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RIJKSINSTITUUT VOOR VOLKSGEZONDHEID EN MILIEU
NATIONAL INSTITUTE OF PUBLIC HEALTH AND THE ENVIRONMENT

RIVM report 601300 002

Environmental risk assessment for veterinary medicinal products Part 2. The phase 1 assessment for immunological products Report on the workshop 23-9-1998

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This investigation has been performed by order and for the account of the Centre for Substances and Risk Assessment and the Agency for the Registration of Veterinary Medicinal Products within the framework of project 601300, Evaluation of Veterinary Medicinal Products.

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Abstract

This report contains a proposal for a simplified Phase 1 assessment for immunological veterinary medicinal products. This scheme was constructed as it was felt that the existing guidance as given by the EMEA was too complex and laborous to reach quick decisions on the acceptability of low-risk products.

Preface

The Umwelt Bundes Amt, the Agency for the Registration of Veterinary Medicinal Products and the Commission on Veterinary Medicinal Products are thanked for their contribution to the CSR workshop. I hope this document will be useful in the process of product registration.

Mark Montforts

All correspondence about the registration procedure should be addressed to BRD, Wageningen.
All correspondence about scientific issues with respect to the methodology should be adressed to the author (e-mail mark.montforts@rivm.nl).

Contents

Samenvatting

In september 1998 organiseerde het Centrum voor Stoffen en Risicobeoordeling van het RIVM een workshop over de milieubeoordeling van diergeneesmiddelen met als doel:

1. de samenwerking tussen de autoriteiten van Duitsland en Nederland stimuleren
2. de mogelijkheden om de risicobeoordeling voor immunologische producten te verbeteren verkennen.

Dit rapport bevat een voorstel voor een vereenvoudigde Fase 1 benadering voor immunologische diergeneesmiddelen. Dit schema is ontworpen omdat bleek dat de bestaande guidance van de EMEA te ingewikkeld en te arbeidsintensief was om efficiënt tot beslissingen over de aanvaardbaarheid van middelen met een laag risico te komen.

Summary

In September 1998 the Centre for Substances and Risk Assessment of the National Institute for Public Health and the Environment of the Netherlands organised a workshop on the environmental assessment for veterinary medicinal products.
The workshop had two goals:

1. to stimulate co-operation in this field between the competent authorities in Germany and The Netherlands
2. to elucidate the possibilities of improving the risk assessment for immunological products.

This report contains a proposal for a simplified Phase 1 assessment for immunological veterinary medicinal products. This scheme was constructed as it was felt that the existing guidance as given by the EMEA was too complex and laborious to reach quick decisions on the acceptability of low-risk products.

1 Introduction

In September 1998 the Centre for Substances and Risk Assessment of the National Institute for Public Health and the Environment of the Netherlands organised a workshop on the environmental assessment for veterinary medicinal products.
The workshop had two goals:

1. to stimulate co-operation in this field between the competent authorities in Germany and The Netherlands
2. to elucidate the possibilities of improving the risk assessment for immunological products.

The second day was reserved for a further exchange on the risk assessment methodology on pharmaceuticals. This report contains the results of the workshop on immunological products and the materials presented.

During the recent meetings on environmental risk assessment for veterinary medicinal products (VMPs) preceding the workshop it became clear that both the Umwelt Bundes Amt of Germany (UBA) and the Centre for Substances and Risk Assessment of the National Institute for Public Health and the Environment of the Netherlands (CSR), were performing or were to perform the assessments for the national registrations, and shared a common view on the approach to do so. In order to stimulate co-operation in this field the UBA was invited to discuss the Dutch methodology (Montforts 1997, 1999).

At the time the methodology for pharmaceuticals was already operational, for immunologicals (including GMO-products) was not. For both groups of products guidance documents of the EMEA were available (EMEA, 1996; EMEA, 1997), but the guidance on immunologicals (including GMO-products) was considered to be too abstract, and could not successfully be used to identify the risk to the environment. Bringing together the expertise on immunological products and GMO-products, the workshop aimed at drawing up a scheme to justify the exclusion for further assessment for products of no concern (the so-called Phase I). To do so, experts from CSR/GMO and ID-DLO were invited.

To inform the national and international organisations on veterinary products, representatives of the Agency for the registration of Veterinary Medicinal Products (BRD) and of the CVMP joined the workshop.

List of participants and expertise.

Name	Institute	Country	Expertise
Jan Linders	CSR-I&B	NL	environmental exposure en effect assessment of substances
Mark Montforts	CSR-M	NL	environmental exposure en effect assessment of substances
Hans Mensink	CSR-M	NL	environmental exposure en effect assessment of microbial pesticides
Peter van Vlaardingen	CSR-M	NL	dossier evaluation
Dennis Kalf	CSR-M	NL	dossier evaluation
Joop de Knecht	CSR-M	NL	dossier evaluation
Birgit Loos	CSR GMO agency	NL	GMO assessment
Frank van Poelwijk	CSR GMO agency	NL	GMO assessment
Johan Schefferlie	CSR-VGZ	NL	project leader, residues of pharmaceuticals
Burkhard Wagner	UBA	D	head of Environmental Exposure Assessment
Ingrid Noeh	UBA	D	Head of GMO agency
Ute Fichna	UBA	D	organisation of assessments
Gera de Bruijn	BRD	NL	organisation of assessments
Johan Bongers	ID-DLO	NL	Head of Department of Control and Standardisation
Hok Oei	ID-DLO	NL	Senior Research Scientist at section Immunobiologicals
Herman Lensing	CVMP/LNV	NL	CVMP member

2 The EMEA assessment for immunological products.

As can be seen in Appendix A, the first workshop day focused on immunological and GMO-containing products. One part of the workshop was reserved for short introductions into relevant aspects of closely related fields of research (see appendices). During the second half a proposal for a Phase 1 assessment was drawn up.

2.1 Framework of the environmental assessment of veterinary medicinal products

In Commission Directive 81/852/EEC it is included that with a request for registration of a veterinary medicinal product information is to be provided to enable an assessment of the safety for the environment. The directive states that:

"the purpose of the study of environmental safety of a veterinary medicinal product is to assess the potential harmful effects which the use of the product may cause to the environment and to identify any precautionary measures which may be necessary to reduce such risks."

Directive 81/852/EEC describes the assessment process in two phases. The first phase (Phase I) shall assess the potential of exposure of the environment to the product and the level of risk associated with any such exposure. The first phase may thus be limited to product identification and exposure assessment. Several exemptions for further testing could be constructed. When these exemptions do not apply, and trigger values are exceeded, one enters Phase II.

This directive is included in the Dutch law on veterinary medicines ('Diergeneesmiddelenwet' 27 June 1985, Stb. 410, last amendment 10 July 1995), and provides since February 1st, 1997, a formal base to reject a request for registration. An elaboration of this directive is given in the EMEA-documents (EMEA, 1996;1997), issued by The Committee for Veterinary Medicinal Products (CVMP) of the European Agency for the Evaluation of Medicinal Products (EMEA).
According to the Dutch law a veterinary medicinal product is a substance, whether or not after preparation or processing, with the intention:

a. to cure, relieve or prevent any affection, illness, morbid symptom, pain, injury, or defect of an animal;
b. to remedy, improve, or change the functioning of organs of an animal;
c. to diagnose a disease or defect in animals at application in an animal.

This definition includes pure substances (organic and inorganic) and preparations (including homeopathic products, vaccines, flee-belts), and excludes disinfectants not used on animals (e.g. for cleaning stables).

The EMEA published guidance on the environmental risk assessment of pharmaceuticals (EMEA, 1997) and immunological products (EMEA, 1996). It is interesting to note the following phrase in the guidance on the immunological products:
"This assessment must address the risks arising from each of the components of the product, not just the risk from live organisms in vaccines." (EMEA 1996).

2.2 The Phase 1 assessment procedure of EMEA

The Guidance of EMEA (1996) does address the two-phase system, but uses the same approach for both phases: should a phase II be necessary, the same procedure should be used again.
In the Background an Introduction already an example for exemption is given:
"For example, for inactivated vaccines to be administered by injection, the hazards and risks from the active ingredients are likely to be negligible.
The main elements (listed by EMEA) are:

i. hazard identification;
ii. assessment of exposure to the hazard and the likelihood that the hazard will occur;
iii. assessment of the consequences of that exposure;
iv. assessment of the level of risk (by consideration of the severity of any adverse consequences and the likelihood that they will occur);
v. selection and assignment of appropriate control measures (risk management), as far as possible.

In Hazard identification the following factors should be included:

- Capacity of live organisms to transmit to non-target species (specificity of host range)
- Shedding of live product organisms (route, numbers, duration)
- Capacity to survive, establish and disseminate
- Pathogenicity to other organisms
- Potential for other effects of live product organisms
- Toxic effects of the product components
- Toxic effects of excreted metabolites

In the assessment of Likelihood, the potential receiving environment is a key factor: climate, soil condition, and demographic considerations are important considerations. Consideration should be given to any potential exposure, its magnitude and duration included. When estimating probabilities and frequencies, consideration should include the number of organisms that might reach the environment."
The exercise should end in an estimation of risk, that determines (although not elucidated in the guidance) whether a Phase II assessment is appropriate. For this purpose the following table was constructed.

Table 1. Estimation of risk according to EMEA (1996).

ESTIMATION OF RISK

Consequence of Hazard	**Likelihood of Hazard Occurring**			
	High	Moderate	Low	Negligible
Severe	High	High	Medium	Effectively Zero
Medium	High	High	Medium/Low	Effectively Zero
Low	Medium/Low	Low	Low	Effectively Zero
Negligible	Effectively Zero	Effectively Zero	Effectively Zero	Effectively Zero

All these elements of guidance (and there are more in the document) are very true; given the nature of live vaccines, the likelihood of exposure and spreading should receive much more attention than is the case for pharmaceutical products. However, converting the seven items for Hazard Identification into a report is a considerable task by itself. Next the assessment is facing the task of describing the “relevant environment”. This environment may be different for many products. Probabilistic risk assessment is considered in many frameworks as a higher Tier exercise. The aim of the workshop was therefore to come to a more Phase I assessment to reach quick decisions on the acceptability of low-risk products.

3 Proposal for phase 1 for immunological products

EMEA excluded the GMO-containing products from the assessment of immunological products. The experiences of CSR in assessing the risks of GMO and of biological plant protection products can be of great help in dealing with the assessment of veterinary products. Principally there are no differences between GMO and non-GMO immunological products. The approaches are the same, and the key point to be solved remains: what risk and what hazard is (not) acceptable. The copies of the presentations (see Appendices) illustrate the frameworks and general points of interest.
To the opinion of the members of this workshop the assessment of GMOs should be dealt with in two parallel procedures: one assessment according to Directive 90/220/EC focusing on the GMO product as such, and one assessment according to the EMEA scheme focusing on the use of the product as a veterinary product.
Starting point of the new scheme was the availability of reliable data and information in the dossier already available. The scheme presented in Figure 1 identifies several elements of the hazard assessment that can serve as safe exemptions for further testing, provided the elements have been addressed adequately. All other efforts should be regarded as Phase II.

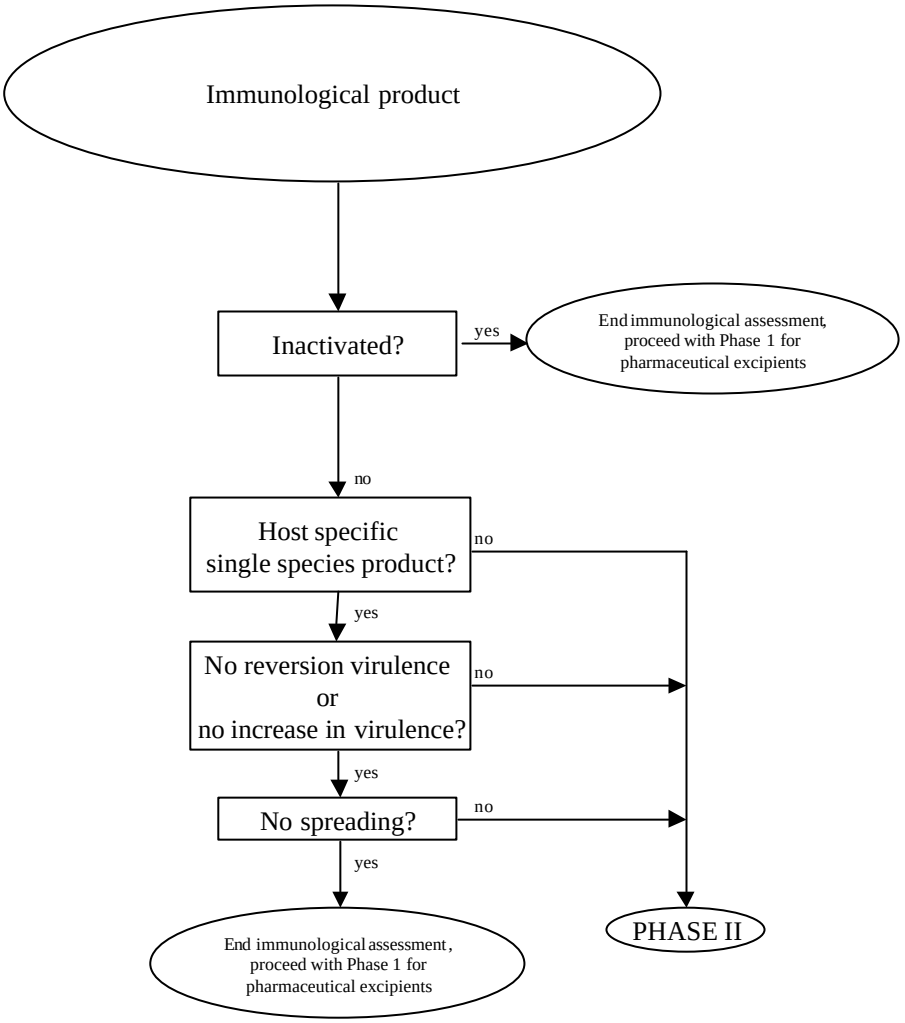

Figure 1. Proposed Phase 1 environmental risk assessment for immunological products.

Literature

Directive 81/852/EEC of the Commission of September 28, 1981 as published in the Official Journal of the European Community of November 6, 1981, No. L317, page 16, amended by:
- Directive 92/18/EEC of the Commission of March 20, 1992 as published in the Official Journal of the European Community of April 10, 1992, No. L97, page 1; and
- Directive 93/40/EEC of the Council of June 14, 1993 as published in the Official Journal of the European Community of August 24, 1993, No. L214, page 31.

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EMEA (1997) Note for guidance: environmental risk assessment for veterinary medicinal products other than GMO-containing and immunological products. European Agency for Evaluation of Medicinal Products, Committee for veterinary medicinal products, EMEA/CVMP/055/96.

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Montforts MHMM. Environmental Risk Assessment for Veterinary Medicinal Products. Part 1. Other than GMO-containing and Immunological Products. RIVM, Report 613310001, Bilthoven, The Netherlands, 1997. First update Report 601300 001, 1999.

Montforts MHMM, Kalf DF, Van Vlaardingen PLA, and Linders JBHJ. The exposure assessment for veterinary medicinal products. The Science of the Total Environment 225 (1999) 119-133.

Appendix A. Program of the workshop

Topics.
1. Administrative and scientific organisation in the Netherlands and in Germany.
2. Designing a toolbox for the ERA for immunological (GMO) products
3. ERA for pharmacological products
   a) experiences in phase I and II
   b) elaboration of phase IIa and IIb.
   c) initiating an EU process on risk assessment (at the authority level)

Wednesday, 23 September 1998	**Activity**
8:30-8:45	Arrival and registration
8:45-9:25	**Introduction to the workshop**
8:45-8:50	Opening address and presentation of targets Hans Könemann, RIVM-CSR
8:50-9:10	Scope of co-operation UBA-RIVM Burkhard Wagner, UBA Jan Linders, RIVM-CSR
9:10-9:20	Embedding of responsibilities in The Netherlands Gera de Bruijn, BRD
9:20-9:30	Embedding of responsibilities in Germany Ute Fichna, UBA
9:30-9:35	Introduction to the program Mark Montforts, RIVM-CSR
9:35-14:45	**Immunological products**
9:35-9:55	Requirements for Genetically Modified Organisms Birgit Loos, RIVM-CSR
9:55-10:15	Risk assessment for biological pesticides Hans Mensink, RIVM-CSR
10:15-10:35	Properties of vaccination products with respect to dossier requirements and the environmental assessment. Johan Bongers/Hok Oei, DLO
10:35-10:55	**Break**
10.55-12:45	Workshop on the phase I for immunological products
12:45-13:45	**Lunch**
13.45-14:45	Conclusions on Phase I, proposals for further work
14:45-16:00	**Organisation**
14:45-15:30	VMP Environmental Risk Assessment: procedures and organisation

	Gera de Bruijn, BRD Johan Schefferlie, RIVM-CSR Ute Fichna, UBA
15:30-16:00	Inventory of questions concerning organisation
16:00-16:15	**Break**
16:15-17:30	**Pharmacological products**
16:15-16:30	Pharmacological products: background to EMEA phases and triggers Jan Linders, RIVM-CSR
16:30-17:30	Setting a target for the future: EU-strategy for technical guidance
17:30-18:00	**Closing of the day;** reception Gerrit Speijers, RIVM-CSR
19:00-	**Dinner at Hotel De Witte Zwaan, De Bilt**

Thursday, 24 September 1998	**Activity**
9:00-9:30	Arrival and coffee
9:30-14:30	**Pharmacological products**
9:30-9:35	Program of the day Mark Montforts, RIVM-CSR
9:35-9:50	Examples of assessment: Experiences in phase I and II Mark Montforts, RIVM-CSR
9:50-10:05	Demonstration of spreadsheet phase I spreading with slurry Peter van Vlaardingen, RIVM-CSR
10:05-12:00	Workshop on exposure and effect assessment; Drawing a frame for Phase IIa and IIb
12:00-13:00	**Lunch**
13:00-14:00	Conclusions on Phase II, proposals for further work
14:00-14:45	**Overall conclusions and Closing of the workshop**

Appendix B. Presentation of H. Oei, ID-DLO department of Control and Standardisation

ID-DLO: Institute for Animal Science and Health
Head: Johan Bongers
Immunobiologicals: Hok Oei DVM (virology)
Jaap Woltjes (bacteriology)
Farmaca: Gerard Prenen
Jan Willem Seinhorst DVM
Miek van der Schaar
Peter Janssen
Ellen Couwenberg

Main activities:

- advice licensing veterinary drugs and vaccines
  - pharmaceuticals: target animal safety and efficacy
  - vaccines: all aspects except ecotoxicology
- quality control of veterinary vaccines
- applied research to support licensing practices

Quality control carried out under supervision of Oei-Bongers within laboratories ID-DLO.

PROPERTIES OF VACCINES WITH RESPECT TO DOSSIER REQUIREMENTS AND THE ENVIRONMENTAL ASSESSMENT.

Requirements: 92/18/EEC
PH.EUR

II Analytical documentation
III Safety documentation
IV Efficacy documentation

II Analytical documentation

IIA Qualitative and quantitative composition active substances:

Vaccines

- Inactivated (adjuvants, preservatives)
- Live:
  - "field strain"/natural low virulence (+/-cloned)
  - attenuated:
    - conventional
    - GMO: deletion
  - recombinant: vector

Type	Status	Example
non GMO	live	ADV
non GMO	inactivated	FMDV
GMO	live	ADV
GMO	inactivated	FeLV

IIC.2.1 Starting materials of biological origin

- seed materials (viruses, bacteria, cells)
- substances of animal origin (serum, trypsin, ….)

IID Control tests during production

- inactivation

IIE Control tests on the finished products

- extraneous agents

Special requirements of live vaccines

- **Spread** of the vaccine strain
  - vaccinated → unvaccinated target animals
  - vaccinated → non-target species
- **Dissemination** in vaccinated animal:
  - faeces, urine, milk, eggs, oral, nasal and other secretions
  - in the body (predilection sites for replication)
- **Reversion** to or increase in **virulence**
  - ≥5 serial passages
- **Biological properties** of the vaccine strain
  - intrinsic biological properties of the vaccine strain (neurotropism)
  - vector vaccines: risk of changing the tropism or virulence
  - foreign gene!
- **Recombination** or genomic reassortment of strain (with field or other strains).

EXAMPLES

- Measles virus
- Chicken herpesvirus ST1
  - residual pathogenicity (ST1: highly oncogenic strains)
  - widely used in Europe
  - →Marek's disease = highly contagious neoplastic disease in chickens
  - Studies: mammalian cells, primates
- Bovine respiratory syncytial virus
- Rotavirus

SAFETY

Risk of live vaccines

- (residual) pathogenicity
- spreading
- revert to virulence
- contamination

ENVIRONMENTAL RISK ASPECTS

- >1 animal species: CDV
- (zoonotic)
- “old”/new
- mass administration (spray, ..)

Appendix C. Presentation of H. Mensink (CSR) on microbial pesticides.

REGISTRATION OF MICROBIAL PESTICIDES: ENVIRONMENTAL ASPECTS

♦ INTRODUCTION

♦ DATA REQUIREMENTS

⇒ recent developments (EU/OECD)

⇒ example: *Spodoptera exigua* NPV

♦ DATA EVALUATION

⇒ guidance?

⇒ example: *Spodoptera exigua* NPV

♦ RISK ASSESSMENT

⇒ guidance/case-by-case?

⇒ example: *Spodoptera exigua* NPV

♦ CONCLUSIONS & DISCUSSION

Table 5. Registered micro-organisms with pesticidal action in the Netherlands (6-1997)

MOPA	TRADE NAME	TYPE PRODUCT	CONTENT OF MOPA
VIRUS			
Cydia pomonella granulose virus	Asepta Carpovirusine	-	-
Spodoptera exiqua nuclear polyhedrosis virus	SPOD-X GH	-	10^8 polyeders/ml
Tomato mosaic virus (weak strain)	Virus No M II	various	0.1 mg viral protein/litre suspension
FUNGI			
Verticillium dahliae Kleb	Trigger	-	10^6 conidia/ml
Verticillium lecanii	Mycotal	WP	10^6 spores/mg
BACTERIA			
Streptomycis griseoviridis	Mycostop	WP	10^8 CFU/g
Bacillus thuringiensis	Bactimos Spuitpoeder	-	-
Bacillus thuringiensis	Abbott-Biob L	-	-
Bacillus thuringiensis	Abbott-Biob WP	-	-
Bacillus thuringiensis	Bactospeine	WP	16000 IU/mg
Bacillus thuringiensis	Bactospeine XLV	WP	13000 IU/mg
Bacillus thuringiensis	Biobit Vloeibaar	SC	13000 IU/mg
Bacillus thuringiensis	Biobit WP	WP	16000 IU/mg
Bacillus thuringiensis	Delfin	WG	32000 IU/mg
Bacillus thuringiensis	Dipel	WP	16000 IU/mg
Bacillus thuringiensis	Dipel ES	-	17600 IU/mg
Bacillus thuringiensis	Kobacthur L	-	-
Bacillus thuringiensis	Kobacthur WP	WP	-
Bacillus thuringiensis	Pokon Bio-Rups	WP	16000 IU/mg
Bacillus thuringiensis	Scutello	-	100%
Bacillus thuringiensis	Scutello L	SC	100%
Bacillus thuringiensis	Turex 50 WP	WP	25000 IU/mg

- = not reported; WP = wettable powder; SC = suspension concentrate; WG = water dispersible granules

Table 6. Registered micro-organisms with pesticidal action in the US (Jan. 1997) Personal communication of EPA to RIVM.

MOPA	
VIRUS	**BACTERIA**
Heliothis nucleopolyhedrosis virus (NPV)	*Bacillus popilliae & B. lentimorbus*
Douglas fir tussock moth NPV	*Bacillus thuringiensis kurstaki*
Gypsy moth NPV	*Agrobacterium radiobacter* K84
Beet armyworm NPV	*Bacillus thuringiensis israelensis*
Autographa californica NPV	*Bacillus thuringiensis san diego*
Autographa falcifera NPV	*Bacillus thuringiensis tenebrionis*
Cydia pomonella granulose virus	*Pseudomonas fluorescens* EG1053
YEAST	*Pseudomonas fluorescens* A506
Candida oleophila I-182	*Pseudomonas fluorescens* 1629RS
FUNGI	*Pseudomonas syringae* 742RS
Phytophthora palmivora MWV	*Bacillus thuringiensis kurstaki* EG2348
Colletotrichum gloeosporioides aeschynomene ATCC 20358	*Bacillus thuringiensis kurstaki* EG2424
Trichoderma harzianum ATCC 20476	*Bacillus thuringiensis kurstaki* EG2371
Trichoderma polysporum ATCC 20475	*Bacillus sphaericus*
Gliocladium virens G-21	*Bacillus subtilis* GBO3
Trichoderma harzianum rifai KRL-AG2	*Bacillus thuringiensis aizawai* GC-91
Lagenidium giganteum	*Bacillus thuringiensis aizawai*
Metarhizium anisopliae ESF1	*Burkholderia cepacia* type Wisconsin
*Puccinia canaliculate (*Schweinitz*)* Langerheim ATCC 40199	*Streptomyces griseoviridis* K61
Ampelomyces quisqualis M10	*Bacillus thuringiensis kurstaki* BMP123
Beauvaria bassiana GHA	*Bacillus subtilis* MBI 600
Beauvaria bassiana ATCC 74040	*Pseudomonas fluorescens* NCIB 12089
PROTOZOA	*Bacillus thuringiensis kurstaki* EG7673
Nosema locustae	*Pseudomonas syringae* ESC 10
	Pseudomonas syringae ESC 11
	Bacillus thuringiensis kurstaki M-200
	Bacillus thuringiensis kurstaki EG7841
	Burkholderia cepacia type Wisc. isol.J82

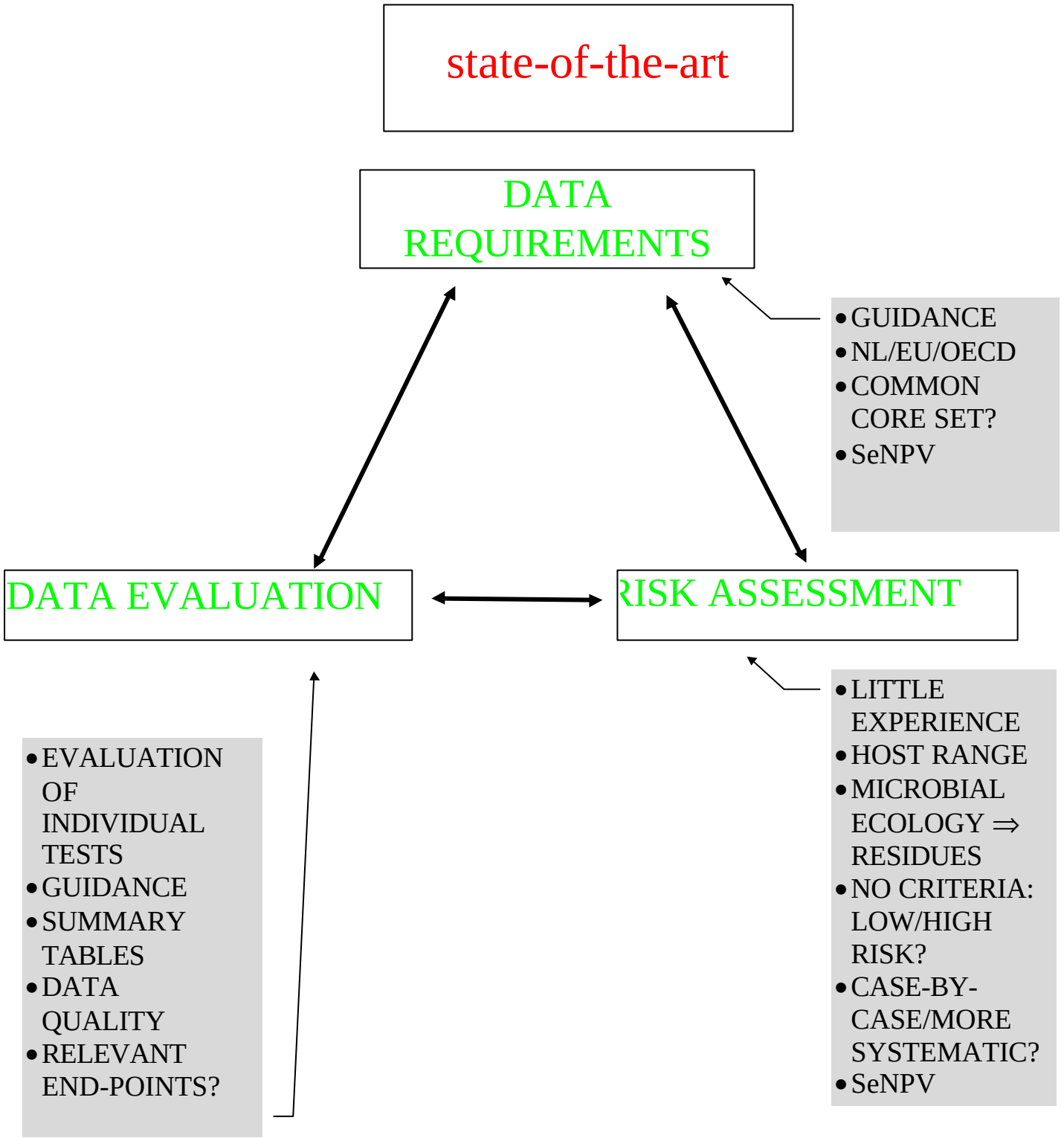

state-of-the-art
DATA REQUIREMENTS
• GUIDANCE
• NL/EU/OECD
• COMMON CORE SET?
• SeNPV
DATA EVALUATION
RISK ASSESSMENT
• EVALUATION OF INDIVIDUAL TESTS
• GUIDANCE
• SUMMARY TABLES
• DATA QUALITY
• RELEVANT END-POINTS?
• LITTLE EXPERIENCE
• HOST RANGE
• MICROBIAL ECOLOGY ⇒ RESIDUES
• NO CRITERIA: LOW/HIGH RISK?
• CASE-BY-CASE/MORE SYSTEMATIC?
• SeNPV

Table 2. Key items for the data evaluation of tests on distribution and fate of MOPAs in the environment

	ITEMS	NOTES	RELIABILITY LOWER ?
METHODOLOGY & TEST DESCRIPTION	1. **test type**	1. **improperly reported?** [*e.g. fate and behaviour in soil, water, air? duration?*]	1. **Y**
	2. **active ingredient, purity**	2. **improper characterisation of the active ingredient? impure?** [*which MOPA — e.g. protozoan, fungus, bacteria, virus? common name? scientific name — down to strain or serotype? mutant? microbiological purity? nature and identity of impurities — e.g. mutated AIs, extraneous MOs? conditions — e.g. a crippled plant pathogen?*]	2. **Y**
	3. **formulation**	3. **(partly) unknown composition?** [*name? type? composition — e.g. quantities and function of non-active ingredients, e.g. wetting agents?*]	3. **Y**
	4. **environmental compartment**	4. **improperly reported?** [*e.g. water, soil, air? natural/artificial? sterile? temperature? light conditions? volume/weight?*]	4. **Y**
	4.1 **abiotic**		
	4.1.1 **water**	4.1.1 [*e.g. pH? sediment type? redox potential/availability of O_2?*]	
	4.1.2 **soil**	4.1.2 [*e.g. soil type? pH? % o.m.? "natural" microbes (quantities, composition)? redox potential/availability of O_2? moisture conditions?*]	
	4.1.3 **air**		
	4.2 **biotic**	4.2 [*e.g. transmission via vectors?*]	
	5. **application**	5. **improperly reported?**	5. **Y**
	5.1 **rate**		
	5.2 **type**	5.2 [*e.g. homogeneously mixed with the medium/substrate? application e.g. as a fluid inoculum, or as encapsulated spores?*]	
	6. **endpoint**	6. **improperly defined?** [*e.g. the amount of AI at the end of incubation, the extent of distribution in the compartment, the extent of interaction — competition? — with other MOs?*]	6. **Y**
	7. **analysis**	7. **invalid? inadequate?** [*e.g. extent of validation? "limit of detection"? proper bioassay?*]	7. **Y**
RESULTS	8. **endpoint**	8. **improperly reported? results non-verifiable?** [*e.g. raw data available for verification?*]	8. **Y**
	9. **statistical analysis**	9. **invalid?** [*all tests with MOs require accurate statistical analysis for proving significant differences between the control and the treatment groups*]	9. **Y**
	10. **test conditions**	10. **improperly reported?** *[are certain ranges of abiotic/biotic parameters exceeded during incubation?]*	10. **Y**
REMARKS	11. *other dissipation routes: e.g. sorption of MOs to glass, or algae?*		11. **E**
	12. *the — e.g. agricultural — history of the environmental compartment under study: does e.g. prior use of compounds may have lead to adapted MOs — e.g. in sewage sludge, or in soil that had been sprayed with chemical pesticides?*		12. **E**
	13. *the handling of the compartment under study: does e.g. the pretreatment indicate microbial populations that cannot be considered resembling "natural" conditions — e.g. soil being stored too dry?*		13. **E**
	14. *the biological meaning of statistically significant differences?*		14. **E**
	15. *microbiological properties: e.g. dispersal mechanism? occurrence of toxins? natural occurrence?* 15.1 *type of propagation: e.g. spores, mycelial fragments?* 15.2 *type of optimal culture media for propagation or growth: e.g. temperature? moisture conditions? pH? % o.m?*		
	16. *pretreatment instability of the AI or product (respecting. light, temperature, "shelf"-storage, and packaging)? instability during incubation?*		16. **Y**

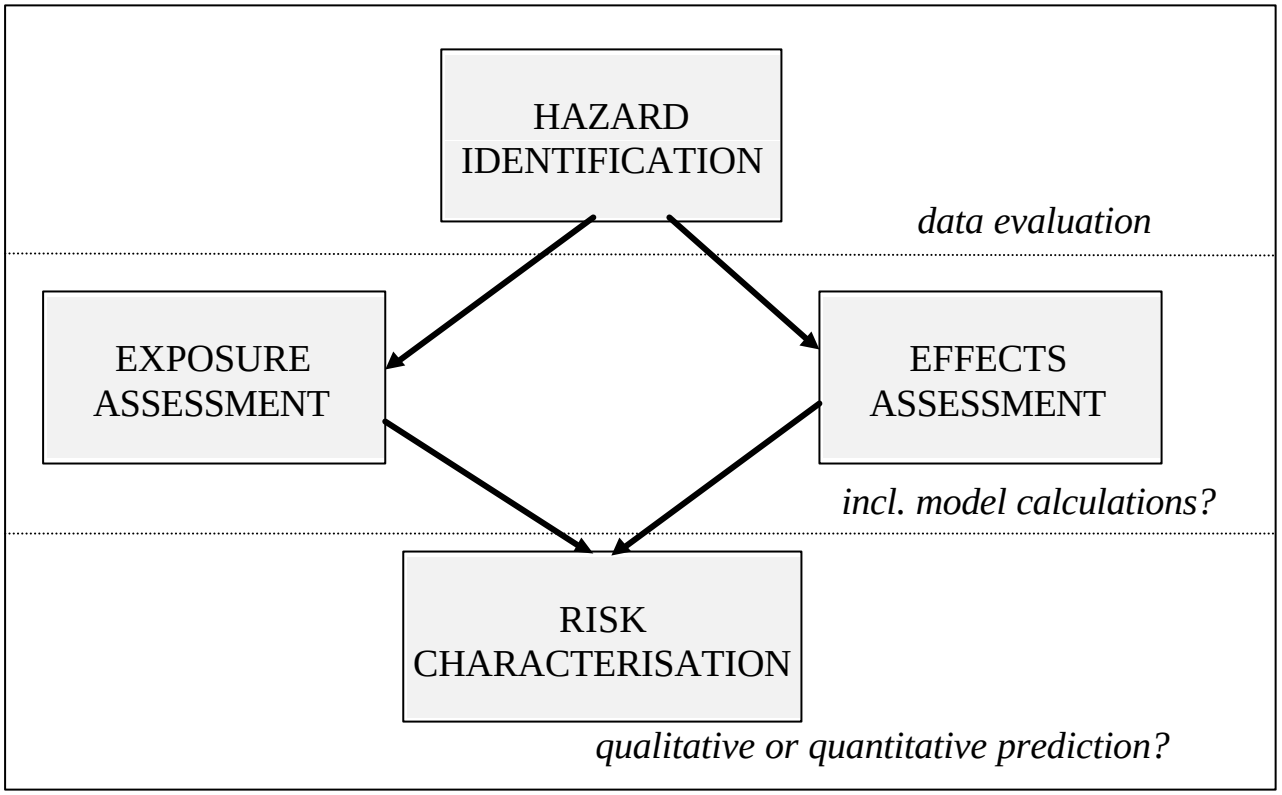


FIG *The systematic procedure of risk assessment for new microbial pesticides (adapted from Van Leeuwen & Hermens, 1995)*

♦ Conclusions SeNPV

1. concise dossier (less reliable data; generally useful)
1A. non-exhaustive literature survey
1B. emphasis on interviewing experts (more communication with e.g. UBA, KEMI, EPA)
2. sufficient data for environmental risk assessment; major assumptions:
2A. non-indigenous in NL (Southern Europe?)
2B. greenhouse ("containment"; restricted area)
2C. NPVs in general→ SeNPV
2D. biological properties (*e.g.* mode of action)/single host species (*Spodoptera exigua*)
2E. "residues" (OBs) in the field absent/low amounts
3. major NTOs of concern (potential exposure):
3A. predatory arthropods and pollinators (IPM!)
3B. predators in the field (in case of "escape")
3C. terrestrial/phyllospheric micro-organisms (competition?)?
4. environmental risks in greenhouses considered to be low, primarily in view of the NPV mode of action, its microbiology, and its narrow host range. [lack of adverse effects confirmed in literature]

♦ Discussion:

1. pragmatic approach (no data for the sake of data alone; is an additional test really necessary?)
2. data requirements should depend on "what to do with the data". Ideally, it is important to discuss the company's test program with the CA prior to performance. Herebye focusing on:
2A. efficacy tests (for determination of the host range) and the intended use (for likely exposure)
2B. potentially exposed NTOs: *e.g.* in the case of SeNPV ⇒ predatory arthropods and pollinators for IPM in greenhouses
3. what about less "well-known" micro-organisms?
4. what about genetical exchange?
5. which taxon should be registred? (e.g. isolate, strain, family..)
6. microbial pesticides ⇔ vaccines

- microorganism/spores ⇔ living/inactivated microorganism
- survival/replication

in the lab/field? ⇔ residues of vaccines?

- characterization/efficacy tests ⇔ characteris./safety test/toxicokinetic test

Appendix D. Presentation of B. Loos (CSR) on the assessment of Genetically modified Organisms.

EU legislation concerning gmo's

- 90/219/EEC Directive contained use gmo's
- 90/220/EEC Directive deliberate release of gmo's, including placing on the market
- 97/258/EEC Novel Foods Regulation

Bureau GGO rivm

Legislation in the Netherlands: granting a permit for the deliberate release into the environment

- Receipt — start (day 1)
- judging completeness — (week 8)
- (if desired) advise COGEM
- Draft decision — (week 12) paraaf LNV/VWS
- Public phase: objections — (during 4 weeks)
- Decision — (6 mnd) paraaf LNV/VWS
- Public phase: appeal — (during 6 weeks)

NB: a license will only come into force after the period for appeal. If there is a call for stay of execution the license will not come into force.

Legislation in the Netherlands: the GMO Decree

- Goal

Working safe with gmo's, preventing undeliberate release by:

- physical containment
- biological containment
- chemical containment

Working with gmo's in the Netherlands: environmental risk assessment

- VROM
  - grant a licence
- RIVM/CSR/Bureau GGO
  - handling unit Decree GMO applications
- COGEM
  - advisory body

Bureau GGO rivm

Advisory bodies concerning gmo's

- COGEM Committee on Genetic Modification
- VCVNV Temporary Committee on Safety of Novel Foods
- CBD Committee on Biotechnology on Animals
- KEMO Central Committee on Ethics of Medical Research

Bureau GGO rivm

Dutch legislation concerning gmo's

- VROM
  - Decree Genetically Modified Organisms
    - ✓ Ministerial Regulation genetically modified organisms and the guideline of the COGEM to this Regulation
- VWS
  - Commodities Act
- LNV
  - Decree on Biotechnology on Animals

Bureau GGO rivm

Legislation in the Netherlands: the application form for deliberate release into the environment

- General data
- Host organism
- Modification
- The GMO
- Mode of introduction
- Mode of observation
- Analysis of the effects of the GMO on Man and the Environment

Bureau GGO rivm

Appendix E. Presentation of J. Schefferlie (CSR) on the procedures and organisation of the assessments.

RIVM - National Institute for Public Health and the Environment

Evaluation of Veterinary Medicinal Products

Johan Schefferlie

Assessments for veterinary drugs at RIVM

- CSR (Centre for Substances and Risk assessment)
  - Part III.B: residues, including the routine analytical method
  - Part III.A 6: user safety
  - Part III.A.5: ecotoxicity
- LGO (Laboratory for Quality Control of Medicines)
  - Part II: pharmaceutical data
- LPI (Laboratory for Pathology and Immunobiology)
  - User and Consumer safety of immunological products

Centre for Substances and Risk assessment (CSR)

Main task:

assessing the risks to human health and the environment resulting from substances and genetically modified organisms

Fields

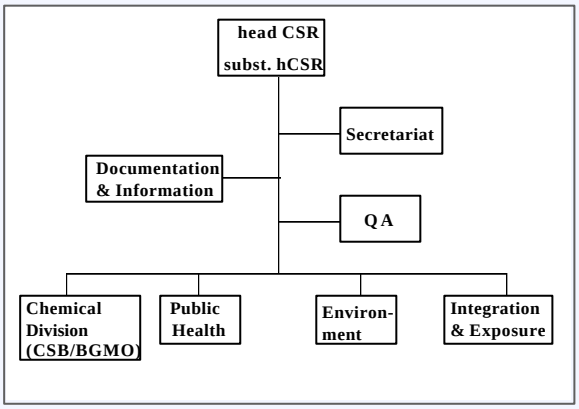
- new chemicals
- existing chemicals
- pesticides
- veterinary drugs
- feed additives
- food additives
- cosmetics
- packaging materials for food
- novel foods
- genetically modified organisms

Organisation of VMP assessments

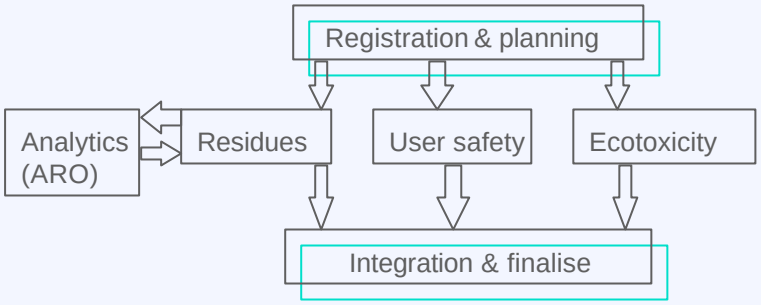
Clients: public authorities only

- Ministries of Public Health (VWS) and Environment (VROM)
- Other public authorities (other ministries, Bureau for the Registration of Veterinary Drugs)
- International organisations
  - European Union
  - OECD
  - WHO
  - FAO
  - IPCS
  - JMPR
  - JECFA

Organogram of CSR

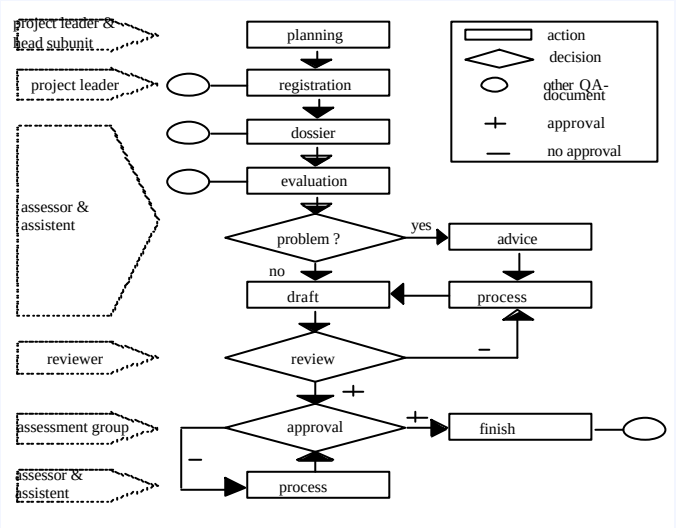


VMP assessments



Organisation of VMP assessments

General process



Organisation of VMP assessments

Number of CSR assessments in 1997

	Ecotoxicity	User safety	Residues
new applications	17	47	36
renewal of registrations	41	0	9
variations	2	4	0

Appendix F. Mailing list

1 Hoofd Bureau Registratie Diergeneesmiddelen, t.a.v. Drs. C. Kuijper
2 Hoofd Centrum voor Stoffen en Risicobeoordeling, t.a.v. Dr. W.H. Könemann
3 LNV, Directeur Veterinaire, Voedings- en Milieuaangelegenheden, t.a.v. Ir. G.A. Koopstra
4 VWS, Directie Gezondheidsbescherming, t.a.v. Mr. J. de Haan
5-7 Bureau Registratie Diergeneesmiddelen, t.a.v. Ir. G. de Bruijn, Wageningen
8 LNV, Directie Veterinaire, Voedings- en Milieuaangelegenheden, t.a.v. dr. ir. M.M.C.G. Peters
9 Depot van Nederlandse publikaties en Nederlandse bibliografie
10 Directie RIVM
11 Sectordirecteur Stoffen en Risico's
12 Sectordirecteur Milieuonderzoek
13-17 Ir. G.J. Schefferlie, projectleider Beoordeling dierbehandelingsmiddelen
18 Dr. L. van Leemput, FEDESA
19 Secretariaat FIDIN
20-24 Dr. B. Wagner, UBA Berlijn
25 Dr. J. Bongers, ID-DLO Wageningen
26 Dr. H. Oei, ID-DLO Wageningen
27 Dr. B. Loos, CSR
28 Dr. F. van Poelwijk, CSR
29 Drs. H. Mensink, CSR
30 Ir. J. Linders, CSR
31 Drs. P.M. Dortant, LPI
32 Auteur
33 Bureau Rapportenregistratie
34 Voorlichting en Public Relations
35 Bibliotheek RIVM
36 Bibliotheek CSR
37–50 Bureau Rapportenbeheer