Danish Environmental Protection Agency

Pesticides November 2006

Health risk assessment of the use of plant protection products:

Pursuant to Directive 91/414/EEC concerning the placing of plant protection products on the market, authorization of plant protection products must as a novelty include a risk assessment of the products' health related (and environmental) properties in relation to their intended use, i.e. the authorization procedure must, to a much greater degree than previously, include quantitative assessments of exposure conditions for spraying personnel, workers and others who are exposed to a plant protection product after its application and livestock. Furthermore the potential exposure of consumers through diet and other possible routes of exposure must be quantified.

The health risk assessment includes traditional hazard identification, and, depending on the context, an assessment of dose-response, exposure and risk characterisation.

The risk assessment provides the basis for the administrative decision on acceptance of the intended use of the plant protection product in relation to the health related aspects of the product's properties. The grounds for the decision can be seen under the section on risk management, which also includes the conditions of use for the product which are a result of the health risk assessment.

In connection with the authorization procedure the case officer fills in the accompanying risk assessment form in accordance with the information supplied in the application. The completed form functions as an internal working document from which relevant information is transferred to the authorization document.

In order to assist completion of the form an outline of the criteria is provided, i.e. prerequisites and assumptions that the Danish Environmental Protection Agency intends to be used for the specific tiers of the health risk assessment. These will be continually updated and will apply until the EU agrees on a common calculation model (as required in the Uniform Principles (Council Directive 94/43/EEC on establishing Annex VI to Directive 91/414/EEC)). At present the calculations are based on elements from both the German database (annex 1) and the British database (annex 2).

NAME:

ACTIVE SUBSTANCE:

1. HAZARD IDENTIFICATION

- Acute toxicity
- Irritation
- Corrosive
- Sensitisation
- Repeated dose toxicity
- Mutagenicity
- Carcinogenicity
- Reproductive toxicity
- Neurotoxicity
- Other

Critical effect(s):

Classification:

Active substance:

Product:

2. ASSESSMENT of DOSE-RESPONSE

LD_{50}:

NOAELs:

Subchronic:

Chronic:

Other:

A. Most relevant **NOAEL** for AOEL:

Safety factor:

AOEL:

B. Most relevant **NOAEL** for ADI:

Safety factor:

ADI:

Comments on plot of dose-response curve:

3. ASSESSMENT OF EXPOSURE

A. Operator exposure:

Concentrations (of active substance in product and application concentration):

Formulation type:

Use (crops and spraying equipment):

Absorption:

Exposure without protective equipment:

Inhalation: Skin:

Mixing:

Spraying:

Total exposure **without** protective equipment, corrected for absorption:

Exposure with protective equipment:

Inhalation: Skin:

Mixing:

Spraying

Total exposure **with** protective equipment, corrected for absorption:

Estimated realistic worst case:

Exposure of workers and others who come into contact with plant protection product after application:

Livestock:

B. Consumer exposure:

(incl. drinking water)

Estimated realistic worst case.

4. RISK CHARACTERISTICS

A. Ratio: User exposure without protective equipment/AOEL:

Ratio: User exposure with protective equipment/AOEL:

B. Ratio: Consumer exposure/ADI:

5. RISK MANAGEMENT

Either:

Product can be authorized as regards toxicological properties:

on condition:

or

Product cannot be authorized as regards toxicological properties:

because:

Annex to risk assessment of plant protection products:

Prerequisites and assumptions that apply to the specific tiers of the risk assessment:

1. Hazard identification:

All inherent dangerous properties of both active substance and product are identified with the toxicological studies. The criteria used for the assessment of the acute effects are described in annex 2 of Statutory Order No. 533 of 18 June 2003 on plant protection products. The criteria used for the assessment of irritant properties and of long-term effects are described in Statutory Order No. 329 of 16 May 2002, on classification, packaging, labelling, sale and storage of chemical substances and products.

The assessment must result in a classification of both the substance and the specific product.

Furthermore, it is decided what effect(s) – known as the **critical effect** – of the substance and/or product must be regarded as significant for the risk when the product is used and which should therefore be used as the basis of the risk assessment.

If the classification results in the product being **classified as dangerous to health for acute toxicity, irritant, sensitization or not within the scope of a hazard class,** as a general rule the product can be authorized (as regards the toxicological properties) without a risk assessment.

If the classification results in the product being **classified as carcinogenic in category Carc1 or Carc2, or as mutagenic in category Mut1 or Mut2 or it is corrosive and/or causes serious eye injuries,** as a general rule the product must be rejected on the basis of these inherent properties. The Danish Environmental Protection Agency has assessed that the possibility of exposure cannot be excluded with a certainty that justifies substances with irreversible toxicological effects being authorised for use as plant protection products, for which reason no further risk assessment is required.

The risk assessment is always completed for the remaining classifications.

2. Dose-response assessment

A. AOEL (Acceptable Operator Exposure Level)

As a general rule, an **AOEL** (Acceptable Operator Exposure Level) must always be determined that is based on the response that is assessed as being the critical effect of the substance and that takes account of the doses that caused an observable effect on test animals. The AOEL expresses the acceptable risk level for the level of the chemical in the operator, i.e. what is available for causing any toxicological effect in the organism. Therefore the AOEL is not a limit value for the content of the substance in any medium.

The **NOAEL** (No Observed Adverse Effect Level) from the most relevant animal test is used as the background for determining the AOEL in order to establish the critical effect. This means that if the critical effect is cancer, then it is the NOAEL from the carcinogenicity test that is used. If the critical effect is harm to the foetus, then the NOAEL from this test is normally used. The NOAEL that is used for the AOEL is defined as the highest daily dose that has not caused an observable adverse effect in the most sensitive species.

However, the lowest relevant NOAEL is used if there are several critical effects. Generally a bodyweight of 70 kg is assumed.

In most cases the results that are used for AOEL are from tests in which animals have been fed the substance with feed through the mouth or directly to the stomach by gavage. In that the majority of user exposure occurs through the skin, any dermal studies that have been carried out ought to be included in the considerations for the AOEL, but it is only in special cases that an NOAEL from such studies should be used as a direct basis for the calculation of the AOEL. An example of these special cases could be that the substance is metabolised via several routes depending on the route of absorption (e.g. this applies to the distribution of cis/trans isomers in certain substances). The same can apply to exposure via the lungs where there also can be metabolic conditions that are different from the oral absorption route. Finally, it may also be necessary to consider whether the substance may be broken down by acid in the stomach or is transformed through microbial action in the intestines and may therefore be more toxic when absorbed in the blood through the skin or lungs.

If the NOAEL from the dermatological toxicity test is used as the basis of the AOEL, then it must be stated that the exposure calculations must not subsequently be corrected for absorption.

In the user-exposure calculations carried out by the applicant, a NOAEL is often automatically chosen from the subchronic studies on the grounds that a plant protection product is used for short periods of time a few times a year. However, in Denmark it is unlikely that we can ever rule out that the product will be widely used at machine pools. In such cases sustained used should be included in the considerations as part of the worst-case estimate.

Safety factor: The NOAEL is reduced by a safety factor that must take account of the uncertainty that lies in the assessment of the study itself, extrapolation from animals to humans, the variations that exist in human sensitivity and lifestyles. A factor of 100 is normally used, for which 10 shows the difference between species and the other 10 show the difference within species. Safety factors larger than the "normal" of 100 are used if data do not provide the basis for an adequately certain assessment, or if the toxicological effect is of such a character that it is judged that a higher safety level must be reflected in the safety factor used. For carcinogenic effects (carc1 or carc2 with R45 or R49 or carc3 with R40) an extra factor of 10 is normally used, and for toxic effects on reproduction (rep1 or rep2 with R60 and/or R61 or rep3 with R62 and/or R63) a factor of 3. In exceptional cases, a safety factor of less than 100 can be used in cases where it is deemed relevant, e.g. if the critical effect is observed at much lower doses in rodents than non-rodents.

B. ADI (acceptable daily intake)

Determination of the **ADI** and associated **MRLs** (Maximum Residue Levels) is only necessary if the product is to be used on crops used for food and feed.

As a main rule, the lowest NOAEL from one of the chronic studies is used as the background for determining the ADI, because in this case the substance is administered to the animals in small doses for the whole or most of their lifespan. The size of the safety factor is assessed according to the same criteria as for user exposure.

3. Exposure assessment:

Exposure to the active substance and/or to toxicologically relevant compounds in the plant protection product is estimated by

normal use - with and without protective equipment

realistic worst case

The term **normal use** means the intended practical conditions of use, i.e. the assessment is based on information on intended use, dose, method, frequency and timing of application as well as the type of product and contents. In all cases where it is possible the principles on integrated control are taken into account.

The size of the exposure is estimated primarily for the spraying personnel, i.e. both during mixing, loading and application of the plant protection product. However, especially in the case of greenhouses, it can be necessary to also estimate the exposure of workers or others who are exposed to the plant protection product after application, just as there can be special reasons for including potential exposure of livestock.

The preliminary estimate of exposure when using the product is carried out on the assumption that protective equipment is not used. If the exposure in this case exceeds the AOEL (see risk characteristics), then the protection offered by protective equipment must be assessed.

Protective equipment:

At present there is no consensus on the extent to which the degree of protection offered by protective equipment should be included in the risk assessment calculations, i.e. fixed values for how much they reduce exposure:

- some models from other countries assume that gloves reduce exposure by 99 % and others by 90 %. The Danish Environmental Protection Agency is in possession of several studies in which gloves reduce exposure by only 60 %. As a consequence of the fact that when labelling there is no established practice of giving instructions for showing which gloves are suitable for the specific plant protection product, the Danish Environmental Protection Agency's assessment of the protection offered by gloves will be very conservative and among other factors it will depend on the characteristics of the solvent.
- the protection that can be achieved by using respiratory protective equipment is defined better because the National Working Environment Authority issues guidelines on protective equipment for using plant protection products that

specify which respiratory protective equipment must be used on the basis of the specific product's classification, formulation type, and method of application. The protection factors that can be provided by correct use of the various types of respiratory protective equipment have been thoroughly studied and for normal filtering respiratory protective equipment will be between 4 and 50.

If it is absolutely necessary to use protective equipment in order to avoid the risk of irreversible harm (e.g. harm to the foetus) or significant risk of acute toxicity, then this is not acceptable.

The calculation of the realistic worst case is used among other things to assess the consequences of mishandling and misuse. For example it can be calculated, possibly with the use of standard values, how large an amount of a specific product could theoretically be spilt on personnel during mixing etc. and it is estimated how serious the consequences of such spillage could be. If the substance has a very steep dose-response curve, then this should also be reflected in the assessment. Furthermore intensive use, for example in machine pools, should be included in determining a realistic worst case.

In addition consideration should also be given in the assessment to the fact that in certain cases exposure can occur when storing and reusing. Furthermore there may be special conditions in relation to degradation and transformation (possibly to more toxic compounds).

Crops:

Every crop that authorization has been applied for must be assessed individually. For each crop the maximum dose applied for is used. In addition, it must be considered whether the crop is tall or short, if it is an outdoor crop.

Certain crops can however be assessed together if the dose and spraying equipment are the same.

Spraying equipment:

For each crop, the spraying equipment to be used is assessed. If there are several possibilities, in principle all possibilities must be assessed, and if only one is assessed it must be the equipment that leads to greatest exposure.

Working conditions:

Mixing and filling:

A distinction is made between preparation of mixture for hand spraying and motorised spraying, and likewise it is important to identify the formulation type (liquid, spray or granulate). Calculations are based on the mixing of the kilograms of active substance that make up one day's application of the plant protection product.

Spraying:

Field crops: It is estimated that 20 ha per day can be sprayed.

Tall crops: Fruit growing etc. It is estimated that 8 ha per day can be sprayed, when the spraying equipment is mounted on a tractor and 1 ha per day when hand-held spraying equipment is used.

Greenhouses: A working day of 6 hours is assumed.

Dressing: As for mixing and filling for hand-held spraying.

Spraying technique: In all ordinary field crops it is assumed that spraying is carried out with tractor-driven spraying equipment with a hydraulic nozzle and that the crop is a short type of crop. For some crops there may be doubt about the spraying technique, and in such cases the instructions for use must be checked, or the enterprise, the Faculty of Agricultural Sciences (DJF) or DEG must be consulted.

DJF will probably provide an overview of some of the special crops used in greenhouses, plant nurseries, fruit growing, municipal use and forestry. Potential exposure for dressing needs to be investigated and recorded.

Exposure routes:

Probable exposure routes and the potential for absorption from the areas of use examined are assessed. Exposure of spraying personnel can be estimated on the basis of exposure through skin and respiratory tracts, and likewise re-entry personnel, while it must normally be expected that consumers are exposed through the gastrointestinal tract.

In most spraying situations the main exposure route is the dermal one, which is why particular importance should be placed on available measurements of dermal exposure of products under assessment with the intended area of use, among other factors significance must be placed on distinguishing between potential exposure i.e. the amount of plant protection product that comes into contact with the user, and the actual exposure i.e. the percentage of the exposure that is located directly on the skin and is available for absorption. Measurements of the absorption percentage from the skin of an actual product or substance can likewise be of great significance for the exposure estimate.

When calculating the contribution from exposure via respiratory tracts, information on the product's particle sizes is particularly significant and it is assessed whether the particles are respirable (i.e. < approx. 5 μm).

Absorption:

One hundred per cent absorption is assumed from all exposure routes unless another figure is rendered probable.

Through the skin:

If a dermal absorption test of the product is available, this is used to estimate the fraction of the exposure on the skin that is absorbed.

At present there is disagreement about the extent to which the already widely used *in-vitro* method of measuring dermal absorption is as good as *in-vivo* studies. When *in-vitro* studies of dermal absorption are developed that are just as good as *in-vivo* studies, the Danish Environmental Protection Agency should encourage the use of *in-vitro* studies instead of using test animals. Until then they can be used to indicate the magnitude of absorption of the substance or product in question.

If a dermal absorption test of the active substance is available, it is assessed whether it can form the basis of an assessment of the product.

If there are no actual dermal absorption tests, there may be useful information on dermal permeability, for example in comparison between dermal and oral toxicity in dermal sub-acute tests or in metabolism tests. It may be possible that the physico-chemical properties (e.g. fat solubility) can form the basis of the assessment.

The British model generally uses 10 % as the standard value for dermal absorption, but this is completely unacceptable because of the fact that our knowledge on absorption of many pesticides shows that 10 % is often too low.

On inhalation:

Unless proven otherwise, 100 % absorption from respiratory tracts is assumed, even though this is probably only the case for gases and respirable particle sizes of aerosols or powders because there is direct absorption in these cases.

From the gastrointestinal tract:

Absorption from here can normally be estimated from metabolism studies.

Exposure:

The amount of exposure of the spraying operator, i.e. user exposure is estimated for all methods of application, either through studies of the product in question or through other relevant studies, for example of products that have a similar area of use (spraying equipment).

If exposure studies of the product in question have been carried out that are comparable with Danish conditions, then such studies are used. In rare cases there will be information on actual exposure from measurements of the active substance in the body fluids of exposed subjects (biological monitoring).

If no relevant figures are available for exposure, the average exposure figure is used, known as a proxy figure, from international databases.

For indoor crops (greenhouses) the figures from the British database for outdoor use of back-mounted spraying (short crops) when the product is sprayed by hand are used, and these are multiplied with the number of hours worked per day (annex 2). If the product is used in a greenhouse with an atomizing sprayer or the like, there are no figures available, and we must assume that no persons are present in the greenhouse during spraying. This can possibly be included as a condition on the label.

For mixing and filling the figures (geometric mean) from the German database (annex 1) are used and are multiplied with the number of kilograms of active substance used in one working day.

For spraying of outdoor crops the figures (geometric mean) from the German database (annex 1) are used and are multiplied with the number of kilograms of active substance used in one working day.

For stored crops each case must be assessed on its own basis as there are no database figures available for this area of use. It may be necessary to carry out new tests or produce more thorough descriptions of working procedures than normal.

Risk characterization:

Under this section conclusions must be given on the extent to which risk of harmful effects arises and in which situations during the use of the plant protection product this may occur. Furthermore, available courses of action must be stated for the actual case with a view to ensuring appropriate risk management.

Firstly, the actual **exposure of spraying personnel** caused by use of the plant protection product is compared to the **AOEL** determined for the critical effect. The resulting ratio is an expression of the risk/safety there is for spraying personnel when using the product.

If the actual exposure without protective equipment is larger than the AOEL, this is compared with the ratio for exposure after use of various types of protective equipment. If it is thereby possible to reduce the ratio to < 1 with a selection relevant of protective equipment, this is acceptable and requirements will be made for the use of this equipment. If exposure cannot be reduced with the aid of relevant protective equipment, authorization will be refused.

Furthermore it will be assessed whether it is only certain methods of application that are problematic, e.g. atomizing sprays, whereas other areas of use can be authorised.

The result from the realistic worst-case calculation can possibly change the decision that was made as a result of the estimate for normal use. For example this applies if in cases of accidents direct poisoning can occur.

This section should as far as possible describe suitable medical treatments of possible poisoning, just as it is important descriptions are given of antidotes that can be used and if the case is such, then how long treatment must last (for example atropine and oximes against poisoning with cholinesterase inhibiting substances).

Information on decontamination methods (neutralising, destruction, disposal) in case of accidents should also be included here.

The actual **exposure of consumers** due to residues in foodstuffs is weighted in relation to the **ADI,** and the ratio is an expression of the risk/safety for consumers when the plant protection product is used.

If the actual exposure through residues is larger than the ADI, authorization must be refused for certain crops or longer preharvest intervals must be calculated, or alternatively authorization must be refused completely. In the assessment of possible conditions for authorization the result from the realistic worst case calculation should be considered.

Finally the risk characterization should include an assessment of whether the plant protection product has undesirable effects other than those that are investigated in the set

predictive toxicological (and ecotoxicological) study program. Examples include metalliferous compounds and ozone-depleting substances.

5. Risk management:

The result of the risk assessment is summarised and the administrative decision that has been made on the basis of this is made known. In the choice of words it is emphasised that this only covers the toxicological part of the total risk assessment that forms the basis of the final decision on authorization.

If the properties of the substance or product applied for require that all parts of the health risk assessment must be carried out, then conditions will in general be placed on the use of the plant protection product. The following conditions can be given:

- limits on spraying methods authorized
- requirements on special permits for spraying personnel
- requirements on special packaging (dimensions, design, possibly water-soluble packaging)
- treatment periods and periods of retainment
- waiting periods for re-entry into treated areas
- specific requirements on the use of protective equipment

Correct use of protective equipment can have great influence on the result of the risk assessment and can therefore be an important tool in risk management. However if approval of the health risks is dependent on the use of gloves that reduce exposure by 90 per cent, for example, according to current requirements on protective equipment a means must be found to communicate the fact that for the product in question it has been determined that an unacceptably high risk is run when not using gloves.