

Antragsformular für die Aufnahme von Wirkstoffen in Anhang I/IA der Biozid-Produkte-Richtlinie

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Pharmaforschung und Klinische Inhalation
Hannover

Österreichisches Biozid-Produkte-Gesetz

Wien - 20. September 2001

Wirtschaftskammer Österreich in Zusammenarbeit mit BMLFUW und FCIO

EU-Projekt "BPD Practicalities Guidelines"

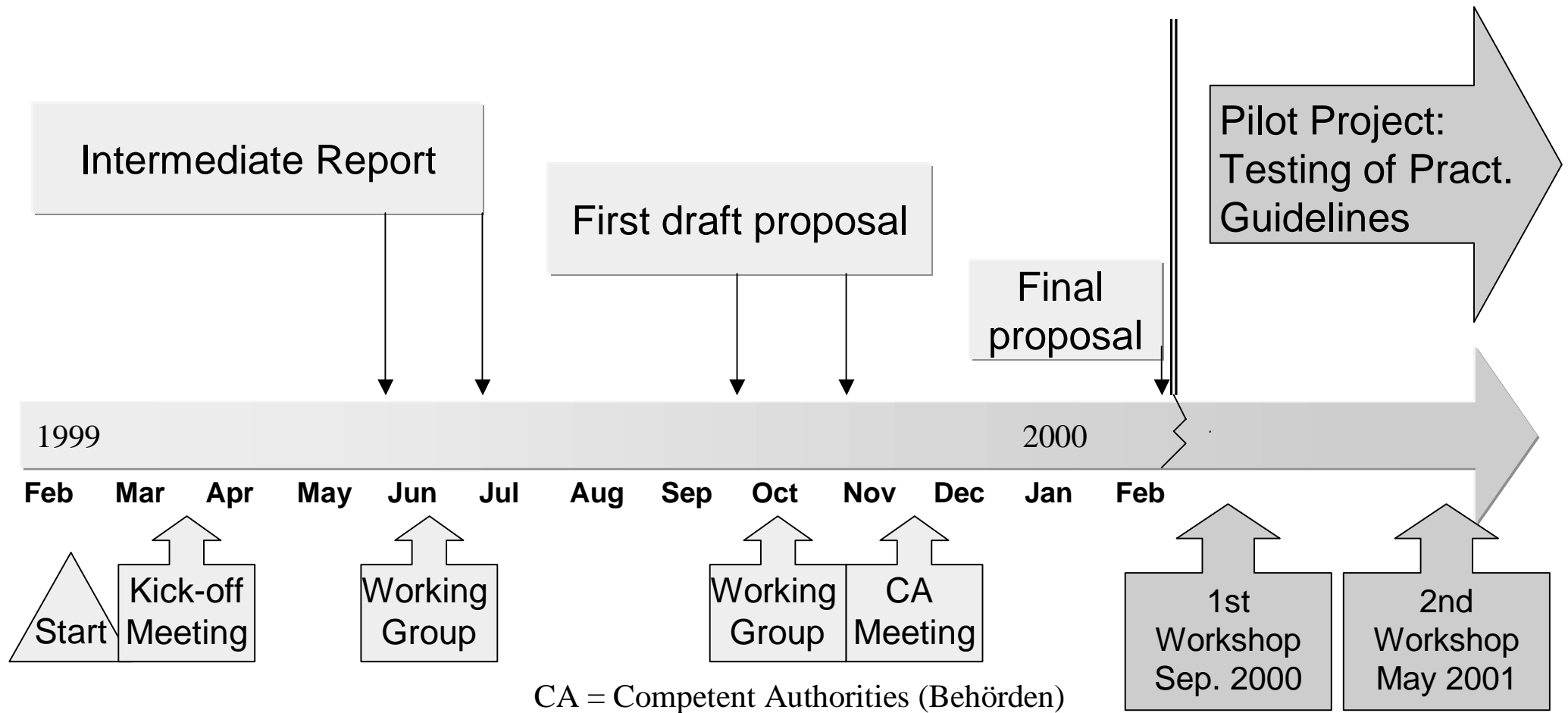
Preparation of Guidelines for the Practical Implementation of Directive 98/8/EC, concerning the Placing of Biocidal Products on the Market

[Erstellung einer Technischen Anleitung zur praktischen Umsetzung der Richtlinie 98/8/EG über das Inverkehrbringen von Biozid-Produkten]

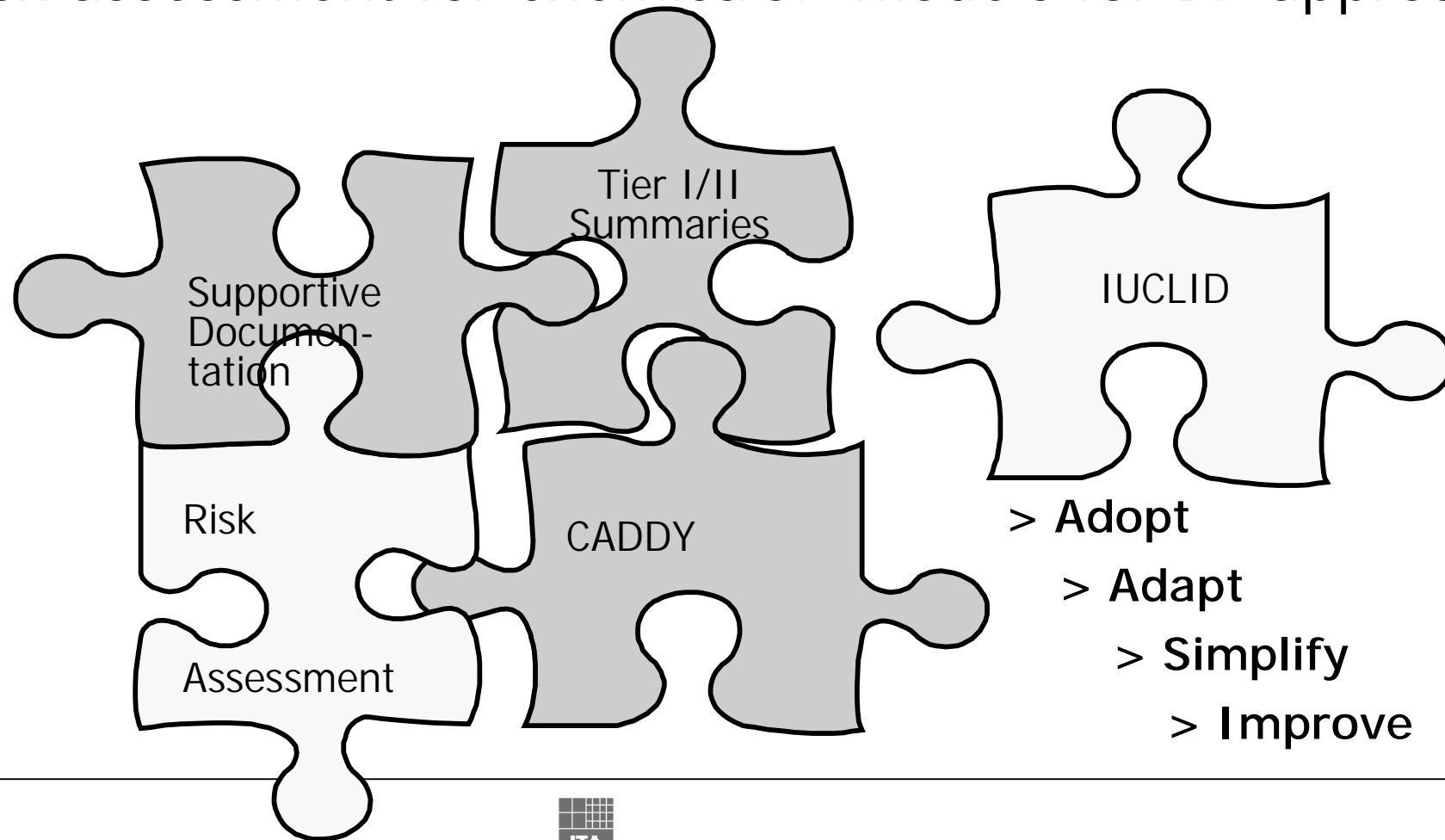
Projektgruppe im Fraunhofer ITA:

- Andrea Boehncke Phys.-chem. Daten, Analytik, Exposition
- Gustav Könnecker Ökotoxikologie, Wirksamkeit
Ingo Meier
- Inge Mangelsdorf Toxikologie (Leiterin Arbeitsgr. Chemikalienbewertung)
- Gerhard Rosner Projektkoordination, Konzeption

Zeitplan: Practicalities-Projekt und Pilot-Projekt



Plant protection products (PPP) approach and risk assessment for chemicals: models for BP approach?



Projektziel

- Technische Anleitung zur Erstellung von Dossiers für Wirksubstanzen und Biozid-Produkte:
 - ✓ nur chemische Stoffe und Produkte
 - ✓ Schwerpunkt: Aufnahme von Wirksubstanzen in Anhang I, IA oder IB
- Technische Anleitung zur Erstellung von Behördenberichten



Applicant's
Dossier



Competent
Authorities'
(CA) Report

Technische Anleitungen zur Biozid-Richtlinie: "Practicalities Guidelines" vs. "Technical Notes for Guidance"

Practicalities Guidelines

Anleitung > WIE soll ein Dossier /
Behördenbericht erstellt werden

- Standardisierung von Gliederung und Format der einzelnen Dossier-/Berichtsteile
- Standardformate für Zusammenfassungen von Testberichten und Literaturdaten ("Study Summaries")

BPD-TNsG

Anleitung > WAS ist erforderlich

- TNsG on data requirements (Datenanforderungen)
- TNsG on inclusion criteria for Annex I, IA or IB (Kriterien für Anhang I-Aufnahme)
- TNsG in support of Annex VI (Gemeinsame Grundsätze für die Bewertung von Unterlagen für Biozid-Produkte)

Vorgeschlagener Ansatz

- Einheitliche Struktur von Dossier und Behördenbericht

- Dossierunterlagen:

- Gesamtzusammenfassung und -bewertung
- Risikobewertung
- Einzelstudien-Zusammenfassungen
- Testberichte

Doc. I: Overall Summary and Assessment

Doc. II: Risk Assessment

Doc. III: Study Summaries

Doc. IV: Original Test and Study Report

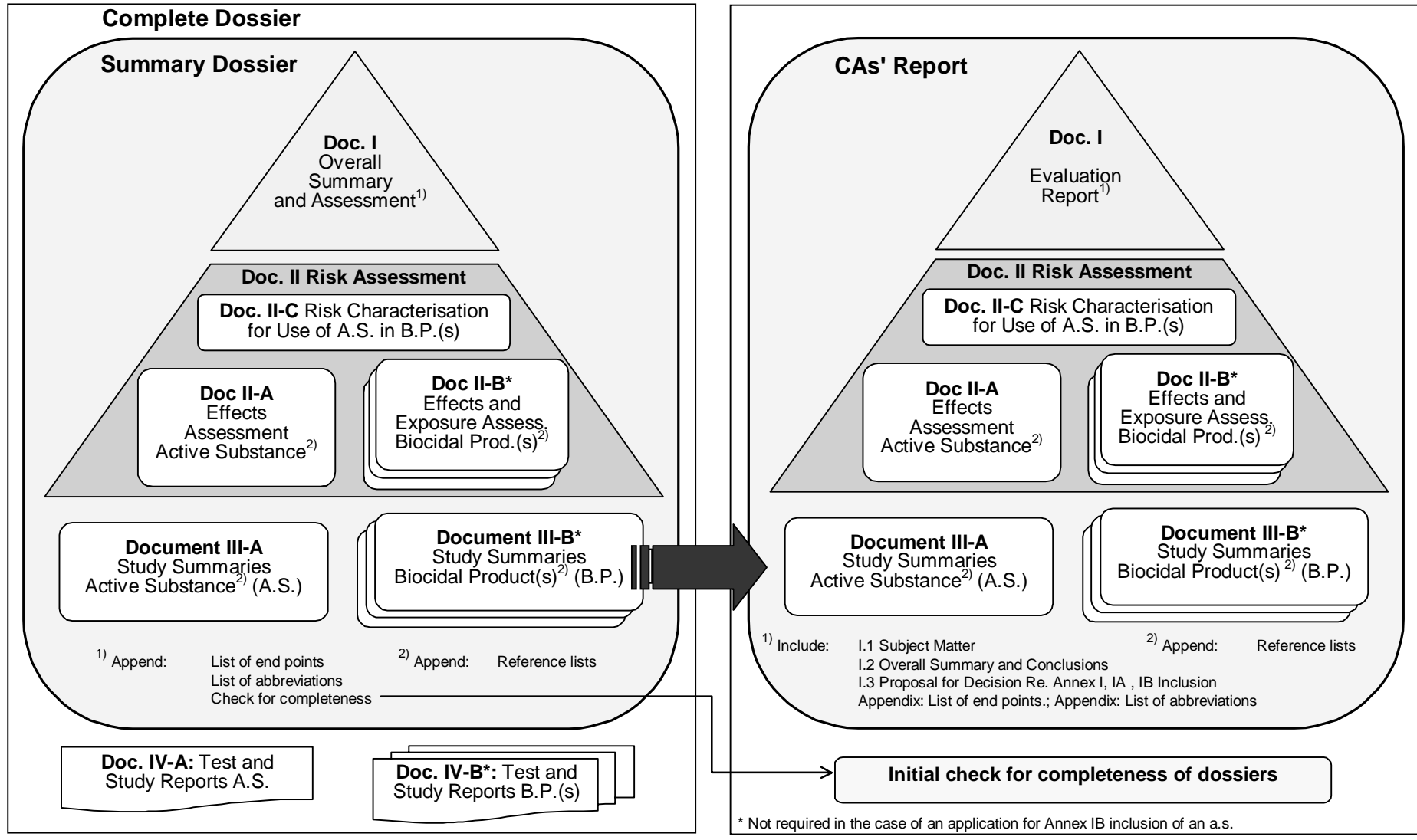
- Anhänge:

- Endpunktliste
- Vollständigkeitsprüfung

List of end points

Check for Completeness

Vorgeschlagene Unterlagen für Dossier / Behördenbericht



Document Type I – Overall Assessment

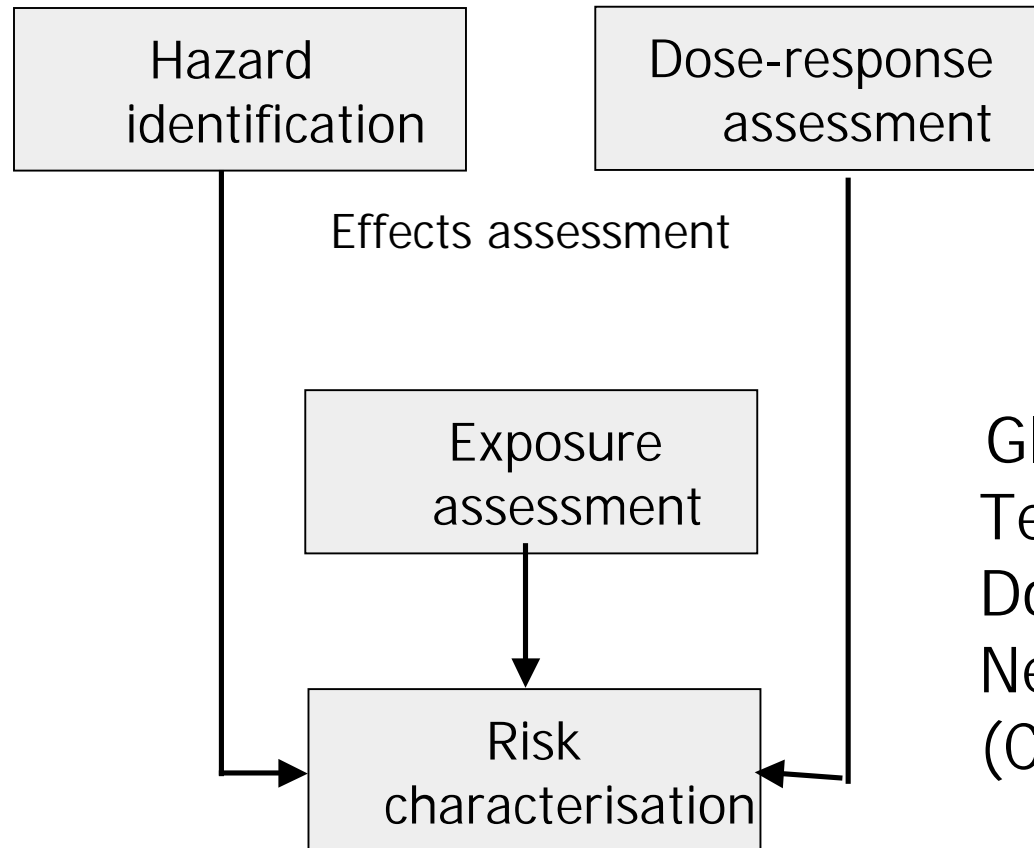
Doc. I.1 Antragsformular

- Zweck der Dossier-Einreichung
- Verwendungsbereich
- Vorschlag für Einstufung und Kennzeichnung
- Bestätigung der Vollständigkeit des Dossiers

Doc. I.2 Gesamtbewertung

- Kriterien für angestrebte Anhang I-Aufnahme
- Annex: Liste der relevanten Endpunkte

Document Type II – Risk Assessment



Gliederung nach
Technical Guidance
Document (TGD) für
Neu-/Altstoffe
(Chemikalien)

Document Type III - Study Summaries

- **Standardformate / Formblätter im WORD-Format**
- **Pro Endpunkt (Kapitel) 1 Standardformat für**
 - Qualitätsprüfung (Quality check = Tier I bei PPP)
 - Studienzusammenfassung (Tier II bei PPP)
- **All-in-one approach:** Synergetische Nutzung für Behördenberichte:
 - Separate Spalte für Anmerkungen
 - Separate "Evaluation box"

Standard formats for study summaries

- Section heading (according to TNsG on Data Requirements)
- Cross-reference to BPD Annex Point

- Reference(s) / Data protection
- Guidelines and quality assurance
- Materials and methods
 - integrated guidance notes
 - default values of standard methods
- Results and discussion
- Applicant's summary and conclusion

End-point specific
(sub)fields

Data input from
applicant

- Separate areas for official use by Competent Authorities:
 - Commentary column
 - Evaluation box for Rapporteur Member State
 - Commentary box for other Member States

Comments and
evaluation by CAs

Beispiel – Annex Point II A6.4

Subchronic oral toxicity test with rodent (rat)

Reference(s) + Guidelines and Quality Assurance

Final proposal by Fraunhofer ITA		28 February 2000
Organics Inc.		XXX-YYY
		Dec./1999
Section A6.4.1 (02) Subchronic oral toxicity test with rodent (rat)		
Annex Point IIA6.4		
	1 REFERENCE	Official use only
1.1 Reference	Elbers R, Hagen E (1992): XXX-YYY - Subchronic toxicity in Wistar rats (13-week administration in the diet with a four-week recovery period). Organics Inc, unpublished report No.: 21627 No. (July 07, 1996); Organics Inc, Institute of Toxicology, Castlebar, Ireland, (Dates of experimental work: April 1991 - May 1991).	
1.2 Data protection	Yes (*)	
1.2.1 Data owner	Organics Inc	
1.2.2 Companies with letter of access	no (*)	
1.2.3 Criteria for data protection	Data on new active substance for first entry to Annex I/IA (*)	
	2 GUIDELINES AND QUALITY ASSURANCE	
2.1 Guideline study	OECD 408 » FIFRA § 83-1 » 67/548/EEC	
2.2 GLP	Yes	
2.3 Deviations	Yes: T3, T4 and thyroxine in the blood were measured in excess of Guideline requirements. In addition P450 levels in the blood were measured.	X

Guidance notes in Practicalities Guidelines

Choose one of the following criteria and delete the others:

- Data on new a.s. for first entry to Annex I/IA
- Data submitted to the MS after 13 May 2000 on existing active substance for the purpose of its entry into Annex I/IA
- Data on existing or new a.s. to maintain or vary a.s. Annex I/IA entry
- No data protection claimed

Demo

Marked by CA to indicate comment

Materials + Methods

3 MATERIALS AND METHODS

3.1	Test material	As given in section 2 (*)
3.1.6	Lot/Batch number	17002/88 (*)
3.1.7	Specification	Deviating from specification given in section 2 as follows: (*)
3.1.7.1	Description	
3.1.7.2	Purity	93.6% (*)
3.4.6	Haematology	Yes number of animals: all animals time points: 5, 13 weeks and 17 weeks (recovery groups) Parameters: see table A6.4.1(02)-1
3.4.7	Clinical Chemistry	Yes number of animals: time points: 5, 13 weeks and 17 weeks (recovery groups) Parameters: total cholesterol, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, P-450
3.4.8	Urinalysis	Yes number of animals: time points: Parameters:

Guidance note

Adopt, change or delete these default values:
yes/no,
number of animals: all animals or other
time points: end of study or other
Parameters: Haematocrit, haemoglobin concentration, erythrocyte count, total and differential leukocyte count, platelet count, clotting time, prothrombin time, thromboplastin time, or other

4 RESULTS AND DISCUSSION

4.1 Observations

4.1.1 Clinical signs At 611 ppm, several animals exhibited a depressed general condition and an ungroomed coat. These findings were reversible.

4.1.2 Mortality X

4.2 Body weight gain The retarded body weight gains observed at the high-dose level were not fully reversible within a post observation period of four weeks (Fig.: A6.4.1(02)-1 and A6.4.1(02)-2).

4.3 Food consumption and compound intake Food intake was not affected at levels up to 611 ppm. Animals drank slightly less water at 611 ppm. In order of increasing doses the treated rats ingested the equivalent of: males: 1.1, 11.1, and 11.1 mg/kg bw/day; females: 1.1, 11.1 and 11.1 mg/kg bw/day of XXX-YYY.

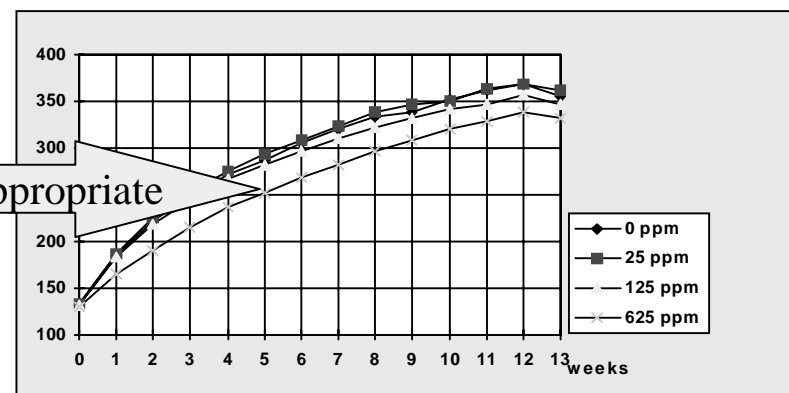
4.4 Ophthalmoscopic examination No effects

4.5 Blood analysis

4.5.1 Haematology White blood cell numbers: no effects
Evidence of impaired blood coagulation (transiently lower thrombocyte counts (THRO) and elevated Hepato-Quick readings (HQUICK) in the high-dose group, but reversible following the recovery period

4.5.2 Clinical chemistry See table A6.4.1(02)-1
Cytochrome P-450 levels (P 450): statistical significant increase at 111 ppm and above in males.
Liver enzyme activities in the serum (aspartate- and alanine-aminotransferase, alkaline phosphatase) elevated in both sexes at 611 ppm.
Blood cholesterol (CHOL) levels: depressed to a statistically significant extent in both sexes at 611 ppm.

Results + conclusions



Copy Fig. from report as appropriate

Table A6.4.1(02)-2: Incidence of treatment related histopathological findings

Parameter	Control		low dose		medium dose		high dose		dose-response +/-	
	m ^a	f ^a	m ^a	f ^a	m ^a	f ^a	m ^a	f ^a	m	f
number of animals examined	10/10	10/10	10/10	10/10	10/10	10/10	10/10	10/10	-	-
BLADDER UROTHEL - hyperplasia (multifocal)	0	0	0	0	0	0	3	4	-	-
TONGUE - hyperkeratosis	0	0	0	0	0	0	7	10	-	-
OESOPHAGUS - hyperkeratosis - hyperplasia	1	0	0	0	9	5	10	10	-	-
- hyperkeratosis	0	0	0	0	1	0	3	8	-	-
LIVER - hyaline droplets	0	0	0	0	0	0	3	0	-	-

Include tables as appropriate

Fraunhofer



Institut für
Toxikologie und
Aerosolforschung

Applicant's Summary + Evaluation by Rapporteur Member State

5 APPLICANT'S SUMMARY AND CONCLUSION	
5.1 Materials and methods	In accordance with method OECD 408 » FIFRA § 83-1 » 67/548/EEC, groups of 10 male and 10 female Wistar rats were administered XXX-YYY (purity 93.6 %) at levels of 0, 11, 111 or 611 ppm in their diet over a period of 90 days. Additional recovery groups made up of ten rats of each sex were treated at levels of 0 or 111 ppm over a period of 13 weeks, and then observed for four weeks. In order of increasing doses the treated rats ingested the equivalent of: males: 1.1, 11.1, and 11.1 mg/kg bw/day; females: 1.1, 11.1 and 11.1 mg/kg bw/day of XXX-YYY.
5.2 Results and discussion	Reversible findings in the high-dose group include a depressed general condition and an ungroomed coat, retarded body weight gains (not fully reversible) transiently lower thrombocyte counts (THRO), elevated Hepato-Quick readings (HQUICK), slight degenerative changes in the urinary bladder epithelium and hyperplastic change in the urinary bladder epithelium. The relevant end points are histopathological changes. In both sexes hyperkeratosis in the superficial epithelium was determined at 111 ppm and above (in oesophagus and forestomach) and at 611 ppm (in the tongue), and was also accompanied by hyperplastic changes and hypertrophy in the oesophagus of the affected animals. Hyperkeratosis, which also occurred in a few control rats, could no longer be observed, or was only seen at a considerably lower incidence, at the end of the recovery period.
5.3 Conclusion	
5.3.1 LO(A)EL	
5.3.2 NO(A)EL	11 ppm, equivalent to: 1.1 mg/kg bw/day (males), 1.1 mg/kg bw/day (females), based on histopathological findings in the liver at 111 ppm
5.3.3 Other	
5.3.4 Reliability	1
5.3.5 Deficiencies	No

Date

Materials and Methods

CAs' comment

Results and discussion

CAs adopt or adapt applicant's text and include comments as appropriate

CAs' comment

Conclusion

Reliability

Acceptability

Remarks

EVALUATION BY RAPPORTEUR MEMBER STATE

Date
14 Feb. 2000

Materials and Methods
In accordance with method OECD 408 » FIFRA § 83-1 » 67/548/EEC, groups of 10 male and 10 female Wistar rats were administered XXX-YYY (purity 93.6 %) at levels of 0, 11, 111 or 611 ppm in their diet over a period of 90 days. Additional recovery groups made up of ten rats of each sex were treated at levels of 0 or 111 ppm over a period of 13 weeks, and then observed for four weeks. In order of increasing doses the treated rats ingested the equivalent of: males: 1.1, 11.1, and 11.1 mg/kg bw/day; females: 1.1, 11.1 and 11.1 mg/kg bw/day of XXX-YYY.

Comments: The purity of the test substance (see 3.1.2.2) is much lower than that given in section 2. No further specification is given in 3.1.2. However, a check of the original study report revealed that the impurities are not of toxicological relevance.

Results and discussion
Reversible findings in the high-dose group include a depressed general condition and an ungroomed coat, retarded body weight gains (not fully reversible), transiently lower thrombocyte counts (THRO), elevated Hepato-Quick readings (HQUICK), slight degenerative liver changes and hyperplastic change in the urinary bladder epithelia.

The relevant end points are histopathological changes: In both sexes hyperkeratosis in the superficial epithelium was determined at 111 ppm and above (in oesophagus and forestomach) and at 611 ppm (in the tongue), and was also accompanied by hyperplastic changes and hypertrophy in the oesophagus of the affected animals.

Comments:
Hyperkeratosis was claimed to be (partly) reversible, but no statistical data were given in 4.6.2. Organ weights and mortality (see 4.12. and 4.6.1) and results of additional determinations, i.e. T3, T4 and thyroxine in the blood (see 2.3), were not reported by the applicant. A check of the original report showed no adverse effects.

Conclusion
NO(A)EL: 11 ppm, equivalent to: 1.1 mg/kg bw/day (males), 1.1 mg/kg bw/day (females), based on histopathological findings in the liver at 111 ppm

Reliability
1

Acceptability
acceptable

Basis für ausführliche ("robust") study summaries

Artikel 8(4) der Richtlinie 98/8/EG:

"Die Unterlagen enthalten eine detaillierte und vollständige Beschreibung der durchgeführten Untersuchungen und der angewandten Methoden ..."

"... Die Informationen ...müssen für eine Bewertung der Wirkungen ausreichend sein."

Vollständigkeitsprüfung

Doc. III-A Section No.	Information, test or study required for active substance	Information, test/study provided Y(n)/P/N/n.a.	Justifi- cation prov'd. Y/N	Confi- dential data Y/N	Relia- bility indicator 0-4/n.a.	Official use only Data Gap Y/N
6.1.	Acute toxicity					
6.1.1	Oral	Y(4)			1/3/2/4	
6.1.2	Dermal	Y(2)			2/2	
6.1.3	Inhalation	N	Y			

Y(n) = Yes (number of tests/studies); P = in part; N = No; n.a. = not applicable;
Reliability indicators: 0, 1, 2, 3 or 4 (provide reliability indicator for each test/study)

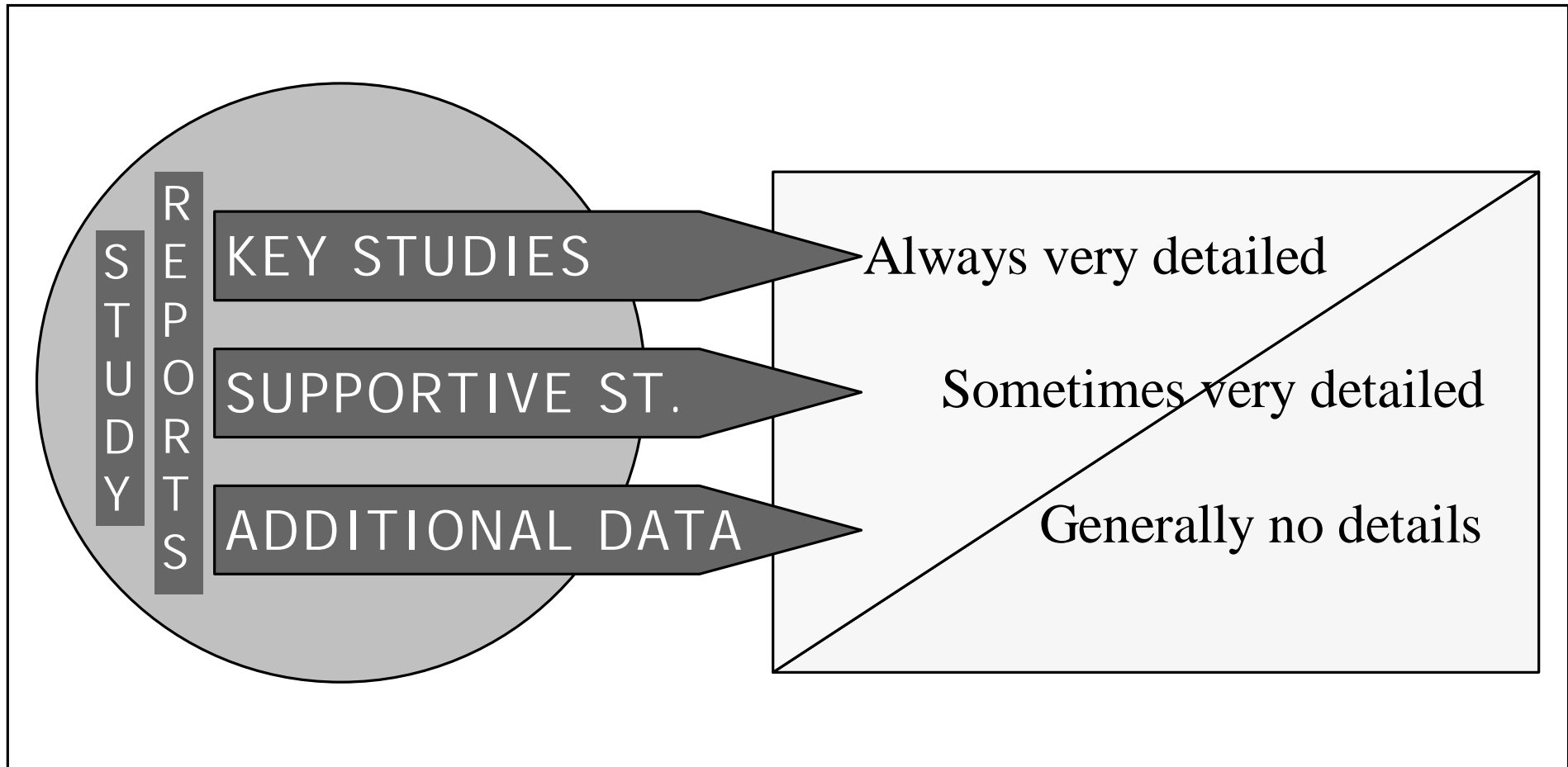
Pilotprojekt "Pilot Evaluation on Existing Biocidal Active Substances"

- Ziel:
 - Validierung des Procedere nach 98/8/EC
 - Prüfung der Praktikabilität der "Practicalities Guidelines"
 - Dossiers für 2 Pilotsubstanzen --> Behördenberichte
- Finnisches Umweltinstitut (FEI) + Dänische Umweltbehörde (Danish EPA)
- 1st Pilot Project Workshop: 28-29 Sep. 2000
- 2nd Pilot Project Workshop: 17-18 May 2001

Feedback Antragsteller im Pilotprojekt

- Anfängliche Skepsis --> weitgehende Akzeptanz
- Standardformate sehr hilfreich zur Erstellung der "robust" study summaries
- Zeit und Manpower abhängig von Qualität der Testberichte!
- Nichtbewertungsrelevante Studien --> kurze Darstellung
- IUCLID für Dossiererstellung: Skepsis

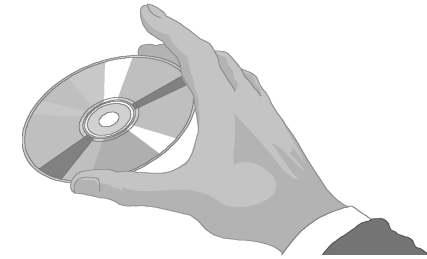
Level of detail for study summary?



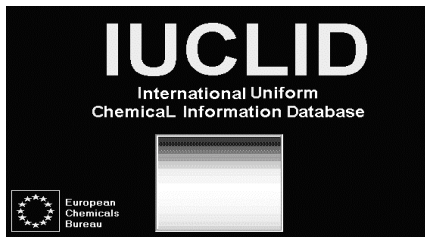
Pilotprojekt 2. Workshop Mai 2001: Schlussfolgerungen zu Practicalities Guidelines

- ▶ Draft Practicalities Guidelines
 - -- can be used as such with minor amendments
 - -- should be revised before data submissions of second phase of Review Program
- ▶ All-in-one approach should be applied
 - -- for Doc. III (Study summaries)
 - -- even for Doc. II, if possible (Risk assessment)
- ▶ Urgent need for modified IUCLID

Electronisches Format IUCLID



CD-ROM submission



IUCLID (International Uniform Chemical Information Database)

- Relationale Datenbank
- Neue Version 4.0: Industriechemikalien + Biozide
- Notifizierung von bioziden Wirkstoffen
- Geplant für Dossiererstellung

