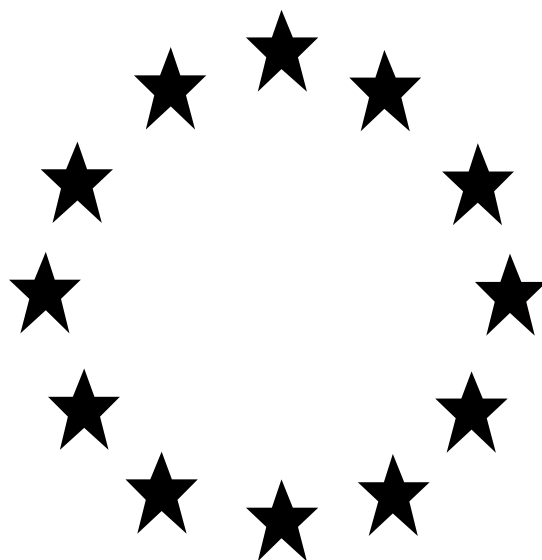




Draft Assessment Report (DAR)

- public version -

**Initial risk assessment provided by the rapporteur Member State
The Netherlands for the existing active substance**

DICHLOBENIL

**of the third stage (part B) of the review programme
referred to in Article 8(2) of Council Directive 91/414/EEC**

Volume 3, Annex B, part 3, B.7

January 2008

B.7 RESIDUE DATA**B.7.1 METABOLISM, DISTRIBUTION AND EXPRESSION OF RESIDUES IN PLANTS
(ANNEX IIA 6.1 AND ANNEX IIIA 8.1)****B.7.1.1 Primary crops****I) Uptake, distribution and metabolism – grapes****Characteristics**

Reference	: Hubert, 1990a	Vehicle	: toluene, cyclohexanone, Igepal CO-710 (non-ionic surfactant) in water
Year of execution	: 1989	Number of treatments	: 1
Guideline	: Directive 91/414/EC; 7028/VI/95 rev.3, Appendix A	Interval	: not applicable
GLP	: yes	Area	: outdoor plots (1.22 m x 3.05 m), Porterville, California
Test substance	: Dichlobenil ([U- ¹⁴ C] 2,6-dichlorobenzonitrile); batch/lot no. AOI87K23B	Total rate	: see application rate
Purity	: radiochem. purity 99.7%, specific activity 0.36 mCi/mmol	DAT	: 159, 190, 222
Application rate	: 6.72 kg a.s./ha	Acceptable	: yes
Concentration	: 0.66 g a.s./L		
Plant	: grape, <i>Vitis vinifera</i> 'Emperor'		

Study design

One application of ¹⁴C-Dichlobenil at a rate of 6.72 kg a.s./ha (1.2N) was made to the soil of grape vine plots. Fruit samples, taken at 159 and 190 DAT and at harvest (222 DAT), were frozen using liquid nitrogen and homogenised with dry ice. Soil samples were taken at 0 (before and after application), 159, 190 and 222 DAT. After combustion, the samples were analyzed for radioactivity by LSC. The grape homogenates of the 222 DAT samples were extracted with methanol and subsequently partitioned with dichloromethane. Analysis was performed by HPLC-UV and 2D-TLC by co-chromatography with known reference compounds in order to identify the major metabolites of Dichlobenil. The LOQ of the method was 0.01 mg/kg.

Results

The levels of ¹⁴C residues in soil after application of 6.72 kg a.s./ha are summarised in table B.7.1.a

Table B.7.1a: Residue levels in soil and grapes after soil application of Dichlobenil (rate 6.72 kg a.s./ha)

	TRR (mg eq/kg) at				
	0 DAT (post application)	60 DAT	159 DAT	190 DAT	222 DAT (harvest)
Soil 0 -7.6 cm	7.9	1.8	0.16	0.39	0.51
Soil 7.6 – 15.2 cm	n.d.	0.21	0.62	0.14	0.22
grapes	n.i.	n.i.	0.32	0.29	0.36

n.d. not detected,
n.i. not indicated

The distribution and identification of radioactive residues in grapes of 222 DAT are summarised in Table B.7.1b. Distribution and identification data were not elucidated in the grapes of 159 and 190 DAT.

Table B.7.1b: Residue characterisation and identification in grapes 222 days after soil application of Dichlobenil (rate 6.72 kg a.s./ha)

	Grapes, 222 DAT (harvest)	
	mg eq/kg	% TRR
TRR	0.39*	100
Organosoluble	0.36	92
<i>Identified</i>	0.32	82
Dichlobenil (parent)	<LOD	
2,6-dichlorobenzamide (BAM)	0.32	82
2,6-dichloro-4-hydroxybenzamide (4-OH BAM)	<0.01	
<i>Characterised</i>		
un-identified metabolite 1	0.04	10
un-identified metabolite 2	0.02	5.1
Water soluble	0.02	5.1
Not extracted	0.03	7.7

* differs slightly from the result of the combustion analysis
LOD limit of detection

After soil application, the parent compound could not be detected in grapes. The major metabolite in the grapes of 222 DAT was 2,6-dichlorobenzamide (BAM), accounting for 82% of the total radioactive residue. Since the level of total radioactivity found during metabolite characterisation was higher than the levels found by combustion, the values for the individual compounds given in Table B.7.1b are indicative of the distribution rather than exact absolute values.

Acceptability

The study is considered acceptable for the overall evaluation.

Conclusions

The radioactive levels in grapes grown in soil treated with Dichlobenil were 0.32, 0.29 and 0.36 mg eq/kg at 159, 190 and 222 DAT, respectively. The parent compound was not detected in the grapes at 222 DAT (no characterization and identification were performed at 159 and 190 DAT). The major residue of Dichlobenil found in the fruit, was 2,6-dichlorobenzamide (BAM). Metabolism of Dichlobenil proceeds through hydroxylation of the cyanogroup.

In soil the radioactive residue did not decline rapidly, accounting for 2.0, 0.78, 0.53 and 0.73 mg eq/kg at 60, 159, 190 and 222 DAT, respectively.

II) Uptake, distribution and metabolism – apples

Characteristics

Reference	: Hubert, 1990b	Vehicle	: toluene, cyclohexanone, Igepal CO-710 in water
Year of execution	: 1989	Number of treatments	: 1
Guideline	: Directive 91/414/EC; 7028/VI/95 rev.3, Appendix A	Interval	: not applicable
GLP	: yes	Area	: outdoor plots (one apple tree per plot), Porterville, California
Test substance	: Dichlobenil ([U- ¹⁴ C] 2,6-dichlorobenzonitrile); batch/lot no. AOI87K23B	Total rate	: see application rate
Purity	: radiochem. purity 99.7%, specific activity 0.36 mCi/mmol	DAT	: 77, 107, 137
Application rate	: 6.72 kg a.s./ha	Acceptable	: yes
Concentration	: 0.66 kg a.s./l		
Plant	: apple, <i>Pyrus mallus</i> 'Gravenstein'		

Study design

One application of Dichlobenil at a rate of 6.72 kg/ha was made to the soil of apple tree plots. Fruit samples were taken at 77 and 107 DAT and at harvest (137 DAT), frozen using liquid nitrogen and homogenised with dry ice. Soil samples were taken at 0, 30, 77, 107 and 137 DAT. After combustion, the samples were analyzed for radioactivity by LSC. The whole apple homogenates (apples without separation of the seeds, pulp and peel) were extracted with methanol and subsequently partitioned with ethyl ether or toluene. Analysis was performed by HPLC-UV and 2D-TLC by co-chromatography with known reference compounds in order to identify the major metabolites of Dichlobenil. The LOQ of the method was 0.01 mg/kg.

Results

The recoveries established for the radioanalysis were 99.7% for apples and 99.2% for soil.

The levels of ¹⁴C residues in soil after application of 6.72 kg a.s./ha is summarised in table B.7.1.c

Table B.7.1c: Residue levels in soil and apples after soil application of Dichlobenil (rate 6.72 kg a.s./ha)

	TRR (mg eq/kg) at				
	0 DAT (post application)	30 DAT	77 DAT	107 DAT	137 DAT (harvest)
Soil 0 -7.6 cm	1.3	0.49	0.49	0.75	0.60
Soil 7.6 – 15.2 cm	n.d.	n.d.	0.098	0.17	0.29
apples	n.i.	n.i.	0.012	0.028	0.025

n.d. not detected;
n.i. not indicated

The distribution and identification of radioactive residues in apples grown in soil treated with Dichlobenil are summarised in Table B.7.1d.

Table B.7.1d: Residues in apples after soil application of Dichlobenil (rate 6.72 kg a.s./ha)

	Apples, 137 DAT (harvest)	
	mg eq/kg	% TRR

	Apples, 137 DAT (harvest)	
	mg eq/kg	% TRR
TRR	0.025	100
Organosoluble	0.024	
<i>Identified</i>	0.024	96
Dichlobenil (parent)	<LOD	
2,6-dichlorobenzamide (BAM)	0.024	96
<i>Characterised</i>		
un-identified metabolite 1	<0.01	
un-identified metabolite 2	<0.01	
Water soluble	<0.01	
Not extracted	<0.01	

LOD limit of detection

The parent compound could not be detected in the fruit. The only metabolite found in the fruit was 2,6-dichlorobenzamide, accounting for 0.024 mg eq/kg.

Acceptability

The study is considered acceptable for the overall evaluation.

Conclusions

The amount of Dichlobenil and its residues in apples following soil treatment with Dichlobenil is very low. Total radioactivity in the fruit was 0.025 mg eq/kg. The only detectable metabolite in the fruit was 2,6-dichlorobenzamide (BAM). Metabolism of Dichlobenil proceeds through hydroxylation of the cyanogroup.

B.7.1.2 Succeeding and rotational crops

No information regarding succeeding and rotational crops are submitted. The current use of Dichlobenil is intended for application to vine, a permanent crop. According to the guideline (Directive 91/414/EC; 7524/VI/95 rev.2, Appendix C) rotational crop studies have to be carried out "if the active substance tends towards an unacceptable accumulation in the soil and can be taken up by the rotational crop in relevant quantities. In general such tests are only required once a plant protection product has been authorized."

Due to the properties of both parent (DT50 of 39 – 296 days) and the main metabolite BAM, which is also the main metabolite in grapes (DT50_(extrapolated) of 404 – 2666 days) (see chapter B.8) an accumulation of especially the metabolite in the ground after application in more than one growing season has to be considered and should be investigated.

In one of the 14 additional trials submitted (Elgar, 1970; not used for the overall evaluation - see B.7.6.2) long term-trials with vine over a period of three years were performed: at the lowest application rate, 8 kg a.s/ha applied in 3 successive years (1968 – 1970), the residues of BAM in grapes accounted for 0.7, 1.9 and 2.3 mg/kg in the first, second and third year, respectively. The

results support the theory that an accumulation of BAM in grapes does occur after annually repeated application.

Additional information about the effect of repeated applications in successive growing seasons of the vine is therefore required. The outcome can influence the view on the MRL as derived based on the currently available data covering one growing season per trial site only.

Furthermore, it is noted that in case the intended use is changed to other - non-permanent - crops, this issue has to be reconsidered.

B.7.1.3 Summary of studies in plants

Uptake, distribution and metabolism of Dichlobenil were investigated after soil application of a slightly exaggerated dose (about 1.2 N) in grapes, the crop of the intended use, as well as in apples. Both belong regarding their metabolism to the same crop group (fruits).

The same metabolism pattern was found in the investigated commodities: at harvest the parent compound was not detectable and 2,6-dichlorobenzamide (BAM) was in both cases the major metabolite.

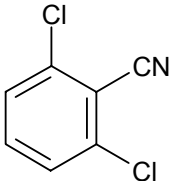
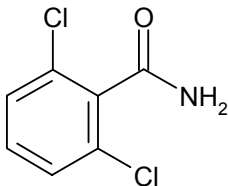
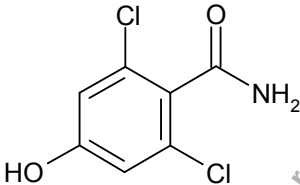
No information about succeeding and rotational crops are submitted. This is acceptable since due to the intended use of Dichlobenil in vine, a permanent crop, succeeding and rotational crops do not have to be considered.

Most likely the conversion of Dichlobenil to BAM occurs in the soil followed by translocation of the metabolite to the grapes (see also B.3.1.2). Since no data on plant metabolism after non-soil application are submitted, no statement regarding the ration and extend of metabolism in soil and possible further conversion in the plant can be made.

In non-GAP residue studies accumulation of residues in grape was observed after repeated yearly application. In B.7.1.1. it was found that residues in soil were 0.20-0.51 mg eq./kg 222DAT. In B.8.3 it was calculated that the PEC_{soil} might be up to 6.88 mg/kg soil. Even when soil-plant transition factors for BAM are low (~1/10, see Appendix C of Guidance Doc 1607/VI/97 rev.1), calculated residues in rotational crops might be above LOQ. Information on the uptake of BAM by rotational crops should be provided. Based on the soil degradation data for Dichlobenil and BAM, an accumulation of especially the metabolite in the ground over more than one growing season is likely and has to be investigated. The performance of a study with repeated application in successive growing seasons in grape is therefore required. Information on repeated application in successive growing seasons might influence the view on the MRL setting as performed based on the currently available data covering only one growing season per trial site.

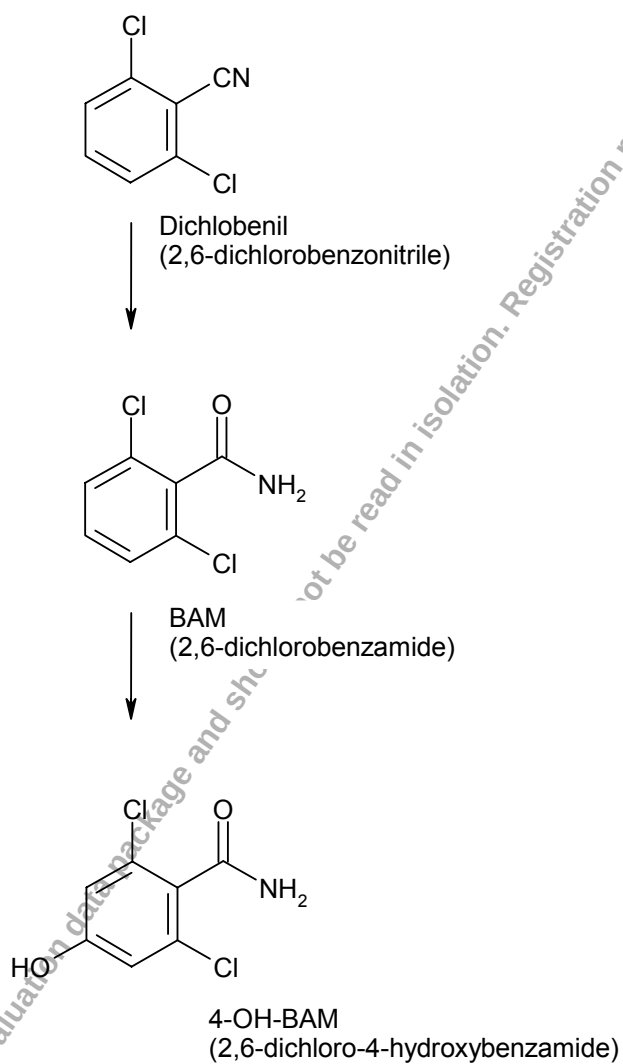
It has to be noted that in case the intended uses will be extended to annual crops, this issue has also to be reconsidered.

B.7.1.4 List of identified compounds

Code	Compounds	Description	Crop/Commodity
Dichlobenil (2,6-dichlorobenzonitrile)		parent compound	grapes and apples
BAM (2,6-dichlorobenzamide)		major metabolite	grapes and apples
4-OH BAM (2,6-dichloro-4-hydroxybenzamide)		metabolite	grapes

B.7.1.5 Metabolic pathway in plants

After soil application, the metabolic pathway of Dichlobenil proceeds through hydroxylation of the cyanogroup resulting in the formation of the main metabolite 2,6-dichlorobenzamide (BAM).



B.7.2 METABOLISM, DISTRIBUTION AND EXPRESSION OF RESIDUES IN LIVESTOCK (ANNEX IIA 6.2 AND ANNEX IIIA 8.1)

No information about metabolism, distribution and expression of residues in livestock is available. However, intake of residues by livestock is possible due to feeding of dry/wet grape pomace to dairy and beef cattle. In the residue trials relevant levels (>LOQ) of the metabolite BAM were found in grapes and the results of the processing study indicate a concentration of this metabolite in fruit pomace. Based on these results, relevant intake levels >0.1 mg/kg dry feed were calculated for cattle (see B.15.1).

Therefore, information on the metabolism, distribution and expression of BAM in ruminants has to be submitted.

B.7.3 DEFINITION OF RESIDUE (ANNEX IIA 6.7; ANNEX IIIA 8.6)

B.7.3.1 Definition of the residue in plant products

The studies on the uptake and metabolism of Dichlobenil in grapes and apples provide sufficient information on the nature and levels of residue after soil application. No detectable levels of the parent compound are found in the fruit grown on the treated soil. The only significant metabolite is 2,6-dichlorobenzamide (BAM). Therefore, the residue definition in plants is 2,6-dichlorobenzamide (BAM) for both monitoring and risk assessment. A conversion factor is not applicable.

It has to be noted that in case the intended use will be modified, this issue has to be reconsidered.

B.7.3.2 Definition of the residue for animal products

No definition of the residue for animal products can be derived, since no data on metabolism, distribution and expression of residues in livestock is available. Considering the relevant intake levels for cattle, information on the metabolism, distribution and expression has to be submitted (see B.7.2).

B.7.4 USE PATTERN

Casoron® G, a 6.75% (w/w) (67.5 g/kg) formulation of Dichlobenil, is submitted for authorisation for use in Northern and Southern Europe as a herbicide for selective, pre-emergence weed control in the cultivation of crops (grapes) and non-crop situations. The different intended uses for Southern and Northern European regions are summarised in Table B.7.4.

Table B.7.4: Intended use pattern of Northern and Southern European regions

INTENDED USE PATTERN, NORTHERN AND SOUTHERN EUROPE; Crompton Crop Protection														
Crop and/or situation	Member State or Country	F, G or I	Pests or group of pests controlled	Formulation		Application				Application rate per treatment			PHI (days)	Remarks:
				type	conc. of a.s. (g/kg)	method kind	growth stage	number (range)	interval (months)	a.s. (kg/hL)	water (L/ha)	a.s. (kg/ha)		
Fruits														
Grapes	Northern and Southern Europe	F	weeds	GR	67.5	broadcast spreading	pre-emergence of the weed (spring)	1	n.a.	n.a.	n.a.	2.7 – 5.4	n.a.	
Non-crop situations														
Non-crops	Northern and Southern Europe	F	weeds	GR	67.5	broadcast spreading	pre-emergence of the weed (spring)	1	n.a.	n.a.	n.a.	2.03 – 5.4	n.a.	
F	field use													
GR	granule													
n.a.	not applicable													

WARNING: This document contains information that is confidential and its use for any purpose other than the evaluation of the product must not be granted on the basis of this document.

B.7.5 IDENTIFICATION OF CRITICAL GAPS

A summary of critical GAPS for crops in Southern and Northern European regions is given in Table B.7.5.

Table B.7.5: Identification of the cGAPs of Southern European regions in crops

INTENDED USE PATTERN, NORTHERN AND SOUTHERN EUROPE, Crompton Crop Protection												
Crop and/or situation	Member State or Country	F, G or I	Pests or group of pests controlled	Formulation		Application			Application rate per treatment		PHI (days)	Remarks:
				type	conc. of a.s. (g/kg)	method kind	growth stage	number (range)	interval (days)	a.s. (kg/hL)		
Fruits												
Grapes	Northern and Southern Europe	F	weeds	GR	67.5	broadcast spreading	pre-emergence of the weed (spring)	1	n.a.	n.a.	5.4	n.a.

WARNING: This document forms part of an EC evaluation. It must be read in isolation. Registration must not be granted on the basis of this document.

B.7.6 RESIDUES RESULTING FROM SUPERVISED TRAILS (ANNEX IIA 6.3; ANNEX IIIA 8.2)**B.7.6.1 Methods of analysis applied in the supervised residue trials**

Residues in crops of the supervised trials performed in grapes were analysed using Agrisearch method Dichlobenil-BAM/Crops/DB/99/1 (see also B.5.2.1, method IV) for the determination of Dichlobenil and its metabolite 2,6-Dichlobenil (2,6-dichlorobenzamide, BAM). The method is based on analyte-dependent extraction, purification by gel permeation chromatography and quantification applying GC-ECD. Procedural validation data are included in the reports. In combination with the validation data as submitted in B.5.2.1 this is considered sufficient to rely on the results obtained by this method. The LOQ account for 0.02 mg/kg for Dichlobenil and 0.003 mg/kg for BAM.

Samples were stored at $\leq -18^{\circ}\text{C}$ and were analysed (Brereton, 2000) within one year after sampling. In the study of Gillis (2004) the samples for the determination of Dichlobenil were extracted within 252 days after storage at $\leq -18^{\circ}\text{C}$ and analysed within 180 days after storage of the extracts at -18°C ; the samples for the determination of BAM were extracted within 429 days after storage at $\leq -18^{\circ}\text{C}$ and analysed within 84 days after storage of the extracts at -18°C . Considering the temperature and duration the sample storage in the study of Gillis (2004), which are not covered by storage stability data, the reliability of the respective results is doubtful (see also remark under applicability). Information about the influence of the storage conditions of the plant extracts on the measured residue levels are required.

B.7.6.2 Supervised residue trails

Supervised trials were submitted for the use of Casoron[®] G on grapes under field conditions in both Northern and Southern European regions. The supervised trials are summarised in table B.7.6.2a (Southern European regions) and table B.7.6.2b (Northern European regions).

All data used for the elaboration of the MRL are underlined. From the original report of Gillis (2004) it was concluded that sample extracts were stored at 4°C . However, An amendment on this report was provided (Harrison and Partington, 2006) showing that storage took place at -18°C .

Table B.7.6.2a: Summary of supervised trials for the Southern European regions

SUPERVISED RESIDUE TRIALS, SOUTHERN EUROPE, Crompton Crop Protection													
Location	Commodity/ Variety	Date of: 1. Planting 3. Harvest	Method of treatment	Application rate per treatment			No. of treatments and dates	Growth stage at last treatment	Portion analyzed	Parent Dichlobenil (mg/kg)	Metabolite BAM (mg/kg)	DAT	Reference, Remark
				a.s. (kg/hL)	water (L/ha)	a.s. (kg/ha)							
FRUIT													
Wine grapes													
Tarn, France (S)	Wine grapes/ Gamay	1. 1974 2. n.i. 3. 06-09-1999	overall broadcast (Fischer granule applicator)	n.a.	n.a.	6.95	1 25-02-1999	00 BBCH	fruit	<0.02	0.076	193	Brereton, 2000 GLP
Tarn-et- Garonne, France (S)	Wine grapes/ Syrah	1. 1982 2. n.i. 3. 24-09-1999	overall broadcast (Fischer granule applicator)	n.a.	n.a.	6.48	1 25-02-1999	00 BBCH	fruit	<0.02	0.090	211	Brereton, 2000 GLP
Tarn-et- Garonne, France (S)	Wine grapes/ Tanant	1. 1975 2. n.i. 3. 14-10-2002	overall broadcast (by hand)	n.a.	n.a.	6.75	1 26-03-2002	05 BBCH	fruit	<0.02	0.080	202	Gillis, 2004 GLP
Tarn-et- Garonne, France (S)	Wine grapes/ Cabernet	1. 1992 2. n.i. 3. 14-10-2002	overall broadcast (by hand)	n.a.	n.a.	6.75	1 27-03-2002	05 BBCH	fruit	<0.02	0.173	201	Gillis, 2004 GLP
Emilia Romagna, Italy	Wine grapes/ Trebbiano	1. 1990 2. n.i. 3. 12-09-2002	overall broadcast (by hand)	n.a.	n.a.	6.75	1 30-04-2002	15 BBCH	fruit	<0.02	0.049	135	Gillis, 2004 GLP
Emilia Romagna, Italy	Wine grapes/ Trebbiano	1. 1978 2. n.i. 3. 16-09-2002	overall broadcast (by hand)	n.a.	n.a.	6.75	1 03-05-2002	15 BBCH	fruit	<0.02	0.015	136	Gillis, 2004 GLP

n.a. not applicable (granular formulation, applied by broadcast spreading)

n.i. not indicated

Registration must not be granted on the basis of this document.

Table B.7.6.2b: Summary of supervised trials for the Northern European regions

SUPERVISED RESIDUE TRIALS, NORTHERN EUROPE, Crompton Crop Protection													
Location	Commodity/ Variety	Date of: 1. Planting 2. Flowering 3. Harvest	Method of treatment	Application rate per treatment			No. of treatments and dates	Growth stage at last treatment	Portion analyzed	Parent Dichlobenil (mg/kg)	Metabolite BAM (mg/kg)	DAT	Reference, Remark
				a.s. (kg/hL)	water (L/ha)	a.s. (kg/ha)							
FRUIT													
Wine grapes													
Loiret, France (North)	Wine grapes/ Cabernet franc	1. 1986 2. n.i. 3. 04-10-1999	overall broadcast (Fischer granule applicator)	n.a.	n.a.	7.02	1 23-02-1999	00 BBCH	fruit	<0.02	0.088	223	Brereton, 2000 GLP
Indre-et- Loire, France (North)	Wine grapes/ Cabernet franc	1. 1989 2. n.i. 3. 23-09-1999	overall broadcast (Fischer granule applicator)	n.a.	n.a.	6.48	1 23-02-1999	00 BBCH	fruit	<0.02	0.097	212	Brereton, 2000 GLP
Spann- berg, Austria	Wine grapes/ Grüner Veltliner	1. 1987 2. n.i. 3. 09-09-2002	broadcast (by hand, manual shaker)	n.a.	n.a.	6.75	1 27-03-2002	00-01 BBCH	fruit	<0.02	0.012	166	Gillis, 2004 GLP
Loiret, France (North)	Wine grapes/ Pinot Meunier	1. 1980 2. n.i. 3. 10-09-2002	overall broadcast (pepperpot construction)	n.a.	n.a.	6.75	1 25-03-2002	01 BBCH	fruit	<0.02	0.146	169	Gillis, 2004 GLP
Saone-et- Loire, France (North)	Wine grapes/ Chardonnay	1. 1996/97 2. n.i. 3. 16-09-2002	overall broadcast (pepperpot construction)	n.a.	n.a.	6.75	1 29-03-2002	05 BBCH	fruit	<0.02	0.152	171	Gillis, 2004 GLP
Loiret, France (North)	Wine grapes/ Pinot noir	1. 1993 2. n.i. 3. 17-09-2002	overall broadcast (pepperpot construction)	n.a.	n.a.	6.75	1 26-03-2002	01 BBCH	fruit	<0.02	0.045	175	Gillis, 2004 GLP

Summary

In total 12 residue trials were submitted – 6 for Northern Europe, 6 for Southern Europe. All trials were performed in 1999 and 2002 with grapes under field conditions and GLP.

In all trials the parent compound Dichlobenil and its main metabolite 2,6-dichlorobenzamide (BAM) were determined. Only for BAM levels above the LOQ were found:

- in Southern Europe the residue levels of 2,6-dichlorobenzamide range from 0.015 mg/kg (at 136 DAT) – 0.173 mg/kg (at 201 DAT),
- in Northern Europe the residue levels of 2,6-dichlorobenzamide range from 0.012 mg/kg (at 166 DAT) – 0.152 mg/kg (at 171 DAT).

All applications were carried out in spring, at the latest at BBCH 15 (5 vine leaves unfolded). In two trials (one Northern and one Southern European trial) the application rates are too high, accounting for more than 25% above the application rate of the critical GAP (>6.75 kg a.s./ha).

Since the residue levels obtained in the Northern and Southern trial are in the same range it is justified to combine the trial data from Northern and Southern Europe for the derivation of the MRL. Based on this approach the available trial data are considered sufficient (n = 10) to derive an MRL for the current intended use of Dichlobenil in vine in Northern and Southern Europe.

It has to be mentioned that the residue levels reported by Gillis (2004) are considered provisional, since the reliability of these data are is questionable due to the sample storage conditions. The plant extracts were stored at -18°C over a considerable amount of time. Additional information has therefore to be submitted in order to enable the assessment if these storage conditions influence the residue levels as measured and documented in the report.

Aside from the trials summarised above, the notifier did also submit in total 14 studies as additional information. However, 9 of the study reports are quite outdated (1966 – 1972) and do not contain all information relevant for an assessment as it is requested in the guideline. Furthermore, in some studies were not performed in Europe, but in Canada. The five more recent studies (1991 -1998) were performed in the United States and are therefore also not suitable for evaluation within the scope of this EU-submission. Therefore, none of the additionally submitted data are considered suitable for the current evaluation and therefore are not included in table B.7.6.2.a/b. However, it is noted that the results reported in these studies do support the results of the trials used for the derivation of the MRL.

Acceptability

Both studies are considered acceptable for the overall evaluation. However the storage stability data available (see B.7.6.3) do not cover the storage period and temperature for the BAM samples in the study of Gillis (2004). The respective information about the storage stability as well as information about the consequences of a possible accumulation of Dichlobenil and its main metabolite BAM in soil on the residue levels in grapes have still to be submitted. Therefore, the MRL based on the trials carried out in accordance with the cGAP (see B.7.12.3) will be considered provisional.

B.7.6.3 Stability of residues prior to analysis

No storage stability study as such is submitted, but storage stability data are provided in one of the processing studies (Maselli, 1998), however these data were obtained without GLP-compliance.

Fortified samples (fortification levels: 0.08 – 0.1 ppm Dichlobenil and 0.02 – 0.1 ppm BAM) were stored at $-20 \pm 5^{\circ}\text{C}$. The following results were obtained:

- grape samples were stable over the whole testing period of 323 days (Dichlobenil) and 345 days (BAM),
- raisin samples were stable over the whole testing period of 273 days (Dichlobenil) and 266 days (BAM),
- grape juice samples were stable over the whole testing period of 322 days (Dichlobenil) and 343 days (BAM).

These storage stability data are accepted to support the storage conditions of the processing study and the residue trial study of Brereton (2000), but do not cover the storage period for the BAM grape samples in the residue study of Gillis (2004), which are stored for 442-443d. However, since the storage stability was proven for 10 months (dichlobenil) and 11 months (BAM) up to a high extent, extrapolation up to 14.5 months was proposed (Yu, 2006) and assumed to be acceptable. Sample extracts were stored at -18°C for up to 180d (dichlobenil) and 84d (BAM). Additional information on sample stability for this period should be provided. The notifier made already clear that 4 additional residue trials with shorter storage intervals of samples and extracts might solve this open point. Furthermore, depending on the outcome on the requested animal metabolism and/or feed intake studies, data on the storage stability of the relevant residue(s) in the relevant animal matrices have to be submitted.

B.7.7 EFFECTS OF INDUSTRIAL PROCESSING AND/OR HOUSEHOLD PREPARATION (ANNEX IIA 6.5, ANNEX IIIA 8.4)

B.7.7.1 Effects on the nature of the residue

No information on the effects of processing on the nature of residue is submitted. According to Annex 1 of the respective guideline (Directive 91/414/EC; 7035/VI/95 rev.5, Appendix E) it has to be investigated if the chemical nature of the residue in the processed commodities is likely to be different from that in the raw agricultural commodity. The relevant processing types for the current intended use are the preparation of wine and the preparation of fruit juice from grapes.

The notifier provided a statement in Annex IIA, point 6.5.1 about the hydrolytical stability of the main residue component BAM. It is concluded from the $\text{Log } P_{\text{ow}} = 0.51$ at PH3 that BAM residue will remain mainly in the water phase. The processing study on grape show that BAM concentrate slightly in grape pomace after pressing juice. Furthermore, BAM is hydrolytically stable for 5d at 50°C at PH 4-9. Therefore, no change in the composition of the residue is foreseen after making juice.

However, no information is provided with regard to the anaerobic process of fermentation from juice to wine. The respective information has to be submitted.

B.7.7.2 Effects on residue levels

I) Processing study – grapes

Characteristics

Reference	: Maselli, 1998	Treatment	: single application
Year of execution	: 1996-1998	Rate	: 8.7 kg a.s./ha (7.8 pounds/acre) 1.6N
Guideline	: Directive 91/414/EC; 7035/VI/95 rev.5, Appendix E	Crop/commodity	: grapes
GLP	: yes		
Test substance	: Casoron 4G (3.75% Dichlobenil), lot no. 505G414		
Formulation	: granules	Acceptable	: yes

Study design

The Dichlobenil formulation Casoron 4G was applied to the soil of grape vines at a level of 8.7 kg a.s./ha (1.6N). Grapes were harvested at maturity. Samples of the grapes of treated and control plots were processed into juice or raisins at two different processing facilities. Grapes and processed fractions were extracted with ethyl acetate in hexane (samples for Dichlobenil analysis) or extracted with ethyl acetate (samples for BAM analysis), cleaned up using an alumina column and analysed for residues of Dichlobenil and BAM by GC-ECD. The limit of quantification (LOQ) for Dichlobenil in all matrices was 0.02 mg/kg; LOQ for BAM were 0.003 mg/kg in grapes and grape juice and 0.03 mg/kg in raisins. The results are corrected for recovery.

Results

Recoveries of Dichlobenil and BAM from fortified control samples ranged from 73% to 111%.

In treated grapes, juice and raisins, no residues of Dichlobenil above the LOQ were found. Residue levels of 2,6-dichlorobenzamide (BAM) are presented in Table 7.7.2.a.

Table 7.7.2a: 2,6-dichlorobenzamide (BAM) levels in grape samples collected during the processing and concomitant transfer factors

Product	Total residue of BAM (mg eq/kg)	Transfer factor
grapes (RAC)	0.004 ^a 0.029 ^b	
juice	0.006 ^a 0.027 ^b	1.5 0.9
raisins	<0.03 ^a 0.083 ^b	n.c. 2.9

RAC raw agricultural commodity

a results from processing facility Fresno, CA

b results from processing facility Madera, CA

n.c. not calculated, levels below the LOQ

No significant concentration occurred during the processing of the grapes into juice.

One of the values for raisins (results from processing facility Fresno, CA) was below the LOQ for raisins (which is 10 times higher than the LOQ for grapes and juice). Therefore, no transfer factor can be determined. The results of the second facility showed a transfer factor of approximately 3 for raisins.

Acceptability

The study is considered acceptable for the overall evaluation.

Conclusions

The transfer factor of 2,6-dichlorobenzamide (BAM), the main metabolite of Dichlobenil, is approximately 3 for raisins and 1.2 for juice .

II) Processing study – grapes

Characteristics

Reference	: Gillis, 2004	Treatment	: single application
Year of execution	: 2002	Rate	: 6.75 kg a.s./ha 1.3N
Guideline	: Directive 91/414/EC; 7035/VI/95 rev.5, Appendix E	Crop/commodity	: wine grapes
GLP	: yes		
Test substance	: Casoron G (6.75% a.s. w/w)		
Formulation	: granules	Acceptable	: yes

Study design

The Dichlobenil formulation Casoron G was applied to the soil of vine plots at a level of 6.75 kg a.s./ha (1.3N). Samples of the grapes of treated and control plots were taken at normal commercial harvest and processed into wine. Grapes and processed fractions were extracted into ethyl acetate/hexane followed by purification of separate aliquots of the extract for Dichlobenil and BAM using gel permeation chromatography. Quantification of each analyte was performed separately using GC-ECD. The limits of quantification (LOQs) for Dichlobenil and BAM were 0.02 mg/kg and 0.003 mg/kg, respectively. The results are corrected for recovery.

Results

Mean procedural recoveries were 84%, 54%, 93%, 82% and 89% for Dichlobenil and 106%, 89%, 102%, 95% and 90% for BAM in grapes, must, wine, wet pomace and young wine, respectively. In treated grapes and wine, no residues of Dichlobenil above the LOQ were found. Residue levels of 2,6-dichlorobenzamide (BAM) are presented in Table 7.7.2b.

Table 7.7.2b: 2,6-dichlorobenzamide (BAM) levels in grape samples collected during the processing and concomitant transfer factors

Product	Total residue of BAM (mg eq/kg)	Transfer factor for BAM	Remarks
grapes (RAC)	0.051 ^a		Variety: Pinot noir 175 DAT
must	0.060	1.2	

Product	Total residue of BAM (mg eq/kg)	Transfer factor for BAM	Remarks
wet pomace	0.047	0.9	
young wine	0.051	1	
wine	0.036	0.7	

grapes (RAC)	0.086 ^b		Variety: Tanat 202 DAT
must	0.073	0.8	
wet pomace	0.20	2.3	
young wine	0.10	1.2	
Wine	0.092	1.1	
grapes (RAC)	0.20 ^c		Variety: Cabernet 201 DAT
must	0.13	0.7	
wet pomace	0.27	1.4	
young wine	0.20	1	
wine	0.33	1.7	

RAC raw agricultural commodity
^a mean of 0.045 and 0.056 mg/kg
^b mean of 0.080 and 0.091 mg/kg
^c mean of 0.173 and 0.219 mg/kg

Concentration of BAM occurs during processing of grapes into wet pomace and wine.

Acceptability

The study is considered acceptable for the overall evaluation.

Conclusions

The transfer factors of the metabolite of Dichlobenil, 2,6-dichlorobenzamide (BAM), range from 0.7 to 1.2 (mean 0.9) for must, from 1.0 to 1.2 (mean 1.1) for young wine, from 0.7 to 1.7 (mean 1.2) for wine and from 0.9 to 2.3 (mean 1.5) for wet pomace.

B.7.7.3 Summary of the processing studies

The effects of processing of grapes to juice and raisins (Maselli, 1998) as well as must, wet pomace and (young) wine (Gillis, 2004) on the residue levels of Dichlobenil and its major metabolite 2,6-dichlorobenzamide (BAM) were investigated. In none of the processed fractions were levels above the LOQ of the parent compound Dichlobenil were measured; only its main metabolite BAM was found. A concentration of BAM occurred during the production of raisins, resulting in a transfer factor of 2.9.

The transfer factors for the production of wet pomace range and juice account for 1.5 (individual results: 0.9, 2.3, 1.4) and 1.2 (individual results: 1.5, 0.9), respectively. The concentration of BAM in

must and wine remain approximately the same, the transfer factors account for 0.9 (individual results: 1.2, 0.8, 0.7) and 1.1 (young wine individual results: 1.0, 1.2, 1.0), – 1.2 (wine, individual results: 1.0, 1.2, 1.0), respectively.

However, since the nature of residue was not further investigated, it can not be assessed if the compounds determined in the two studies do cover all residue components which occur after processing. Therefore information regarding the influence of the relevant processing processes (preparation of wine from grapes) on the chemical nature of the residue has still to be submitted. Only based on this information a final conclusion about the appropriateness of the above mentioned processing studies can be drawn.

B.7.8 LIVESTOCK FEEDING STUDIES (ANNEX IIA 6.4; ANNEX IIIA 8.3)

No livestock feeding studies were submitted by the notifier.

However, since relevant intake levels >0.1 mg/kg dry feed occur for cattle (see B.7.15.1), data on animal metabolism is required for ruminants (see B.7.2). In case these data indicate that significant residues (≥ 0.01 mg/kg) occur in any edible part of the animal after intake of the residue levels in potential feeding stuff at the 1x dose rate, a feeding study with BAM in ruminants will be required as well.

B.7.9 RESIDUES IN SUCCEEDING OR ROTATIONAL CROPS (ANNEX IIA 6.6; ANNEX IIIA 8.5)

No information on residues in succeeding or rotational crops are submitted. Considering the intended use in vine, a permanent crop, such information is also not required. However, data about the influence of repeated application in successive growing seasons on the residue levels in grapes should be submitted (see B.7.1.2. for further explanation).

B.7.10 PROPOSED PRE-HARVEST INTERVALS FOR ENVISAGED USES, OR WITHHOLDING PERIODS, IN THE CASE OF POST-HARVEST USES (ANNEX IIA 6.8; ANNEX IIIA 8.7)

Proposed post harvest intervals (PHIs) are:

Crop group	Crops	PHI (days)
Berries and small fruit	Table and wine grapes	Not applicable: application is envisaged in early spring, before the emergence of the grapes

B.7.11 COMMUNITY MRLs AND MRLs IN EU MEMBER STATES (ANNEX IIIA 12.2)

Country	Commodity	MRL (mg/kg)	Residue definition
EU MRL			
EU	-	Not derived	-
Community MRLs			
Austria	Crops, other animal product Fish	0.05 5.0	Dichlobenil/2,6-dichlorobenzamide (BAM)
Belgium	Fruit Others	0.1 0.02*	including 2,6-dichlorobenzamide (BAM) and chlorthiamid
Germany	Vegetables, cereals, fruit Others Grapes Other berries & small fruit (except strawberries) Pit & pome fruit, wild toadstools	0.1 0.05 1.0 0.5 0.1	Dichlobenil Dichlobenil 2,6-dichlorobenzamide (BAM) 2,6-dichlorobenzamide (BAM) 2,6-dichlorobenzamide (BAM)
	Others	0.05	2,6-dichlorobenzamide (BAM)
Hungary	Fruit	0.1	Dichlobenil
Italy	Apple, pear, grape, olive, wheat, fodder from pasture/grassland, medicinal herbs, clover	0.1	Dichlobenil
Luxembourg	Blackberry bush, European blackberry bramble, raspberry, raspberry bush, small fruit, red currant, white currant, gooseberry bush, blueberry, cranberry, pineapple, kiwi, fruit, fig, kumquat, litchee, mango, banana, olive, passion fruit, avocado, date, pome granat, strawberry (cultivated), other fruit from nursery, quinces, apple, pears, cashew nuts, other shell fruit, Brazil nut, coconut, European chestnut, pecan nut, hazelnut, pistachio nut, pine seed, almond, other nut fruit, apricot, peaches, nectarines, cherries, plum, other citrus fruit, limes, grapefruit, lemon, mandarin, and orange	0.1	Dichlobenil
Netherlands	Fruit Other food crops Table & wine grapes Other fruits Other food crops	0.1 0.02* 1.0 0.5 0.05*	dichlobenil 2,6-dichlorobenzamide (BAM)
Poland	Fruit	0.1	Dichlobenil
Portugal	Apple, pear, grape	0.1*	Dichlobenil
Spain	Pome & stone fruit	0.2	Dichlobenil

* Limit of detection
STMRs not indicated

B.7.12 PROPOSED EU MRLS AND JUSTIFICATION FOR THE ACCEPTABILITY OF THOSE MRLS (ANNEX IIA 6.7; ANNEX IIIA 8.6)

B.7.12.1 Proposed MRLs by notifier

The MRLs proposed by the notifier Crompton Uniroyal Chemical are listed in the table below.

Crop group	Crops	MRL	STMR
Berries and small fruit	Table and wine grapes	Dichlobenil: 0.02 mg/kg (LOQ) BAM: 0.3 mg/kg	not indicated

B.7.12.2 Justification of proposed MRL

Berries and small fruit

Crop : grapes

Part of plant : fruit

Based on the results of the metabolism study in grapes (see B.7.1.1.) 2,6-dichlorobenzamide (BAM), the main metabolite of Dichlobenil, is the residue definition for grapes at the current intended use. Residue trial data are available to derive an MRL (see B.7.6.2). Twelve trials were submitted, 6 trials in Southern Europe and 6 trials in Northern Europe. The studies were conducted in 1999 and 2002. Two trials were not compliant with the cGAP because of a too high application rate. Five trials in Northern Europe and 5 trials in Southern Europe are compliant with the cGAP. Due to the comparable residue levels found, the results from Northern and Southern European trials are combined for the derivation of the MRL.

However, the MRL as derived below is considered provisional since the following relevant issues have to be clarified:

- Based on the soil degradation data (see B.8.3) it has to be concluded that an accumulation of especially the metabolite BAM in soil after application in more than one growing season occurs. Since it seems likely that this results in increasing residue levels in grapes in the successive growing seasons, the influence of repeated applications in successive growing seasons on the residue levels in grapes over the years has to be elucidated (see B.7.1.2).
- The reliability of the data as reported in the study of Gillis (2004) is questionable, due to the storage of the plant extracts at -18°C over a considerable amount of time (see B.7.6.1). Additional information has therefore to be submitted before a definite MRL can be established for grapes.

Grapes: Residues of BAM (mg/kg)

NMS	0.012		0.045				0.097	0.146	0.152	
SMS		0.015		0.049	0.080	0.090				0.173

Southern and Northern Europe

Method 1:	R(max) =	0.25
Method 2:	R(cal) =	0.30

MRL for grapes:	0.3 mg/kg BAM (provisional)
STMR:	0.085 mg/kg BAM (provisional)
Highest residue value (HR)	0.17 mg/kg BAM (provisional)

The MRL for grapes as proposed by the notifier is not confirmed. In contrast to the MRL as proposed by the notifier, the parent compound Dichlobenil is not included in the residue definition and therefore no MRL for dichlobenil was derived by the RMS. The MRL for grapes expressed as 0.3 mg/kg BAM, as also proposed by the notifier, is confirmed by the RMS. However this MRL is considered provisional, due to the data gaps as described above.

B.7.12.3 Summary of the proposed MRL

The provisional MRL and STMR as proposed by the RMS based on the available residue data in grapes after soil application of Dichlobenil are given in the following table.

Crop group	Crops	MRL (provisional)	STMR (provisional)
Berries and small fruit	Table and wine grapes	0.3 mg/kg 2,6-dichlorobenzamide (BAM)	0.085 mg/kg BAM

B.7.13 PROPOSED EU IMPORT TOLERANCES AND JUSTIFICATION FOR THE ACCEPTABILITY OF THOSE RESIDUES

Not applicable, since no applications outside the EU are proposed in the intended use pattern.

B.7.14 BASIS FOR DIFFERENCES, IF ANY, IN CONCLUSIONS REACHED HAVING REGARD TO ESTABLISHED OR PROPOSED CAC MRLS

Not applicable, since no Codex MRL has been established or proposed yet.

B.7.15 ESTIMATION OF POTENTIAL AND ACTUAL DIETARY EXPOSURE THROUGH DIET AND OTHER MEANS (ANNEX IIA 6.9; ANNEX IIIA 8.8)

Theoretical maximum daily intakes (TMDIs) from feed were calculated for livestock based on the in this monograph submitted residue trial data and processing data.

B.7.15.1 Intakes by domestic animals**Cattle**

Based on the intended use of Dichlobenil in grapes, intake by livestock is considered to occur via feeding of dry/wet grape pomace to dairy and beef cattle. Relevant levels (>LOQ) of BAM, the main metabolite of Dichlobenil, were found in the residue trials in grapes and due to the results of the processing study, a concentration of these content in fruit pomace is expected. No data on the transfer during processing of dry pomace are available.

Since no livestock feeding studies were submitted, it cannot be stated if the plateau levels are reached slowly or within 7 days. Therefore intake calculations were performed with the provisional MRL and STMR, accounting for 0.3 mg/kg BAM and 0.085 mg/kg BAM, respectively.

In both cases a transfer factor of 1.5 (mean value for the transfer during processing to wet pomace) was applied, resulting in levels of 0.45 mg/kg and 0.13 mg/kg BAM if calculated with the provisional MRL and STMR, respectively. Due to the provisional data used for the calculation, the resulting TDMIs have to be considered provisional as well.

The following calculations were applied:

$$C = (A/100) \cdot B$$

$$E = (C/D) \cdot 100$$

$$G = F \cdot E$$

- A Daily Maximum Feed intake (DryMatter) DM
 B % of diet as crop
 C Intakes of dry matter from crop (kg/animal/day)
 D % dry matter
 E Intake fresh material (kg/animal/day)
 F Residues in crop (mg/kg)
 G Residue intake (mg/animal/day)

Dairy cattle

Group/Crop	% of diet as crop	Intakes of dry matter from crop (kg/animal/day)	% dry matter	Intake fresh material (kg/animal/day)	Residues in crop (mg/kg)	Residue intake (mg/animal/day)
Intake calculation based on the provisional STMR (0.085 mg/kg BAM) and processing factor 1.5:						
I) wet/dry grape pomace	10	2	23	8.7	0.13	1.13
Intake calculation based on the provisional MRL (0.3 mg/kg BAM) and processing factor 1.5:						
I) wet/dry grape pomace	10	2	23	8.7	0.45	3.91

Total intake:

Group/Crop	mg/animal/day (based on provisional STMR)	mg/animal/day (based on provisional MRL)	percent of diet
I) wet/dry grape pomace	1.1	3.9	10
Total	1.1	3.9	10

TMDI dairy cattle (550 kg) (provisional):

= 0.002 – 0.007 mg/kg bw/day

= 0.06 – 0.21 mg/kg diet (dry weight)

Beef cattle

Group/Crop	% of diet as crop	Intakes of dry matter from crop (kg/animal/day)	% dry matter	Intake fresh material (kg/animal/day)	Residues in crop (mg/kg)	Residue intake (mg/animal/day)
Intake calculation based on the provisional STMR (0.085 mg/kg BAM) and processing factor 1.5:						
l) wet/dry grape pomace	30	4.5	23	19.6	0.13	2.5
Intake calculation based on the provisional MRL (0.3 mg/kg BAM) and processing factor 1.5:						
l) wet/dry grape pomace	30	4.5	23	19.6	0.45	8.8

Total intake:

Group/Crop	mg/animal/day (based on provisional STMR)	mg/animal/day (based on provisional MRL)	percent of diet
l) wet/dry grape pomace	2.5	8.8	30
Total	2.5	8.8	30

TMDI beef cattle (350 kg) (provisional): = 0.007– 0.025 mg/kg bw/day
= 0.17 – 0.59 mg/kg diet (dry weight)

Poultry

No intake of residues by poultry is expected after application of Dichlobenil based on the current intended use.

Pigs

No intake of residues by pigs is expected after application of Dichlobenil based on the current intended use.

B.7.15.2 Intakes by humans (long-term)

Intake calculations for humans were performed based on the established provisional MRL (see section B.7.12). As described in chapter B.7.15.1, relevant intake of BAM occurs in livestock, but no information on the nature of the residue and the residue levels in animal parts used for human consumption are available. Therefore, all further intake calculations for human are provisional. Depending on the additional information (influence on repeated treatment in successive growing seasons on the residue levels in grapes, influence of the storage conditions of the plant extracts in the residue trial study of Gillis (2004) on the residue levels measured, influence of processing on the nature of residue and data on animal metabolism, eventually followed by a feeding study), the calculation of the human intake levels have possibly to be reconsidered.

International theoretical maximum daily intake (provisional ITMDI)

The provisional ITMDI for humans was determined on the basis of an ADI for BAM of 0.022 mg/kg bw/day or 1.3 mg/person/day (assumed body weight is 60 kg), the proposed provisional MRL and the FAO/WHO EURdiet as shown in table B. 7.15.2a.

Table B.7.15.2a ITMDI (provisional)

Product	Consumption products	Intake (g/person/ day)	provisional MRL (mg/kg BAM)	ITMDI (mg/person/day)	% of the ADI
grapes	fresh, dried, wine	n.d.	0.3	0.0041	0.3
Total (excl. water)				0.0041	0.3

Drinking water derived from ground water or surface water might contain BAM at relatively high levels. A worst case estimation for BAM was up to 0.38 mg/L BAM under the Hamburg scenario, see B.8.5.2. When taking an additional residue intake through drinking water of 0.38mg/L (corresponding to 0.76 mg/person/d (consumption of 2L/person/d) , a total provisional ITMDI of 58% of the ADI is calculated for the FAO/WHO EURdiet. When assuming that during processing of potable water all BAM will be removed up to the legal value of 0.1 µg/L BAM, the additional intake for consumers by the intake of water is less than 0.1% of the ADI and filling the ADI for 0.3%. If based on the provisional STMR of 0.085 mg/kg BAM and considering the highest processing factor, 2.9 for wine, an IEDI (provisional) of 58% of the ADI (intake via water included) is calculated for the WHO European diet.

National theoretical maximum daily intake (provisional NTMDI) for adults

The provisional NTMDI for humans was determined on the basis of an ADI for BAM of 0.022 mg/kg bw/day or 1.4mg/person/day (assumed body weight is 63 kg), the proposed provisional MRL and the Dutch TMDI model (RIKILT-DLO, the Netherlands) as shown in table B. 7.15.2b.

Table B.7.15.2b NTMDI for adults (provisional)

Product	Consumption products	Intake (g/person/ day)	provisional MRL (mg/kg BAM)	ITMDI (mg/person/day)	% of the ADI
grapes	Table grapes	14.44	0.3	0.0043	0.3
	Wine grapes	39.68	0.3	0.012	0.9
Total (excl. water)				0.016	1.2

When taking an additional residue intake through drinking water of 0.38 mg/L BAM, corresponding to 0.76 mg/person/d (consumption of 2L/person/d), a total provisional NTMDI of 55% of the ADI is calculated for the Dutch TMDI model. . When assuming that during processing of potable water all BAM will be removed up to the legal value of 0.1 µg/L BAM, the additional intake for consumers by consumption of is less than 0.1% of the ADI and the ADI is filled for 1.2%.

National theoretical maximum daily intake (provisional NTMDI) for children (1-6 y)

The provisional NTMDI for humans was determined on the basis of an ADI for BAM of 0.022 mg/kg bw/day or 0.38 mg/person/day (assumed body weight is 17.1 kg), the proposed provisional MRL and the Dutch TMDI model (RIKILT-DLO, the Netherlands) as shown in table B. 7.15.2c.

Table B.7.15.2c NTMDI for children (1-6 y) (provisional)

Product	Consumption products	Intake (g/person/ day)	provisional MRL (mg/kg BAM)	ITMDI (mg/person/day)	% of the ADI
grapes	Table grapes	12.98	0.3	0.0039	1.0
	Wine grapes	0.02	0.3	0.00001	0.0
Total (excl. water)				0.0039	1.0

When taking an additional residue intake through drinking water of 0.38 mg/L, corresponding to 0.76 mg/person/d (consumption of 2L/person/d), a total provisional NTMDI of 203% of the ADI is calculated for the Dutch TMDI model. When assuming that during processing of potable water all BAM will be removed up to the legal value of 0.1 µg/L BAM, the additional intake for consumers by consumption of is less than 0.1% of the ADI and the ADI is filled for 1.1%.

If based on the provisional STMR of 0.085 mg/kg BAM and the highest processing factor 2.9, provisional NEDIs of 1.0% of the ADI (intake via water included) for both adults and children were calculated for the Dutch model.

Based on the foregoing calculations and considerations, the use of Dichlobenil according to the intended uses for which MRLs are proposed, is not considered to result in an unacceptable risk on adverse health effects due to long-term exposure to residues in food products.

B.7.15.3 International estimate for short term intake by humans (acute)

The provisional IESTI for humans was determined on the basis of an ARfD for BAM of 0.14 mg/kg bw/day or 9.81 mg/person/day (assumed body weight is 70.1 kg for UK adults), the proposed provisional HR and processing factor for wine of 1.2, and the UKdiet as shown in table B. 7.15.3a (UK adults)

Table B.7.15.3a IESTI UK, adult (provisional)

Product	Consumption products	Intake (g/person/ day)	provisional HR (mg/kg BAM)	P-factor	IESTI (mg/person/day)	% of the ARfD
Table grapes	fresh, dried	317	0.173	1	0.27	2.8
Wine grape	wine	1261	0.173	1.2	0.24	2.4

The ARfD for UK toddlers was 2.03 mg/kg/person/day (assumed body weight is 14.5 kg). The calculated IEST for UK toddlers is shown in Table B.7.15.3b.

Table B.7.15.3b IESTI UK, toddlers (provisional)

Product	Consumption products	Intake (g/person/day)	provisional HR (mg/kg BAM)	P-factor	IESTI (mg/person/day)	% of the ARfD
Table grapes	fresh, dried	177	0.173	1	0.15	9.7
Wine grape	wine	68	0.173	1.2	0.01	0.9

B.7.15.4 National estimate for short term intake by humans (acute)

The provisional NESTI for humans was determined on the basis of an ARfD for BAM of 0.14 mg/kg bw/day or 8.82 mg/person/day (assumed body weight is 63 kg for UK adults), the proposed provisional HR and processing factor for wine of 1.2, and the NLdiet as shown in table B. 7.15.3a (NL general population)

Table B.7.15.4a NESTI NL, general population (provisional)

Product	Consumption products	Intake (g/person/day)	provisional HR (mg/kg BAM)	P-factor	NESTI (mg/person/day)	% of the ARfD
Table grapes	fresh, dried	400	0.173	1	0.35	3.9
Wine grape	wine	-	0.173	1.2		

The ARfD for NL children of 1-6y was 2.39 mg/kg/person/day (assumed body weight is 17.1 kg). The calculated NEST for NL children of 1-6y is shown in Table B.7.15.3b.

Table B.7.15.4b NESTI NL, children 1-6y (provisional)

Product	Consumption products	Intake (g/person/day)	provisional HR (mg/kg BAM)	P-factor	NESTI (mg/person/day)	% of the ARfD
Table grapes	fresh, dried	200	0.173	1	0.17	7.2
Wine grape	wine	-	0.173	1.2		

B.7.16 SUMMARY AND EVALUATION OF RESIDUE BEHAVIOUR (ANNEX IIA 6.10; ANNEX IIIA 8.9)

Dichlobenil (2,6-dichlorobenzonitrile) is the active substance of Casoron® G, submitted for authorisation for use in Northern and Southern Europe. Casoron® G, a ready-to-use granular formulation containing 6.75% (w/w) (67.5 g/kg) formulation of Dichlobenil, intended to be used for the cultivation of grapes as pre-emergence herbicide for selective weed control of most germinating seeds and seedlings from both annual and perennial weeds.

Uptake, distribution and metabolism of Dichlobenil were investigated after soil application of a slightly exaggerated dose (about 1.2 N) in grapes, the crop of the intended use, as well as in apples. Both belong regarding their metabolism to the same crop group (fruits). The same metabolism pattern was found in the investigated commodities: at harvest the parent compound was not detectable and 2,6-dichlorobenzamide (BAM) was in both cases the major metabolite. The metabolic pathway of Dichlobenil after soil application proceeds via the hydroxylation of the cyanogroup resulting in the formation of the main metabolite 2,6-dichlorobenzamide (BAM). It is likely that the conversion of Dichlobenil to BAM occurs in the soil followed by the translocation of the metabolite to the fruits. No information regarding succeeding and rotational crops is submitted, which is due to the intended use of Dichlobenil in vine, a permanent crop, also not required. However, based on the soil degradation data for both parent (DT50 of 39 – 296 days) and the main metabolite BAM (DT50_(extrapolated) of 404 – 2666 days) (see chapter B.8) an accumulation of especially the metabolite in the ground after application in more than one growing season is likely. Supplementary residue trials performed with repeated yearly applications show increasing residue levels in time. Furthermore, a PEC soil of 6.88 mg/kg is calculated. Therefore, the influence of repeated applications in successive growing seasons on the residue levels in grapes has to be elucidated. This additional information on repeated application in successive growing seasons might influence the view on the MRL setting as performed based on the currently available data of only one growing season per trial site. Furthermore, it is noted that in case the intended use is changed to other - non-permanent – crops or other crop groups, new metabolism studies have to be provided and this issue has to be reconsidered.

The submitted studies on the uptake and metabolism of Dichlobenil in grapes and apples provide sufficient information on the nature and levels of residue after soil application. Since no detectable levels of the parent compound were found in fruits grown on the treated soil and the only significant metabolite is 2,6-dichlorobenzamide (BAM), the residue definition in plants is 2,6-dichlorobenzamide (BAM) for both monitoring and risk assessment.

It has to be noted that in case the intended use will be modified, this issue has to be reconsidered.

No information about metabolism, distribution and expression of residues in livestock is available.

Therefore, no definition of the residue for animal products can be derived,

However, based on the intended use of Dichlobenil in grapes, intake of residues by livestock is possible due to feeding of dry/wet grape pomace to dairy and beef cattle. Since relevant intake levels

(>0.1 mg/kg dry feed) of the metabolite BAM were calculated to occur for cattle, data on the metabolism of BAM in ruminants have to be submitted.

In case these data indicate that significant residues (≥ 0.01 mg/kg) occur in any edible part of the animal after intake of the residue levels in potential feeding stuff at the 1x dose rate, a feeding study with BAM in ruminants will be required as well.

In total 12 residue trials were submitted – 6 for Northern Europe, 6 for Southern Europe. All trials were performed in 1999 and 2002 with grapes under field conditions and GLP.

All applications were carried out in spring, at the latest at BBCH 15 (5 vine leaves unfolded) but two trials (one Northern and one Southern European trial) the application rates are too high, accounting for more than 25% above the application rate of the critical GAP (>6.75 kg a.s./ha).

In all trials the parent compound Dichlobenil and its main metabolite 2,6-dichlorobenzamide (BAM) were determined. Only for BAM levels above the LOQ were found: in Southern Europe the residue levels of 2,6-dichlorobenzamide range from 0.015 mg/kg (at 136 DAT) – 0.173 mg/kg (at 201 DAT) and in Northern Europe the residue levels of 2,6-dichlorobenzamide range from 0.012 mg/kg (at 166 DAT) – 0.152 mg/kg (at 171 DAT).

Since the residue levels obtained in the Northern and Southern trials are in the same range it is justified to combine the trial data from Northern and Southern Europe for the derivation of the MRL. Based on this approach the available trial data are considered sufficient ($n = 10$) to derive an MRL for the current intended use of Dichlobenil in vine in Northern and Southern Europe.

However it has to be mentioned that the eight residue trials reported by Gillis (2004) are considered provisional, since the reliability of these results is questionable due to the sample extract storage conditions. The plant extracts were stored at -18°C over a considerable amount of time. Additional information has therefore to be submitted in order to enable the assessment if these storage conditions influence the residue levels as measured and documented in the report.

Aside from the 12 trials summarised above, the notifier did also submit in total 14 studies as additional information but none of the additionally submitted data are considered suitable for the current evaluation. However, it is noted that the results reported in these studies do support the results of the trials used for the derivation of the MRL.

The provisional MRL for grapes as elaborated by the RMS accounts for 0.3 mg/kg 2,6-dichlorobenzamide (BAM), the provisional STMR accounts for 0.085 mg/kg BAM.

MRL and STMR are considered provisional since the influence of repeated applications in successive growing seasons on the residue levels in grapes over the years has to be elucidated and additional information is available in order to enable the assessment if the storage conditions as applied in the study of Gillis (2004) do influence the accuracy of the residue levels measured.

No storage stability study as such is submitted, storage stability data are provided in one of the processing studies (Maselli, 1998); these data were obtained without GLP-compliance. Fortified samples were stored at $-20 \pm 5^{\circ}\text{C}$. The following results were obtained:

- grape samples were stable over the whole testing period of 323 days (Dichlobenil) and 345 days (BAM),
- raisin samples were stable over the whole testing period of 273 days (Dichlobenil) and 266 days (BAM),
- grape juice samples were stable over the whole testing period of 322 days (Dichlobenil) and 343 days (BAM).

These storage stability data are accepted to support the storage condition for the processing study and the residue trial study of Brereton (2000), but do not cover the storage period for the BAM grape samples extracts in the residue study of Gillis (2004), see B.7.6.2. Therefore, the respective data on the storage stability of BAM in sample extracts has still to be submitted (Furthermore, depending on the outcome on the requested animal metabolism and/or feed intake studies, data on the storage stability of the relevant residue(s) in the relevant animal matrices have to be submitted.

The effect of processing of grapes to juice, raisins, must, wet pomace and (young) wine on the residue levels of Dichlobenil and its major metabolite 2,6-dichlorobenzamide (BAM) was investigated. In none of the processed fractions levels above the LOQ of the parent compound Dichlobenil were found. In all cases only its main metabolite BAM was detected. A concentration of BAM occurred during the production of raisins, resulting in a transfer factor of 2.9. The transfer factors for the production of wet pomace range and juice account for 1.5 and 1.2, respectively. The concentration of BAM in must and wine (young and ripe wine) remain approximately the same, the transfer factors account for 0.9 and 1.1, respectively.

It was concluded that processing to juice did not result in changes in residue composition since BAM is stable during heating to 50°C at PH4. However, since the effect of processing on the nature of residue was not investigated during fermentation, it can not be assessed if the compounds determined in the two studies do cover all residue components which occur after processing. Therefore information regarding the influence of the relevant processing processes (preparation of wine from grapes juice) on the chemical nature of the residue has still to be submitted. Only based on this information a final conclusion about the appropriateness of the above mentioned processing studies can be drawn.

Based on the available information intake calculations for livestock and humans were performed.

Since the data used for the calculation are provisional, the outcome of the intake calculations has to be considered provisional as well.

Due to the intended use of Dichlobenil in grapes, livestock intake occurs via feeding of dry/wet grape pomace to dairy and beef cattle. Relevant levels (>LOQ) of BAM, the main metabolite of Dichlobenil, were found in the residue trials in grapes and due to the results of the processing study, a concentration of these content in fruit pomace is expected. No data on the transfer during processing of dry pomace are available.

Since no livestock feeding studies were submitted, it cannot be stated if the plateau levels are reached slowly or within 7 days. Therefore intake calculations were performed using both the provisional MRL and STMR, accounting for 0.3 mg/kg BAM and 0.085 mg/kg BAM, respectively.

In both cases a transfer factor of 1.5 (mean value for the transfer during processing to wet pomace) was applied, resulting in levels of 0.45 mg/kg and 0.13 mg/kg BAM for the provisional MRL and STMR, respectively. This results in provisional TDMLs, ranging from 0.057 – 0.20 mg/kg diet (dry weight) for dairy cattle and 0.17 – 0.59 mg/kg diet (dry weight) for beef cattle. Since these levels are above the limit value as set in the guideline, the metabolism in ruminants has to be investigated.

Long-term intake calculations for humans were performed based on the provisional MRL. As described above, relevant intake of BAM is considered to occur in livestock, but no information about the consequences regarding the residue levels in animal parts used for human consumption are available. Therefore are all further intake calculations for human provisional. Depending on the additional information (influence on repeated treatment in successive growing seasons on the residue levels in grapes, influence of the storage conditions of the plant extracts in the residue trial study of Gillis (2004) on the residue levels measured, influence of processing on the nature of residue and data on animal metabolism, eventually followed by a feeding study), the calculation of the human intake levels have to be reconsidered.

The provisional human ITMDI for the FAO/WHO EUR diet accounts for 0.3% of the ADI and was determined on the basis of an ADI for BAM of 0.022 mg/kg bw/day or 1.3 mg/person/day (assumed body weight is 60 kg) and the proposed provisional MRL for grapes Taking an additional residue intake through drinking water of 0.38 mg/L into account, the ADI is filled for 58%

If based on the provisional STMR of 0.085 mg/kg BAM and considering the processing factors, an IEDI (provisional) of 0.3% of the ADI (intake via water included) is calculated for the WHO European diet.

The provisional NTMDI based on the Dutch TMDI model for adults accounts for 1.2% of the ADI and was determined on the basis of an ADI for BAM of 0.022 mg/kg bw/day or 1.4 mg/person/day (assumed body weight is 63 kg) and the proposed provisional MRL for grape, the ADI is filled for 1.2%. Taking an additional residue intake of 0.38 mg/L through drinking water into account .

The ADI is filled for 55%.

The provisional NTMDI based on the Dutch TMDI model for children of 1 - 6 years accounts for 1.1% of the ADI and was determined on the basis of an ADI for BAM of 0.022 mg/kg bw/day or 0.38 mg/person/day (assumed body weight is 17.1 kg) and the proposed provisional MRL of grape. Taking an additional residue intake through drinking water of 0.38 mg/kg into account, the ADI is filled for 202%. A risk for (young) children cannot be excluded,

If based on the provisional STMR of 0.085 mg/kg BAM and the highest processing factor 2.9, provisional NEDIs of 1.0% of the ADI (intake via water included) for both adults and children were calculated for the Dutch model.

An acute reference dose for 2,6-dichlorobenzamide, as the main residue of Dichlobenil, was set at 0.14 mg/kg bw/d. From the consumption of grapes, a maximal intake of 2.8% and 9.7% is derived for

UK adults and UK toddlers, respectively for table grapes. For the Dutch population, the NESTI was maximal 3.9% and 7.2% for the general population and children of 1-6y, respectively.

Based on these calculations (although partly based on provisional data) and the information available, the use of Dichlobenil according to the intended uses for which a provisional MRL is proposed, is not considered to result in an unacceptable risk on adverse health effects due to long-term exposure to residues in food. However, due to the consumption of drinking water an unacceptable risk for young people cannot be excluded. Therefore, the rapporteur recommends to make an overview of clearing methodology used for processing of ground and surface water into potable water throughout the member states of the European Union.

B.7.17 REFERENCES RELIED ON**Section B.7 Residue data (Annex IIA, point 6, Annex IIIa, point 8)**

Annex point / reference no.	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Data protection claimed Y/N	Owner
IIA, 6.1/01	Hubert, T.D.	1990a	Dichlobenil: nature of the residue in grapes Report Hazleton Laboratories America Inc., U.S.A. No. HLA 6248-102 CA – 2909 GLP, Unpublished	Y	CHEM
IIA, 6.1/01	Hubert, T.D.	1990b	Dichlobenil: nature of the residue in apples Report Hazleton Laboratories America Inc., U.S.A. No. HLA 6248-101 CA – 2894 GLP, Unpublished	Y	CHEM
IIA, 6.3/01	Brereton, R.	2000	To determine the magnitude of Dichlobenil and its metabolite 2,6-dichlorobenzamide (BAM) residues at harvest after treatment in the raw agriculture commodity wine grapes resulting from a single overall application to the ground of Casoron G in France Report Agrisearch UK Limited, England No.AF/4481/UR (Uniroyal Chemical Europe B.V. No.C.201.60.009) CA – 3911 GLP, Unpublished	Y	CHEM
IIA, 6.3/02	Gillis, N.	2004	To determine the magnitude of Dichlobenil and BAM residues at harvest in the raw agricultural commodity grapes from a single application of Casoron G to the ground, in Austria, France and Italy during 2002 Report Agrisearch UK Ltd, England No.AF/6262/UR CA – 4173 GLP, Unpublished	Y	CHEM
IIA, 6.3/03	Harrison, C. Partington, K.	2006	To determine the magnitude of Dichlobenil and BAM residues at harvest in the raw agricultural commodity grapes and processed fractions from a single application of Casoron G to the ground, in Austria, France and Italy during 2002 Report Agrisearch UK Ltd, England No.AF/6262/UR Amendment 2 CA – 4173 GLP, Unpublished	Y	CHEM
IIA, 6.3/04	Yu, W.	2006	Freezer Storage Stability of Dichlobenil and BAM in Grapes – Extrapolation of data. Non-GLP, Unpublished	Y	CHEM
IIA, 6.5.2/01	Gillis, N.	2004	To determine the magnitude of Dichlobenil and BAM residues at harvest in the raw agricultural commodity grapes from a single application of Casoron G to the ground, in Austria, France and Italy during 2002 Report Agrisearch UK Ltd, England No.AF/6262/UR CA – 4173 GLP, Unpublished	Y	CHEM

IIA, 6.5.2/02	Maselli, C.V.	1998	Casoron 4G on grapes: processing study at 1.3x rate for raisins and juice Report Uniroyal Chemical Inc., U.S.A. RP-96005 CA – 3843 GLP, Unpublished	Y	CHEM
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