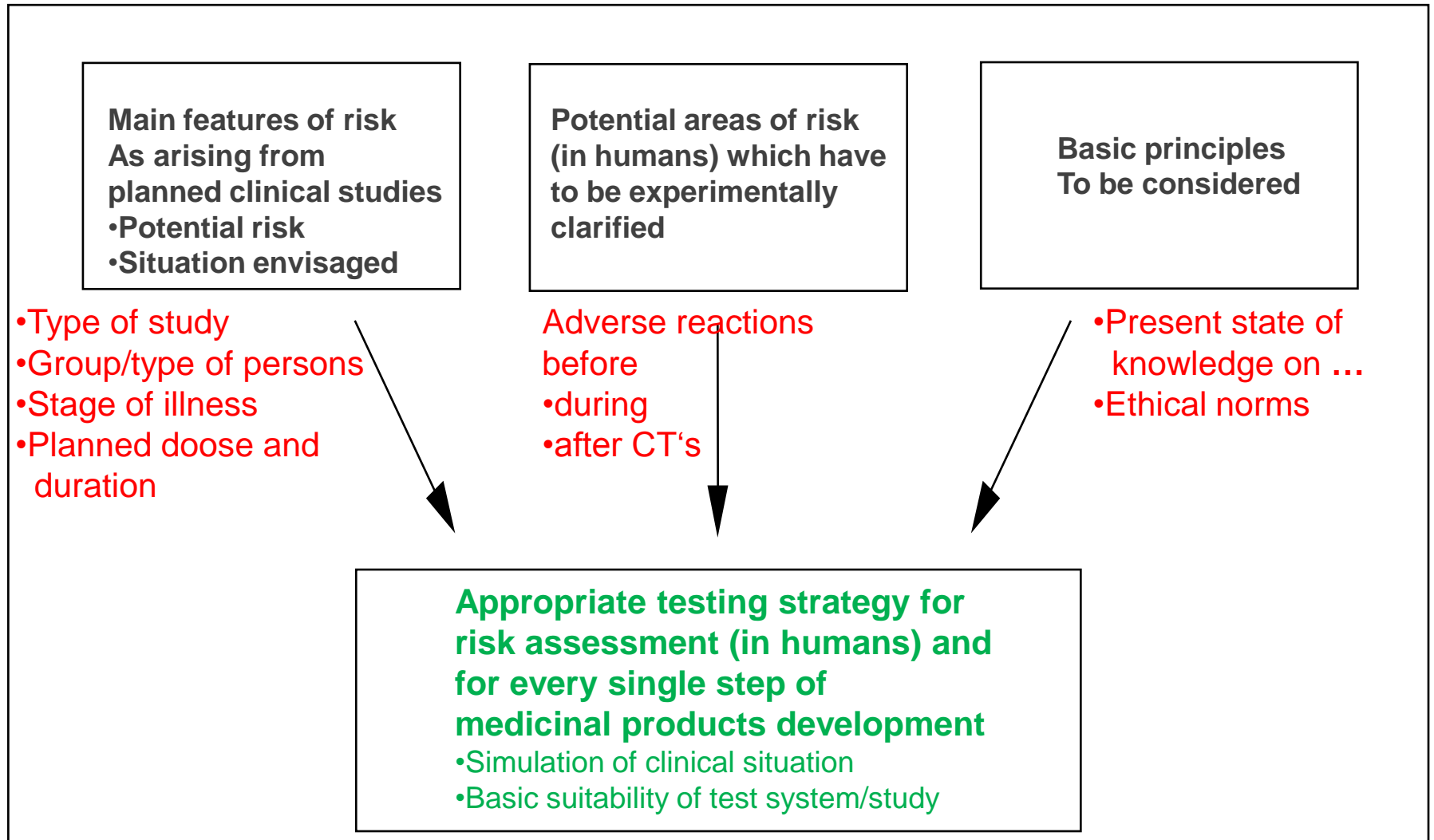
# RISK ASSESSMENT FOR THE USE IN HUMANS



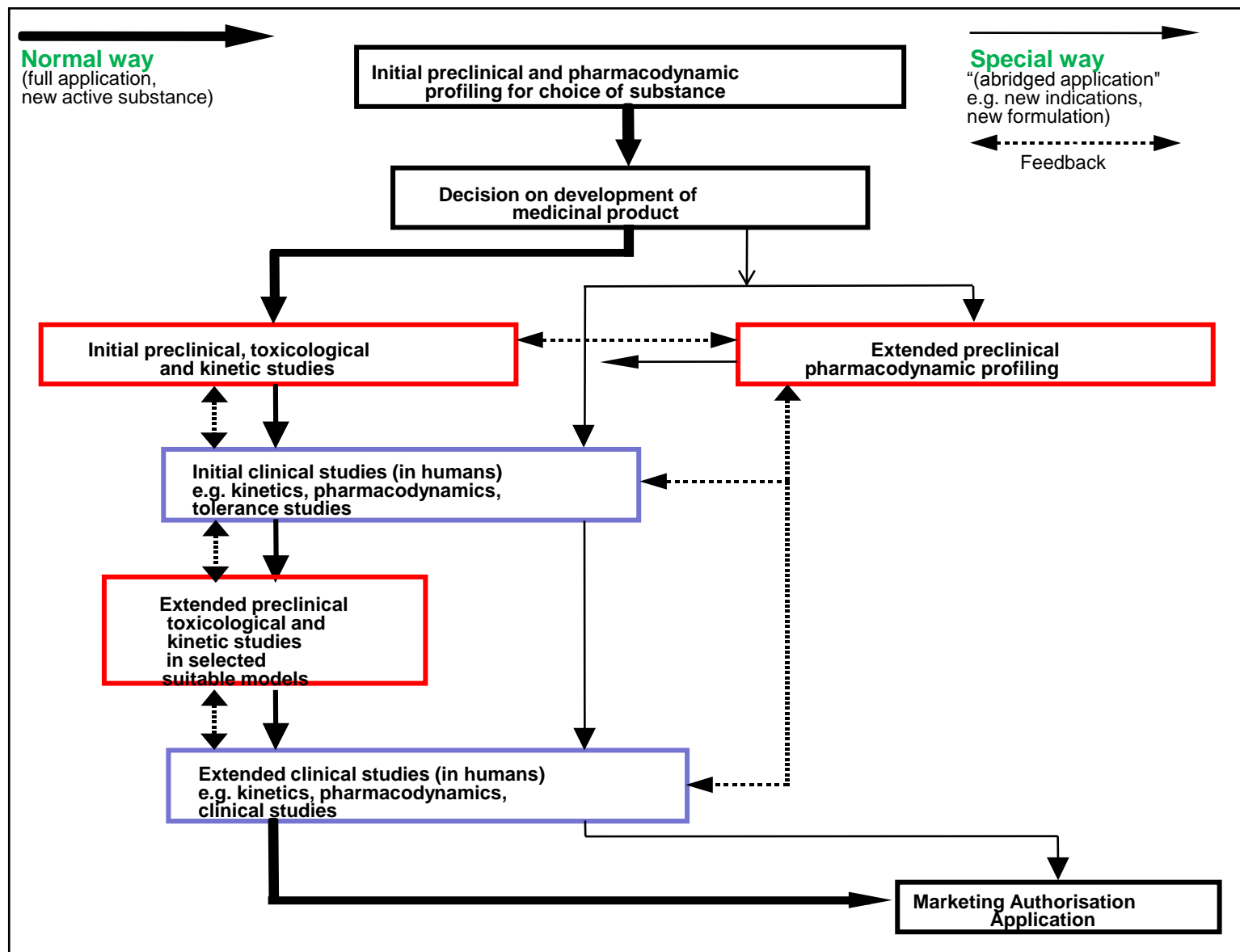
➔ basic flow of information

*feedback of information  
on planning and validation of studies*

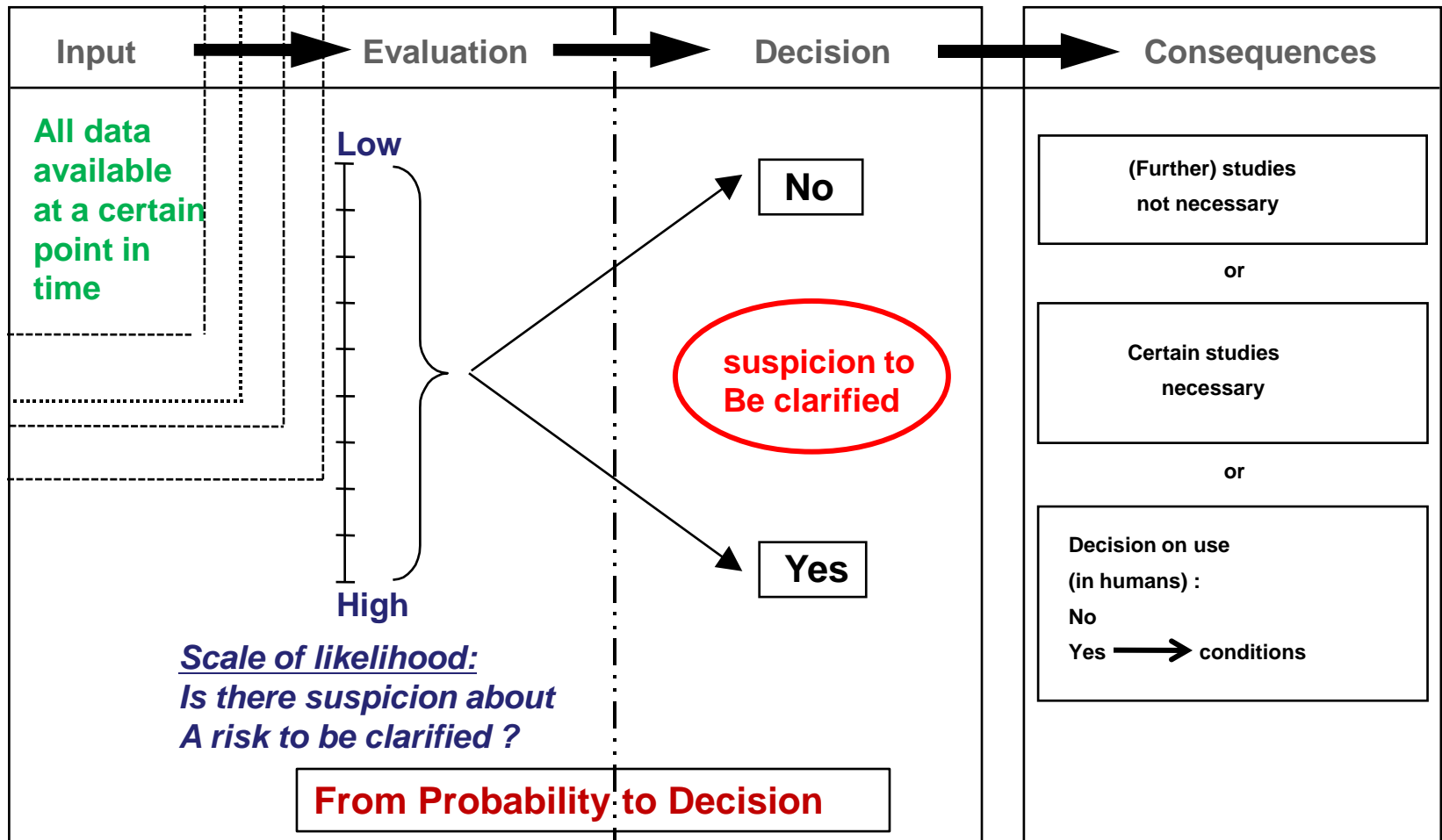
# Development of Individual Testing Strategies



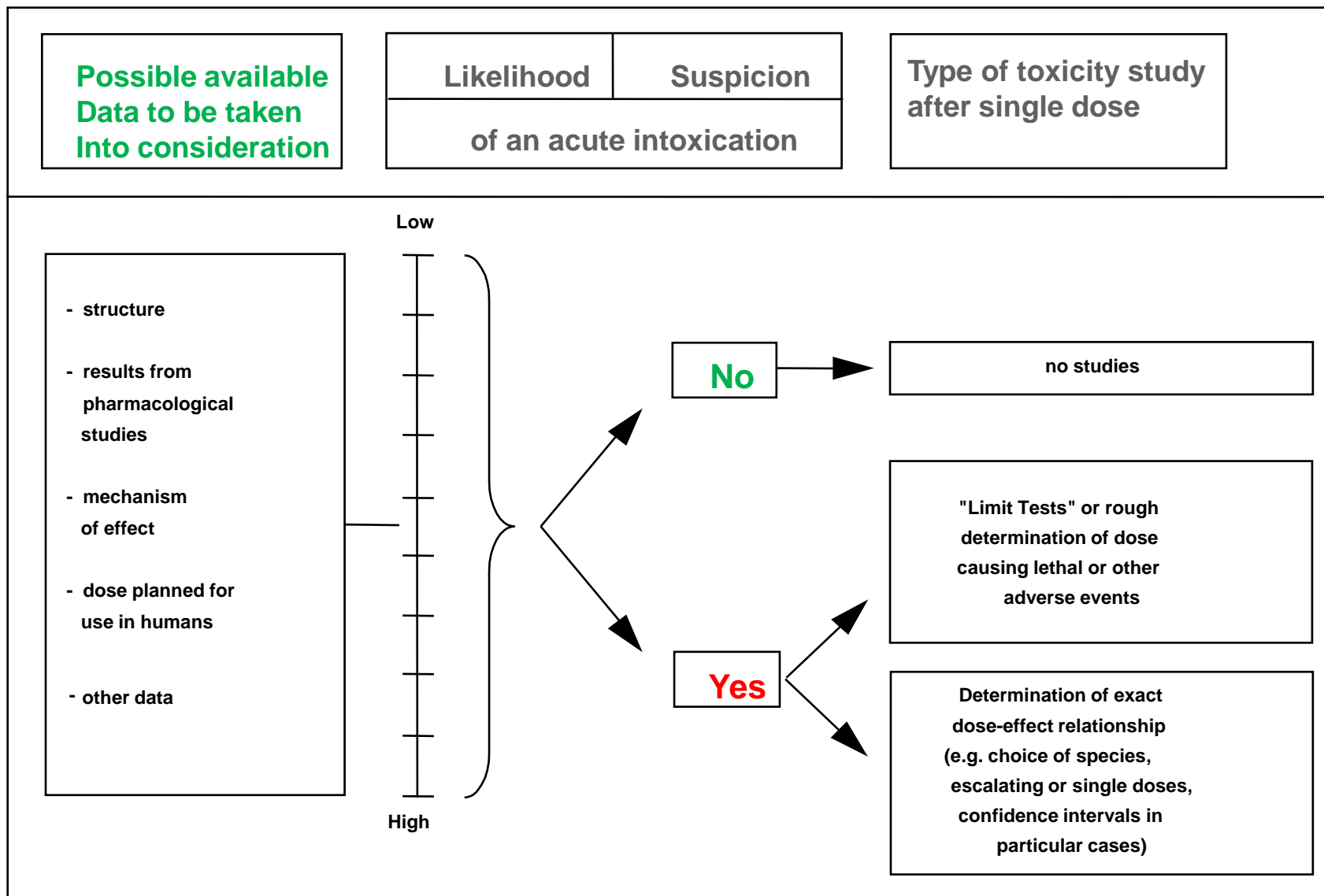
# Coordination Plan for Stepwise Progress



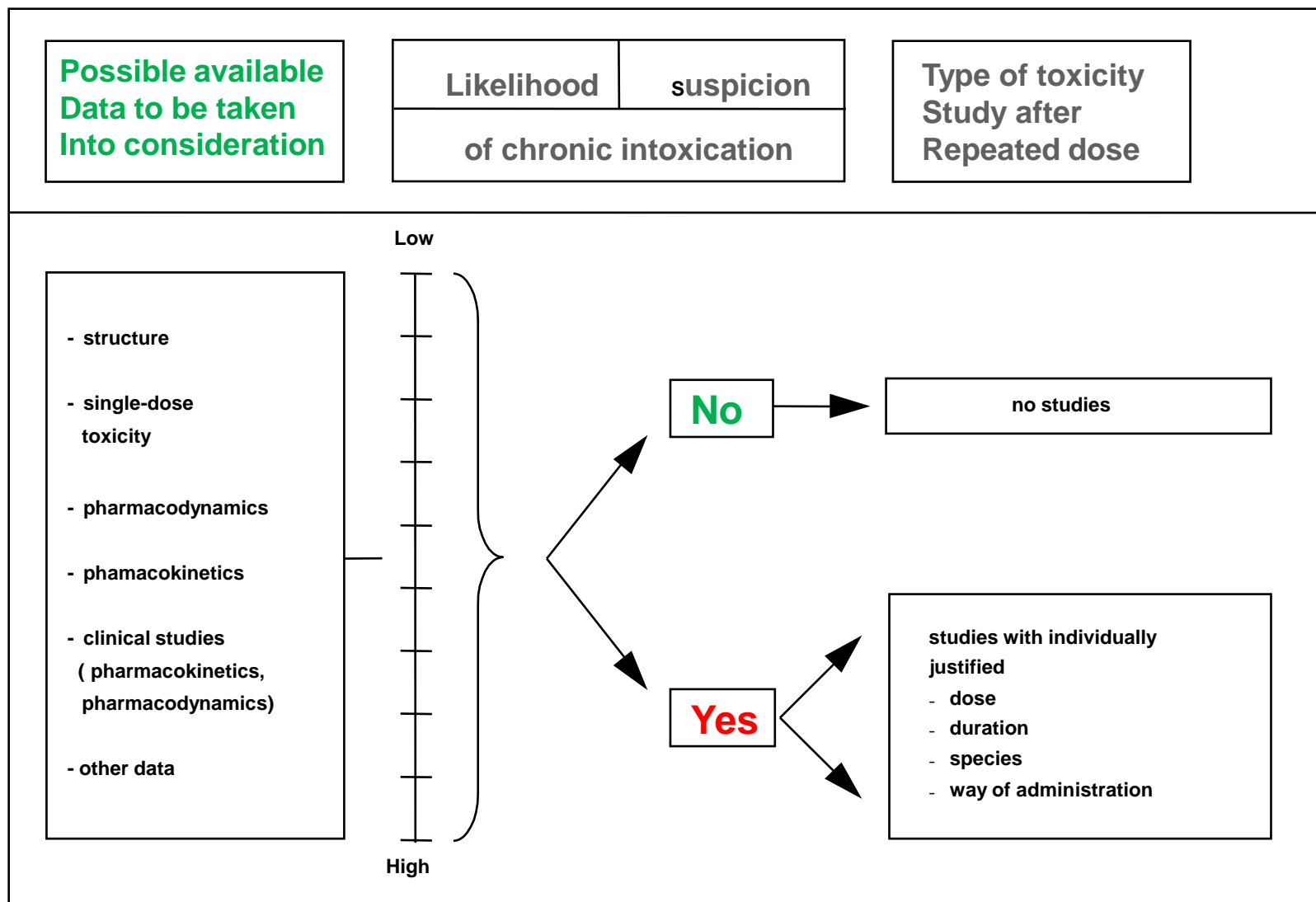
# Generic Principle of Flowchart



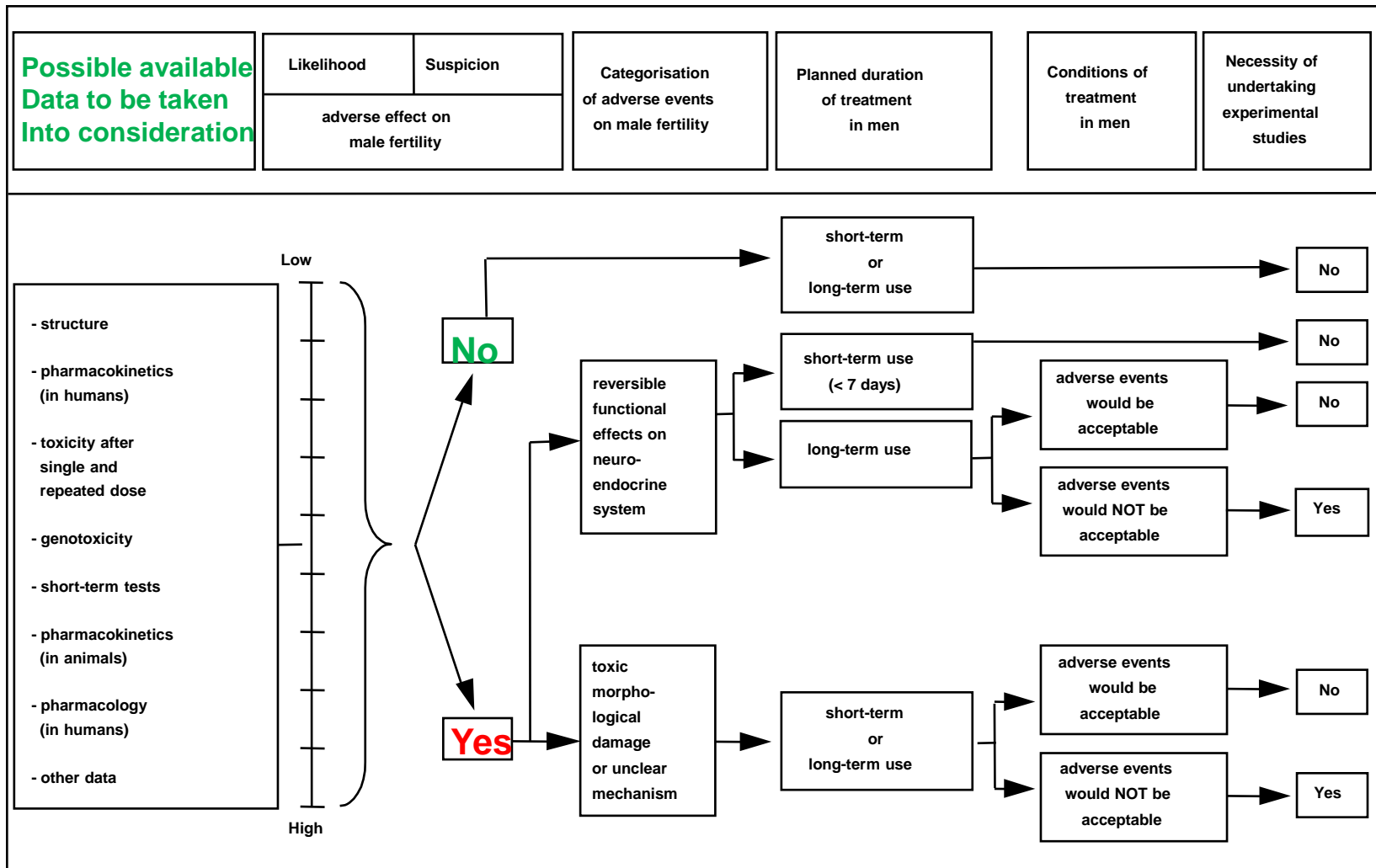
# Discussion about Single Dose Toxicity Testing



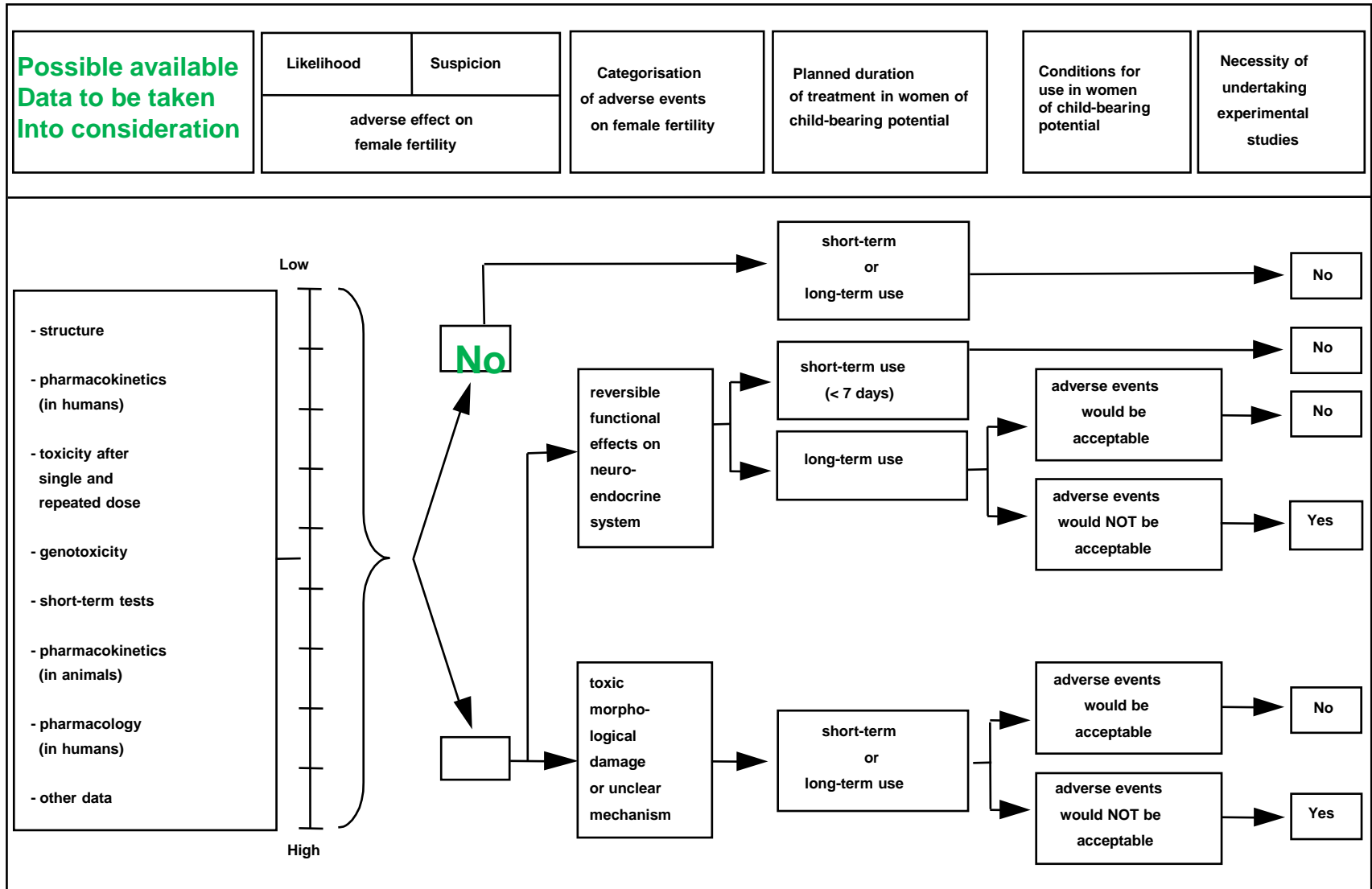
# Discussion about Repeated Dose Toxicity Testing



# Discussion about Toxicity to Male Fertility Testing

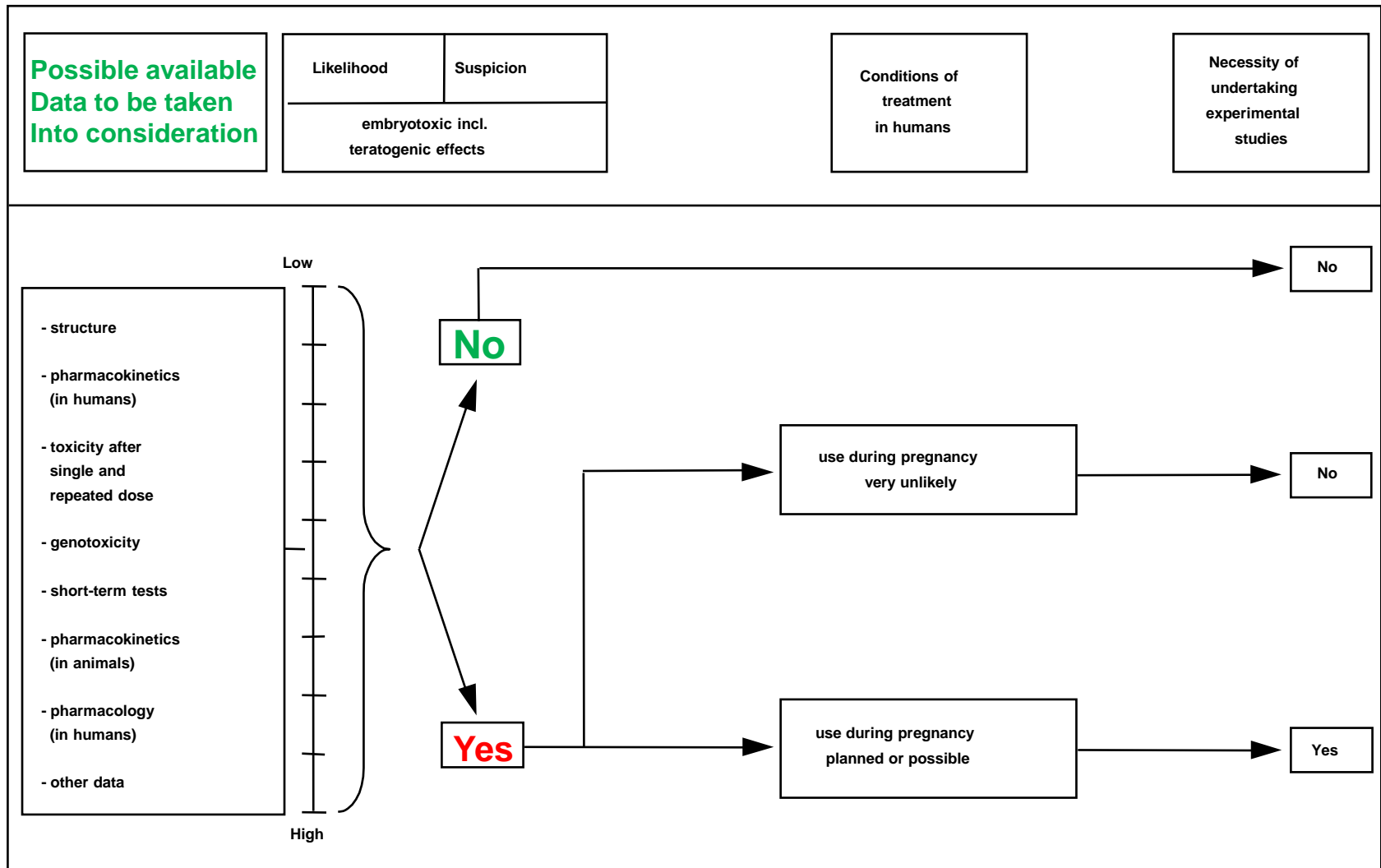


# Discussion about Toxicity to Female Fertility Testing

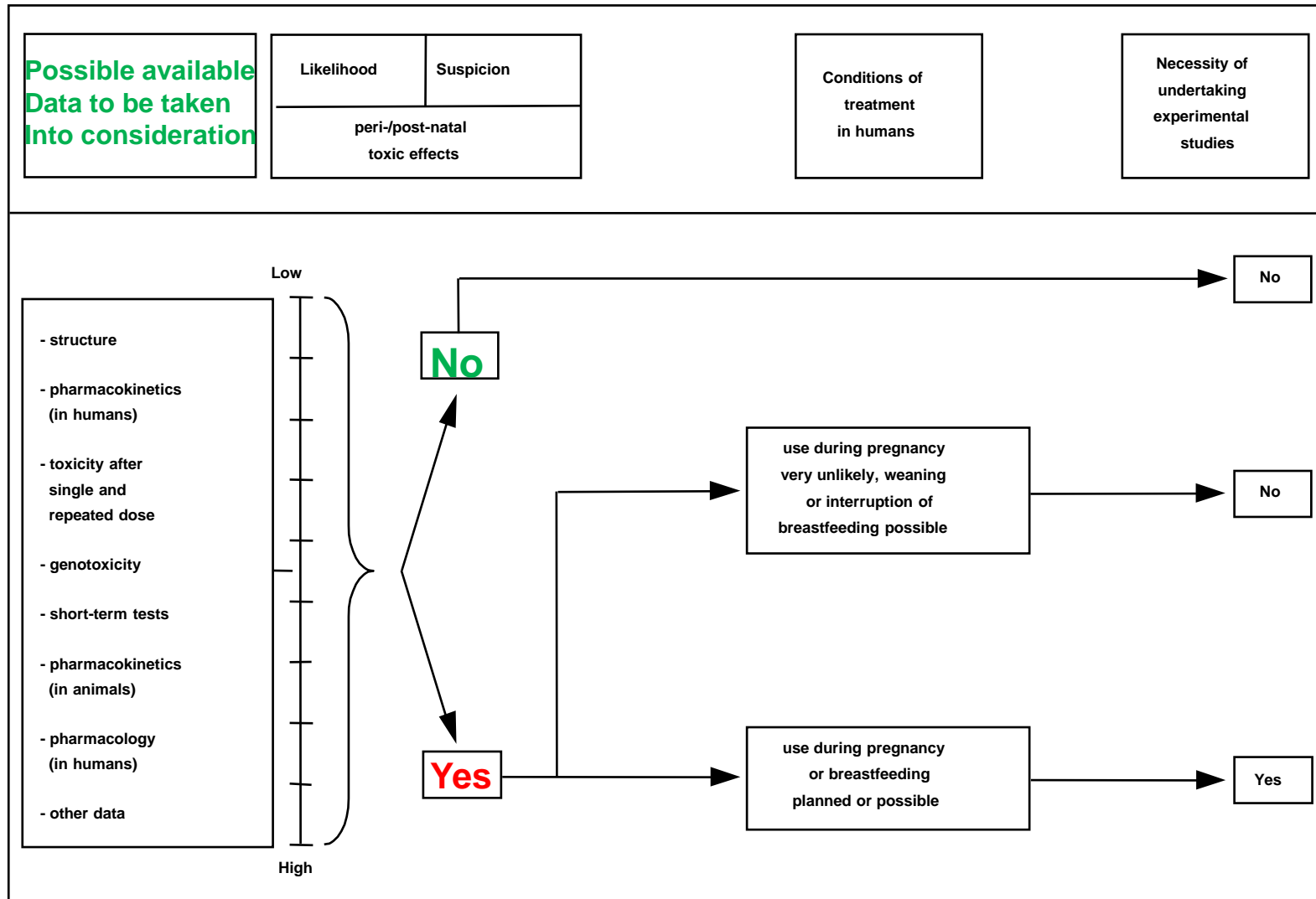




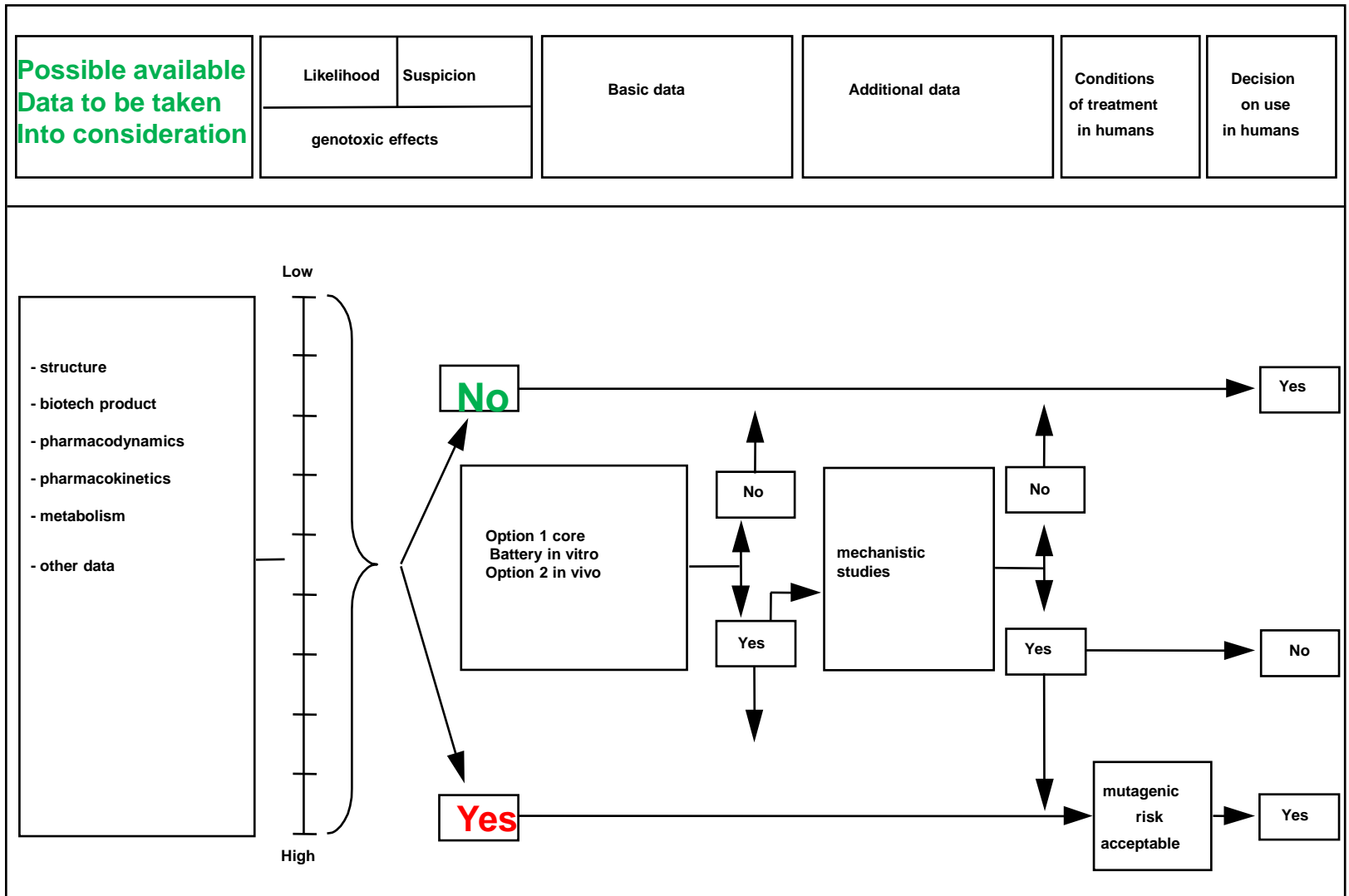
# Discussion about Embryonal / Foetal Toxicity Testing



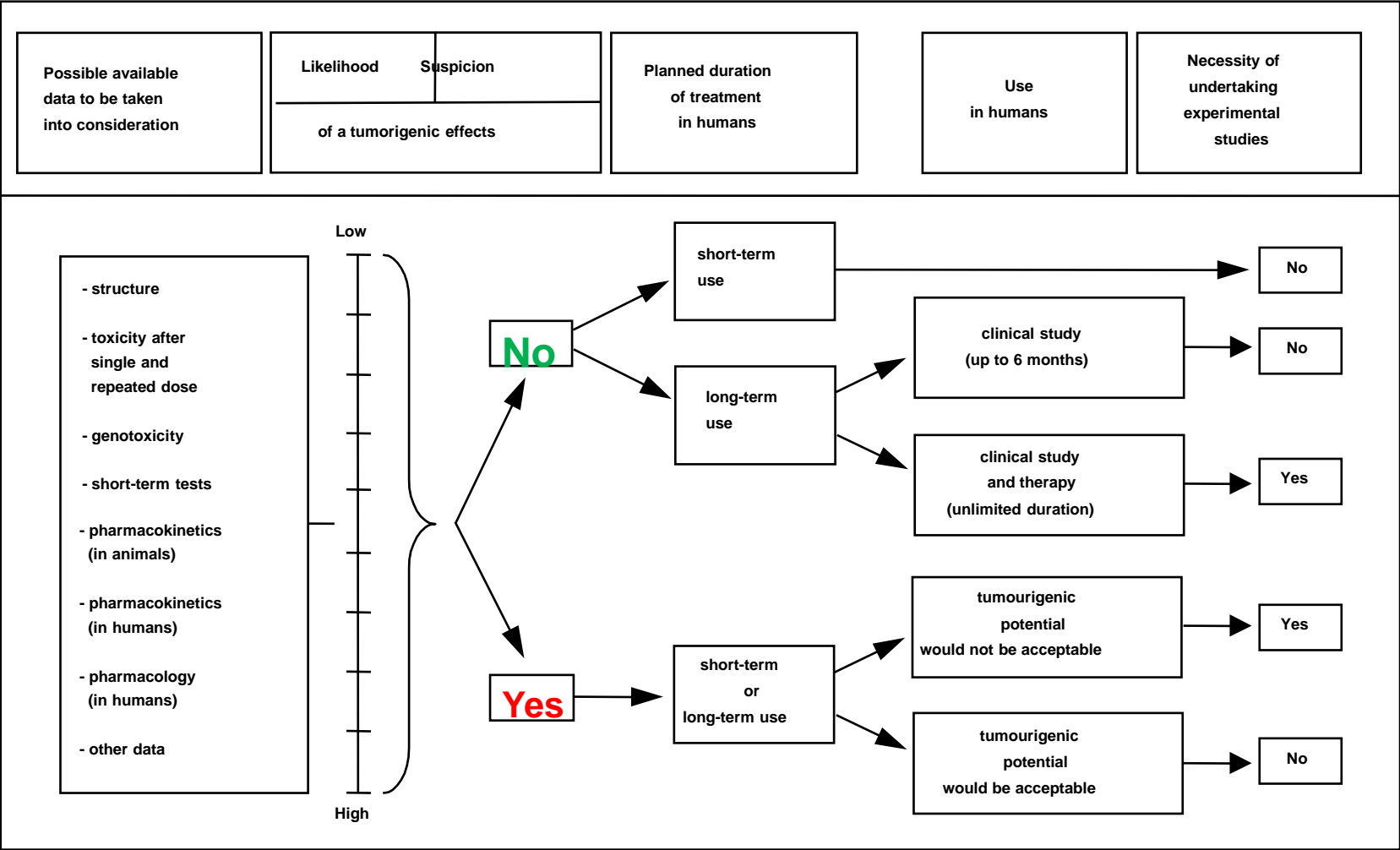
# Discussion about Postnatal Development Toxicity Testing



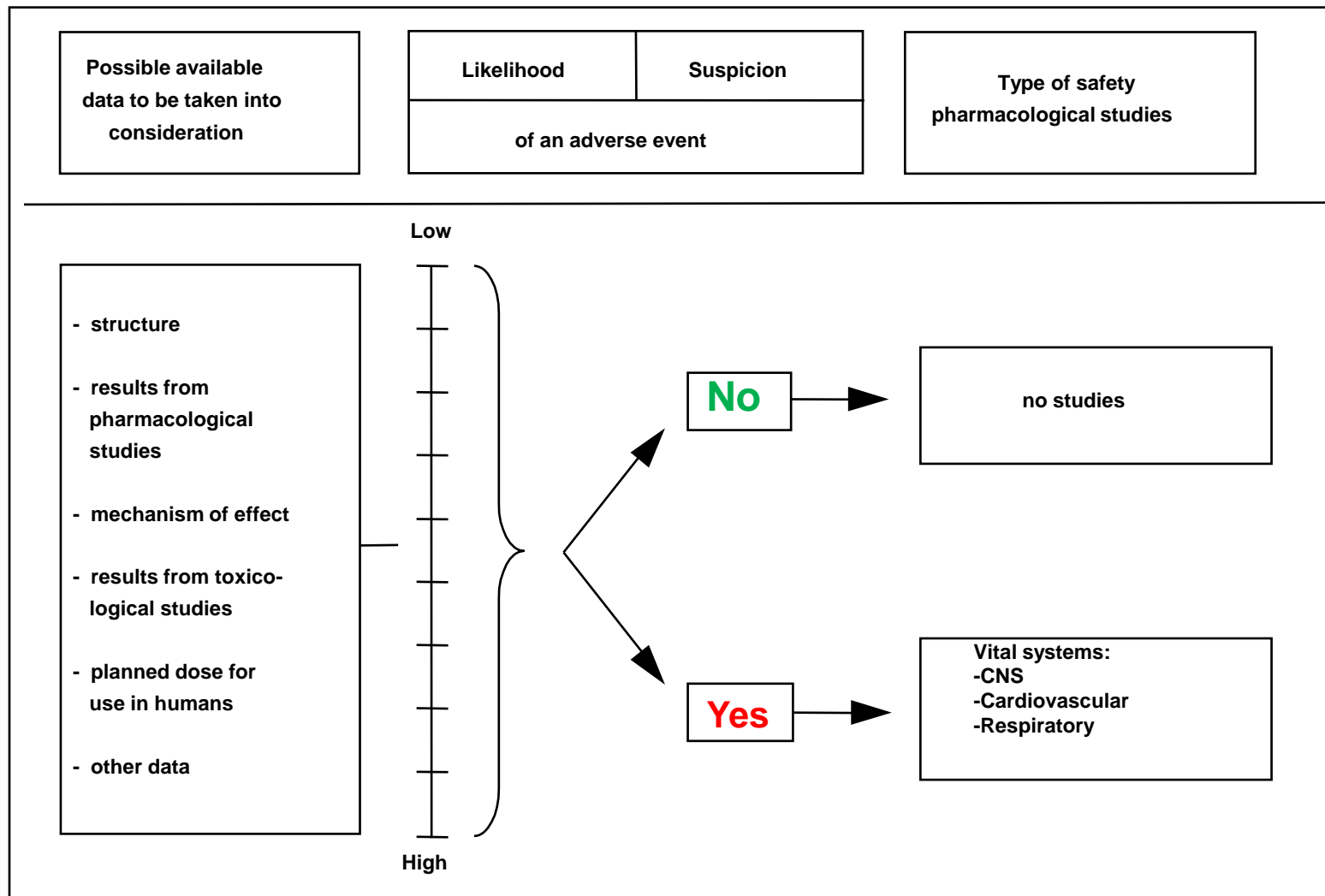
# Discussion about Genotoxicity Testing



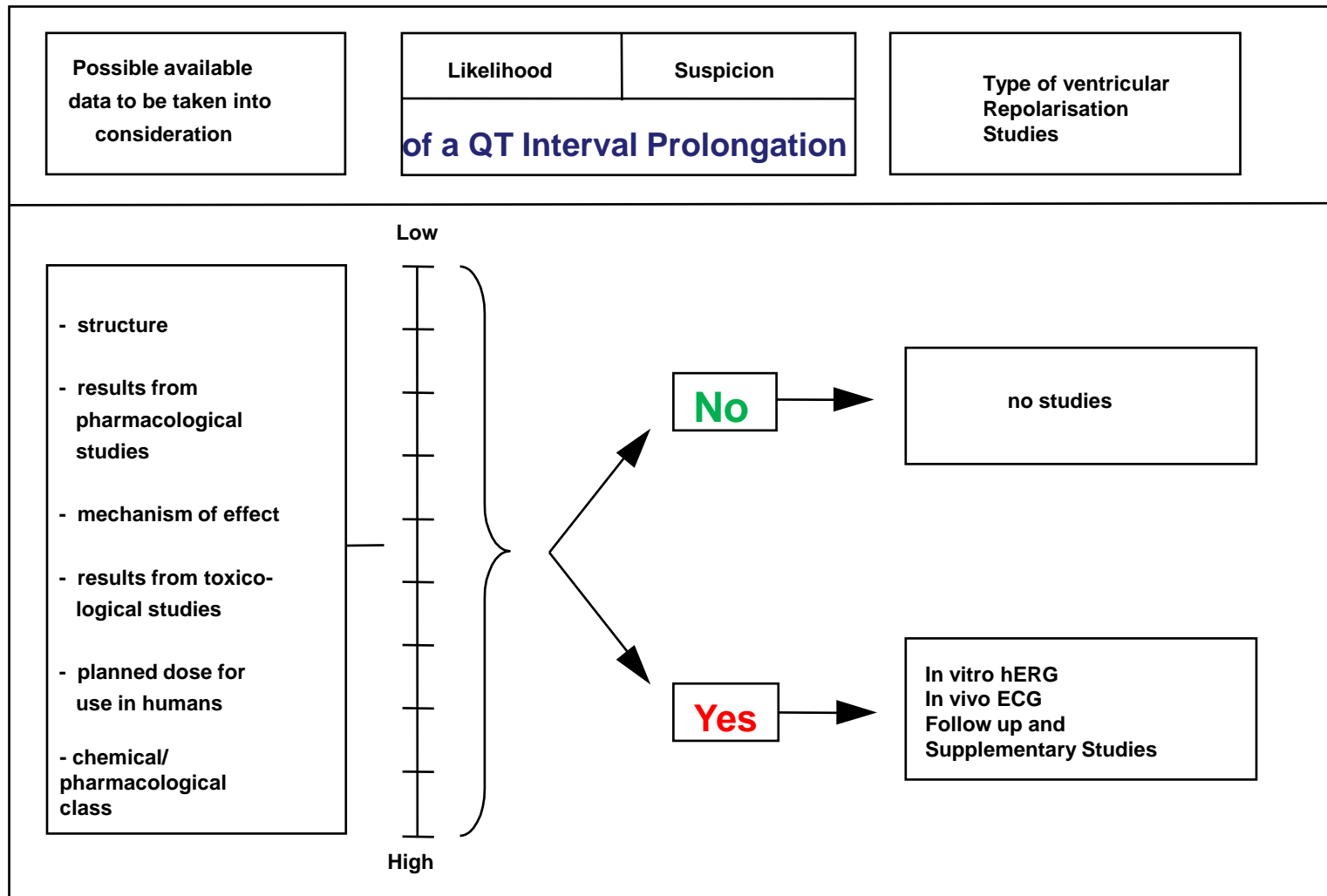
# Discussion about Tumourigenicity Testing



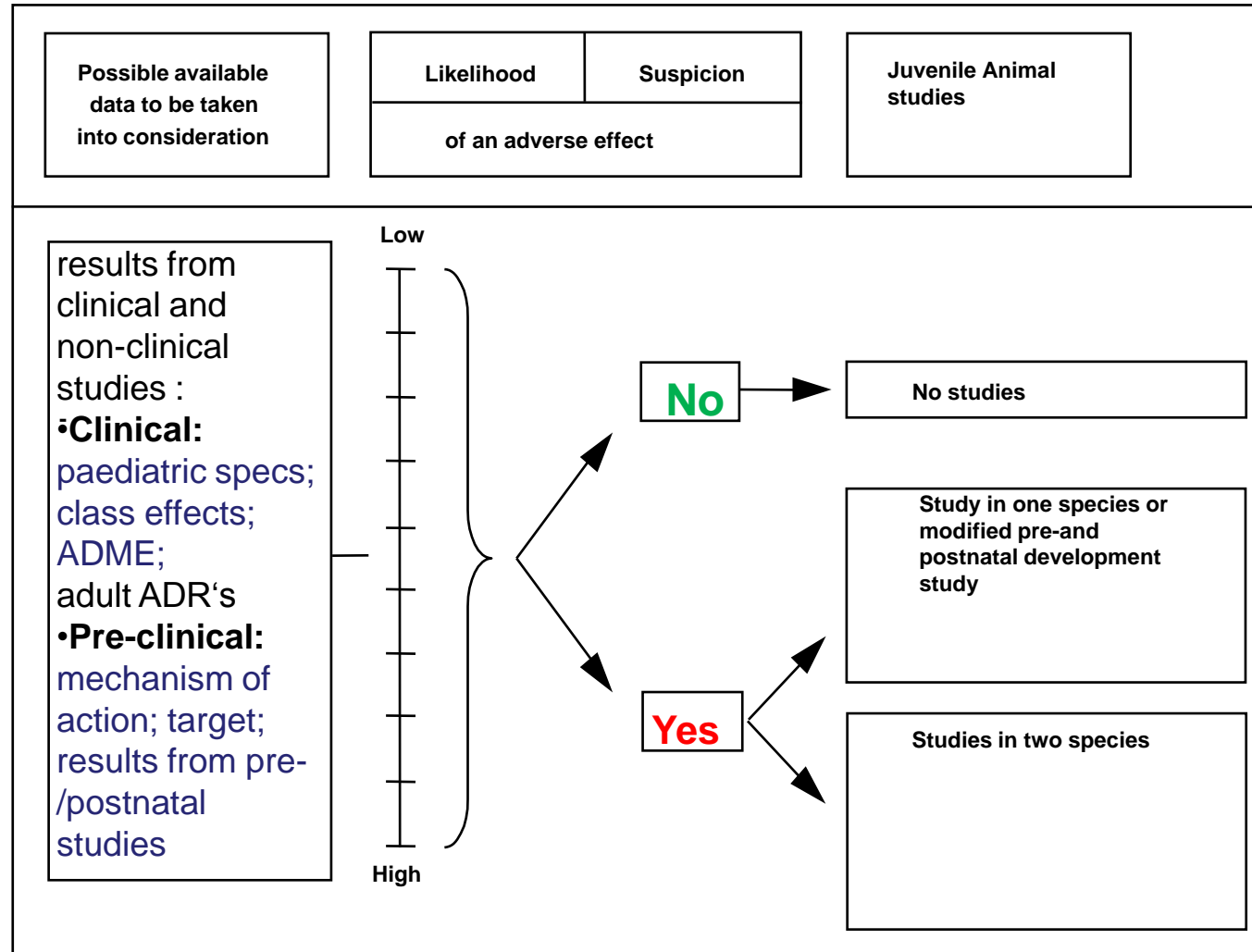
# Discussion about Safety Pharmacology Testing



# Discussion about Safety Pharmacology Testing



# Discussion about Juvenile Animals Testing



# Summary and Conclusions

- Strategy for Testing: case by case
- Strategy for Testing: discussion based on use of flow-charts
- Strategy for Testing: re-iterative process (taking into due consideration the increase in knowledge over time)
- Strategy for Testing: based on judgment of probabilities
- Strategy for Testing: further support from ICH-Guideline