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PRELIMINARY REPORT ON

THE RISK ASSESSMENT FOR ANIMAL POPULATIONS

DISCUSSED BY THE SCIENTIFIC STEERING COMMITTEE

AT ITS MEETING OF 7-8 NOVEMBER 2002

NOTE :

This report was discussed by the SSC on 7-8 November 2002 as a preliminary document. It is based on data published in scientific journals or available from ongoing research projects. Other relevant information may, however, be available from other sources that do not commonly report on scientific or technical press. Scientists, industrial associations, research institutes, veterinary pathology laboratories, etc… are therefore invited to comment on the attached documents and, if appropriate, provide additional information. These contributions should be sent **before 3 January 2003** to the secretariat of the SSC. The SSC will, if appropiate, integrate them in its final opinion. The industry is invited to, as far as possible, co-ordinate its comments and channel them through existing associations. Individual comments are, however, also welcomed.

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DRAFT DOCUMENT FOR CONSULTATION AND COMMENTS

TASK FORCE ON HARMONISATION OF RISK ASSESSMENT

WORKING GROUP ON THE ENVIRONMENT

REPORT ON A MORE CONSISTENT APPROACH TO THE RISK ASSESSMENT FOR ANIMAL POPULATIONS

Several SANCO Scientific Committees are involved in the risk assessment of different stressors on farm and wild animal populations.

The requirements for assessing the risk on farm animals are basically covered in a general assessment of "health risks" were, in addition to human health risk, a secondary assessment covers the risk on animal health. No proper definitions on "which animals" should be covered under this assessment are normally found in the regulations or in the risk protocols. However, current practice indicates that the assessments mostly focus on farm animals and in particular mammals and birds. Only under certain conditions other animal populations, such as fish from aquaculture facilities or honeybees, could be considered in the assessment of animal health, although the common practice is to include all animals other than farm/domestic mammals and birds in the environmental assessment, even if there are managed by humans. The typical example are honeybees, their assessment is a key issue for the evaluation of pesticides. It focus on human handle populations that should be strictly considered as farm animals, however it is not included in the animal health assessment but in the environmental evaluation.

The assessment of wild populations is mostly covered in the ecological (often termed the enviromental) risk assessment. For allowing comparisons this document will focus on the effect assessment for wild mammals and birds, although when required, other animal groups will be mentioned.

Therefore, the main aim of this document is to compare the premises an methodologies employed for assessing animal health and those described for assessing population (not communities or ecosystems) risks under the environmental evaluation, focusing on the mammals and bird population assessment. Different kinds of stressors, of biological or chemical nature, will be compared. The risk related to Genetically Modified Organism requires an in-depth conceptual analysis and has not been included in this document.

The risk associated to infections agents, mostly focuses on farm animals (and frequently includes or even focuses on the Human Health risk associated to zoonotic diseases). Some opinions can focus on wild populations, such as the SCAHAW on Classical Swine Fever in Wild Boar or the opinion of the SCVMPH on *Vibrio vulnificus* and *Vibrio parahaemolyticus* in raw and undercooked seafood. However, it is clear that although these opinions cover environmental aspects, the basic aim is the protection of domestic animals and Human Health.

A significant innovation comes from the opinion of the SCP on the Data Requirements for Active Substances consisting of Micro-organisms, including viruses as Plant Protection Products (PPP). The opinion stressed the need for assessing the short-term and long-term implications of micro-organisms on ecosystems and human health, the differences in the behaviour between micro-organisms and chemicals as PPP, as well as the fact that test protocols that have been developed for chemical substances may not be appropriate for micro-organisms.

The risk of chemicals for animal populations is directly included in the comprehensive risk assessment. For pesticides, wild and domestic populations are considered independently, on the basis of different scenarios. For general chemicals, wild populations are part of the general assessment of ecological (environmental) effects, while domestic animals are not considered as an issue. However the assessment includes estimations of several environmental exposure pathways, and the effect assessment for Human Health and secondary poisoning is obviously based on the toxicity on mammals. Therefore, although no specific risk characterisation criteria for domestic animals are included, the basic principles can be extrapolated from the TGD.

Several risk assessment protocols, covering animal populations, are described below.

1. PRINCIPLES FOR ASSESSING THE RISK OF MICRO-ORGANISMS ON ANIMAL POPULATIONS

1.1 PRINCIPLES FOR RISK ASSESSMENT OF INFECTIOUS AGENTS

Aims and purpose of infectious disease risk assessment:

The aims and purpose of infectious disease risk assessment is dependent on the risk question being asked. For instance, the question, “What is the probability of a random animal in country A becoming infected with disease X?” will be concerned with considering the likelihood of a single animal becoming infected. In contrast, the risk assessment for the question, ‘What is the probability of a random animal in country A becoming infected with disease X and an epidemic resulting?’ will consider not only the likelihood of one animal becoming infected but the agent subsequently spreading and infecting further animals such that an epidemic results. A further risk assessment may consider not only the animal health but also the economic implications of an epidemic.

Ecological consequences can also be assessed. For example the risk question may be ‘What is the probability of an epidemic infecting species Z and subsequently reducing

the population of species Z to a level likely to result in its eventual extinction?' A further consequence, and again the subject of a further stage in the assessment, may take into account the reduction in biodiversity if a single species population is reduced. Each of these questions are sequential in that the first question must be asked before answering the second question. However, more importantly, each question results in a slightly different aim for the risk assessment despite all the questions collectively applying to infectious disease risk assessment.

Infectious disease risk assessment can be applied in two main circumstances. Firstly, a risk assessment could be undertaken to determine the probable amount of infectious agent already present, either in the specified country/region, or species, or both. This is based directly on an assessment of the prevalence of the agent in the specified population. Secondly, in all other circumstances, infectious disease risk assessment can be broadly thought of as an 'import' risk assessment since in order for an animal(s) to become infected, by definition the infectious agent has to 'move' or be 'imported' into a population from another location or population. The aim of an import risk analysis, as applied to investigating the risk of importing an agent from a particular country, is to provide importing countries with a defensible and transparent means of assessing this risk and also in identifying potential safeguards if the risk is unacceptably high (OIE, 2001). However this aim is also applicable to a risk analysis examining the risk of 'importing' a biological agent via movement of animals from one region to another within a country.

Most commonly, infectious disease risk assessment is undertaken to assess the risks associated with a biological agent for domestic populations. However, the same techniques can be utilised for assessing the risks to wild populations specifically. It is therefore obvious that the consequences of a domestic animal disease entering into a wild population or wild animal reservoir could be considered within a disease risk assessment undertaken for domestic animals.

Overall, the aim of any risk assessment with regard to protecting either animal health or considering economic consequences of a biological agent entering into an indigenous population, is primarily directed by the overall purpose and hence risk question being asked. This is important to note when considering harmonisation of risk assessment procedures that focus on the environment. However, most importantly, all risk assessments should be transparent in order that data deficiencies can be highlighted and to provide reviewers and policyholders with logical reasons for deriving the final outcome of risk, and effect of any potential safeguards.

Methodology:

The Office of International Epizootics (OIE) has outlined specific guidelines on the format to be utilised when undertaking import risk analyses for animals and their products. This methodology is also the most appropriate for risk analyses analogous to importation, as indicated in the previous section. (Figure 1).

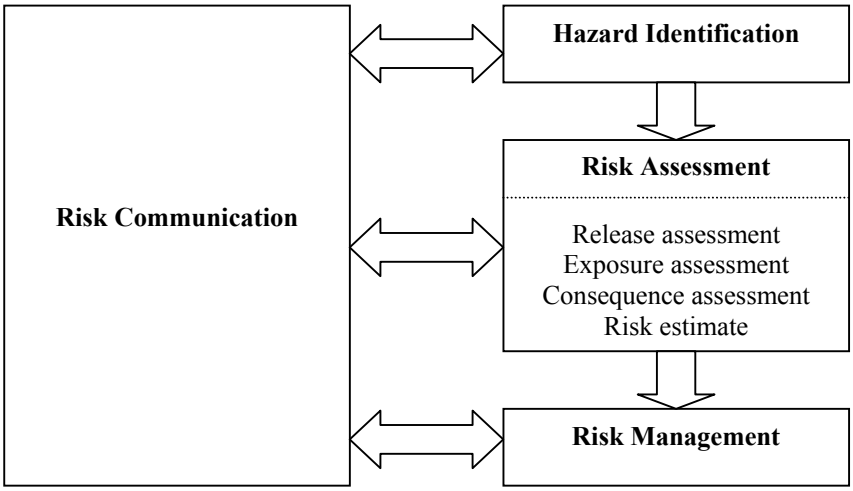

Figure 1: Summary of the components of an infectious disease risk analysis

Initially in order to undertake an infectious disease risk assessment, the risk question must be defined. For example, a risk question may be,

- "If animals of species X are moved from region A to region B what is the probability of epidemics of exotic disease occurring in region B due to hazards carried by X?"

This risk question will be used to illustrate the factors that are necessary to consider within the hazard identification and risk assessment procedures (as outlined with boxes after each step).

After defining the risk question, the next crucial stage is hazard identification, a categorisation step in which biological (and sometimes other) agents carried by, or present on, the animals and their products are identified as potential hazards or not. If no hazards are identified at this stage, then (unless there is the possibility of cross-contamination of animal products, for example) a risk assessment is not required. The hazard identification process will include consideration of viruses, rickettsiae, bacteria, fungi, protozoa, and parasites and may also include both chemical and physical agents. This process may involve literature reviews, data searches, and consultation with experts in order to identify all the potential biological hazards, especially in the case of importation of animal products (OMAFRA, 1997) (Roth, 1995). An example of the hazard identification process for the example risk question is outlined below.

Hazard Identification process for the example risk question:

- Consider and gather all information on the biological agents to which Species X is susceptible, in particular starting with the probability of their presence in Region A

After the hazard identification process is complete, the risk assessment can be undertaken. Infectious disease risk assessment, as outlined by the OIE, comprises four

main steps, namely release assessment, exposure assessment, consequence assessment and risk estimate. Each stage will now be briefly discussed in terms of the aim and some of the basic factors considered within each step.

Within a release assessment, the probability is estimated that a biological agent is 'released' under a specific set of conditions with respect to amounts and timing of release and how these might be influenced by various actions, events or measures (OIE, 2001). Release, in this context, means the 'import' into a particular country, region or site the animal or animal product (for example meat, milk, hide, exhaled air, vesicle fluid) containing or carrying the hazard(s) under consideration. Some of the factors that may be considered in order to determine this probability include the prevalence of the agent, the species and breed susceptible to the agent, and whether testing, quarantine, and/or vaccination takes place.

Example factors to consider within a release assessment for the example risk question:

- Prevalence of hazards identified in species X from region A
- Outcome of infection to each hazard (infectious, carrier, immune, latent infection etc)
- Whether any testing is undertaken
- Sensitivity and specificity of any testing
- Whether any quarantine is used
- Incubation periods for each hazard if quarantine is used
- Number and rate of animals of species X moved to region B

An exposure assessment describes the qualitative or quantitative evaluation of an animal being exposed to a biological agent. Once the biological agent is 'released' into the new location, as determined in the previous step, an assessment of the probability that animals are exposed to the agent is undertaken. In order to determine this probability, factors such as the mechanism by which the agent is transmitted from infected or contaminated animal or animal product, to susceptible animals, the mode of infection, the survival ability of the agent, the effects of meteorological conditions, and the variety of susceptible species and their distribution need to be considered. For animal products intended for particular uses (food, hides, semen for example) that may contain an infectious agent, pathways for use and disposal of unconsumed or unused product of need to be taken into account.

Example factors to consider within an exposure assessment for the example risk question:

- Susceptibility of resident populations of all species of region B to identified hazards
- Demography of resident populations of all species of region B to identified hazards
- Intended use(s) of species X (i.e. breeding, zoo, direct to slaughter for food, etc)
- Farming or husbandry practices that influence contact between X and resident populations of B (e.g. indoor housing)
- Other uses of species X that influence contact between products of X and resident populations of B (e.g disposal of food waste)
- Environmental characteristics, including meteorological, of region B that may influence the viability of the hazard(s)
- Management of X, or processing of products of X that may influence the viability of the hazard(s)
- Presence of any necessary vectors or intermediate hosts in region B

Within a consequence assessment, the relationship between specified exposures to the biological agent and the consequences of those exposures is assessed (OIE, 2000). Specifically, it describes the probability of a consequence, or unwanted outcome such as disease or illness, occurring given exposure to an infectious agent. The impact, or effect, that a biological agent may have can be determined from either an animal health, zoonotic, environmental or economic perspective. Further, there may be an interaction between these elements and the probability of different consequences may need to be separately assessed depending upon the risk question(s) asked.

In terms of animal health consequences, factors such as the range of potential hosts, the impact of the agent on the host's health, the expected severity of the disease and the morbidity and mortality rates should be considered. For some biological hazards identified in the hazard identification process, there may be an adverse effect on human health which would be need to be considered within the assessment. When taking into account the environmental impact, factors that should be considered include the effects of the agent on endangered or threatened species, the potential reduction in biodiversity and susceptibility of wild species, and also the impact of the ecosystem if an entire species was eradicated due to an infectious agent. In terms of economic consequences factors which are important to consider once the agent is present in the population, are the cost of increased surveillance, compensation to farmers, treatment for ill or diseased animals, and trade restrictions.

Example factors to consider within a consequence assessment for the example risk question:

- Dose and route of infection for each susceptible species (e.g inhalation, ingestion)
- Susceptibility by species and route (dose-response)
- Vaccination status of resident populations
- Outcome of infection in susceptible domestic and wild populations (morbity, mortality, production loss etc)
- Transmissibility of hazard once infection established in index case in resident population

The final stage of risk assessment, risk estimation, consists of evaluating the results from the previous stages to produce an overall measure of the risk associated with the infectious agent identified within the hazard identification process (OIE, 2001). Risk estimation takes into account the entire risk pathway, or the steps that have to occur in order for an unwanted outcome to occur resulting from the identified hazard.

Undertaking a risk assessment for infectious agents:

Infectious disease risk assessment can be undertaken either qualitatively or quantitatively. The former is usually undertaken in the first instance in order to gather available data and consider whether the probable magnitude of risk requires further

quantification. In a qualitative risk assessment descriptive terms such as low risk, negligible risk etc are used to describe the overall estimate of risk, and these are necessarily subjective. Therefore transparency is crucial in overcoming problems which might otherwise result from this subjectivity, and allowing further decisions to be made based on a qualitative assessment. If a quantitative assessment is required, then depending on available data, the probability of the unwanted outcomes defined in the risk question can be determined quantitatively. In some cases, a scoping study may be undertaken specifically to evaluate if there is appropriate quantitative data available to undertake a quantitative risk assessment (QRA).

QRA are undertaken using either deterministic or stochastic models. A deterministic risk assessment utilises point values for each variable within the assessment and hence the final output is a single value. In contrast, the stochastic approach enables real life variation and uncertainty in the data to be incorporated, primarily through the use of probability distributions. Within this framework output estimates of risk will be characterised by probability distribution and thus can be described with a level of confidence. As such, a stochastic model provides a more useful and realistic estimate of the risk being assessed since it can account for inherent variation and uncertainty within the system. For this reason, stochastic risk assessments are generally considered more appropriate for decision-making but, due to their structure, stochastic QRAs are more time consuming and require more resources. In summary, the two approaches for undertaking a QRA and their relationship in terms of complexity is shown diagrammatically in Figure 2.

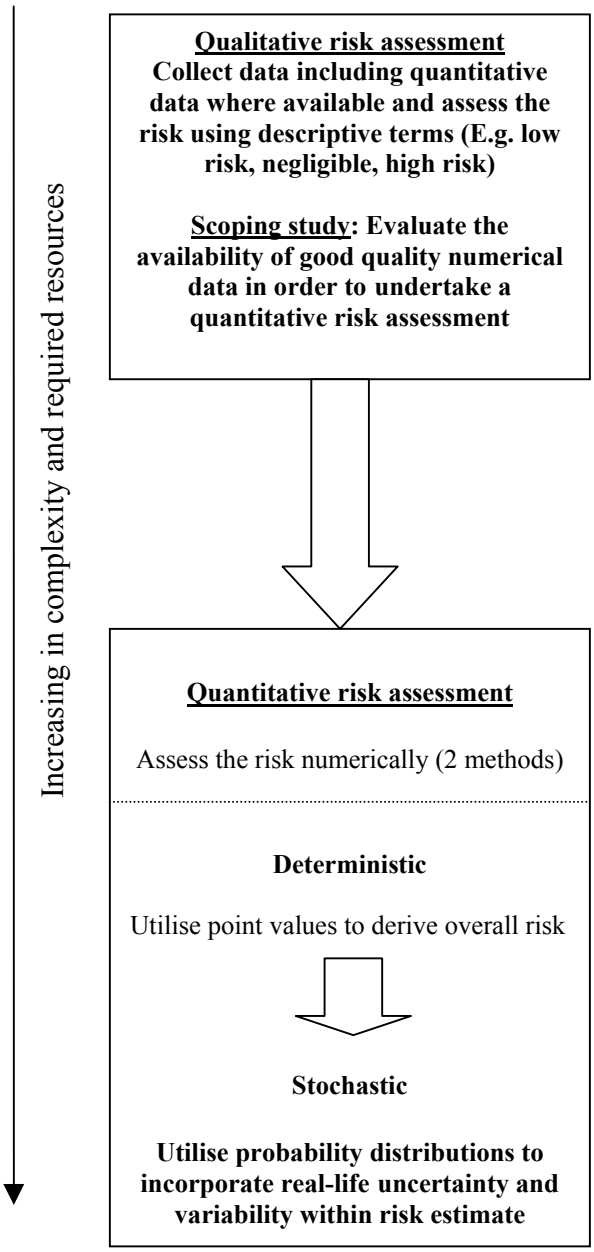

Figure 2: A summary of the increasing complexity of the methods for undertaking an infectious disease risk assessment.

1.2 RISK ASSESSMENT FOR IMMUNOLOGICAL MEDICINES.

The DG Enterprise is responsible for the European legislation on the registration of medicinal products. The registration process is mandated to the 'European Medicines Evaluation Agency' (EMEA). Within EMEA, scientific committees advise on the requests for marketing authorisation with respect to quality, efficacy and safety of the products. These committees are the CVMP for veterinary medicines and the CPMP for human (proprietary) medicines. Member states appoint two independent experts to both the CVMP and CPMP, that can be regarded as a "Scientific Board for Registration" Members states are involved in the process through their formal representatives in de

Standing Committees (SC) and Pharmaceutical Committee (PhC). The SC, as part of the DG Enterprise, decide on the proposals of the CVMP/CPMP and turn them into binding law. DG Enterprise has the PhC at its disposal, which was installed by Directive 75/320, for advice on interpretation of the directives, compulsory consultation when changing directives, and other issues.
The assessment of veterinary medicines is required by the Directive 2001/82/EC. Veterinary products applied for under article 13 of the 2001/82 directive are not deemed to be assessed on environmental risks according to Annex V of the directive; only the UK and NL assess 'old products'.
The EMEA published guidance on the environmental risk assessment of veterinary pharmaceuticals (EMEA, 1996).The assessment for veterinary products has been implemented in 1997. For the ERA of immunological products for human use no guidance is available.

The assessment is based on the risk-approach. 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

For veterinary medicines the guidance 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 repeated. 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."
In the Background and Introduction of the 1996 guidance already an exemption for further assessment 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 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.

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 applicable; 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. The guidance is sometimes considered as being too abstract, and not useful to identify the risk to the environment. A joint workshop has attempted to design a more practical strategy (Montforts, 2000). Expertise in the field of infectious diseases has not been used so far.

1.3 RISK ASSESSMENT OF MICRO-ORGANISMS USED AS ACTIVE SUSTANCES FOR PLAN PROTECTION PRODUCTS.

The assessment of plant protection products containing micro-organisms is covered by the general directive on plant protection products Directive 91/414/EC. However the level of guidance for these microbial PPP is less avanced than for active substances of chemical nature.

No specific guidance document exist for the moment. Currently, there are documents which include proposals on the criteria for evaluation and authorisation of plant protection products containing micro-organisms. These documents cover both the regulatory aspects that must be included in the directive adaptation and the technical guidance. The data requirements in Annex II Band IIIB were published in the O.J. 20 June 2001 (L164 page 1). The Council directive establishing Annex IVB on microbials PPP SANCO/108/2002 was prepared and a question was sent to SCP early 2002. An opinion is expected early 2003.

Considering the importance of these evaluation for getting a proper view of the harmonization needs, a summary of the proposed approach, based on the latest draft version available has been included. Obviously, it must be noted that this summary corresponds to a draft version, not to an adopted decision, and may still suffer some changes.

The proposal includes two specific chapters which are considered relevant for this assessment, one covers the assessment of animal health (included in a more general chapter covering human and animal health) and the other covers the assessment of environmental risks, which are addressed as independent evaluations.

Risk assessment for animal health

The draft guidelines include the assessment of adverse effects on human and animal health as a single point of the evaluation.

The hazards associated to these active substances are defined by three main categories:

1. The pathogenicity of the micro-organism on humans and animals
2. Infectivity and colonisation of the micro-organism
3. Toxicity of metabolites/toxins and substances added to formulate the product.

It is recognised that pathogenicity, infectivity and toxicity comprise a complex set of microorganism – host interaction and that the above endpoints may not be resolved easily as independent endpoints.

This evaluation takes into consideration the microorganism potential ability to infect and multiply in mammalian host systems. The mode of action and studies on mammalian toxicity, pathogenicity and infectivity are the key information. Therefore, it is assumed that animal health refers specifically to farm animals, and in particular to mammals.

When the hazard is related to toxins, and therefore is of a chemical nature, the risk assessment must consider two phases. First, the assessment of exposure, as the likelihood for production of the toxins under different use patterns. Second, an effect assessment which can perfectly follows the general principles of chemicals` risk assessment.

However, the effect assessment part requires different approaches when the hazards are of biological nature. An assessment of infectivity and pathogenicity is necessary even if the potential of exposure is deemed low. The evaluation must include skin and respiratory irritation. No specific guidance for the exposure assessment of animal population has been developed.

The effect assessment is based on the following studies
- acute oral toxicity, pathogenicity and infectivity
- acute inhalation, pathogenicity and infectivity
- genotoxicity testing
- cell culture studies
- short-term toxicity and pathogenicity

Additional information, such as:
- specific toxicity
- in vivo studies in somatic cells
- genotoxicity – in vivo studies in germ cells

The risk assessment is based on the identification of potentially unacceptable risks. It is assumed that the evaluation is a tiered process, however, no specific triggers are recommended.

Environmental risk assessment

The generic paradigm for environmental risk assessment; based on exposure assessment, effect assessment and the combination of both results in the risk characterisation is applied to microorganisms as PPP active substances.

For the exposure assessment, the evaluation of the fate and distribution of the plant protection product in the environment must cover all aspects of the environment, including biota. The potential for persistence and multiplication of the microorganism has to be assessed in all environmental compartments unless it can be justified that the microorganism will not reach a specific compartment. The mobility of the microorganism and its residual metabolites/toxins has to be considered.

The microorganism may give rise to risks from its potential ability to establish itself in the environment (by multiplication) and can therefore have a long-lasting or permanent impact on the microbial community or their predators

The aquatic compartment covers, both groundwater and surface water. For the atmosphere, transport, short-range and long-range, of the microorganism is considered a key issue. The terrestrial compartment, including abiotic and biotic sub-compartments, is in most cases the compartment receiving initially the release of the product containing the microorganisms.

The effect assessment is distributed into specific evaluations for several taxonomic groups, which are basically similar to those selected for chemical pesticides.

The assessment includes:

Effects on and exposure of terrestrial wildlife (wild birds, mammals and other terrestrial vertebrates). The rationale is similar to that presented for the assessment of animal health, but including studies on avian toxicity, pathogenicity and infectivity.
Effects on and exposure of aquatic organisms
Effects on and exposure of bees.
Effects on and exposure of other arthropods than bees
Effects on and exposure of earthworms
Effects on and exposure of soil micro-organisms
Effects on and exposure of other species

In all these cases, the assessment includes two different aspects, the potential ability to infect and multiply in the non-target organisms, and the possibility for production of toxins, which are evaluated following the standard procedure for chemical pesticides of Toxicity/Exposure ratios.

The criteria for decision-making in the case of pathogenicity/infectivity is the following:

- No authorisation shall be granted when the microorganism has turned out to be infectious or pathogenic to the non-target organisms (mammals, birds, fish, bees, other non-target arthropods, earthworms).

For hazards related to toxicity, criteria applied to chemical pesticides are considered.

For assessing effects on microbial population, the evaluation of environmental impacts includes:

- impact of the micro-organism (if non-indigenous) on the total microbial population dynamics and activity
- interferences with biogeochemical nutrient cycles
- impact of the micro-organism on predators of non-target micro-organisms
- interference with nutrient uptake in mycorrhiza

2 PRINCIPLES FOR ASSESSING THE RISK OF CHEMICALS ON ANIMAL POPULATIONS

2.1 INDUSTRIAL CHEMICALS

No specific protocols or guidance for assessing the risk of chemicals to animal populations is defined in the TGD for industrial chemicals. However, the risk analysis conducted for terrestrial vertebrates, mostly mammals, and described as secondary poisoning should be considered a population risk assessment. Laboratory toxicity data are used in the assessment, and a set of risk factors is applied for covering the extrapolation between measured and relevant long-term effects as well as species sensitivity differences. Specific population risk assessments should consider the taxonomic, physiological, etc. proximity between the populations that should be protected and the species for which information is available, as well as the specific parameters controlling population dynamics under the assessed circumstances. Literature offers some examples where all these aspects have been taken into account (e.g. examples presented by the US EPA) but not general guidance is available in Europe as this aspect is not currently a key issue in the chemicals' registration area.

2.2 CHEMICAL PLANT PROTECTION PRODUCTS (PESTICIDES)

For plant protection products some recommendations are however available. First, because the environmental assessment does not focus on full ecosystem protection but on the protection of non-target species, which in most cases focuses at the population level. Second, because in certain cases the assessment can include domestic animals exposed to treated residues, which represents an individual/population assessment.

Annex VI of Directive 91/414/EEC describes the "Uniform Principles" for the authorisation of Plant Protection Products, which include assessment of potential effects on animal health and non-target species. The risk for wild animal populations is included in the ecotoxicological assessment, while the impacts on domestic animals are covered, simultaneously to the human health impacts, in the chapters of toxicology and residues. This distinction creates difficulties for setting comparisons between both assessments, because of the methodology and the level of description for each assessment present significant differences. The ecotoxicological assessment includes a set of acceptability triggers in the Directive, and the assessment, in the first tier, focus on a quantitative estimation on the fulfilment of those triggers. In addition, guidance documents have been developed to describe the assessment procedures. For birds and mammals, the triggers represent a margin of safety of 10 for acute toxicity and 5 for chronic toxicity. The (domestic) animal health estimation follows, however, the methodology adopted for human health. No specific triggers or guidance document are available, and the methodology consist on independent evaluations of the toxicity and the possible level of exposure and a final, case-by-case, evaluation on the reliability of the margin of safety identified in the assessment, considering also the remaining uncertainty in the estimations.

From a regulatory perspective, the first procedure is clearly preferable. However, the scientific basis of these procedures must be transparent and the assumptions presented in a clear way. In fact, in a recent opinion on the SCP (**Opinion on the draft Guidance Documents on Risk Assessment for Birds and Mammals under Directive**

91/414/EEC) it is pointed out that the current ecotoxicological evaluation of the risk for birds and mammals does not allow setting the level of protection which is achieved within the proposed procedures. Even more, the SCP also states that the degree of certainty that would be afforded by the assessment factor is undefined, and does not distinguish between the level of effect and the certainty. The second procedure obliges to case-by-case assessments, although some general rules can be observed from the current practice. For example, a margin of safety of at least 100 is applied to the most sensitive chronic toxicity (i.e., multigeneration study) endpoint for the derivation of the ADI. In some cases, it is stated that this margin comes from the application of a factor of 10 to cover intra-species variability and a factor of 10 to cover inter-species variability. Setting some general assessment principles have clear benefits, while still allows for a rapid incorporation of scientific developments. For example, these defaults factors of 10 could be modified according to toxicokinetic and toxicodynamic considerations (i.e., Heinrish-Hirsch et al., 2001; Gunder-Remy and Sonich-Mullin, 2002) for each chemical. In the particular case of animal health, the assessment of intra-species variability could be reduced if only certain population groups are exposed. In addition, interspecies variability is a key issue and should be afforded according to the best available options (i.e., Gibson and Starr, 1988; Walton et al., 2001) considering the physiological differences between the tested animals and the domestic species.

Some provisional comparisons between the risk for domestic and wild animal populations can, however, being done for pesticides. Assuming that the animal health assessment uses the ADI developed for human health, the margin of safety considered for domestic animals should be 20 times higher than for wild populations. It must be considered however that although it is clear that a level of residues in animal feed below the ADI implies low risk for domestic animals, a level above the ADI is not necessarily interpreted as a significant risk, and the uncertainty in the assessment takes a significant role in the final decision. Unfortunately, the animal health risk is assumed in most cases as covered by the human health risk, and although residue estimations in animal feed is included in the report, the list of endpoints and the public summary usually only present the human health calculations and the assumption of low risk for animals. In addition, consultations to the SCP normally cover human health and/or ecotoxicological issues, and therefore a "*doctrine corpus*" on animal health issues is not available.

Within the opinions adopted by the SCP a specific case related to wild animals welfare, is found for paraquat (Opinion on specific questions from the Commission on the evaluation of paraquat in the context of Directive 91/414/EEC adopted by the SCP on 20 December 2001). The SCP stated that Directive 91/414/EEC article 4 states that "Member States shall ensure that a plant protection product is not authorised unless….(iii) it does not cause unnecessary suffering and pain to vertebrates to be controlled…(v) it has no unacceptable influence on the environment, having particular regard to the following considerations…. Its impact on non-target species. It seems open to interpretation whether impacts in the form of suffering and pain should be assessed for non-target species (SCP 2002). No guidance is available on how to assess the humaneness for non-target species. However, some countries (e.g. the United Kingdom[1]) have developed guidance for the assessment on humaneness for compounds (vertebrate control agents) and target species. The starting point could be that it should

[1] Chapter 9 of the Data Requirements Handbook of the UK Pesticides Safety Directorate, http://www.pesticides.gov.uk/applicant/registration_guides/data_reqs_handbook/contents.htm

be assumed, until convincing evidence is available to the contrary, that procedures that cause pain or distress in humans would do so in animals.

The SCP also stated that the absence of comments on animal welfare in opinions of the SCP on other active substances is not to be interpreted as an absence of an animal welfare issue for all those substances.

2.3. PHARMACEUTICALS AND FEED ADDITIVES.

The risk assessment of the treated animals is, obviously, an essential element in the evaluation of veterinary medicines and feed additives. However, the evaluation, as expected, considers a comparative assessment between the benefits expected from the use of the pharmaceutical or additive and the risk for potential secondary effects. The information available for assessing the efficacy of these chemicals also offers in most cases the required information for addressing non-desired secondary effects. A typical assessment method is the comparison between the therapeutic and the toxic doses; obviously, the margin of safety should consider the benefits obtained with the treatment versus the likelihood and severity of the secondary effects. In most cases, trials have been conducted on the species for which the treatment is intended, and therefore the likelihood for each effect can be directly estimated from the percentage of observations for each particular secondary effect found at the recommended dose. This risk/benefit approach based on the same population is not suitable for assessing effects on populations exposed though unintended routes, such as residues in food items or through the environment. Most regulatory guidance documents assume, however, that accounting for the large differences in the exposure, this risk is expected to be negligible when compared to the risk from the intended application. Although this assumption can be acceptable in most cases, specific evaluations should be considered, at least in those case when the possibility for unintended exposures of animal populations is much higher than for humans, and therefore, the human health risk assessment does not cover that expected risk for domestic animals.

3. CONCLUSIONS AND RECOMMENDATIONS

The risk for animal populations related to different stressors, including infectious agents, non-infectious microorganisms and several types of chemicals is assumed as an essential part of several risk assessment processes.

As expected the risk associated to infectious diseases is a targeted risk assessment covering only populations of susceptible species. Most guidance documents focus on domestic animals and considers a very specific issue, the introduction of the disease associated to intended animal movements.

A more generic assessment is conducted to cover the risk associated to some specific uses of potentially harmful agents, either microorganisms or chemical substances. In this particular case, the risk for domestic animal populations is covered as a subchapter in the human health risk assessment, while the environmental/ecological risk assessment may include specific assessments of non-target populations, such as wild birds and mammals.

In general, the guidance documents for human and animal health do not include specific considerations on the margins of safety considered to be acceptable, and, as pointed out by the SCP, the triggers established for the ecotoxicological assessment do not distinguish between variability and uncertainty, being impossible to determine which level of protection is achieved with the proposed values. Therefore, quantitative estimations are very difficult.

Several qualitative comparisons can however be established, both for microorganisms and for chemicals.

3.1 MICRO-ORGANISMS

The risk assessment of microorganisms, including infectious diseases and those intentionally used as immunological or plant protection products, is in all cases a risk assessment focused on populations. Even in the case of immunological and plant protection products, were the assessment goals are environmental protection and therefore the risk to all relevant taxa must be addressed, the guidelines establish clearly independent evaluations for each taxonomic group.

Two main hazards are basically considered, first biological interactions based mainly in the infectivity and pathogenicity of the stressor to different groups of species; second the potential for producing toxins. Both will be treated independently.

Risk related to biological interactions.

As mentioned before, the basic hazard considered for this assessment is the infectivity and pathogenicity of the stressor to different species. Therefore, this approach must be considered as an species-species relationship, based on agent-host interactions.

The risk assessment for the outbreak of infection diseases presents the higher level of development and knowledge. It focuses, from the very beginning, on the available information on species susceptibility to the agent, and can be designed to cover a single species (e.g. a farm species) or the whole range of susceptible species from domestic to wild animals.

The approach is basically a case-by-case approach, using quantitative assessments whenever possible or qualitative alternatives. No specific criteria for covering uncertainty and setting triggers associated to specific margins of safety considered adequate at the generic level have been established.

For immunological products the level of guidance is clearly lower, however, a similar approach should be taken, assuming that basically the assessment covers an infectious agent modified for reducing infectivity/pathogenicity, and therefore, a significant potential for harmonisation may be expected.

The situation is different when assessing the potential risk of the agent in a broad environmental spectrum. The assessment must cover all relevant taxonomic groups, and the information on the pathogenicity/infectivity of the agent to different vertebrate and

invertebrate animals is in most cases no available, and therefore, screening tests or uncertainty assessments on the likelihood for infectivity/pathogenicity of different taxa must are required. No quantitative screening models, equivalent to the QSAR methods for chemicals, are available, and therefore the assessment requires expert judgement and a clear uncertainty statement for providing the required transparency.

The OECD methodology for infectious diseases considers the release estimation and the exposure assessment as independent phases. However, the release/emission assessment is part of the exposure assessment in the assessment of immunological and plant protection products as well as for chemicals.

The advantages and disadvantages of these approaches should be investigated, for harmonisation purposes, a single framework should be proposed.

The guidelines do not provide recommendations for assessing the ecological consequences of the infectious risk. The potential applicability of the general recommendations for covering effects on wild species is clear, however, the available information on the consequences of the infectious outbreak in term of population dynamics and the role of ecological parameters are less understood.

The current possibilities for extrapolating population effects to community effects and alterations of the ecosystem structure and function are quite limited. However, this problem is not exclusive for infectious agents but general for any kind of stressor.

The recommendations for micro-organisms containing plant protection products also include the requirement for assessing additional species-species interactions other than agent-host relationships, and in particular, potential modification of the soil microbial community. In theory at least, this hazard could be also relevant for infectious agents and immunological products, although in addition to soil, other microbial populations such as those from sewage treatment plants or those responsible for manure ageing and composting should be included in the targeted assessment.

It is not clear if the standard tests (i.e. OECD respiration and nitrification) designed for addressing the effects of chemicals are or not suitable for the assessment of these interactions. The draft guideline includes a set of endpoints that must be addressed but no standard tests are currently available and therefore additional research is required.

In the particular case of sewage and compost ageing population, the situation is better because these are targeted oriented processes, and at least, tools for assessing the final results, such as sewage treatment possibilities and fertilisation capacity improvement, are available.

Risk related to the production of toxic substances.

When the mechanism of action is related to the production of toxic substances, the assessment should include two consecutive steps. First, quantification of the amount of toxin expected to be produced in/released to food items or environmental compartments; second, the risk associated to these levels of emission. The first part requires a specific assessment, while once the level of exposure is estimated, the effect

assessment and risk characterisation can follows the methodologies and approaches developed for chemicals.

A critical aspect is however the consideration of the spatial and temporal variability in the exposure profile, and the need for assessing effects related to non-continuous exposures.

3.2 CHEMICALS

In general, the risk for domestic animal populations is covered as part of the human health assessment while wild animal populations are part of the environmental risk assessment.

This distinction presents significant difficulties for comparing the level of protection intended and achieved in each assessment, due to methodological differences. The human health risk mostly focuses on independent estimations of the exposure and effects, and the case-by-case decision on the margin of safety achieved in the assessment. Environmental risk assessment usually includes a quantitative tier 1, based on fixed risk criteria (representing fixed margins of safety).

Only in the particular case of plant protection products, both independent assessments are required, and therefore comparisons should be possible. Initial assessment would suggest a much higher margin of safety applied for the protection of farm animals *versus* wild animal populations. However, this initial estimation is based on assumptions of "current practices", as guidance documents for animal health risk are not available, and it has been impossible to confirm the working hypotheses within the time frame of this work and the publicly available information.

Regulatory protocols also include comparative risk assumptions, suggesting that certain risks do not need any evaluation because are expected to be much lover than others already assessed. In the particular case of animal population, these assumptions are particularly relevant for products intended to be applied on animals (veterinary medicines, feed additives) where it is assumed that considering that the exposure to animals associated to non-intended routes (i.e. contaminated food, environmental compartments) will be so low when compared to the intended exposure (use as pharmaceutical or additive) the risk associated to these un-intended exposures will also be lower than, and therefore covered by, the risk associated to the animal use. Although this assessment can be acceptable in most cases, it should be considered that the risk/benefit analysis, which drives the decision for the intended use, does not apply to the unintended exposures, where the animals are not expected to obtain any benefit from this exposure.

3.3 Issues with harmonisation:

It is observed that the traditional format internationally accepted for undertaking chemicals' risk assessment differs from that internationally accepted for undertaking risk assessments concerned with animals and their products. Primarily, traditional chemicals' risk assessment defines the stages within risk assessment based on the NAS-NRC paradigm, namely hazard identification, exposure assessment, hazard characterisation and risk characterisation. The primary difference between the two

approaches is the inclusion of an assessment of the likelihood of the release of an agent within the OIE format. Within the chemical risk assessment format, this likelihood of release is incorporated within the exposure assessment. A further less intuitive difference between the two systems appears in the practical application of the protocols.

In the NAS-NRC risk assessment framework exposure and effects are assessed in parallel, being common in current practice that independent teams perform each assessment. The exposure assessment considers the estimation of expected levels. The effect assessment has traditionally been used as a regulatory tool for setting allowable or acceptable levels of contaminants, for example in foods or the environment. Then the risk characterisation considers the expected risk as the combination of the outcomes from both processes, e.g. if the predicted exposure levels are expected to be above or below the allowable levels.

The OIE framework was initially designed to estimate of the magnitude of risk in any given situation and hence can be applied directly to any risk question. It is a conceptually logical and transparent method where the elements of the analysis plan follow a specific order. The output enables risk managers to compare directly the assessed risk with any defined, identified or agreed national or international acceptable level of risk and to implement safety measures if required.

It must be, however, considered that these differences are based on the regulatory framework, not on the differences in the type of stressors. As pointed out in this report, the risk associated to microorganisms used as plant protection products has been structured following the protocols adopted for chemicals, i.e according to the NAS-NRC risk assessment framework. It is obvious that assessing the likelihood for release for a product that will be intentionally spread on the environment does not require a significant effort. Examples from the opposite situation can also be found, particularly in site-specific risk assessment for chemicals where the process starts with the exposure assessment, using model predictions or real measurements, and the effect assessment follows this process, in order to estimate the likelihood for effects associated to that particular exposure levels, an approach that mimics the OIE framework.

Thus, in terms of overall harmonisation, the aims and purposes for undertaking a risk assessment for infectious agents or non-infective micro-organisms, can, if required, be similar to those for chemicals and other stressors that focus on the population level – it merely depends upon the risk question initially asked.

Getting harmonisation of the general procedures would also represents a significant benefit for those risk assessments that require combinations from the methodologies adopted for each kind of stressor. The risk associated to microorganisms producing toxins is a perfect example, as the exposure part must consider the characteristics of the microorganisms while the final effect is of chemical nature.

3.4 General Recommendations

Several Scientific Committees have included the need for a proper assessment of the real level of protection offered by the different risk assessment protocols.

Two particular comparisons should be of high interest.

- Comparisons on the level of protection (what consequences are likely to be) of the current procedures, for the same population exposed to different stressors (infectious diseases; immunological agents, microbial and chemical PPP, etc.)
- Comparisons on the level of protection considered for farm *versus* wild populations.

Considering the lack of specific guidance for most of the assessments, this objective can only be conducting by an in-depth analysis of a large set of individual risk assessment. The WG recommends conducting such study, establishing parallel assessments for setting up differences between the variability and the uncertainty of the assessments.

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