Update of the risk assessment of the foot-and-mouth disease virus (FMDV) antigen production plant (APP), Houtribweg, Lelystad, The Netherlands

A study commissioned by the Dutch Ministry of Agriculture (LNV)

Dates of Mission: 5 to 7 October 2009

Date of report: 16 October 2009

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2. Executive summary

1. The expert team considered the risk assessment of the foot-and-mouth disease (FMD) antigen production plant (APP) study of March 2007 commissioned by the Dutch Ministry of Agriculture (LNV) as generally still valid.
2. In cases were the expert team concluded that new developments and insights have to be taken into account, the respective parts of the 2007 risk assessment were updated.This applies in particular to the risk associated with disposal of waste water from antigen production: this most plausible explanation of the 2007 outbreak in the UK neccessitated a revision of the 2007 risk assessment.
3. It was considered unneccessary to reassess the four scenarios described under 5.1.1 to 5.1.4 of the 2007 risk assessment.
4. In consultation with the Ministry of LNV, it was decided to analyse two scenarios. The first scenario was outlined by the potential buyer - extend the production and R&D facilities, utilize the infrastructure of the CVI and work within the biorisk management structure of the CVI. The second scenario was an extension of the production and R&D facilities in Lelystad in an independent infrastructure and with an independent biorisk management structure, under the responsibility of the buyer but close to the CVI.
5. It was concluded that the risk associated with the first scenario was not significantly greater than that that associated with the activities of CIDC-Lelystad during 2004/2005/early 2006
6. It was concluded that the risk associated with the second scenario was somewhat greater than that in the first scenario by maintaining two separate HCU's and biorisk management systems (in close vicinity) under separate responsibilities/legal entities.
7. It was concluded that a situation where it is unclear who is responsible for certain parts of the infrastructure or the equipment has to be avoided.
8. The expert team has recommended a series of conditions for inclusion in the contract with the buyer to ensure that the company complies unconditionally with the biorisk and GMP requirements and thereby maintains the relatively low risk profile of the APP. A requirement of GMP is that personnel must be qualified and experienced. This gives a safeguard against the possible employment by a new owner of unqualified personnel.

3. Background and terms of reference

The foot-and-mouth disease (FMD) Antigen Production Plant (APP), located in the High Containment Unit of the Central veterinary institute (CVI),Houtribweg, Lelystad, belongs to Lelystad Biologicals b.v.. FMD antigen is produced at the HCU-facilities of CVI-Lelystad but vaccine formulation and filling is done at the facilities at Edelhertweg about 5 km away. CVI-Lelystad belongs to Wageningen University and Research Centre (Wageningen UR). Before the operation of the APP was taken over by Lelystad Biologicals b.v, the Dutch Ministry of Agriculture (LNV) had commissioned a risk assessment of the foot-and-mouth disease (FMD) antigen production plant (APP) hereinafter called the 2007 study.

In 2009, another expert team was asked to comment and advise on the following key questions:

What has changed compared to the situation analysed in the 2007 risk assessment?

What are the biorisk implications of the two situations decribed below?

> *1. The company producing FMD vaccines will extend the production and R&D facilties and utilizes the infrastructure of the CVI and works fully within the biorisk management structure of the CVI*
>
> *2. The company producing FMD vaccines will extend the production and R&D facilties and has its own infrastructure and biorisk management system - in close vicinity to the HCU of the CVI*

4. What has changed compared to the situation analysed in the 2007 study?

Compared to the situation 2007, the following changes have to be taken into account:

a. In 2007, there was an epidemic (8 infected premises) of FMD in the UK due to an escape of FMDV (O_{BFS}) from either the Institute for Animal Health (IAH) or the Merial vaccine plant in Pirbright. The most likely explanation is a leakage of contaminated waste water from a pipe that ran through the ground without double walls or regular pressure testing to the waste water treatment plant of the IAH. This pipe was used by both facilities. There are concerns that infectious cell sludge from a centrifuge on the Merial site was released to this pipe without proper inactivation. However, this could not be proved beyond doubt. Further factors potentially involved were flooding due to heavy rainfall and construction works on the IAH site. As a consequence of the events in the UK, the risk

analysis of activities at the CVI, including the APP, was amended and considerations on the disposal of virus culture fluid or cell debris from production vessel or other production equipment before inactivation was added (see No. 10 of Appendix 2).
For the disposal of virus culture fluid or cell debris from production vessels or other production equipment (e.g. disposal of unsuitable virus cultures) a reliable inactivation before release into the waste water system has to be required as a standard procedure. Especially when this waste water system (including all pipes) is not completely in full containment (khaki area) this inactivation at source is an absolute necessity.

b. The CIDC was merged with the division for infectious disease of ID Lelystad into the Central Veterinary Institute (CVI) (Letter of LNV, DK.2007/3424 13 December 2007). The responsibilities and the tasks of the former CIDC were taken over by the CVI and as before, have to be performed under the Statutory Statute (CVI-stat. tasks, formerly called CIDC). This statute is intended to guaranty the independence of the statutory work. The tasks of the former ID Lelystad were also taken over by CVI which is allowed under restrictions to perform contract research.

c. The new MINIMUM CONTAINMENT STANDARDS FOR FMD LABORATORIES were adopted by the 38th General Session of the European Commission for the Control of FMD (EUFMD), Rome, April 2009 and it is planned to include them into Annex XII of Council Directive 2003/85/EC. In this document, the terms biorisk, biosafety and biosecurity are defined as in the latest available draft of the CEN/CWA "Laboratory Biorisk Management Standard", Edition April 2008. In this update these terms were used accordingly.

d. A potential international buyer with huge experience in the production of FMD vaccines has announced his interest in purchasing the APP in Lelystad and expanding R&D and production capacity. The buyer has indicated that he would like to concentrate R&D and QC activities in the currently unused second floor of the APP-unit. He has also indicated that he is considering building a new wing to the present production building. It was suggested by the buyer that all the extensions will still operate under the biorisk management system of the CVI.

There are considerations whether the extension beyond a certain level would require a new HCU infrastructure which operates completely independently from the CVI and its services/utilities but still in its close vicinity.

Despite the changes outlined above, the expert team considered the risk assessment of the foot-and-mouth disease (FMD) antigen production plant (APP) (2007 study) as generally still valid.

5. What are the risks of selling the FMD antigen production plant Lelystad according to two scenarios:

5.1 The company producing FMD vaccines will extend the production and R&D facilties and still utilizes the infrastruture of the CVI and works fully within the biorisk management structure of the CVI.

The buyer, an experienced international FMD vaccine producer, plans to take over the APP, including most of the staff. In future, it plans to enlarge the R&D capacity (now situated in the CVI-part of the HCU) and to concentrate this by renovating the currently unused second floor of the lab building and to extend the production capacity by adding a new wing to the current building.

As the buyer is a very experienced FMD vaccine producer and works strictly according to GMP rules the conditions mentioned in the 2007 study will, in principle, be met.

The expert team considers the use of the existing infrastructure of the CVI also for a moderately expanded APP to be feasible and reasonable. The full capacity for waste water treatment in each of the two existing waste water treatment plants is about 70 tons per day. (It is not advisable to base the estimate of the spare capacity of the existing infrastructure on the use of both plants, as one is considered a back-up in case of problems or sheduled maintainance. If in exceptional cases, both plants are used, they could process about 140 tons of water per day.) As currently 30 to 50 tons of water have to be treated daily, the spare capacity is 20 to 30 tons. One batch of antigen produces about 10 tons of waste water over 3 days, so spare capacity for a significant increase of production is available. The capacity for steam production as well as the normal and back-up supply of electricity was described by the facility engineer as fully sufficient even in case of significantly increased antigen production. He also stated that they could be upgraded within the existing building if needed.

The number of animal challenge experiments performed at the CVI and the competition for the resources of the CVI will be limited as the buyer indicated that these experiments will normally only be performed with "new" strains, but not for routine batch release.

The first scenario is comparable to the one analysed in point 5.1.2 of the 2007 study, except that the buyer will significantly upgrade and enlarge the facilities and there will be a sharp spatial separation of CVI and APP activities. If properly managed, in the first scenario there will be no additional risks compared to the situation analysed under point 5.1.2 in the 2007 study.

The expert team recommends that the following conditions should become part of the contract with the buyer:

The biorisk management system must **comply with the new MINIMUM CONTAINMENT STANDARDS FOR FMD LABORATORIES** adopted by the 38th General Session of the European Commission for the Control of FMD.

There has to be **one biorisk management system** under the responsibility of the CVI statutory tasks.

The **responsibilities** of the CVI and the buyer have to be **clearly defined**. This is the more important when changes in infrastructure and engineering are to be implemented.

There has to be a **responsibility of the buyer to comply** with the CVI biorisk management system.

The buyer has to **grant** the CVI BSO and the CVI facility engineer **access** to the APP. The **CVI BSO has the right to inspect** the APP without anouncement.

The **CVI-BSO has the right to immediately suspend operations** in the APP and/or associated facilities if he considers that there has been a breach of the biorisk management rules or if such a breach is likely or imminent. The BSO must inform the Director of CVI-Lelystad without delay.

The buyer has to appoint **qualified staff members who can be contacted by the CVI BSO or facility engineer in case of (potential) biorisk incidents** 24 h / 7 days a week.

The buyer has to appoint a **staff member with biorisk responsibilites** (e.g. QA manager) who also attends the CVI biorisk committee meetings as an advisor.

The buyer has to **seek approval** of the CVI for all modifications of the building and all major changes of equipment (e.g. new vessels, water and steam lines).

The **buyer has to inform the CVI BSO** about all activities and incidents in the APP with a **potential biorisk relevance**. In particular, the buyer has to notify the CVI BSO about

1) all biorisk incidents
2) all changes in SOPs
3) all changes potentially affecting the secondary containment
4) all changes potentially affecting the infrastructure of the site
5) all changes affecting the inactivation of antigen

5.2 The. company producing FMD vaccines will extend the production and R&D facilities and has its own infrastructure and biorisk management system - in close vicinity to the HCU of the CVI

The expert team concluded that if the buyer intends to expand the antigen production capacity in Lelystad to a level approching it´s current major European production site, the current infrastructure would not be sufficient. In this case, there could be a tendency to add new parts to the infrastructure under the responsibility of the buyer. The interference between two connected technical infrastructures could create management problems and it would become more difficult to separate the responsibilities of the CVI from that of the buyer, leading to potential biorisk problems.

On the other hand, maintaining two separate HCU's and biorisk management systems (in close vicinity) under separate responsibilities/legal entities could also lead to potential biorisk problems. Currently the CVI has intimate knowledge of the biorisk situation of Lelystad biologicals and of the third parties involved in reconstruction, engineering and maintenance and related biorisk issues, e.g. contractors. This advantage of an intimate knowledge will no longer apply to the facility operated by the buyer in the second scenario. In case of a very unlikely outbreak of FMD in the vicinity of the two HCU-plant a complex situation will arise when investigating the cause of the outbreak and the responsibilities involved.

Nevertheless, it was concluded that setting up an independent infrastructure with a clear division of responsibilities between the buyer and the CVI would be preferable to a situation in which the buyer is responsible for parts of the enlarged infrastructure and the CVI for other parts and both parts interfere with each other. In case the buyer operates his own independent infrastructure, the biorisk management system of the buyer should be harmonized as far as possible with that of the CVI and must be strictly supervised by the competent authority.

Even in case the antigen production capacity is enlarged to an extent that the option of setting up an independent infrastructure operated by the buyer has to be considered, the number of animal challenge experiments performed in Lelystad probably will not increase significantly. For economic reasons as well as due to the increased acceptance of in-vitro results for batch release, challenge experiments will normally only be performed with "new" strains. It is therefore unlikely that the buyer would like to set up his own animal challenge facilities in Lelystad. The competition for the animal testing resources of the CVI will still be limited.

The expert team recommends that for this second scenario the following conditions should become part of the contract with the buyer:

The buyer´s biorisk management system must comply with the new **MINIMUM CONTAINMENT STANDARDS FOR FMD LABORATORIES** adopted by the 38th General Session of the European Commission for the Control of FMD.

The buyer is **responsible for the infrastructure and the biorisk management on his site -** which should be independent from those of the CVI.

Nevertheless, it should be attempted to **harmonise the biorisk management systems of the CVI and the buyer** as far as possible.

The **biorisk management system of the buyer has to be audited independently** on a regular basis.

The buyer has to **inform the responsible authority** about all activities in the APP with a biorisk relevance.

The responsible authority has the **right to inspect** the APP without anouncement.

The responsible authority has the **right to immediately suspend operations** in the APP and/or associated facilities if it considers that there has been a breach of the biorisk management rules or if such a breach is likely or imminent.

The buyer has to arrange as part of the biorisk management system that qualified **staff members are available in case of (potential) biorisk incidents** 24 h / 7 days a week and systems are in place to alert them also outside of normal working hours of any such incident.

The **waste water treatment has to be done within the containment** and all waste water pipes have to be in the containment.

It is recommended that the buyer´s BSO attends the CVI **biorisk committee meetings** as an advisor and vice versa, the BSO of the CVI attends the biorisk management committee meetings of the buyer as an advisor.

6. General recommendations

It is recommended that guidelines are created which allow a fruitful research co-operation (e.g. use of valuable samples from experiments by both parties, joint research projects) of the CVI and the buyer while ensuring that the CVI statutory tasks are not affected.

Future renovations should be considered an opportunity to introduce double piping or similar provisions against leakage in case a pipe potentially containing infectious virus passes through an area which has a lower biorisk status (e.g. the downstream processing area for inactivated antigen or the "khaki area").

7. Acknowledgements

The members of the expert team gratefully acknowledge and thank Peter de Leeuw, Katharina Kardinal, Kees de Roos, Derk Hulleman, Herman Louwes, Marlies Kolkman, Michel Dauvergne, Dick Pouwels, Johan Bongers, Hans Kramps, Martin Schutte, Johan IJzerman, Douwe Kuperus and Phaedra Eble, for helpful discussions and constructive advice.

8. Appendices

Appendix 1: Meetings and visits during the mission to Lelystad.

Appendix 2: Risk analysis of activities at CVI, including the APP, with modifications suggested by the expert team 2009

Members of the expert team:

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, QA/QP Lelystad Biologicals b.v.
. QA officer Lelystad Biologicals b.v.
, Directeur des Productions Biologiques France, Merial.
. Director Operations. Animal Sciences Group
, Head of Virology department, CVI
. Head of Biosafety office CVI
, facility Manager CVI
, biosafety officer CVI
, biosafety officer CVI
, FMD expert CVI.

Appendix 1

Meetings and visits during the mission to Lelystad

Monday October 5th 2009

Frenkelzaal	***Plenary Session***
14.00 – 14.30	Introduction to Lelystad Biologicals BV
14.30 – 15.00	Summary recommendations and conclusions of previous risk assessment
15.00 – 16.30	Presentation of proposed changes in working procedures, production scale and infrastructure by potential new owner
	Bilateral session
16.30 – 17.30	Director ASG
18.00 onwards	Departure to hotel / restaurant for dinner

Tuesday 6th October 2009

	Visits of critical areas
8.30 – 11.00	Visit to cell culture, FMD production facilities, virus Culture, DSP area, engineering areas, "unused 2nd floor" and other "khaki aeras"
Frenkelzaal	***Bilateral session***
11.00 -12.30	Facility Manager High Containment Unit; Manager operations CVI
12.30 -13.30	***Lunch***
	Bilateral session
13.30 – 15.30	Biosafety Officer High Containment Unit
16.00 – 17.00	Research vesicular diseases

Wednesday 7th October 2009

Frenkelzaal	
8.30 – 12.00	Discussion / preparation of report

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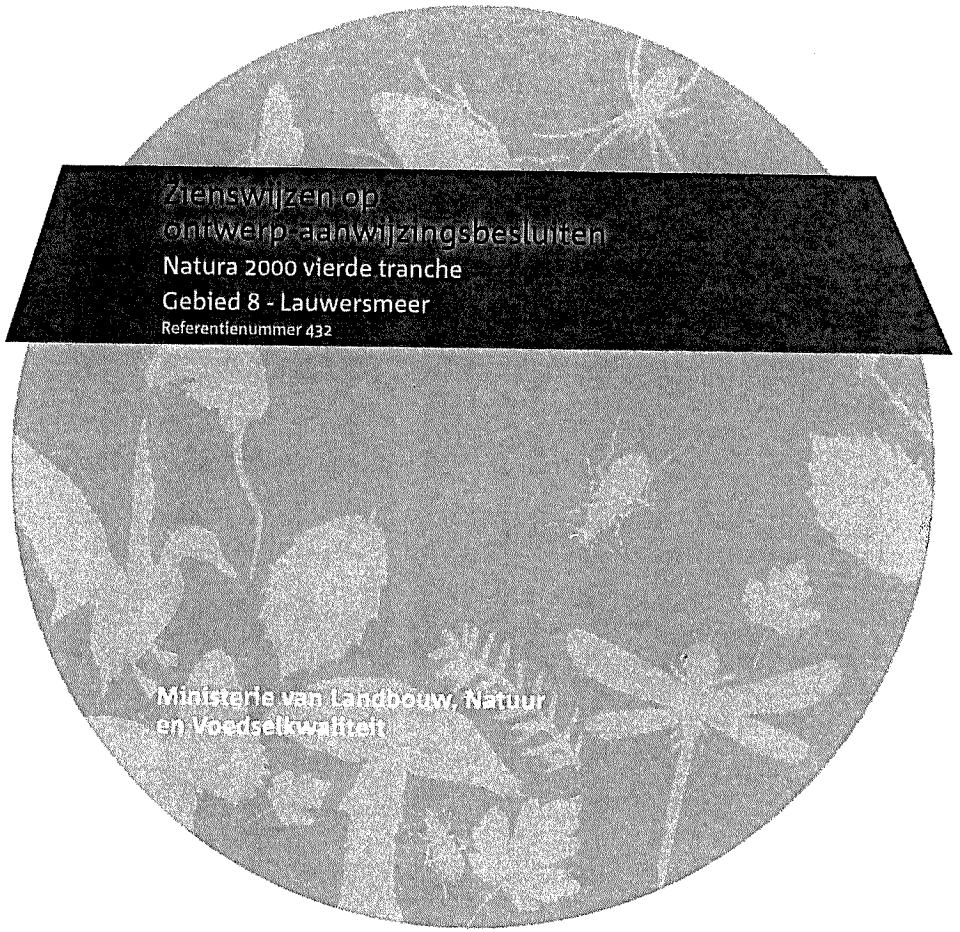

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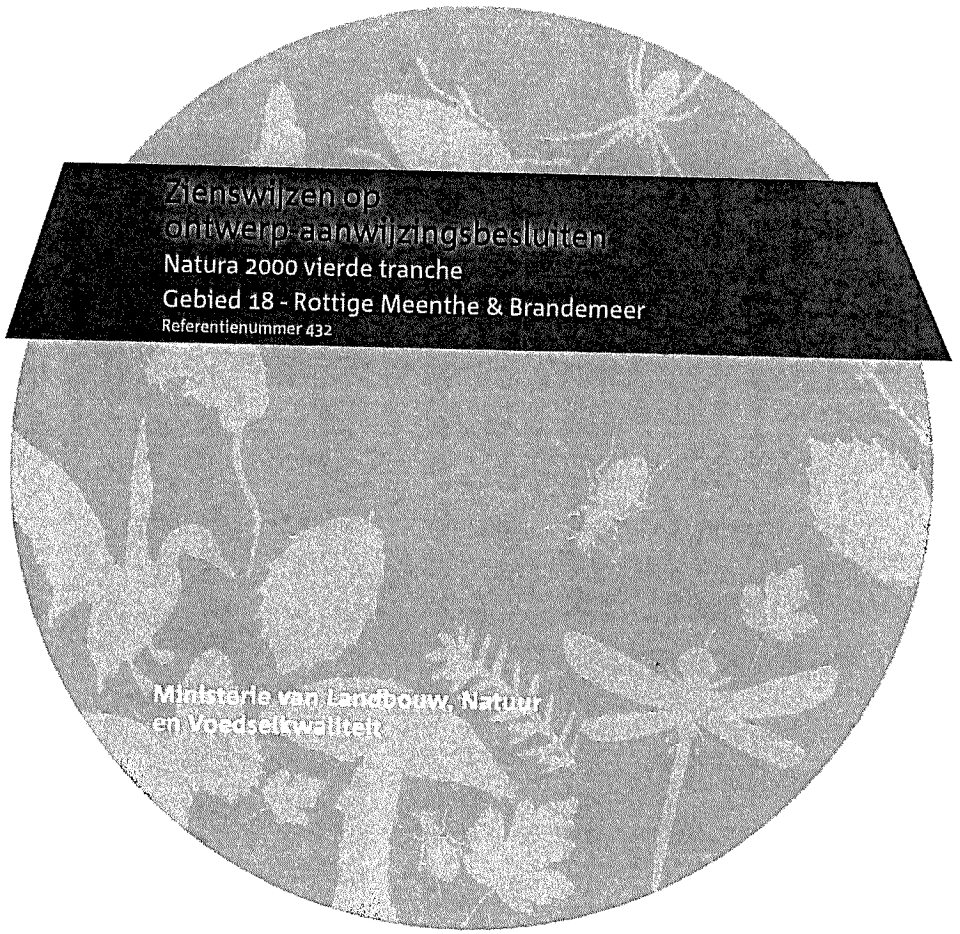

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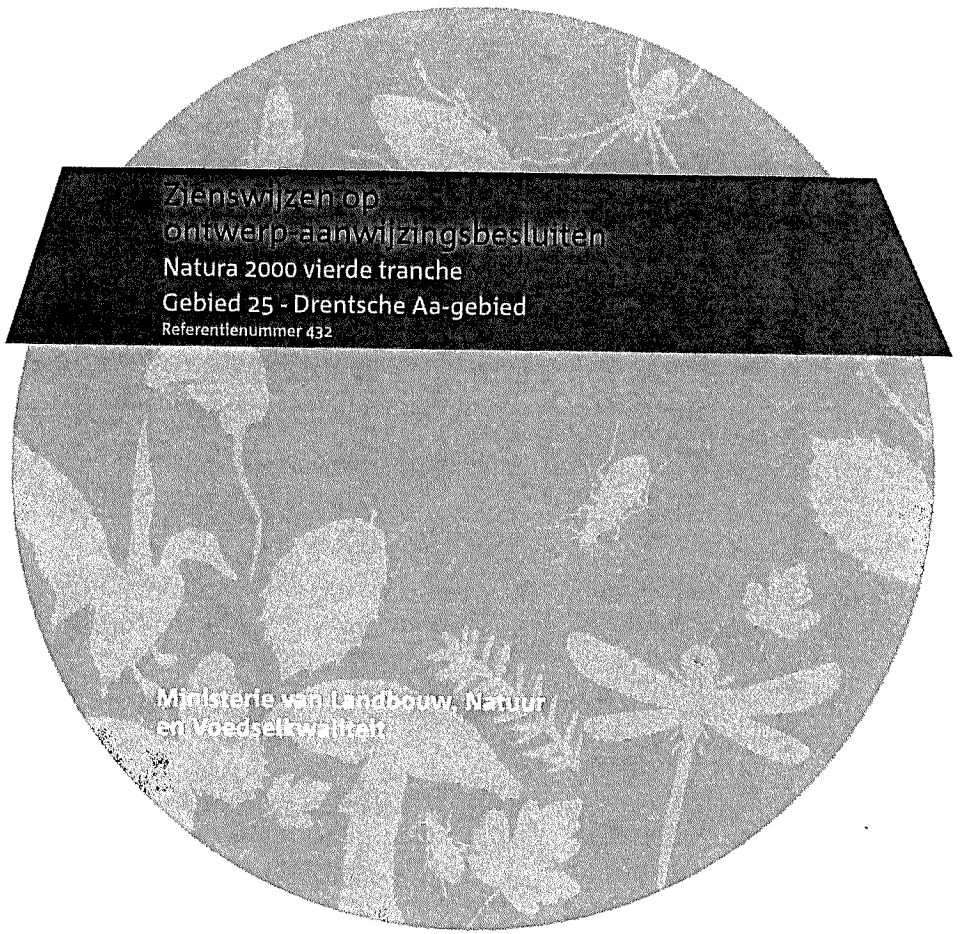

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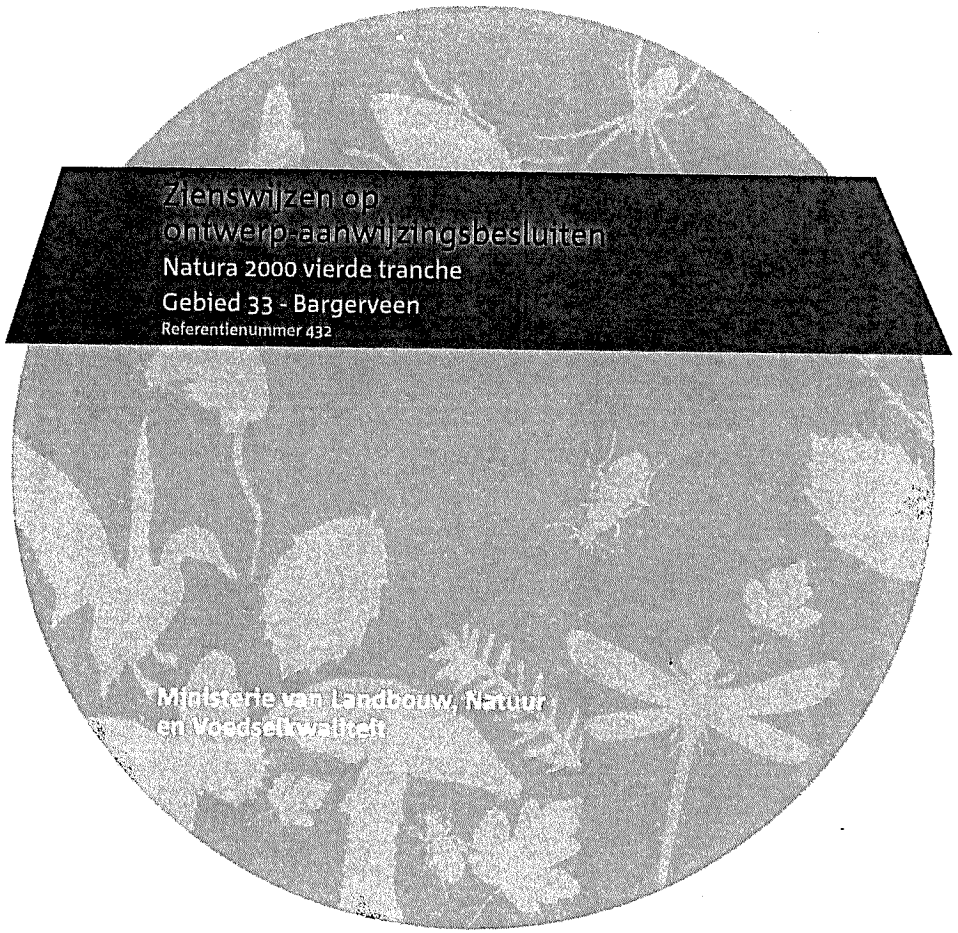

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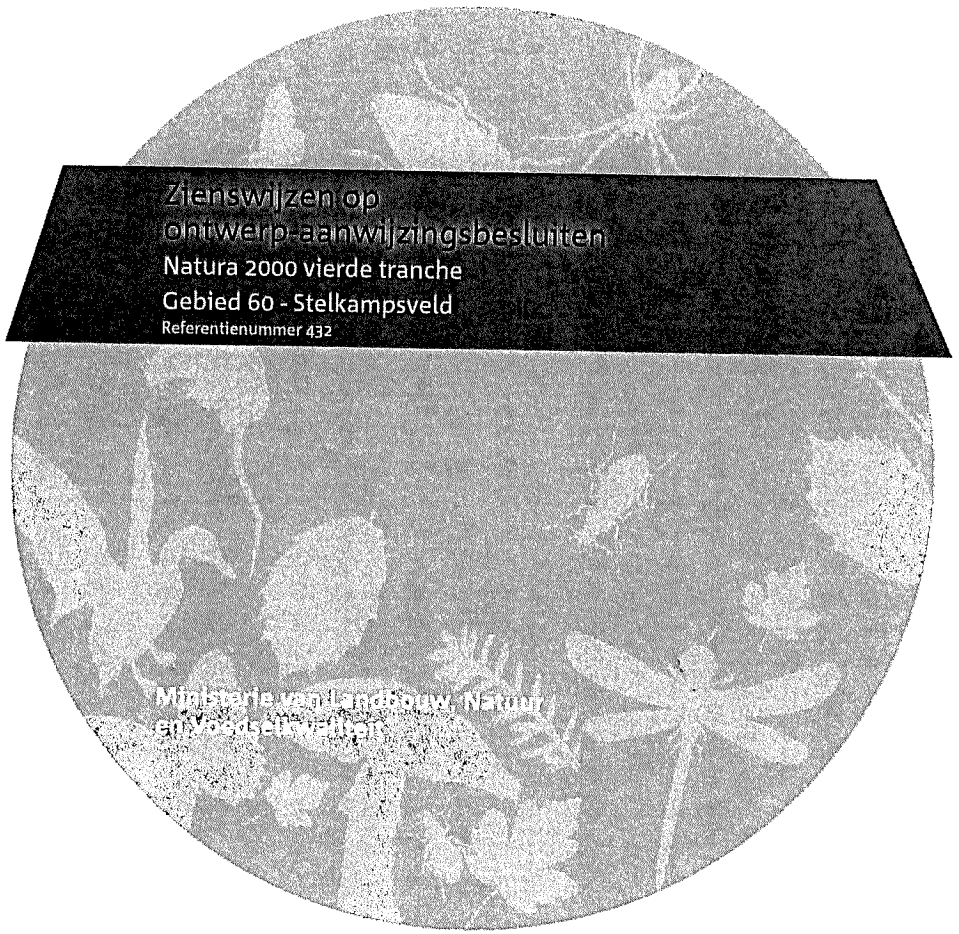

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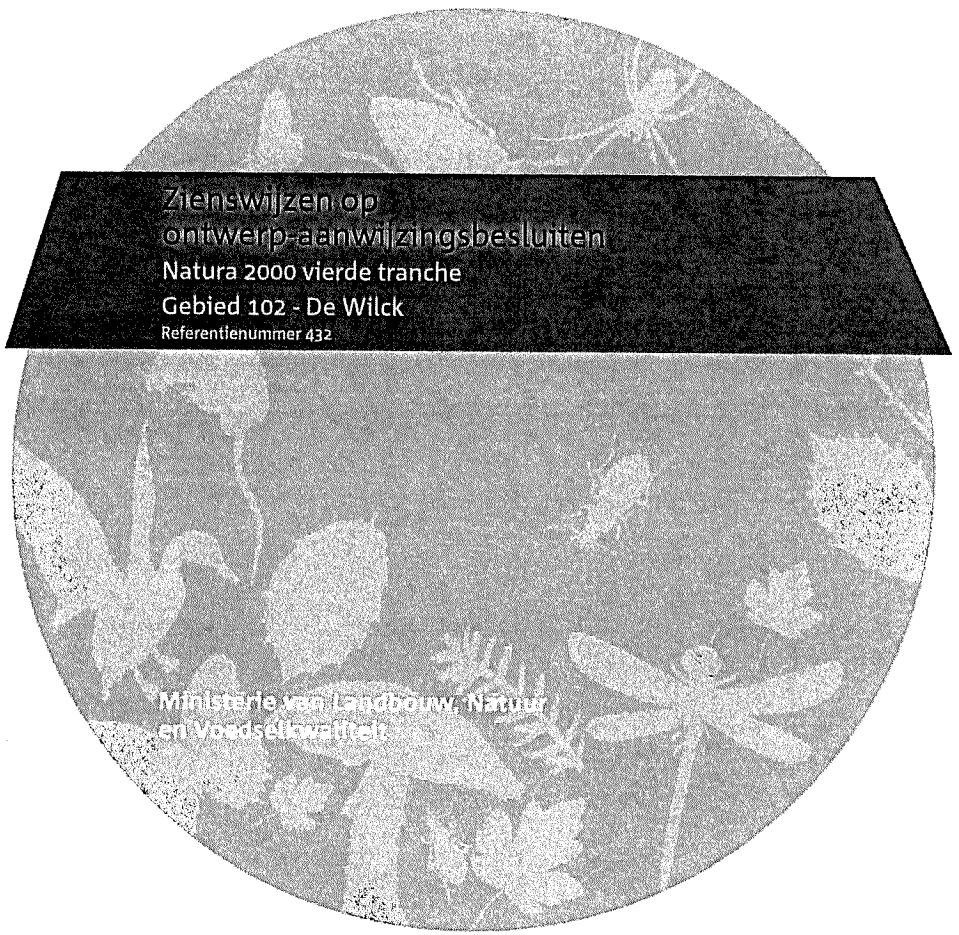

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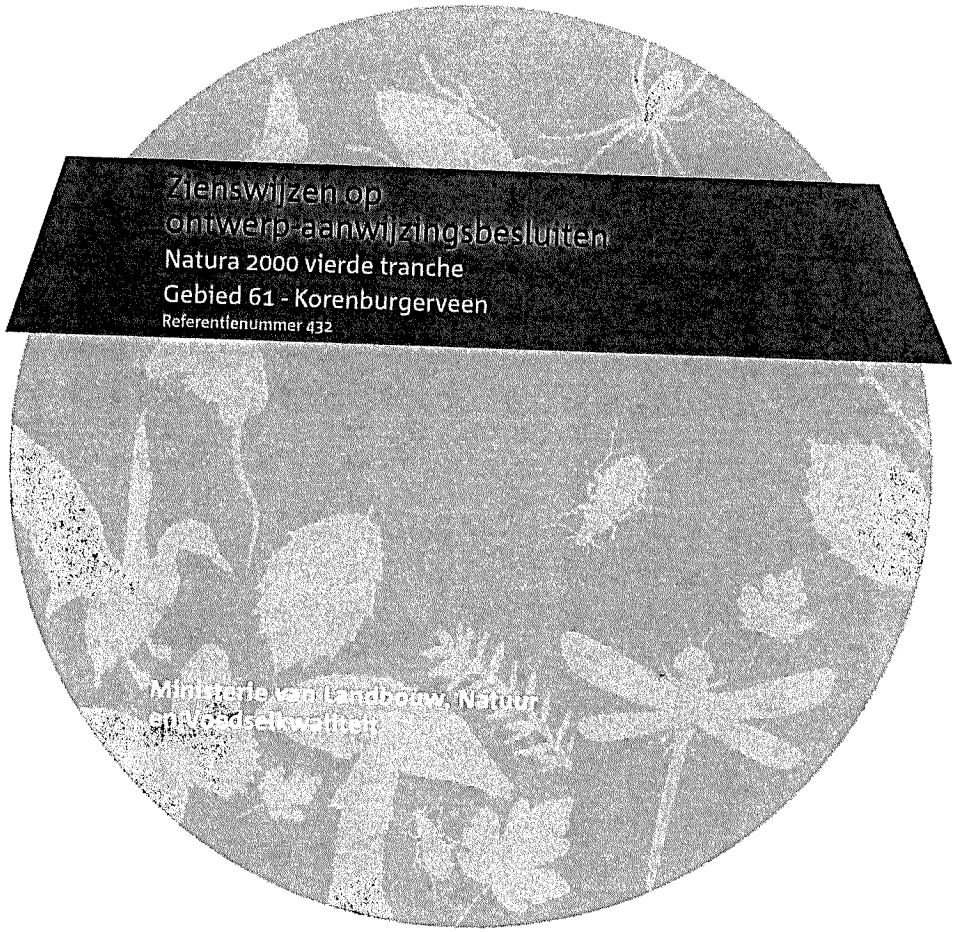

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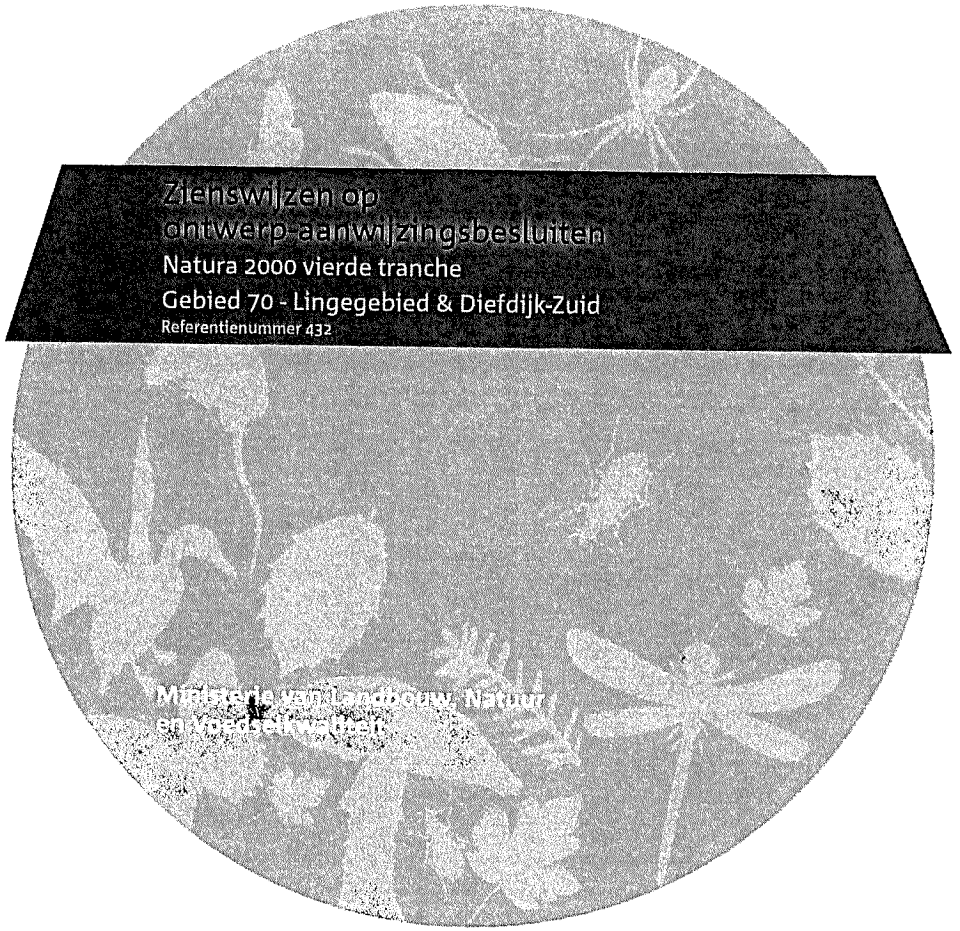

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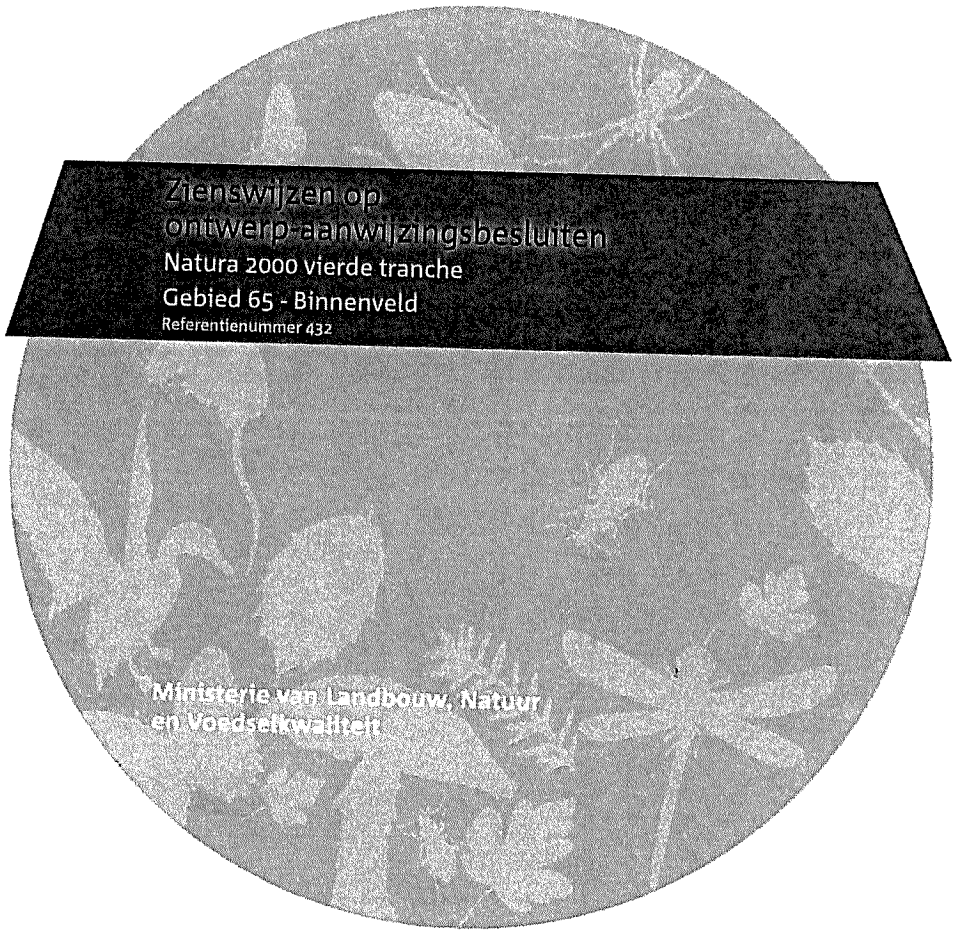

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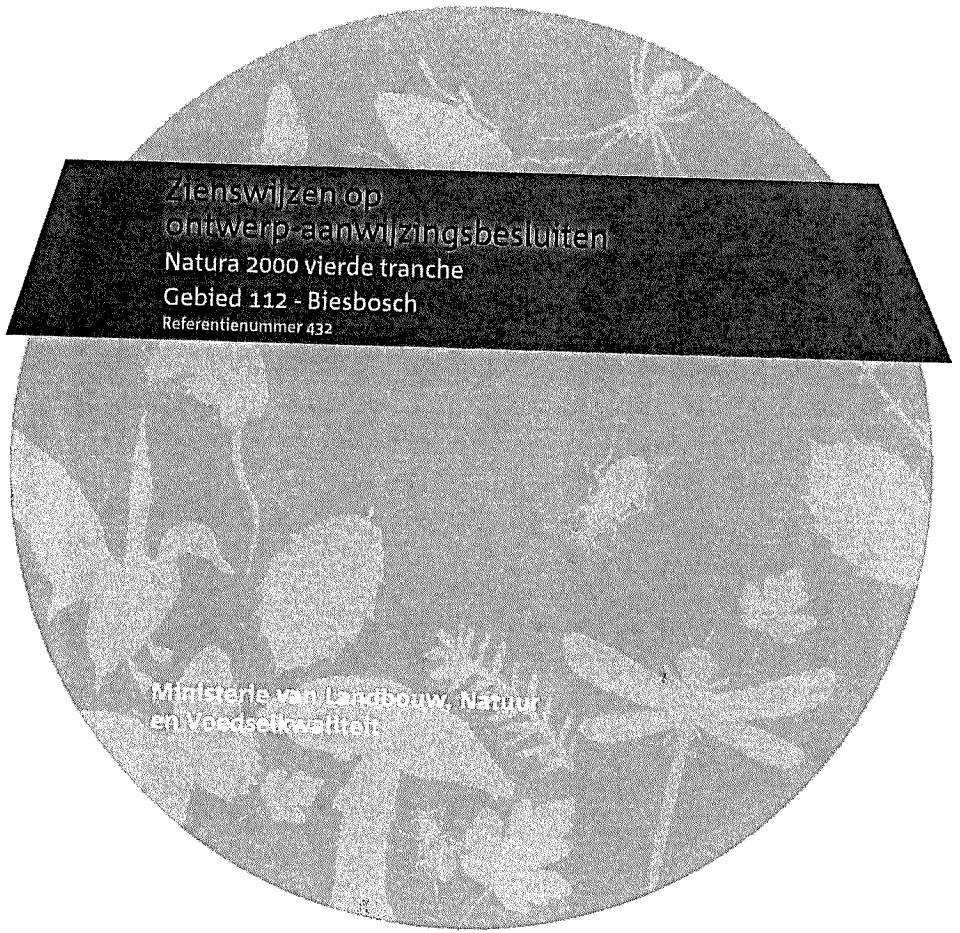

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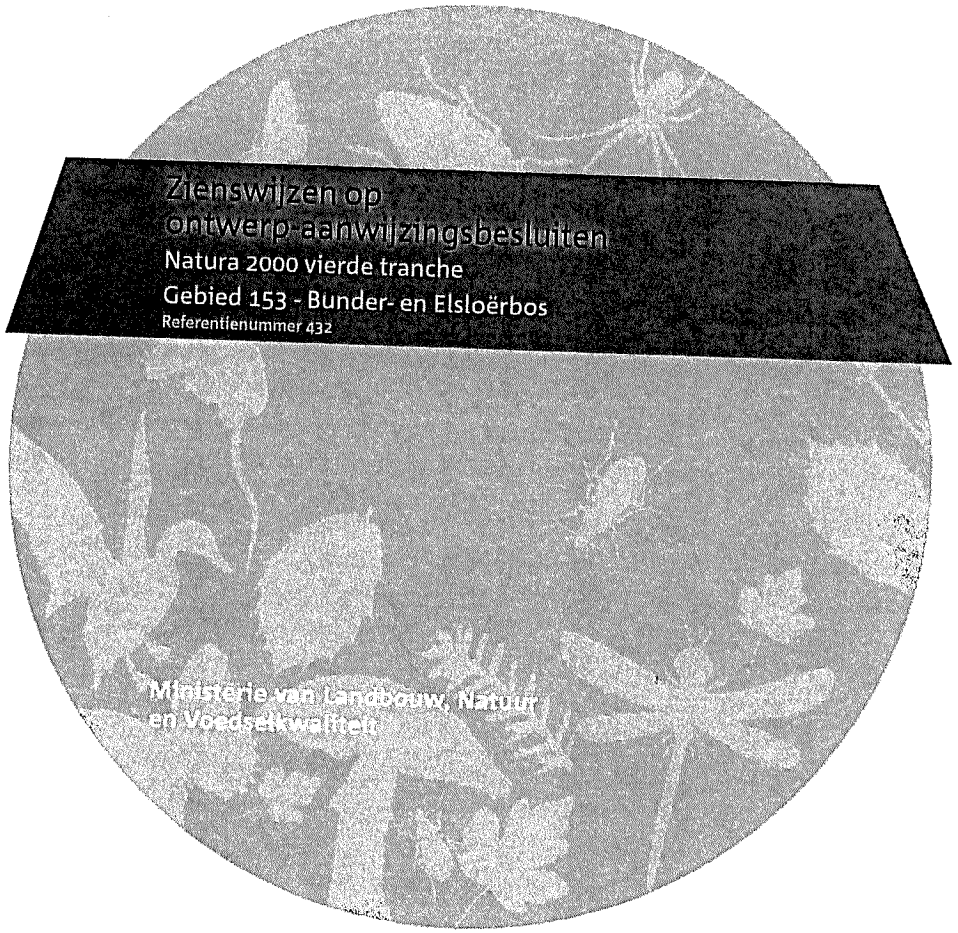

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