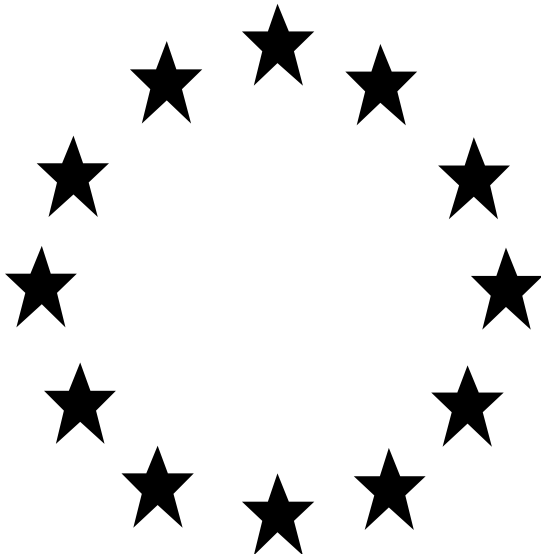

Draft Assessment Report (DAR)

- public version -

Initial risk assessment provided by the rapporteur Member State Germany for the existing active substance

CHLORIDAZON

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

Volume 3, Annex B, B.6, part 3

July 2005

Report: Leuschner F. et al., 1977(b)
Oral toxicity of metabolite B, assay 98 %, in the Sprague-Dawley rat - repeated dosage over 3 months
[redacted]
unpublished
BASF RegDoc# 1977/0156

GLP: No, studies were conducted prior to the implementation of GLP but are scientifically valid

Guideline: Comparable to OECD 408

Deviations: Batch of test substance not identified. No analytical data on the test substance provided. No investigation of phosphorus and creatinine in clinical biochemistry.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Test substance was identified as follows:
BH 119-metabolite B (chloridazon metabolite B, 4-amino-5-chloropyridazone(6))
Purity: 98 %
Batch: not indicated
Test animals: Sprague-Dawley rats

Chloridazon metabolite B was administered to 20 male and 20 female Sprague-Dawley rats over a period of 3 months via the feed. The dose levels were weekly adapted to the body weight and food consumption of the animals to achieve a test substance intake of 0; 30; 90 and 270 mg/kg bw.
The animals were examined each day for clinical symptoms and mortalities. Food consumption was determined daily. Body weight was recorded at weekly intervals.
Hematology was investigated before the start, after 6 weeks of administration and at the end of the study. It consisted of: hemoglobin, erythrocyte and leukocyte count, differential blood count and haematocrit. The following parameters were determined only at the end of the study: platelets, reticulocytes, prothrombin time and blood clotting time.
Clinical-chemistry was performed before the start, after 6 weeks of administration and at the end of the study. It consisted of: Alanine aminotransferase, glucose, blood urea and alkaline phosphatase. The following parameters were determined only at the end of the study: aspartate aminotransferase, total bilirubin, total protein, sodium potassium, calcium, chloride and uric acid.
Urinalysis was also performed before the start, after 6 weeks of administration and at the end of the study.
An auditory response test was performed towards the end of the study.
An ophthalmological examination was carried out prior to sacrifice.
Terminal investigations consisted of organ weight determination, gross necropsy followed by a full histopathological evaluation.

Findings:
There are no data on the stability of the test substance. The stability of the test substance in the food has been demonstrated in other studies. There are no data on the homogeneity and the correctness of the dietary concentrations.

Table B.6.8-9: Test substance intake (mg/kg bw)

Males	Females
29.2	28.7
86.5	86.3
259.2	257.4

There were no mortalities at any dose level. The only sign of clinical toxicity was a slight sedation in high dose animals from week 7 onwards.
There were no test substance related effects on food consumption.
Body weight gain was reduced in high dose animals from week 7 onwards. At the end of the study body weights in high dose males were 7.5 % lower than controls, high dose females 7.3 % lower than controls.
There were no test substance related changes in haematology, clinical chemistry, urinalysis, ophthalmoscopy or auditory response at any dose level.
Relative kidney weight was slightly higher in high dose females.
Macroscopic investigation demonstrated at the high dose level a delation of the renal pelvis and urinary bladder as well as deposits in these organs in individual females.
Histopathological examinations revealed the following changes at the high dose level only:
Increased epithelial dysplasia on the associated apices of the renal papillae and changes in the parenchyma up to scar formation, predominantly in the females. Increased epithelial dysplasia of the mucosa of the urinary bladder.
There were no other test substance related changes observed.

Discussion:
As the batch of test substance was not identified and no analytical data on the test substance was provided this study should only be considered as supportive. The derived NOAEL should not be used in the consideration of the ADI.

Conclusion:
This study identified the kidney and bladder as target organs.
The NOAEL for this study was 86 mg/kg bw. It should, however, not be used in the risk assessment.

Report: Engelhardt G., Hoffmann H. D., 1992
Report on the study of chloridazon-metabolite B; Reg. No. 14 456 (ZST test substance No.: 90/435) in the Ames test (standard plate test and preincubation test with *Salmonella thyphimurium*)
BASF AG, Ludwigshafen/Rhein, Germany,
unpublished
BASF RegDoc# 1992/10844

GLP: Yes (laboratory certified by Ministerium fuer Umwelt und Gesundheit, Postfach 31 60, 6500 Mainz)

Guideline: OECD 471

Deviations: Substances used for positive controls were 2-AA (2-aminoanthracene) with S9 mix and MNNG (N-methyl-N-nitroso-N-nitroso-guanidine), NPD (4-nitro-o-phenyldiamine) and AAC (9-aminoacridine chloride monohydrate) without S9 mix.

Acceptability: The study is considered to be supplementary.

Material and Methods:
Test material: Test substance was identified as follows:
BH 119-metabolite B (chloridazon-metabolite B; Reg. No. 14 456), white grey powder
Purity: 98.2 %
Batch No.: L 45/253
Test substance No.: 90/435
Test system: *Salmonella typhimurium* tester strains TA 1535, TA 100, TA 1537 and TA 98

Chloridazon metabolite B was tested for mutagenicity in the reverse mutation assay on bacteria with and without metabolic activation (S-9 mix from male Sprague Dawley rats treated with Aroclor 1254). The following *Salmonella typhimurium* tester strains were used in this assay: TA 1535, TA 100, TA 1537 and TA 98. The testing was performed according to the standard plate assay as well as preincubation assay.

The study consisted of 4 experiments:
1st experiment: the strains TA 1535, TA 100, TA 1537 and TA 98 were exposed at chloridazon metabolite B doses ranging from 20 to 5000 µg/plate in the standard plate test with and without metabolic activation (standard plate test).
2nd experiment: the strain TA 100 was exposed to chloridazon metabolite B at doses ranging from 20 to 5000 µg/plate in the standard plate test with and without metabolic activation.
3rd experiment: the strain TA 100 was exposed to chloridazon metabolite B at doses ranging from 20 to 5000 µg/plate in the standard plate test with and without metabolic activation. This experiment was performed due to unusually low spontaneous rates for TA 100 in the previous experiments.
4th experiment: the strains TA 1535, TA 100, TA 1537 and TA 98 were exposed to chloridazon metabolite B doses from 20 to 5000 µg/plate in the preincubation test with and without metabolic activation.

Dimethylsulphoxide (DMSO) was used to solve the test substance and was used as solvent control. The positive controls (prepared in DMSO) were: 2-AA (2-aminoanthracene) with S9 mix and MNNG (N-methyl-N-nitroso-N-nitroso-guanidine), NPD (4-nitro-o-phenyldiamine) and AAC (9-aminoacridine chloride monohydrate) without S9 mix.

Findings:
Bacteriotoxicity or precipitation of test substance was not observed in any *Salmonella typhimurium* strain in any assay. The test substance and DMSO did not induce two-fold increases in the number of revertant colonies at any dose level, which would be a criteria for a positive response. The mutagenic response of the positive controls indicates that the test system was able to detect mutagens.

Conclusion:
According to the results of the present study chloridazon metabolite B is not mutagenic in the bacterial reverse mutation assay with S. typhimurium under the experimental conditions chosen.

Report:	Wollny H. E., Arenz M., 1999 Gene mutation assay in Chinese hamster V79 cells in vitro (V79/HPRT) with Reg. No. 14 456 RCC Cytotest Cell Research GmbH, Rossdorf, Germany unpublished BASF RegDoc# 1999/11478
GLP:	Yes (laboratory certified by Hessisches Ministerium fuer Umwelt, Energie, Jugend, Familie und Gesundheit, Wiesbaden)
Guideline:	OECD 476, EEC 87/302, EPA 870.5300
Deviations:	None
Acceptability:	The study is considered to be acceptable.

Report:	Wollny H. E., 1999 First amendment to report: Gene mutation assay in Chinese hamster V79 cells in vitro (V79/HPRT) with Reg. No. 14 456 RCC Cytotest Cell Research GmbH, Rossdorf, Germany unpublished BASF RegDoc# 1999/1003077
GLP:	Yes (laboratory certified by Hessisches Ministerium fuer Umwelt, Energie, Jugend, Familie und Gesundheit, Wiesbaden)
Guideline:	OECD 476, EEC 87/302, EPA 870.5300
Deviations:	None
Acceptability:	The study is considered to be acceptable.

Material and Methods:
Test material: Test substance was identified as follows:
BH 119-metabolite B (Reg. No. 14 456, chloridazon metabolite B), light brown powder
Purity: 99.8 %
Batch No.: 41-216
Test system: Chinese hamster V79 (V79) cells

Chloridazon metabolite B was examined for mutagenic activity (using the HPRT locus) by assaying for the induction of 6-thioguanine resistant mutants in Chinese hamster V79 (V79)

cells after in vitro treatment. The test was performed with and without metabolic activation (S-9 mix from the liver of phenobarbital and beta-naphthoflavone induced male Wistar rats). The test concentrations were chosen on the results of a preliminary cytotoxicity test. Two independent experiments were carried out. Concentrations of the test substance were:

without S9 mix: 31.3, 62.5, 125, 250 and 500 µg/mL
with S9 mix: 31.3, 62.5, 125, 250 and 500 µg/mL

The solvent 0.5 % DMSO (final concentration in the culture medium) was used as negative control while ethylmethanesulphonate (EMS) and dimethylbenz(a)anthracene (DMBA) were used as positive controls without or with S9-mix activation, respectively.

Findings:
The stability of the test substance in water and DMSO was analytically confirmed. The stability of the test substance was guaranteed.
The maximal concentration was limited by the solubility of the test substance in DMSO. The substance solution in DMSO formed a fine suspension. Higher concentrations yielded inhomogeneous suspensions. No relevant cytotoxic effects were observed.
No biologically significant or reproducible increases in mutant frequency were observed with and without metabolic activation.
The positive controls demonstrated that the system was able to detect known mutagens.

Conclusion:
According to the results of the present study chloridazon metabolite B is not mutagenic in the in vitro mammalian cell (V79 / HPRT) test under the experimental conditions chosen.

Report:	Engelhardt G., Hoffmann H. D., 1993 In vitro cytogenetic investigations of chloridazon-metabolite B; Reg. No. 14 456 in human lymphocytes BASF AG, Ludwigshafen/Rhein, Germany, unpublished BASF RegDoc# 1993/10075
GLP:	Yes (laboratory certified by Ministerium fuer Arbeit, Soziales, Familie und Gesundheit, Postfach 31 80, 6500 Mainz)
Guideline:	OECD 473
Deviations:	None
Acceptability:	The study is considered to be acceptable.

Material and Methods:
Test material: Test substance was identified as follows:
BH 119-metabolite B (chloridazon-metabolite B; Reg. No. 14 456), grey powder
Purity: 98.2 %
Batch No.: L 45/253
Test system: human lymphocytes

Chloridazon metabolite B was examined for the ability to cause chromosomal damage in human lymphocytes. The test was performed with and without metabolic activation (S-9 mix from the liver of Aroclor 1254 induced male Sprague-Dawley rats). The test concentrations were chosen on the results of a preliminary cytotoxicity test. The dose selection was based on the quality of the metaphases and not on the mitotic index because the test substance concentrations causing a reduction of the mitotic index are at dose levels that severely affect the quality of the chromosome preparation, thus no longer allowing evaluation.
The chromosome preparation was performed 24 hours after test substance application without S-9 mix. In presence of metabolic activation test substance treatment lasted for 3 hours followed by a reincubation for 24 hours using fresh medium culture. The solvent DMSO (dimethylsulfoxide) was used as negative control while mitomycine (without metabolic activation) and cyclophosphamide (in tests without metabolic activation) were used as positive controls. The test concentrations chosen for the main experiment were 2; 5 and 10 µg/mL without metabolic activation and 100; 500; 1000; 1500 and 2000 µg/mL with S-9 mix.
A second experiment was carried out using a concentration of 2000 µg/mL with S-9 mix. After preparation of the chromosomes, 100 metaphases of each culture were analysed for the test substance, untreated and solvent controls. For the positive controls 50 cells were evaluated.

Findings:
The stability of the test substance in DMSO and water was determined analytically. The homogeneity of the preparation was ensured by constant shaking.
Test substance precipitation was reported for concentrations of 1000 µg/mL and higher. The determination of mitotic index indicates a reduction at 2000 µg/mL.
In the first experiment chloridazon metabolite B resulted in an increase in the number of aberrant metaphases including and excluding gaps when compared to the solvent control with metabolic activation. This increase, however was not statistically significant.
Therefore, a second experiment was performed with a concentration of 2000 µg/mL with S-9 mix. In this experiment no increase in aberrant chromosomes were observed.
The positive controls demonstrated that this system is able to detect mutagens.

Conclusion:
Based on the results of this in vitro cytogenetics study in human lymphocytes chloridazon metabolite B does not have a chromosome damaging (clastogenic) effect under the test conditions chosen.

Report: Hellwig J., Hildebrand B., 1997
Reg. No. 14 456 - Prenatal toxicity in rats after oral administration (gavage)
[redacted]
unpublished
BASF RegDoc# 1997/10597

GLP: Yes (laboratory certified by Ministerium fuer Arbeit, Soziales, Familie und Gesundheit, Postfach 31 80, 6500 Mainz 1)

Guideline: EEC 87/302, EEC 67/548, OECD 414, EPA 83-3, JMAFF

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:

Test material: Test substance was identified as follows:

BH 119-metabolite B (Reg. No. 14 456; chloridazon metabolite B), white grey solid
Purity: 98.2 %
Batch No.: L 45/253
Test Substance No.: 90/435

Test animals: Wistar rats

Chloridazon metabolite B was examined for its prenatal toxicity in Wistar rats. The dams (25 per test group) were treated from day 6 through day 15 post coitum (p.c.) with doses of 0 (0.5 % aqueous carboxymethylcellulose); 20; 60 and 120 mg/kg body weight by gavage and a constant dosing volume of 5 mL/kg body weight.
The animals were observed for food consumption and body weight gain regularly throughout the study period. Their state of health was checked daily.
On day 20 p.c., all females were sacrificed and assessed by gross pathology. The fetuses were dissected from the uterus, sexed weighed and further investigated for any external, soft tissue and/or skeletal findings.

Table B.6.8-10: Dosing scheme – prenatal toxicity gavage study in Wistar rats

Group number	Number of females mated/pregnant	Concentration (mg/100 mL)	Dose volume	Dosage level
0	25/22	-	5 mL/kg*	0 mg/kg bw*
1	25/23	400	5 mL/kg	20 mg/kg bw
2	25/23	1200	5 mL/kg	60 mg/kg bw
3	25/22	2400	5 mL/kg	120 mg/kg bw

*0.5 % aqueous carboxymethyl cellulose (CMC)

Findings:

The test substance was demonstrated to be stable and homogeneous over the test period. Homogeneity and stability of the test substance in the vehicle was verified. The correctness of the prepared concentrations was also proven.
At the high dose level (120 mg/kg bw) signs of maternal toxicity consisted of a marginally but statistically significant impaired body weight gain at the beginning of the treatment period (day 8-10 p.c.). In controls body weight gain between days 8 to 10 p.c. was 8.6 g, whereas this value was 3.5 g at 120 mg/kg bw. Moreover, hematurea was observed in six high dose dams during and after the treatment period.
At the lower dose levels there were no signs of maternal toxicity.
Developmental toxicity was not observed at any dose level.
In the report it is stated that in a preceding range-finding study massive signs of maternal toxicity (reduced food consumption, body weight gain and clinical signs of toxicity, including hematurea) were found at 500 and 250 mg/kg bw. At the high dose level all dams died, whereas at 250 mg/kg bw. 8 out of 10 dams died before scheduled sacrificed. Therefore, the selection of a dose level of 120 mg/kg in the present study was justified and sufficiently close to a maximum tolerated dose level.

Conclusion:
Chloridazon metabolite B causes some signs of maternal toxicity during treatment at the 120 mg/kg bw dose level. There was no indication of malformations or developmental toxicity at any dose level tested. Thus the following NOAELs were achieved:

NOAEL maternal toxicity: 60 mg/kg bw
NOAEL developmental toxicity: 120 mg/kg bw.

B.6.8.1.2 Metabolite B-1

Report: Manciaux X., 1999
Metabolite B-1: Acute oral toxicity in rats
[redacted]
unpublished
BASF RegDoc# 1999/10903

GLP: Yes (laboratory certified by Secrétariat du GIPC, 3/5 rue Barbet de Jouy, 75353 Paris CEDEX)

Guideline: OECD 401, EEC 92/69 B 1, EPA 870.1100, JMAFF

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Metabolite B-1, chloridazon
Purity: 99.7 %
Batch No.: 01196-259: 99.7 %
Test animals: Wistar rats

Five male and female Wistar rats per dose group were treated with chloridazon metabolite B-1 in 0.5 % carboxymethylcellulose by gavage at dose level of 5000; 1000 and 200 mg/kg bw. The animals were examined for clinical signs and mortality. All rats that died and the surviving rats at the end of the study (14 days observation period) were examined macroscopically.

Findings:
Chemical analysis confirmed homogeneity, stability and correctness of the concentration of the test substance preparation. In addition, the storage stability of the test substance was guaranteed for the duration of the study.
At the 5000 mg/kg dose-level all animals died on day 1 (5/5 males and 4/5 females) or day 6 (one female).
At the 1000 mg/kg dose-level, 1/5 males and 2/5 females died on day 1 and one female was found dead on day 2. No clinical signs were recorded.
At the 200 mg/kg dose-level no mortality occurred and no clinical signs were noted.
The body weight gain of the surviving animals in the group, which received 1000 mg/kg bw and of the females given 200 mg/kg bw was reduced between day 1 and day 8; it returned to normal thereafter.

The body weight gain of the males at the 200 mg/kg dose-level was not affected by the treatment.
There were no gross pathological findings in animals, which died or in the surviving rats.

Conclusion:
The LD_{50} in rats was calculated to be 1200 (615 – 2340) mg/kg bw.

Report: Mellert W. et al., 2001
Metabolite B-1 - Subchronic oral toxicity study in Wistar rats - Administration in the diet for 3 months
[redacted]
unpublished
BASF RegDoc# 2001/1014868

GLP: Yes (laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 87/302 B, OECD 408

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Metabolite B-1, chloridazon
Purity: 99.7 %
Batch No.: 1520-061
Test animals: Wistar rats

Chloridazon metabolite B-1 was administered to groups of 10 male and 10 female Wistar rats in the diet for 3 months. As recommended by the CTB Guidance Document on relevant metabolites (February 1999), 50 mg/kg bw/day were selected as highest dose level to be tested. As additional dose levels, 10 and 2 mg/kg bw/day were selected.
Food consumption, water consumption and body weights were determined weekly. The animals were examined for clinical signs of toxicity or mortality at least once a day. Detailed clinical examinations in an open field were conducted prior to the start of the administration period and weekly thereafter. A functional observational battery (FOB) and measurement of motor activity was carried out towards the end of the administration period. Ophthalmological examinations were carried out prior to the start and towards the end of the administration period. Clinicochemical and hematological examinations were carried out towards the end of the administration period, urinalyses were carried out after 40 days as well as towards the end of the administration period. All animals were assessed by gross pathology, followed by histopathological examinations.

Findings:
The stability of the test substance was proven by reanalysis. The stability and homogenous distribution of the test substance in the diet was proven over the study period. The correctness of the test substance concentrations was analytically determined.

The following test substance-related findings were obtained:
50 mg/kg bw/d - decreased alanine aminotransferase activities in the females
10 mg/kg bw/d - decreased alanine aminotransferase activities in the females
2 mg/kg bw/d - no treatment-related effects

Thus, the oral administration of the test compound caused decreases in alanine aminotransferase activities in the mid and high dose females. The liver enzyme alanine aminotransferase is generally determined as a parameter for liver toxicity in case of an increase. A decrease of these enzymes is not associated with any pathological changes and is not considered to represent an adverse effect
Therefore, the no observed adverse effect level in this study was 50 mg/kg bw.

Conclusion:
The no observed adverse effect level (NOAEL) under the conditions of this study was 50 mg/kg bw.

Report: Engelhardt G., Hoffmann H. D., 1999
Salmonella typhimurium / *Escherichia coli* reverse mutation assay (Standard plate test and preincubation test) with metabolite B-1
BASF AG, Ludwigshafen/Rhein, Germany,
unpublished
BASF RegDoc# 1999/11415

GLP: Yes (laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 471, EEC 92/69 B 13, EEC 92/69 B 14

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Metabolite B-1, chloridazon
Purity: 99.7 %
Batch No.: 01196-259: 99.7 %
Test system: *Salmonella typhimurium* TA 1535, TA 100, TA 1537 and TA 98, *E. coli* WP2 uvrA

Chloridazon metabolite B-1 (Reg. No. 035 375) was tested for mutagenicity in the reverse mutation assay on bacteria with and without metabolic activation (S-9 mix from male Spraque-Dawley rats treated with Aroclor 1254). The following bacterial strains were used in this assay: *Salmonella typhimurium* TA 1535, TA 100, TA 1537 and TA 98 and *E. coli* WP2 uvrA. The testing was performed according to the standard plate assay (with doses ranging from 20 to 5000 µg/plate) as well as preincubation assay (with doses ranging from 20 to 5000 µg/plate).
Three plates were used per dose for each strain and test condition.
For control purposes and to demonstrate the sensitivity of the test system, negative controls (with and without S-9 mix) and positive controls (with S-9 mix: 2-aminoanthracene; without

S-9 mix: N-methyl-N'-nitro-N-nitrosoguanidine, 4-nitro-o-phenylendiamine, 9-aminoacridine and 4-nitroquinoline-N-oxide) were tested.

A substance is considered positive in this test if the following criteria are met:
- there is at least a doubling of the negative control mutation rate with or without S-9 mix,
- there is a dose-response relationship, and
- the results are reproducible.

The study consisted of 2 experiments:
1st experiment: the strains TA 1535, TA 100, TA 1537 and TA 98, and *E. coli* WP2 uvrA were exposed to the test substance at doses of 0; 20; 100; 500; 2500 and 5000 µg/plate in the standard plate test with and without metabolic activation.
2nd experiment: the strains TA 1535, TA 100, TA 1537 and TA 98, and *E. coli* WP2 uvrA were exposed to the test substance at doses 0; 20; 100; 500; 2500 and 5000 µg/plate in the preincubation test with and without metabolic activation.

Findings:
The stability of the test substance throughout the study period was guaranteed. The stability of the test substance in the vehicle DMSO over a period of 4 hours and in water over a period of 96 hours has been verified analytically. The homogeneity of the test substance was guaranteed by mixing before preparation of the test substance formulations.
Precipitation of test substance was not observed.
A bacteriotoxic effect was observed occasionally in the standard plate test at 5000 µg/plate and in the preincubation assay depending on the strain and test conditions from about 500 - 2500 µg/plate.
The negative controls did not lead to an increase of revertant colonies and the mutagenic response of the positive controls indicated that the test system was able to detect mutagens.
The test substance did not lead to an increase in revertant colonies either without S-9 mix or after adding a metabolising system in two experiments carried out independently of each other.

Conclusion:
According to the results of the present study chloridazon metabolite B-1 is not mutagenic in the *Salmonella typhimurium/Escherichia coli* reverse mutation assay under the experimental conditions chosen.

Report: Engelhardt G., Hoffmann H. D., 2000(a)
In vitro gene mutation test with metabolite B-1 in CHO cells (HPRT locus assay)
BASF AG, Ludwigshafen/Rhein, Germany,
unpublished
BASF RegDoc# 2000/1010207

GLP: Yes (laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 476, EEC 87/302

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Chloridazon, metabolite B-1
Purity: 99.7 %
Batch No.: 1520-061
Test system: Chinese hamster ovary (CHO) cells

Chloridazon metabolite B-1 (Reg. No. 035 375) was tested for its ability to induce gene mutations at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster ovary (CHO) cells in vitro. Two independent experiments were carried out, using two parallel cultures each either with or without the addition of Aroclor 1254-induced Sprague-Dawley rat liver S-9 mix (exogenous metabolic activation).
According to an initial range-finding cytotoxicity test for the determination of the experimental doses and taking into account the cytotoxicity actually found in the main experiment, the following doses were evaluated in the 1st experiment after an exposure period of 4 hours:
1st experiment (with and without S-9 mix):
0; 50; 100; 200; 400; 800 and 1600 µg/mL.
A 2nd experiment for confirmation was performed using the following doses (4 hours exposure):
2nd experiment (with and without S-9 mix):
0; 50; 100; 200; 400; 800 and 1600 µg/mL.

After an attachment period of 20 - 24 hours, a treatment period of 4 hours both with and without metabolic activation and an expression phase of about 7 - 9 days and a selection period of about 1 week, the colonies of each test group were fixed with methanol, stained with Giemsa and counted.
For control purposes and to demonstrate the sensitivity of the test system, negative controls and two appropriate positive control chemicals methylcholanthrene (with S9 mix) and ethyl methane sulfonate (without S9 mix) were tested.
No changes in osmolarity and pH-values were observed.

The criteria for a positive response are:
- Increases of the corrected mutation frequencies above the concurrent negative control values and above 15 mutants per 10^6 clonable cells and/or the evidence of a dose-response relationship in the increase in mutant frequencies.
- Evidence of reproducibility of any increase in mutant frequencies.
- A statistically significant increase in mutant frequencies and the evidence of a dose-response relationship.

Findings:
The stability of the test substance throughout the study period was verified by reanalysis. The stability of a comparable batch (01196-259) of the test substance in the vehicle DMSO over a period of 4 hours and in water over a period of 96 hours has been verified analytically. The homogeneity of the test substance was guaranteed by mixing before preparation of the test substance formulations.
The negative controls gave mutant frequencies within the range expected for the CHO cell line.

Both of the positive control chemicals led to the expected increase in the frequencies of forward mutations.
The test substance did not cause any increase in the mutant frequencies either without S-9 mix or after adding a metabolising system in both main experiments performed independently of each other.
Thus it can be stated that in this mutagenity assay and under the experimental conditions reported the test substance did not induce gene mutations at the HPRT locus in V 79 cells.

Conclusion:
Under the experimental conditions of this assay, chloridazon metabolite B-1 (Reg. No. 035 375) has no mutagenic activity in vitro in the CHO/HPRT forward mutation assay.

Report:	Engelhardt G., Hoffmann H. D., 2000(b) In vitro unscheduled DNA synthesis (UDS) assay with metabolite B-1 in primary rat hepatocytes BASF AG, Ludwigshafen/Rhein, Germany, unpublished BASF RegDoc# 2000/1018811
GLP:	Yes (laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)
Guideline:	EEC 87/302, OECD 482
Deviations:	None
Acceptability:	The study is considered to be acceptable.

Material and Methods:
Test material: Metabolite B-1, chloridazon
Purity: 99.7 %
Batch No.: 1520-061
Test system: primary Wistar rat hepatocytes

Chloridazon metabolite B-1 (Reg. No. 035 375) was tested for its ability to induce DNA repair synthesis (unscheduled DNA synthesis (UDS)) in primary Wistar rat hepatocytes *in vitro*. Three independent experiments were carried out. The quantification of UDS was performed microscopically using 3 or 4 slides per test group. 25 – 50 cells in good morphological conditions were randomly selected per slide and examined to achieve a total number of 100 cells/dose group.
Both, test substance treatment and labeling with ^{3}H-thymidine lasted for about 18 - 20 hours.

For each cell, the following counts were performed with an automatic image analyser:
- the nuclear grain (NG) count (= number of silver grains overlying the nucleus)
- the cytoplasm grain (CG) count (= number of grains in two or three nucleus-equivalent areas adjacent to the nucleus).

According to an initial range-finding cytotoxicity test for determining the experimental doses and taking into account the cytotoxicity actually found in the main experiment the following doses were evaluated in the 1st experiment:

- 0; 31.25; 62.5; 125 and 250 µg/mL

However, the values of both the NG counts and the CG counts in all test groups including the negative control groups (untreated and vehicle control) exceeded the historical control data base for unknown reasons. Thus, these values were not taken into consideration for a final conclusion.

Therefore, a 2nd experiment was carried out and, based on the cytotoxicity found in the 1st experiment, the following doses were evaluated:

- 0; 25; 50; 100 and 200 µg/mL

In a 3rd experiment for confirmation of the results of the 2nd experiment the following doses were evaluated:

- 0; 37.5; 75; 150 and 300 µg/mL

A test substance is considered positive if a dose-related increase is demonstrated in both of the following:

- The mean number of NNG (net nuclear grains) counts, which must exceed zero at one of the test points.
- The percentage of cells in repair must be equal to or exceed 20, with a NNG of ≥ 5.

A dose-related increase in % cells in repair ≥ 5 outside the values of both the concurrent negative control and the historical control data base (≥ 3 < 20) and a dose-related increase in the mean number of NNG counts near to but without exceeding zero is considered to be an indication for a marginal response which needs to be confirmed / clarified in a further experiment.
A test article producing NNG counts and % cells in repair in the range of the negative control data is considered to be negative in the *in vitro* UDS assay.

Findings:
The stability of the test substance throughout the study period was verified by reanalysis. The stability of a comparable batch (01196-259) of the test substance in the vehicle over a period of 4 hours and in water over a period of 96 hours has been determined analytically. The homogeneity of the test substance was guaranteed by mixing before preparation of the test substance formulations.
Cytotoxicity was observed from about 250 µg/mL onward.
The negative controls (untreated and vehicle controls) gave UDS activities within the range expected for rat hepatocytes.
The positive control chemical 2-acetylaminofluorene (2-AAF) revealed a distinct increase in the mean number of nuclear and net grain counts.
On the basis of the results from the present study, the test substance did not lead to an increase in the mean number of net nuclear grain counts at any dose level in isolated rat hepatocytes in two experiments performed independently of each other.

Conclusion:
The test substance chloridazon metabolite B-1 (Reg. No. 035 375) is considered to be negative in the *in vitro* UDS assay using primary rat hepatocytes.

Report: Engelhardt G., Hoffmann H. D., 2000(c)
Bone marrow chromosome analysis in vivo with metabolite B-1 in Wistar rats single oral administration
[redacted]
unpublished
BASF RegDoc# 2000/1018864

GLP: Yes (laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 92/69 B 11, OECD 475

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Metabolite B-1, chloridazon
Purity: 99.7 %
Batch No.: 1520-061
Test animals: Wistar rats

Chloridazon metabolite B-1 was tested for clastogenicity in Wistar rats using the bone marrow chromosome analysis method. For this purpose, the test substance, suspended in an aqueous 0.5 % CMC formulation, was administered once orally to male animals at dose levels of 250 mg/kg, 500 mg/kg and 1000 mg/kg bw in a volume of 10 mL/kg bw in each case.
For control purposes as a negative control male animals were administered merely the vehicle (0.5 % CMC formulation) by the same route and as positive control the chemical cyclophosphamide was administered.
The animals were sacrificed and the bone marrow of the two femora was prepared 20 and 44 hours after administration in the highest dose group of 1000 mg/kg body weight and in the vehicle controls. In the test groups of 500 mg/kg and 250 mg/kg bw and in the positive control group, the 20-hour sacrifice interval was investigated only. About 2 – 3 hours before the animals were sacrificed, they were intraperitoneally injected with 3.3 mg Colcemid/kg bw in order to arrest mitosis in the stage of metaphase. After preparation of the bone marrow and staining of the preparations with Giemsa, 100 metaphases were analysed per animal.

Findings:
The stability of the test substance throughout the study period was verified by reanalysis. The homogeneity of the test substance was guaranteed on account of the high purity.
The stability of a comparable batch (01196-259) of the test substance in water over a period of 96 hours has been determined analytically. The homogeneity of the test substance in the vehicle was provided by stirring during removal and administration.
The positive control chemical cyclophosphamide led to the expected increase in the number of chromosomally damaged cells.
Animals which were administered the vehicle or the positive control substance cyclophosphamide did not show any signs of toxicity.

The administration of the test substance up to a dose of 1000 mg/kg bw was tolerated by all animals without any signs or symptoms.
According to the results of the present study, the single oral administration of chloridazon metabolite B-1 did not lead to any increase in the number of chromosomally damaged cells. The rate of aberrant metaphases was always within the same range as that of the concurrent negative control in all dose groups and at all sacrifice intervals.
Thus, under the experimental conditions chosen here, the test substance chloridazon metabolite B-1 does not have any in vivo chromosome-damaging (clastogenic) effect in bone marrow cells of Wistar rats.

Conclusion:
The test substance chloridazon metabolite B-1 has no in vivo chromosome-damaging (clastogenic) effect in bone marrow cells of Wistar rats.

Report: Kaspers U. et al., 2002
Metabolite B-1 - Prenatal developmental toxicity study in Wistar rats, oral administration (gavage)
[redacted]
unpublished
BASF RegDoc# 2002/1000102

GLP: Yes (laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 87/302, OECD 414, EPA 870.3700

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: Metabolite B-1 chloridazon
Purity: 99.7 %
Batch No.: 1520-061: 99.7 %
Test animals: Wistar rats

Chloridazon metabolite B-1 was tested for its prenatal developmental toxicity in Wistar rats. The test substance was administered as an aqueous suspension to 25 mated female Wistar rats/group by stomach tube at doses of 2; 10 and 50 mg/kg body weight on day 6 through day 19 post coitum (p.c.). A standard dose volume of 10 mL/kg body weight was used for each group. The control group, consisting of 25 females, was dosed with the vehicle only (0.5 % carboxymethylcellulose CB 30.000 in doubly distilled water). 22 - 24 females/group had implantation sites at terminal sacrifice.
Food consumption and body weights of the animals were recorded regularly throughout the study period. The state of health of the animals was checked each day.
On day 20 post coitum, blood was taken from all surviving females, which were subsequently sacrificed and assessed by gross pathology (including weight determinations of the unopened uterus, the liver, the kidneys and the placentae). For each dam, corpora lutea were counted and number and distribution of implantation sites (differentiated as resorptions, live and dead

fetuses) were determined. The fetuses were removed from the uterus, sexed, weighed and further investigated for any external findings. Thereafter, nearly one half of the fetuses of each litter was examined for soft tissue findings and the remaining fetuses for skeletal (incl. cartilage) findings.

Findings:
The stability of the test substance was given. The stability of aqueous test substance suspensions over a period of 96 hours could be demonstrated. The homogenous distribution of the test substance in the vehicle was demonstrated. The correctness of the test substance concentrations was analytically determined.

The following substance-related findings were obtained:
At 50 mg/kg body weight/day:
- statistically significantly impaired absolute body weight gain (about 11 % below controls if calculated for days 0 – 20 p.c.) and - without statistical significance - about 9 % below controls if calculated for the entire treatment period (days 6 – 19 p.c.)
- lower corrected body weight gain (about 13 % below controls without statistical significance)
- statistically significantly decreased mean gravid uterus weight (about 12 % below controls)
- increased red blood cells, hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH), glucose, triglycerides and cholesterol
- decreased alanine aminotransferase and total bilirubin values
- distinctly lower mean fetal body weights (about 17 % below controls if both sexes are combined)
- statistically significantly increased rates of fetuses/litter with certain skeletal variations (i.e. delays in ossification of skull, vertebral column and sternum and rudimentary cervical rib(s)) and consequently of total skeletal variations

At 10 mg/kg body weight/day:
- no substance-related effects on dams, gestational parameters or fetuses

At 2 mg/kg body weight/day:
- no substance-related effects on dams, gestational parameters or fetuses.

Thus, under the conditions of this prenatal developmental toxicity study, the oral administration of chloridazon metabolite B-1 to pregnant Wistar rats from implantation to one day prior to the expected day of parturition (days 6 - 19 p.c.) elicited maternal toxicity at 50 mg/kg body weight/day. Maternal toxicity was substantiated in this group mainly by impairments in absolute and corrected body weight gain, effects on clinical chemistry parameters indicative for changes in the metabolic process of the liver and mild polycythemia.
No signs of substance-induced maternal toxicity occurred at the low and the mid dose level (2 or 10 mg/kg body weight/day).
There were no substance-related influences on the gestational parameters up to and including the highest dose level (50 mg/kg body weight/day).
Clear signs of substance-induced prenatal developmental toxicity, but no indications for teratogenicity occurred exclusively at the high dose level. The mean fetal body weights were distinctly diminished. Correspondingly, the rates for certain skeletal variations (i.e. some delays in skeletal maturation and rudimentary cervical rib(s)) were statistically significantly increased and occasionally outside historical control ranges. These variations mirror common

findings on fetal morphology most probably due to fetal growth retardations and/or due to maternal stress, but are not indicative for selective effects on the fetal organism.
At 2 and 10 mg/kg body weight/day no substance-induced signs of embryo-/fetotoxicity were observed.

Conclusion:
Based on these results, the no observed adverse effect level (NOAEL) for maternal and prenatal developmental toxicity was 10 mg/kg body weight/day. Thus, signs of prenatal developmental toxicity did only occur at a dose level, which was also toxic to the dams.

B.6.8.2 Supplementary studies on pharmacological effects of chloridazon

Report: Bloch I. et al., 1987
Study of effect on vital functions of animals: general pharmacology - of chloridazon
[redacted]
unpublished
BASF RegDoc# 1987/0431

GLP: Yes (laboratory certified by Eidgenössisches Departement des Inneren, Bern, Schweiz)

Guideline: JMAFF

Deviations: Not available

Acceptability: The study is considered to be supplementary.

Material and Methods:
Test material: Test substance was identified as follows:
Chloridazon, solid
Purity: 95.3 %
Batch No.: K 50 / 16A
Test Substance No.: 86/99
Test animals: NMRI mice, Wistar rats, New Zealand White rabbits, Hartley guinea pigs

Chloridazon was tested in a series of in vivo and in vitro studies to investigate the safety pharmacology of this compound.

1. General observations on native behaviour in mice
Three male NMRI mice per dose group received a single oral administration (suspension) of either 0; 500 or 1000 mg/kg bw by gavage. After dosing the behaviour of the animals was observed for 3 hours immediately after dosing and again 24 hours later.

2. Prolongation of sleeping time induced by hexobarbitone
Groups of six male NMRI mice per dose group received a single oral administration (suspension) of either 0; 500 or 1000 mg/kg bw by gavage. Valium was used as a positive control. At 60 minutes after the administration the animals were intraperitoneally administered with hex-

abarbitone (70 mg/kg bw). The duration of sleeping time was measured by disappearance and reappearance of the righting reflex.

3. Effect on convulsion induced by pentetrazole
Groups of six male NMRI mice per dose group received a single oral administration (suspension) of either 0; 500 or 1000 mg/kg bw by gavage. Valium was used as a positive control. At 60 minutes after the administration the animals were intraperitoneally administered with pentetrazole (150 mg/kg bw). The time until convulsions appeared was measured and mortality in each group was recorded.

4. Effect on convulsion induced by strychnine
Groups of six male NMRI mice per dose group received a single oral administration (suspension) of either 0; 500 or 1000 mg/kg bw by gavage. Valium was used as a positive control. At 60 minutes after the administration the animals were intraperitoneally administered with strychnine (2 mg/kg bw). The time until convulsions appeared was measured and mortality in each group was recorded.

5. Effect on body temperature in rats
Groups of six male Wistar rats per dose group received a single oral administration (suspension) of 1000 mg/kg bw by gavage. The rectal temperature of the animals was recorded every hour for a total of six hours. The first interval was recorded 30 minutes before test substance administration.

6. Effect on body temperature in rabbits
Five male New Zealand White rabbits received a single oral administration (suspension) of either 0; 500 or 1000 mg/kg bw by gavage. The rectal temperature of the animals was recorded every hour for a total of six hours. The first interval was recorded 30 minutes before test substance administration.

7. Effect on locomotor activity in mice
Groups of four male NMRI mice per dose group received a single oral administration (suspension) of either 0; 500 or 1000 mg/kg bw by gavage. Valium was used as a positive control. The activity was recorded 45 – 60 minutes after treatment in an activity cage. The mice were then removed and placed in their maintenance cages. A second period (in the activity cage) was recorded at 105 – 120 minutes after treatment, and a third at 165 – 180 minutes.

8. Effects on blood pressure, heart rate and respiration in rabbits
Three male New Zealand White rabbits per dose group received a single intraperitoneal administration of 500 mg/kg bw dissolved in physiological saline solution and 3.5 % polyvinylpyrolidone. After dosing blood pressure, heart rate and respiration were recorded. The agonists histamine, acetylcholine and noradrenaline were injected intraveneously.

9. Effects on skeletal muscle
Four male Wistar rats were anesthetised and the schiatic nerve was electrically stimulated. The contractility response was measured using a force displacement transductor. Blood pressure and heart rate were recorded. The animals received a single intraperitoneal administration of 250 mg/kg bw dissolved in physiological saline solution and 3.5 % polyvinylpyrolidone.

10. Effects on the isolated ileum from guinea pigs

A 20 cm segment of the terminal ileum was removed from four male Hartley guinea pigs and divided into 2 - 3 cm long strips. Four strips were selected and were each suspended in an organ bath. The contraction strength of the ileum was recorded in the presence and absence of the test substance. In addition, the potential effect of the test substance on ileum contraction in presence of histamine and acetylcholine was determined. Moreover, dose response curves of chloridazon and acetylcholine were determined with and without atropine.

11. Effects on the isolated vas deference from guinea pigs
Both vas deferentia were removed from four male Hartley guinea pigs. Four pieces were selected and were each suspended in an organ bath. The contraction strength of the vas deference was recorded in the presence and absence of the test substance. In addition, the potential effect of the test substance on vas deference in presence of acetylcholine and epinephrine was determined.

12. Effects on the isolated trachea from guinea pigs
The trachea from six male Hartley guinea pigs was removed and prepared. Four strips were selected and were each suspended in an organ bath. The contraction strength of the trachea was recorded in the presence and absence of the test substance. In addition, the potential effect of the test substance on trachea contraction in presence of histamine, epinephrine and acetylcholine was determined.

13. Effect on intestinal motility – charcoal propulsion
Groups of 10 male NMRI mice per dose group received a single subcutaneous administration of either 0 or 2000 mg/kg bw. Atropine was used as a positive control. At 45 minutes after the subcutaneous administration, the mice were orally dosed with a charcoal suspension. Ninety minutes after dosing of the charcoal the animals were sacrificed. Inhibition of charcoal propulsion was demonstrated if the cecum was charcoal free.

14. Effect on gastric secretion
Groups of five male Wistar rats received a single oral administration (suspension) of either 0; 500 or 1000 mg/kg bw by gavage. Atropine was used as a positive control. The animals were anesthetised and a pyloric ligation was performed. Immediately after recovery of the anesthetic the administration was performed. Six hours later the animals were re-anesthetised and the stomach removed. Gastric juice was collected and analysed for pH.

15. Effect on blood coagulation
Groups of seven male Wistar rats received a single oral administration (suspension) of either 0; 500 or 1000 mg/kg bw by gavage. Three hours after the administration blood was withdrawn and the following coagulation tests were performed; thromboplastin time (PT), partial thromboplastin time (PPT) and thrombine time (TT).

16. Effects on hemolysis in vitro
Blood was taken from two male New Zealand White rabbits and the erythrocytes were collected after centrifugation as a 10 % suspension. A 10 % suspension of the test substance, dissolved in physiological saline and 0.4 % Tween 20 was added for two hours to the test tube and the occurrence of hemolysis was recorded.

Findings:
The test substance was stable over the entire experimental period, and stable in water for at least 24 hours.

1. General observations on native behaviour in mice
At the high dose one animal died. At this dose tonic clonic convulsions were initially observed after stressing the animals, later without stressing. Passivity and ptosis was observed at 1000 and 500 mg/kg bw.

2. Prolongation of sleeping time induced by hexobarbitone
There was no effect at 500 and 1000 mg/kg bw.

3. Effect on convulsion induced by pentetrazole
There was no effect at 500 and 1000 mg/kg bw.

4. Effect on convulsion induced by strychnine
There was no effect at 500 and 1000 mg/kg bw.

5. Effect on body temperature in rats
At 500 and 1000 mg/kg body temperature in rats was reduced. The highest decrease was 1.8 degrees at 500 mg/kg bw and 2.7 degrees at 1000 mg/kg bw.

6. Effect on body temperature in rabbits
There was no effect at 1000 mg/kg bw.

7. Effect on locomotor activity in mice
At 500 mg/kg bw locomotor activity was slightly reduced (13 %). At 1000 mg/kg bw a 73 % reduction was noted.

8. Effects on blood pressure, heart rate and respiration in rabbits
There was no effect at 500 mg/kg bw.

9. Effects on skeletal muscle
There was no effect at 250 mg/kg bw.

10. Effects on the isolated ileum from guinea pigs
Cloridazon had an acetylcholine like effect, which was approximately 1000-fold less than acetylcholine itself. This effect was inhibited by atropine. Histamine and acetylcholine induced contractions could be inhibited by chloridazon at concentrations of 10^{-3} and 10^{-4} g/mL.

11. Effects on the isolated vas deference from guinea pigs
Chloridazon at concentrations of 10^{-3}, 10^{-4} and 10^{-5} g/mL had only a slight effect (reduction) on acetylcholine induced contractions.

12. Effects on the isolated trachea from guinea pigs
Chloridazon at concentrations of 10^{-4} and 10^{-5} g/mL had very slight effects (increase) on acetylcholine induced contractions. At a concentration of 10^{-3} g/mL the induced contractions were reduced by 26 – 36 %.
Chloridazon at concentrations of 10^{-4} and 10^{-5} g/mL had very slight effects (increase) on histamine induced contractions. At a concentration of 10^{-3} g/mL the induced contractions were clearly reduced.

Chloridazon at concentrations of 10^{-3} and 10^{-4} g/mL almost completely inhibited the epinephrine induced relaxation. At a concentration of 10^{-5} g/mL the induced relaxation was reduced by 30 %.
A chloridazon related relaxation was noted at concentrations of 10^{-4} and 10^{-3} g/mL.

13. Effect on intestinal motility – charcoal propulsion
Charcoal propulsion was inhibited by 2000 mg/kg bw chloridazon (subcutaneous) by 37.5 %.

14. Effect on gastric secretion
There was no effect at 500 and 1000 mg/kg bw.

15. Effect on blood coagulation
There was no effect at 1000 mg/kg bw.

16. Effects on hemolysis in vitro
A 10 % suspension of chloridazon caused a moderate hemolysis in vitro after two hours of incubation.

Discussion:
The authors of this study suggest that the motoric cortex of the cerebrum may be depressed based on the reduction of locomotor activity but then disappears based on the onset of tonic-clonic convulsions. A depressing effect on lower brain centres is suggested by the observed body temperature decrease. However, these observations may also be explained taking into account the induced toxicity by dose levels of 1000 mg/kg bw. One animal died and under such circumstances decreased motor activity and (prefinal) tonic clonic convulsions may not necessarily be indicative of an effect of the central nervous system. Taking into account the results of the study of the effects of chloridazon on the EEC at similar dose levels [see 1987/0461, Teschendorf H. J., 1988], in which no pathological changes of the EEC were observed, it may be concluded that the observed motoric changes were not related to an effect on the central nervous system.
The effect on body temperature was observed only in rats but not in rabbits. It should be considered that the toxicity and reduced activity of the rats may also explain the reduction in body temperature.
The effect on the vegetative nervous system in vitro is predominantly parasympathicomimetic. This is suggested by the acetylcholine like effects on the isolated ileum, which could be inhibited by atropine.
It is considered that chloridazon has slight effects on the muscarinergic and nicotinergic receptors. This is suggested by the increased contractile responses of the isolated trachea at the lower (10^{-4} and 10^{-5} g/mL) concentrations, but with strongly decreased contractile response at the high (10^{-3}g/mL) concentration. The question of unspecific effects at this very high in vitro concentration, however, should also be considered.
There were no effects on the intravasal and cardiovascular systems.

Conclusion:
The effect of chloridazon on the vegetative nervous system in vitro is predominantly parasympathicomimetic. This is suggested by the acetylcholine like effects on the isolated ileum, which could be inhibited by atropine. There were no effects on the intravasal and cardiovascular systems.
Other test substance related changes were less specific, contradictory, observed at toxic dose levels or at very high in vitro concentrations only.

Report: Teschendorf H. J., 1988
Study on the EEG effects in the conscious rat of chloridazon
[redacted]
unpublished
BASF RegDoc# 1987/0461

GLP: Yes, OECD and U.S. FDA-GLP-regulations

Guideline: JMAFF

Deviations: Not available

Acceptability: The study is considered to be supplementary.

Material and Methods:
Test material: Test substance was identified as follows:
Chloridazon, solid
Purity: 95.3 %
Batch No.: K 50/16A
Test Substance No.: 86/99
Test animals: Sprague Dawley rats

Chloridazon was administered orally by gavage to male Sprague Dawley rats per group as a 0.5 % aqueous CMC suspension at dose levels of 0; 316; 681 and 1000 mg/kg bw. For control, low and high dose level two animals per group were used, for the mid dose level four animals. At least 10 days before administration of the test substance, the animals were anesthetised and electrodes were implanted into the brain at the following locations:
subcortical: amygdala nucleus and hippocampus
cortical: frontal, occipital and neutral (anterior to the bregma midline).
Only those animals from which the EEC was normal and regular were included in the test. After 27 – 38 minutes of EEC recording the test substance was administered. Thereafter, the EEC was continuously recorded for 402 – 480 minutes. The EEC was evaluated optically including changes of amplitude and frequency as well as pathological waves.
In addition, the time pattern of waking / sleeping stages was evaluated, according to the following stages: waking, sleeping - non REM sleep, - transitional stage to REM sleep, - REM sleep.
The status of health of the animals was regularly monitored.

Findings:
The dose of 1000 mg/kg bw resulted in a poor general condition of the animals, with shaggy hair, ataxia, stereotyped chewing movements as well as muscle twitching. One animal died 48 hours after the administration.
The dose of 681 mg/kg bw resulted in the following observations: shaggy hair, mild ataxia, stereotyped chewing movements as well as muscle twitching. Motor activity was not increased.
The low dose (316 mg/kg bw) did not result in clinical signs of toxicity.
Pathological irregularities in the EEC were not observed at any dose level.

There was a dose related prolongation of the waking phase in the EEC, with a concomitant reduction of the sleep phase, notably the REM phase. This occurred without simultaneous stimulation of motor activity. These changes may be attributable to a cholinergic effect of the test substance.

Conclusion:
Chloridazon did not induce pathological changes to the EEC at any dose level. There was a dose related prolongation of the waking phase in the EEC without stimulation of motor activity. These changes may be attributable to a cholinergic effect of the test substance.

B.6.9 Medical data and information (Annex IIA 5.9)

B.6.9.1 Medical surveillance on manufacturing plant personnel

The personnel handling chloridazon in manufacturing, research and formulation is observed regularly by medical examinations. However, this surveillance program is not aimed at specifically detecting chloridazon-related symptoms or diseases. Thus, no adverse effects on health have been observed which could be related to an exposure to chloridazon.

B.6.9.2 Direct observation, e.g. clinical cases and poisoning incidents

A few cases of irritation of skin and eyes were reported in the published literature. One case of sensitisation with allergic contact dermatitis and a positive patch-test was observed. There was no positive patch-test reaction in 149 tested persons (40 of them worked as farmers). No poisoning incidents were reported in the published literature.

B.6.9.3 Observations on exposure of the general population and epidemiological studies if appropriate

No observations regarding health effects after exposure of the general public are known to us.

B.6.9.4 Diagnosis of poisoning (determination of active substance, metabolites), specific signs of poisoning, clinical tests

Methods for determination of active substance or metabolites in biological fluids are not established. Specific signs of poisoning or clinical test are not known.

B.6.9.5 Proposed treatment: first aid measures, antidotes, medical treatment

See safety data sheet/precautions; symptomatic and supportive treatment, no specific antidote known.

B.6.9.6 Expected effects of poisoning

No effects were reported.

B.6.10 Summary of mammalian toxicology and proposed ADI, AOEL, ARfD and drinking water limit (Annex IIA 5.10)

B.6.10.1 Metabolism / Toxicokinetics

After single oral administration of ^{14}C-chloridazon to male and female rats at dose levels of 20 mg/kg bw and 200 mg/kg bw, the active ingredient was rapidly absorbed from the gastro-intestinal tract. The absorbed material was rapidly excreted mostly via urine (between 85 % and 90 %) and feces (7 % - 26 %) with a half-life of 16 to 49 hours. There were no significant differences between the high and low dose level or any sex-related differences regarding rates and routes of excretion. A comparison of the excretion balance after oral vs. intravenous administration showed that virtually all radioactivity in the feces was related to biliary excretion, which was found to be 12 % to 37 % of the dose. The bioavailability was approximated to be 96-100 %.
Excretion after a 14-day pre-treatment was even faster than after a single low dose. C_{max} increased less than proportionally with dose. The AUC was linear over the tested dose range for male rats, while in females the AUC value increased slightly less than proportionally with the dose indicating a marginally lower absorption at the high dose level.
After a 7-day treatment with 20 mg/kg bw/day, highest amounts of radioactivity were found in the heart, adrenal glands, and in the gastro-intestinal tract. There was a steady decline in the radioactivity in all organs and tissues indicating that chloridazon has no accumulating potential.

After oral dosing, chloridazon was rapidly metabolised in the rat by oxidative mechanisms. The main transformation is the hydroxylation of the parent compound at the phenyl ring moiety. This metabolite is then converted either to its glucuronide or sulfate. Subsequent hydroxylation at the phenyl ring or - to a lesser extent - dechlorination of the sulfate conjugate was also observed. Three major of at least 9 metabolites were found in urine.

The dermal absorption of ^{14}C-BAS 119 H in the formulation (BAS 119 50 H) and 1:6 and 1:33 aqueous dilutions thereof was studied in male Wistar rats following a single dermal administration. The dermal absorption was found to be approximately 4 % (10 h exposure; including skin residues) both for the diluted and undiluted product.

B.6.10.2 Acute toxicity studies, local irritation and skin sensitising properties

The acute oral toxicity of isomer reduced chloridazon in rats is low. Female rats were more sensitive (LD_{50} 2140 mg/kg bw) than males (> 3830 mg/kg bw). Chloridazon with higher isomer content appears to be slightly more toxic after acute oral exposure to rats, however a different rat strain (Sprague Dawley oppose to Wistar) might have also influenced the results (LD_{50} >1000 < 1470 mg/kg bw). The acute oral LD_{50} in mice was determined to be 605 mg/kg bw for males and 598 mg/kg bw for females.

Chloridazon, whether isomer reduced or isomer rich, was virtually non toxic to Wistar or CRJ-SD rats after dermal application. The LD_{50} values were above 2000 mg/kg bw causing neither mortality nor systemic toxicity. In addition, no local reaction was observed in these studies at the application site.

The inhalation toxicity of aerosols of chloridazon, both isomer reduced and isomer rich, is low (LC_{50} > 5.4 or > 30.8 mg/L over 4 h, respectively). There was only a slight irritation of the airways during exposure in the dust aerosol study. Minor differences in clinical signs in the two inhalation studies might be due to differences in the exposure techniques and the fact that a different rat strain was used.

Isomer reduced chloridazon was not irritant in a skin irritation study in rabbits. Both - isomer reduced and non-reduced forms - of chloridazon were non irritant to the eye. Isomer reduced chloridazon was not a skin sensitiser in the Guinea pig maximisation test.

B.6.10.3 Short-term toxicity

The 4-week short term oral toxicity of chloridazon was investigated in rats and dogs. For both species a dose level of 10000 ppm proved to be too high (animals in moribund condition).

To determine whether there are differences in toxicity between both qualities of chloridazon, chloridazon isomer rich (original lower purity) and isomer reduced (higher purity) were tested comparitively in two 4-week feeding studies in Wistar rats. A dose of 5000 ppm in rats resulted in reduced food consumption, body weight and slight clinical chemical changes (e.g. increased cholesterol values). Target organs were the kidneys and liver. There were no major differences between the two qualities.

Beagle dogs dosed up to 2700 ppm did not demonstrate test substance related effects. At 5000 ppm reduced food consumption and body weight development were noted. There was a slight anemic effect in females. A few clinical chemical parameters (e.g. increased cholesterol) were affected. The target organs were the liver and the kidneys.

The 4-week toxicity of chloridazon is comparable in rats and dogs. The NOAEL in dogs is 81.9 mg/kg bw/day, in rats 40 mg/kg bw/day. The latter value, however, is the result of a wide spacing of the dose levels (500 ppm as NOAEL and 5000 ppm as LOAEL).

The subchronic toxicity of chloridazon was studied in 90 days studies in rats, mice and dogs.

In Sprague Dawley rats a dose of 19200 ppm proved to be too high and was reduced to 9600 ppm after 5 weeks. At this dose and at 4800 ppm reduced food consumption and body weight gain was observed. Reduced erythrocyte and hemoglobin values in females and altered clinical chemical changes (indicating an impairment of liver function) were observed at the high dose level only. The target organ was the liver: increased weight (4800 ppm and higher – both sexes and 1200 ppm females), hepatocyte enlargement, decreased glycogen content (4800 ppm and higher). The NOAEL was 300 ppm (approximately 21 mg/kg bw/day).

In B6C3F1 mice reduced food consumption and body weight was noted at 7500 ppm. Body weight was also reduced in 1500 ppm males. At 1500 ppm and higher reduced triglyceride and cholesterol values were seen in males. The target organ was the liver: increased weight (7500 ppm both sexes, 1500 ppm males). The NOAEL was 300 ppm in males (65 mg kg/bw/day) and 1500 ppm in females (467 mg/kg bw/day).

In Beagle dogs three 90 days studies were carried out. Toxicity was observed at dose levels of 4000 ppm and higher. Toxicity consisted of reduced body weight gain and reduced protein

values suggesting impaired liver function. The target organs were the liver (increased weight) and the kidneys (increased weight in males and vacuolisation of distal renal tubules in females). The overall NOAEL was established at 3000 ppm (97 mg/kg bw/day).

The 12-month oral toxicity of chloridazon was studied in beagle dogs. Toxicity was observed at dose levels of 1200 ppm and higher. Toxicity consisted of slightly reduced food consumption in both sexes (6000, 8000 ppm) and reduced body weight gain in females (1200, 3600 ppm), increased inorganic phosphate in both sexes (6000, 8000 ppm) and reduced bilirubin in males (8000 ppm). Target organs were the kidneys and the gastric mucosa, possibly due to local irritation. The LOEL in dogs is 1200 ppm and the NOAEL 400 ppm equivalent to 11 mg/kg bw/day.

In conclusion, the short-term oral toxicity of chloridazon was characterised by effects on the body weight and the liver in all three species tested. At high dose levels liver function was impaired resulting in clinical chemical changes, whereas at lower dose levels only liver weight increases were seen. Kidney toxicity and effects on the gastric mucosa were observed in dogs at very high dose levels.

In a 21-day dermal study in New-Zealand White rabbits neither systemic toxicity nor signs of local irritation were observed at a dose level of 1000 mg/kg bw/day indicating the very low toxic potential of the test substance after dermal exposure.

Based on the above described findings, the relevant NOAELs from the short-term toxicity studies are listed below.

Table B.6.10-1: NOAEL´s from short-term studies in different species (mg/kg bw/day)

Species	Route	Males	Females
Rat	oral – 4 weeks	40	40
Dog	oral – 4 weeks	81.9	81.9
Rat	oral – 3 months	21	23.5
Mouse	oral – 3 months	65	467
Dog	oral – 3 months	97	97
Dog	oral - 12 months	11	11
Rabbit	dermal – 3 weeks	1000	1000

B.6.10.4 Genotoxicity studies

Chloridazon was evaluated for possible mutagenic/genotoxic effects *in vitro* and *in vivo*. It was negative in 4 out of 5 reverse mutation assays in bacteria (Ames test). The only positive response was obtained in one of the oldest tests with the isomer rich quality at doses causing test substance precipitation. In this study precipitation was observed at very low doses (1000 µg/plate) in contrast to the other studies. In addition, the effect observed was marginal (maximum 1.5 fold increase with and without metabolic activation). The marginally increased mutation frequency suggests that an impurity or physical properties (precipitation) may have been responsible for this finding. This interpretation is further supported by the negative results obtained in tests with other batches conducted under the same test conditions. Therefore, it is concluded that the present isomer reduced technical active ingredient is negative in the Ames test including *Salmonella* and *E. coli* test strains. Chloridazon showed also negative results in a reverse mutation assay in a special *E. coli* strain (*E. coli* K 12 (343/113)).

Point mutations in mammalian cells were assessed in Chinese hamster ovary cells (HPRT assay). In this study no mutagenic effects were observed.

In the chromosome aberration test *in vitro* in human lymphocytes no increase of mutation frequency was noted.

DNA damage and repair was investigated *in vitro* in bacterial cells (Recombination assay with *Bacillus subtilis*) in two experiments and in the UDS test in primary rat hepatocytes. In all 3 experiments there was no indication of DNA damage and repair caused by chloridazon.

In two *in vivo* studies NMRI in mice, a micronucleus tests (single oral application) and a dominant lethal assay (gavage for five consecutive days), the absence of a genotoxic potential of chloridazon was confirmed.

The studies conducted sufficiently cover all endpoints to be investigated in mutagenicity and genotoxicity testing. Chloridazon has no mutagenic and no genotoxic potential.

B.6.10.5 Long-term toxicity / carcinogenicity studies

In a recent long-term study in Wistar rats body weight gain was reduced at doses of 1000 and 2000 ppm. At the high dose level (2000 ppm) several red blood cell parameters were reduced indicating an anaemic effect. In addition, the thromboplastin time was decreased and a few clinical chemical parameters were altered. There were no specific target organs in the long-term rat study. The NOAEL in this study was 300 ppm (13 mg/kg bw/day).

In a recent carcinogenicity study in Wistar rats the only effect seen in the high dose groups (1000 ppm) was reduced body weight. The NOAEL in this study was 300 ppm (13 mg/kg bw/day).

In an older study in Sprague Dawley rats food consumption and body weight gain was impaired in males and females at 4050 ppm. At this dose level red blood cell parameters were reduced mainly in females. In high dose females cholesterol was increased and several organ weights were altered, however, without corresponding histopathological changes.
The increased incidence of muscular atrophy in high dose females correlates with the observation of “prominence of shoulder blades” in these animals. An increased incidence and grade of muscular atrophy was also observed in high dose males. The observations were confirmed in the additional histopathological examinations. The only test substance related change in the 1350 ppm group was a slight increase in the incidence and grade of muscular atrophy in females. That similar observations were not found in the more recent long-term studies in rats, in doses up to 2000 ppm, may be related to different sensitivities of the different rat strains implied. The NOAEL of this study was 450 ppm (20 mg/kg bw/day).

The overall NOAEL for the chronic rat toxicity was 300 ppm (13 mg/kg bw/day).

Chloridazon was not carcinogenic in any of the long-term studies in rats.

In a more recent carcinogenicity study, B6C3F1 mice treated with a very high dose level (5000 ppm) showed reduced body weight gain and an increase of relative liver weights only. The NOAEL in this study was 1000 ppm equivalent to 134 mg/kg bw/day in males and 158 mg/kg bw/day in females.

In an older long-term study in CFLP mice reduced body weight gain, increased liver weights and histopathological signs of an adaptation of the liver were observed at 20000 ppm. The NOAEL in this study was 4000 ppm (351 mg/kg bw/day in males and 423 mg/kg bw/day in females).

The overall long term NOAEL in mice was 1000 ppm (134 mg/kg bw/day).

Chloridazon was not carcinogenic in both long-term studies in mice.

The relevant NOAELs are shown in the table below.

Table B.6.10-2: Long-term NOAELs in mg/kg bw/day

Study	Males	Females
long-term rats	13	18
long term mouse	134	158

In conclusion, chloridazon was not carcinogenic in rats and in mice. Long-term studies in rats and mice identified kidney, liver, blood and sceletal muscle as target organs.

B.6.10.6 Reproductive toxicity / developmental (teratogenicity) studies

In a recent study chloridazon was administered via the feed to Wistar rats for two consecutive generations at dose levels of 0, 100, 400 and 1600 ppm. Effects on parental animals (body weight, body weight gain, increased triglycerides and liver weights, hepatocyte swelling and lipid deposits) were noted at the high dose. The only finding in pups was a reduced body weight and body weight development at this dose level. No effects were noted at the low and mid dose level for parental animals and their offspring. The NOAEL for systemic toxicity in parental animals and offspring was 400 ppm (37 mg/kg bw/day). There was no indication of an impairment of fertility in both sexes at all dose levels, thus the NOAEL for reproductive performance and fertility was 1600 ppm (about 148 mg/kg bw/day)

In an older multigeneration study, where CFY rats had been treated via the feed over three consecutive generations with doses of 0, 150, 440 and 1350 ppm, no effects on parental animals and pups were noted at any dose level. Similarly there were also no adverse effects on reproduction and fertility parameters. The dose levels were in the same range as in the above-mentioned 2-generation study, however, the scope of examination was not as extensive. The relevant NOAELs should therefore be derived from the more recent 2-generation study.

In a pre-, peri-, postnatal feeding study in NMRI mice according to FDA method (segment II and III) no effects were noted in the prenatal phase (segment II) in dams treated with 0, 5000 and 10000 ppm. There was also no indication of embryo-/fetotoxicity and no malformations were noted. In the peri-/postnatal phase (segment III) with identical doses the pup vitality index was slightly reduced at 10000 ppm (1742 mg/kg bw/day) in the test group where dams received chloridazon throughout pregnancy up to day 21 post partum. The effect was not noted in the test group when the dams had only been treated during the gestation period. In addition there was a slight increase in liver weights of dams and pups. No other adverse effects were noted for dams and pups including pup examination for anomalies, variations or

malformations. No adverse effects were noted at the 5000 ppm dose level (905 mg/kg bw/day).

When chloridazon was administered by gavage to Wistar rats in a prenatal toxicity study maternal toxicity was marked at the high dose of 250 mg/kg bw/day leading to reduced food consumption, impairment of body weight and body weight development (including corrected body weight gain), and clinical symptoms (piloerection). At 50 mg/kg bw/day there was a slight effect on food consumption and body weight gain. The effects were not seen at a lower dose of 10 mg/kg bw/day. There was no indication that the administration of chloridazon caused embryo-/fetotoxicity or malformations at any dose levels.

When chloridazon was administered by gavage to Chinchilla Russian rabbits, maternal toxicity at the doses of 165 mg/kg bw/day and 495 mg/kg bw/day in form of impairment of food consumption and body weight was observed. The NOAEL was 55 mg/kg bw/day. No adverse effects on embryo-/fetal development - including the occurrence of malformations - could be noted even at the high dose of 495 mg/kg bw/day which showed clear maternal toxicity.

The following NOAELs have been established for reproduction toxicity including fertility and prenatal toxicity of chloridazon:

Table B.6.10-3: Reproduction toxicity NOAELs in mg/kg bw/day

Study	Parental/maternal toxicity	Developmental toxicity	Fertility
2-generation rat	37	37	148
pre-, peri-, postnatal mouse	905	905	-
prenatal toxicity rat	10	250	-
prenatal toxicity rabbit	55	495	-

In conclusion there were no adverse effects on reproduction and fertility and also no adverse effects in fetuses of rats, mice and rabbits.

B.6.10.7 Neurotoxicity / Delayed neurotoxicity studies

With regard to neurotoxicity no indications of an acute or subchronic neurotoxic effect could be derived from the toxicity studies performed with chloridazon. Chloridazon showed no clinical signs in any of the toxicity studies which could be attributed to neurotoxicity and no indications on histopathological changes on the central or peripheral nerve system were seen in the short-term, long-term or reproductive/developmental studies in rats, mice and dogs.

B.6.10.8 Further toxicological studies

A number of toxicological studies with metabolites of chloridazon was performed.
The metabolite B (Reg. No. 14456) was demonstrated to be virtually non-toxic after acute oral administration with a LD_{50} in rats of approx. 5000 mg/kg bw for males and > 5000 mg/kg bw for females.

Chloridazon metabolie B did not show mutagenic or genotoxic properties in three tests (Ames test, V79/HPRT test, *in vitro* cytogenetics).

The short-term toxicity of chloridazon metabolite B is characterised mainly by kidney and descending urinary tract toxicity. Increased drinking water consumption and altered urinalysis parameters are considered to be related to the kidney toxicity. Kidney and urinary tract toxicity was observed in several studies. Female rats were more affected than males. The second target organ was the liver, with weight increases, altered fat distribution and increased number and size of vacuoles. At very high dose levels food consumption and body weight gain were impaired.

In a 4-week study in rats a NOAEL of 90 mg/kg bw/day was obtained. Three 3-month studies were conducted in rats. In an early study in Sprague-Dawley rats a NOAEL of 86 mg/kg bw/day was obtained. However, as the batch of the test substance was not identified and no analytical data provided the study was not used for the establishment of the most relevant NOAEL. In the second 3-month study in Wistar rats the LOEL was 750 ppm. A NOAEL was not established in this study. In a follow up 3-month study a NOAEL of 200 ppm (15 mg/kg bw/day) was obtained. The overall NOAEL for the short term toxicity of chloridazon metabolite B was 15 mg/kg bw/day.

In a prenatal toxicity study in rats maternal toxicity (reduced body weight gain and hematurea indicating kidney toxicity) was observed at 120 mg/kg bw/day, the NOAEL being 60 mg/kg bw/day. These findings are consistent with the observations in the short term feeding studies in rats. There were no signs of developmental toxicity including no test substance related malformations up to the top dose level of 120 mg/kg bw/day.

In conclusion chloridazon metabolite B was virtually not toxic after acute oral administration, it was not mutagenic, not genotoxic and demonstrated no developmental toxicity. In short term feeding studies the target organs were liver and kidney. The overall NOAEL for the short term toxicity of chloridazon metabolite B was 15 mg/kg bw/day.

An acute oral toxicity study with chloridazon metabolite B-1 (Reg. No. 035 375) revealed an LD_{50} of 1200 mg/kg bw.

Chloridazon metabolite B-1 was found to be not mutagenic in the *Salmonella typhimurium/Escherichia coli* reverse mutation assay and not mutagenic in the CHO/HPRT mutation assay. It was negative in the *in vitro* UDS assay using primary rat hepatocytes. Additionally, chloridazon metabolite B-1 had no *in vivo* chromosome-damaging (clastogenic) effect in bone marrow cells of Wistar rats.

The no observed adverse effect level in a 3-month dietary rat study was 50 mg/kg bw/day for males and females (highest dose tested).

In a prenatal developmental study in Wistar rats maternal toxicity was seen at 50 mg/kg bw/day (highest dose level). Signs of substance-induced prenatal developmental toxicity (reduced mean fetal weight, delayed ossification, rudimentary cervical ribs), but no indications for teratogenicity occurred exclusively at the high dose level, which can be interpreted as secondary effect due to maternal toxicity. At 2 and 10 mg/kg bw/day no substance-induced signs of embryo-/fetotoxicity were observed. The no observed adverse effect level (NOAEL) for maternal and prenatal developmental toxicity was 10 mg/kg bw/day.

In conclusion chloridazon metabolite B-1 was moderately toxic after acute oral administration, it was not mutagenic nor genotoxic. The NOAEL for maternal and prenatal develop-

mental toxicity was 10 mg/kg bw/day. The NOAEL for short-term toxicity of chloridazon metabolite B-1 was 50 mg/kg bw/day.

Based on these data and according to the EU guidance document on groundwater metabolites, both metabolites are considered toxicologically not relevant. A number of toxicological studies has been performed but a complete data package including long-term and multi-generation studies is lacking. Therefore, a higher safety factor of 1000 has to be applied when an ADI for these metabolites is derived on the basis of toxicological data obtained with the parent compound. Assuming a daily intake of 2 L water, a bodyweight of 70 kg and a 10 % contribution of drinking water to the whole daily exposure, a maximum groundwater concentration of up to 35 µg/L for the metabolites B and B1 would be acceptable. However, as stated in the guidance document, a pragmatic limit value of 10 µg/L should not be exceeded. If this would happen, regulatory decisions must be taken on Member state level.

The results of the pharmacology testing of chloridazon can be summarised as follows:
The effect of chloridazon on the vegetative nervous system *in vitro* is predominantly parasympathicomimetic. This is suggested by the acetylcholine like effects on the isolated ileum, which could be inhibited by atropine. There were no effects on the intravasal and cardiovascular systems.

Other test substance related changes were less specific, contradictory, observed at toxic dose levels or at very high *in vitro* concentrations only.

Chloridazon did not induce pathological changes to the EEC at any dose level. There was a dose related prolongation of the waking phase in the EEC without stimulation of motor activity. These changes may be attributable to a cholinergic effect of the test substance.

B.6.10.9 Human Data

The personnel handling chloridazon in manufacturing, research and formulation is observed regularly by medical examinations. However, this surveillance program is not aimed at specifically detecting chloridazon-related symptoms or diseases. Thus, no adverse effects on health have been observed which could be related to an exposure to chloridazon.
A few cases of irritation of skin and eyes were reported in the published literature. One case of sensitisation with allergic contact dermatitis and a positive patch-test was observed. There was no positive patch-test reaction in 149 tested persons (40 of them worked as farmers). No poisoning incidents were reported in the published literature.
No observations regarding health effects after exposure of the general public are known. Methods for determination of active substance or metabolites in biological fluids are not established. Specific signs of poisoning or clinical test are not known.
See safety data sheet/precautions; symptomatic and supportive treatment, no specific antidote known.

B.6.10.10 ADI

For the determination of the acceptable daily intake (ADI), the results of the long-term administration studies as well as those from reproduction toxicity have the greatest relevance.

The relevant NOAELs obtained in long-term studies are shown in the table below.

Table B.6.10-4: Chronic NOAELs in mg/kg bw/day

Study	Males	Females
12 month feeding dog	11	11
long-term feeding rats	13	18
long term feeding mouse	134	158
2-generation feeding rat	37	37

The NOAEL derived from the long-term study in rats (13 mg/kg bw/day for males and 18 mg/kg bw/day for females) is lower than any of the other long-term studies. However, the NOAEL for maternal toxicity in the prenatal toxicity study in rats was slightly lower with 10 mg/kg bw/day. As the LOEL in this particular study was 50 mg/kg bw/day and as at this dose level only marginal signs of toxicity were observed, the NOAEL from the long-term study in rats of 13 mg/kg bw/day should be used for the calculation of the acceptable daily intake (ADI). The value is rounded according to the rules to 10 mg/kg bw/day.

Chloridazon has no genotoxic potential, is not teratogenic, has no effects on fertility and is not neurotoxic. Chloridazon is not carcinogenic in any species tested.

A full toxicology database, evaluating all toxicity endpoints required, was developed for chloridazon. Clear no effect levels have been determined for all treatment related effects.

Using the conventional safety factor of 100, the proposed ADI is 0.1 mg/kg bw.

B.6.10.11 AOEL (systemic)

For the calculation of the acceptable operator exposure level (AOEL) and a risk assessment made thereof, the NOAELs of short-term toxicity studies as well as reproduction/developmental toxicity studies will be taken into account.

The AOEL relevant NOAELs are listed below.

Table B.6.10-5: NOAELs from AOEL relevant studies in different species (mg/kg bw/day)

Species	Route	Males	Females
Rat	oral – 4 weeks	40	40
Dog	oral – 4 weeks	81.9	81.9
Rat	oral – 3 months	21	23.5
Mouse	oral – 3 months	65	467
Dog	oral – 3 months	97	97
Rat	dermal – 3 weeks	1000	1000
Mouse	Pre-, peri-, postnatal	-	905
Rat	2-generation study	37	37
Rat	prenatal toxicity study	-	10
Rabbit	prenatal toxicity study	-	55

The apparently lowest NOAEL of 10 mg/kg bw/day was observed in a prenatal toxicity study in rats, based on only marginal signs of maternal toxicity at the next higher dose level of 50 mg/kg bw/day: slightly reduced food consumption as well as a marginal impairment of body weight gain at the start of the treatment period (days 6 – 8 post coitum).

The applicant suggests that since these effects at 50 mg/kg bw/day were marginal, the NOAEL of 10 mg/kg bw/day should not be used for the AOEL determination. Instead the NOAEL of 17 mg/kg bw/day derived from a long-term feeding study in rats should be used for the calculation of the AOEL. He considers this approach acceptable as the NOAEL in this study is still clearly below the LOAEL of the prenatal toxicity study in rats (50 mg/kg bw/day).

However, the rapporteur considers it more appropriate to use the NOAEL of 21 mg/kg bw/day from the 3-month rat study.

Taking into account a bioavailability of 100 %, and the safety factor of 100, the systemic acceptable operator exposure level is calculated to be 0.2 mg/kg bw/day.

B.6.10.12 ARfD (acute reference dose)

Chloridazon is of low acute oral, dermal and inhalation toxicity. After single oral dosing mortalities were only observed in several studies starting at dose levels of approximately 1000 mg/kg bw and higher. Under the conditions of the rules of good agricultural practice the risk of an acute intoxication by chloridazon can be ruled out. No acute effects have been observed after single exposure in repeat-dose studies. Considering the low acute toxicity of the active substance and it's use patterns, the establishment of an acute reference dose is not considered necessary.

B.6.10.13 Drinking water limit

The determination of a MAC value is not necessary, because according to Directive 91/414/EC only the ADI and AOEL values have to be determined. Therefore, the establishment of a maximum admissible concentration for drinking water from an ADI value is not yet confirmed by a harmonised EU proposal. In addition to that, the maximum admissible concentration of an active substance is 0.1 µg/L, as established by the Directive 89/778/EEC.

B.6.11 Acute toxicity including irritancy and skin sensitisation of preparations (Annex IIIA 7.1)

BAS 119 33 H (trade names: Pyramin WG; Pyramin DF) is formulated as water-dispersible granules containing nominal 650 g/kg of the active ingredient chloridazon.
The acute oral toxicity of BAS 119 33 H in rats is moderate. Females appear slightly more sensitive after oral exposure. When tested by the dermal route BAS 119 33 H is virtually non-toxic and only minimal skin irritation was observed. BAS 119 33 H is moderately toxic when inhaled as a liquid aerosol.
BAS 119 33 H is not irritant to the skin and eyes of rabbits. All findings are very mild and show a fast reversibility. It is not a skin sensitiser in the modified Buehler test (9 induction applications) and in the Open Epicutaneous Test according to the method of Kleczak. The acute toxicity data after various routes of application (oral, dermal, inhalative) including the primary skin/eye irritation and dermal sensitisation data of BAS 119 33 H are summarised inTable B.6.11-1.

Table B.6.11-1: Acute toxicity including skin/eye irritation and dermal sensitisation of BAS 119 33 H

Study type	Results	Reference
Acute oral LD_{50} rat	m: 1690 mg/kg bw f: 825 mg/kg bw m + f: 1160 mg/kg bw	Kieczka H., Kirsch P.; 1987d
Acute dermal LD_{50} rat	> 2000 mg/kg bw	Kieczka H., Kirsch P.; 1987e
Acute inhalation LC_{50} rat	m: 2.62 mg/L (4 h) f: 3.57 mg/L (4 h) m + f: 3.28 mg/L (4 h)	Klimisch H.-J. et al.; 1987
Skin irritation	Not irritating	Kieczka H., Kirsch P.; 1987a
Eye irritation	Not irritating	Kieczka H., Kirsch P.; 1987b
Skin sensitisation (Buehler test: 9 Inductions)	Not sensitising	Wiemann C., Hellwig J. 2001

On the basis of the acute toxicity data in accordance with the Directive 1999/45/EC a classification/labelling with Xn, R 20-22 is required.

B.6.11.1 Oral

Report: Kieczka H., Kirsch P., 1987(d)
BAS 119 33 H: Report on the study of acute oral toxicity on the rat based on OECD and EPA (FIFRA)
[redacted]
unpublished
BASF RegDoc# 1987/032

GLP: Yes (laboratory certified by Ministerium fuer Umwelt und Gesundheit, Postfach 3160, 6500 Mainz)

Guideline: OECD 401, EPA 81-1

Deviations: Testing method 401 has been deleted from OECD guidelines since December 2002 but the experiments described were performed in 1987.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: BAS 119 33 H; Batch/purity: 85-1; chloridazon: 68 %.
Test animals: Wistar rats/Dr. Thomae
Five male and five female Wistar rats per dose group were administered doses from 261 to 3160 mg/kg body weight BAS 119 33 H as an aqueous preparation in 0.5 % carboxy methyl cellulose (CMC) by gavage (for detail of dosing see Table B.6.11-2). Chemical analysis with respect to stability and concentration control analysis of the test substance preparation was performed. The animals were examined for clinical signs and mortality throughout the study. Body weight was examined on day 0, 7 and 13 of the study. All rats that died and the surviving rats at the end of the study (14 days observation period) were examined macroscopically.

Table B.6.11-2: Dosing scheme – acute toxicity study in rats with BAS 119 33 H

Number of rats/sex	Dose (mg/kg bw)	Concentration (g/100 mL)	Administered volume (mL/kg bw)
5	3160	31.60	10
5	2150	21.50	10
5	1470	14.70	10
5	825	8.25	10
5	464	4.64	10
5	261	2.61	10

Findings:
The stability of the test substance itself was verified by reanalysis after termination of the study. Homogeneity was guaranteed by shaking. The stability of the test substance preparation was confirmed by analysis. The correct concentration was confirmed by a concentration control analysis in one dose.

Table B.6.11-3: Mortality in the acute oral toxicity study in Wistar rats with BAS 119 33 H

Dose (mg/kg bw)	Mortality (no. of deaths/no. of total rats)			Time of death after dosing
	Male	Female	Combined	
3160	5/5	5/5	10/10	Day 1
2150	3/5	5/5	8/10	Day 1
1470	1/5	5/5	6/10	Day 1
825	1/5	2/5	3/10	Day 1
464	0/5	1/5	1/10	Day 1
261	0/5	0/5	0/10	-

There were no clinical symptoms at 261 mg/kg body weight and this concentration was also non-lethal to the rats. Clinical symptoms at higher doses included dyspnoea, apathy, abnormal position, staggering, paresis, tremors, twitching spastic gait, tonic cramps, convulsions, piloerection, exophthalmus and poor general state in a dose dependent manner.
There was one male rat (high dose group) which died within 1 h after dosing. All other rats died within day 1 of the study (Table B.6.11-3). All surviving rats gained weight, however, body weights of surviving animals were slightly lower at doses of 464 mg/kg and above when compared to the lowest non-toxic dose of 261 mg/kg body weight. While necropsy of surviving rats was unobtrusive, general congestive hyperemia was noted as the only macroscopic finding in animals that died.

Conclusion:
BAS 119 33 H has a moderate acute toxicity after oral exposure in rats.
The acute oral LD_{50} in Wistar rats was calculated as follows:

Males:	1690 mg/kg body weight
Females:	825 mg/kg body weight
Males and females:	1160 mg/kg body weight

A classification/labelling with Xn, R 22 is needed.

B.6.11.2 Percutaneous

Report: Kieczka H., Kirsch P., 1987(e)
BAS 119 33 H: Report on the study of acute dermal toxicity on the rat based on OECD and EPA (FIFRA)
[redacted]
unpublished
BASF RegDoc# 1987/033

GLP: Yes (laboratory certified by Ministerium fuer Umwelt und Gesundheit, Postfach 31 60, 6500 Mainz)

Guideline: OECD 402, EPA 81-2

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: BAS 119 33 H; Batch/purity: 85-1; chloridazon: 68 %.
Test animals: Wistar rats/Dr. Thomae
The dermal LD_{50} of BAS 119 33 H was determined using five male and five female Wistar rats. The animals were treated with a 50 % (w/v) aqueous preparation (containing 0.5 % carboxy methyl cellulose). The dose level selected was 2000 mg/kg body weight and the test substance preparation was applied to an area of approximately 50 cm² of the dorsal/dorsolateral flank under semi-occlusive conditions for 24 hours (for details see Table B.6.11-4). After 24 hours of exposure the treated skin was cleaned with water. Chemical analysis with respect to stability of the test substance preparation was performed. Verification of the dose level was not performed. The animals were examined for clinical signs and mortality. Body weight was determined on day 0, 7 and 13 of the study. The local skin reaction was evaluated 30 to 60 minutes after removal of the dressing, about 1 week later and at study termination. All surviving rats at the end of the study (14 days observation period) were examined macroscopically.

Table B.6.11-4: Dosing scheme – acute dermal toxicity study in Wistar rats with BAS 119 33 H

Number of rats/sex	Dose (mg/kg bw)	Concentration (% w/v)	Administered volume (mL/kg bw)
5	2000	50	4.0

Findings:
The stability of the test substance itself was verified by reanalysis after termination of the study. Homogeneity was guaranteed by shaking. The stability of the test substance preparation was confirmed by analysis and the homogeneity was guaranteed by shaking.

Table B.6.11-5: Mortality, systemic/local toxicity in the acute dermal toxicity in Wistar rats with BAS 119 33 H

Dose (mg/kg bw)	Mortality (no of deaths/no of total rats)			Findings
	Males	Females	Combined	
2000	0/5	0/5	0/10	No systemic toxicity, erythema on day 1 after exposure

There was no mortality in this study and no clinical symptoms were noted. Local symptoms of exposure were restricted to transient erythema formation on study day 1 (Table B.6.11-5). A satisfactory body weight gain was recorded during the study period. No macroscopic pathological findings were observed at study termination.

Conclusion:
BAS 119 33 H is of no toxicity following acute dermal application.
Thus the LD_{50} value is > 2000 mg/kg body weight for Wistar rats of both sexes.
A classification/labelling is not needed.

B.6.11.3 Inhalation

Report: Klimisch H.-J. et al., 1987
Test Report: Acute inhalation toxicity LC_{50} 4 hours (rat); liquid aerosol study of BAS 119 33 H (Pyramin DF)
[redacted]
unpublished
BASF RegDoc# 1987/099

GLP: Yes (laboratory certified by Ministerium fuer Umwelt und Gesundheit, Postfach 31 60, 6500 Mainz)

Guideline: OECD 403

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: BAS 119 33 H; Batch/purity: 85-1; chloridazon: 68 %.
Test animals: SPF-Wistar rats/Chbb: THOM

Five male and five female Wistar rats per dose group were exposed to a liquid aerosol with head-nose exposure to concentrations of 0.73; 2.62 and 4.68 mg/L BAS 119 33 H in the air for a period of 4 hours (Table B.6.11-6). The concentrations were verified analytically. The MMAD (mass median aerodynamic diameter) and the fraction of respirable dust were determined (Table B.6.11-7). During and after exposure behaviour and general conditions were recorded. Body weight was determined once a week. All rats were subjected to gross pathology 14 days after exposure.

Table B.6.11-6: Experimental Procedure in the LC_{50} determination in rats with BAS 119 33 H (liquid aerosol)

Dose group	Analytical concentration (mg/L air)	Number of animals
1	0.73	5 males and 5 females
2	2.62	5 males and 5 females
3	4.68	5 males and 5 females

Table B.6.11-7: Analytical results in the LC_{50} determination in rats with BAS 119 33 H (liquid aerosol)

Dose group	**Concentration in mg/L air**		**MMAD**	**Standard deviation**	**% Respirable aerosol fraction**
	Analytical	Nominal			
1	0.73	16.3	2.8 µm	3.5	87.6
2	2.62	98	4.6 µm	2.8	79.2
3	4.68	244	3.8 µm	2.8	84.7

Findings:
A stability of the test substance was ensured for at least 2 years and the homogeneity of the test substance was guaranteed.

Table B.6.11-8: Mortalities in the LC50 determination in rats with BAS 119 33 H (liquid aerosol)

Dose group	Analytical concentration (mg/L air)	Mortality (dead animals/animals exposed)	
		Males	Females
1	0.73	0/5	0/5
2	2.62	3/5	2/5
3	4.68	3/5	3/5

In this study mortality was recorded within day 1 at the mid and high dose group (Table B.6.11-8). Clinical symptoms noted during exposure were slight attempts to escape, accelerated breathing and reddish discharge in some animals. After exposure all animals showed deteriorated general state of health, unsteady high-stepping gait, abdominal respiration, accelerated respiration. At the mid and high dose group isolated tremors, abdominal or intermittent breathing, stained fur in the genital area (blood test positive) and loss of hair in the region of the head were noted. Additionally, high dose animals showed piloerection. Symptoms were reversible by day 6 (low dose group) or day 12 (medium dose group). At the high dose group piloerection was still present at the end of the study.
The only effect on bodyweight was noted in males of the mid and high dose group, when compared to historical (air) control data. While there was retardation after 1 week compared to the historical control, this was adjusted to normal in the second week. Animals that had died during the study showed focal hyperemia with oedematisation in the lungs and general congestion. No gross pathological changes were observed in surviving animals examined at study termination.

Discussion:
In order to determine the acute inhalation toxicity (single 4-hours-exposure) BAS 119 33 H was tested as a liquid aerosol. According to the requirements of OECD-guideline 403 particle

size spectrum of the aerosol was quite well within the respirable range with mass median aerodynamic diameters between 2.8 to 4.6 µm. Comparison of analytical with nominal concentrations of BAS 119 33 H in each dose group of the aerosol (see Table B.6.11-8) reveals that there were technical difficulties to produce fines effectively. The notifyer proposed not to classify the preparation and argues that not only under experimental but also under in use conditions it seems unlikely that respirable dust or liquid of BAS 119 33 H could occur in high amounts.

Conclusion:
BAS 119 33 H has a moderate acute inhalation toxicity when tested as liquid aerosol by head/nose exposure. The 4-hour LC_{50} was calculated to be:

Males	2.62 mg/L air
Females	3.57 mg/L air
Males and females	3.28 mg/L air

A classification/labelling with Xn, R 20 is needed.

B.6.11.4 Skin irritation

Report: Kieczka H., Kirsch P., 1987(a)
BAS 119 33 H: Report on the acute dermal irritation/corrosivity to the intact dorsal skin of the white rabbit based on OECD and EPA (FIFRA)
[redacted]
unpublished
BASF RegDoc# 1987/004

GLP: Yes (laboratory certified by Ministerium fuer Umwelt und Gesundheit, Postfach 31 60, 6500 Mainz)

Guideline: OECD 404, EPA 81-5

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: BAS 119 33 H; Batch/purity: 85-1; chloridazon: 68 %.
Test animals: White Vienna rabbits

BAS 119 33 H was tested for skin irritation on rabbit skin (White Vienna) according to OECD method 404. About 0.5 g of an 80 % (w/w) aqueous preparation of BAS 119 33 H was applied onto the shaven back of 6 rabbits (4 males and 2 females) under semi-occlusive conditions. The test substance was moistened with distilled water in order to mimic physiological conditions. The patch size was 2.5 x 2.5 cm. At the end of the 4 hour exposure period the test substance was removed with Lutrol (polyethylene glycol 400 and water, 1:1) and the exposed skin sites were evaluated 30-60 minutes after removal of the test patch (i.e. 4 hour interval) and 24, 48 and 72 hours after beginning of the application.

Findings:
The stability of the test substance was verified by reanalysis. The stability of the test substance preparation in distilled water was verified analytically. The homogeneity of the test substance preparation was guaranteed by shaking.
The only finding observed was very slight erythema at the 4 hour reading interval. No other skin findings were noted on day 1, 2 or 3 after exposure, thus the study was terminated (Table B.6.11-9).

Table B.6.11-9: Skin irritation results of BAS 119 33 H in White Vienna rabbits

Rabbit No.	Reaction	4 h	24 h	48 h	72 h
		after beginning of the application			
1	Erythema	1	0	0	0
	Oedema	0	0	0	0
2	Erythema	1	0	0	0
	Oedema	0	0	0	0
3	Erythema	0	0	0	0
	Oedema	0	0	0	0
4	Erythema	1	0	0	0
	Oedema	0	0	0	0
5	Erythema	1	0	0	0
	Oedema	0	0	0	0
6	Erythema	1	0	0	0
	Oedema	0	0	0	0
Mean (animal 1 - 6, 24 - 72 h)	Erythema	0.0			
	Oedema	0.0			

Conclusion:
BAS 119 33 H was not irritant to rabbit skin. A classification/labelling is not needed.

B.6.11.5 Eye irritation

Report: Kieczka H., Kirsch P., 1987(b)
BAS 119 33 H: Report on the acute irritation to the eye of the white rabbit based on OECD and EPA (FIFRA)
[redacted]
unpublished
BASF RegDoc# 1987/005

GLP: Yes (laboratory certified by Ministerium fuer Umwelt und Gesundheit, Postfach 31 60, 6500 Mainz)

Guideline: OECD 405, EPA 81-4

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: BAS 119 33 H; Batch/purity: 85-1; chloridazon: 68 %.
Test animals: White Vienna rabbits

A bulk volume of 0.1 mL (about 45 mg) of unchanged BAS 119 33 H was instilled into the right eye of three male and three female White Vienna rabbits. The animals were scored for corneal changes, iris effects, and conjunctival reaction 1, 24, 48 and 72 hours after test substance application.

Findings:
The stability of the test substance was verified by a reanalysis. The homogeneity of the test substance was guaranteed by shaking.

Table B.6.11-10: Results of the primary eye irritation test in White Vienna rabbits with BAS 119 33 H

Animal / time of examination	Cornea	Iris	Conjunctivae	
	Opacity		Redness	Chemosis
1h				
Animal 1	0	0	2	0
Animal 2	0	0	2	0
Animal 3	0	0	2	0
Animal 4	0	0	2	0
Animal 5	0	0	2	0
Animal 6	0	0	2	0
24 h				
Animal 1	0	0	2	0
Animal 2	0	0	2	0
Animal 3	0	0	1	0
Animal 4	0	0	2	0
Animal 5	0	0	1	0
Animal 6	0	0	1	0
48 h				
Animal 1	0	0	0	0
Animal 2	0	0	0	0
Animal 3	0	0	0	0
Animal 4	0	0	0	0
Animal 5	0	0	0	0
Animal 6	0	0	0	0
72 h				
Animal 1	0	0	0	0
Animal 2	0	0	0	0
Animal 3	0	0	0	0
Animal 4	0	0	0	0
Animal 5	0	0	0	0
Animal 6	0	0	0	0
Mean	0.0	0.0	0.5	0.0

There were no effects on cornea and iris in this study [see Table B.6.11-10] At the first reading interval 1 h after exposure well defined conjunctival redness was noted as the only finding in all animals gradually disappearing. 48 hours after exposure redness has completely disappeared. There were no effects on cornea and iris throughout the study. Thus, the study was terminated after 72 hours.

Conclusion:
BAS 119 33 H was not irritant to rabbit eyes. A classification/labelling is not needed.

B.6.11.6 Skin sensitisation

Report: Wiemann C., Hellwig J., 2001
BAS 119 33 H - Modified Buehler Test (9 inductions) in guinea pigs
[redacted].
unpublished
BASF DocID 2001/1009207

GLP: Yes (laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: EEC 96/54 B 6, OECD 406, EPA 870.2600, JMAFF

Deviations: None

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: BAS 119 33 H; Batch/purity: 97-1: 65.4 %.
A 70 % (w/w) aqueous preparation was used for induction applications and 25 % (w/w) for challenge applications.
Test animals: SPF-Guinea pigs/Hsd Poc: DH

BAS 119 33 H was investigated for its sensitising effect in the modified Buehler Test with nine inductions. The study was performed in 20 guinea pigs in the test group and 10 animals in each of the control groups 1 and 2.
All inductions were performed with a 70 % test substance preparation in double distilled water. The inductions were performed on days 0 - 2, 7 - 9 and 14 - 16. For the induction, 2 x 2 cm gauze patches containing the test substance were applied to the skin of the left anterior flank under an occlusive dressing. A volume of 0.5 mL of the test substance was applied to each animal. The control animals were not treated. The duration of exposure was 6 hours; the material was applied to the anterior left flank. Reading of the skin was performed at 24 h after the beginning of application.
A challenge was performed 13 days after the ninth induction. A volume of 0.5 mL of a 25 % test substance preparation in double distilled water was applied to each animal. The test group and control group 1 were treated with the test substance (control group 2 remained untreated). The duration of exposure was 6 hours; the test substance was applied on the posterior right flank. Readings were performed at 24 and 48 h after the removal of the patch.
A positive control (reliability check) with a known sensitiser is performed twice a year in the laboratory. The positive control with Alpha-Hexylcinnamaldehyde techn. 85 % showed that the chosen guinea pig strain was able to detect sensitising compounds under the laboratory conditions chosen.

Findings:
The stability of the test substance was guaranteed over the study period and it was homogeneous.
The stability of the test substance in double distilled water was confirmed by analysis. The homogeneity of the test substance preparation was provided by stirring with a pestle and mortar (inductions), resp. with an ultra turrax and a magnetic stirrer (challenge).

The concentrations of the test substance suitable for use in the main experiment were determined in pretests. Four 6-hour epicutaneous occlusive applications were performed (three resp. one application per week). After a single application the minimum irritant concentration was found to be a 70 % test substance preparation in doubly distilled water. The maximum non-irritant concentration was found to be a 25 % test substance preparation in doubly distilled water. (Findings 24 hours after beginning of application).
After the third and seventh induction no signs of skin irritation could be observed, while after all other inductions 1 to 4 animals (total 11 animals) reacted with discrete or patchy erythema. The application areas were yellow-brown discoloured, however, this did not impair evaluation of erythema formation. Additionally, partially pulled out hair, due to adhesive properties of the test substance were observed.
The challenge with a 25 % test substance preparation in double distilled water did not cause any skin reactions, neither in control group 1 nor in the test group 24 and 48 hours after removal of the patches. The application areas were yellow-brown discoloured, however, this did not impair evaluation of erythema formation. Since no borderline results were observed, a 2nd challenge was not performed. Control group 2 that had been intended for a potential 2nd challenge was not treated and therefore not reported.
The number of animals with skin findings after the challenge is summarised in Table B.6.11-11:

Table B.6.11-11: Skin findings after challenge

	Challenge (number of animals with skin finding / number of animals tested)
	Test substance 25 % in double distilled water
Control group 1	0 / 10
Test group	0 / 20

Under the test conditions chosen BAS 119 33 H does not have a sensitising effect on the skin of the guinea pig.

Conclusion:
BAS 119 33 H has no sensitising effect to the skin of the guinea pig in the modified Buehler Test (9 inductions). A classification/labelling is not needed.

Report: Kieczka H., Kirsch P., 1987(c)
Report on the open epicutaneous test (OET) for the sensitising potential of BAS 119 33 H in the guinea pig
[redacted]
unpublished
BASF RegDoc# 1987/008

GLP: Yes (laboratory certified by Ministerium fuer Umwelt und Gesundheit, Postfach 31 60, 6500 Mainz)

Guideline: OECD 406

Deviations: None

Acceptability: The study is considered to be supplementary.

Material and Methods:
Test material: BAS 119 33 H; Batch/purity: 85-1; chloridazon: 68 %.
Test animals: SPF-Guinea pigs

Pirbright White, Dunkin; Hartley HOE DHP K [SFP-LAC] BÖ
BAS 119 33 H was examined in the Open Epicutaneous Test according to the method of Kleczak [G. Kleczak: Identification of Contact Allergens (Predictive Tests in Animals) in: Advances in Modern Toxicology Vol. 4 – Dermatotoxicology and Pharmacology – ed. F.N. Marzuli, H.I. Maibach – p 321 - 324 (1971)].
The aim of this test is to identify the threshold level of skin sensitisation in guinea pigs by using a series of induction and challenge concentrations. The doses were selected by a pretest in which the test substance preparations were applied to the shaven flank of the guinea pigs. The test side was not covered with any material throughout the study (open application). In the main study the minimum irritant concentration (in the case of this study the maximum technically applicable dose was 60 % w/w) and diluted concentrations (20 %, 7 % and 2 % w/w) were applied open on 8 guinea pigs per test group for 4 weeks (5 applications per week in total 20 applications) during the induction phase. Each animal was treated with 0.1 mL test compound of one appropriate concentration that was applied to 8 cm^2 of its' right flank. Readings were done 24 hours after application (no readings were carried out on Saturday and Sunday). Challenge was performed using four different concentrations per animal applying 0.025 mL test compound to 2 cm^2 of the animals' left flank each at day 3 and 17 after the last induction. Reading of skin findings was done 24, 48 and 72 hours after the test substance application. If one out of 8 guinea pigs of a particular concentration group shows a positive skin reaction 48 h after application this will be interpreted as a positive result in this test system provided that appropriate control animals will show no skin reactions.

Findings:
The stability of the test substance was confirmed by reanalysis. The stability of the test substance formulation in water was confirmed by analysis and the homogeneity was guaranteed by shaking.
The results of the pretest indicated that a 60 % aqueous preparation of BAS 119 33 H was the minimum irritant dose level but this was also the maximum concentration which could be applied technically. This dose produced skin staining and residues of the test substance remained on the skin of the guinea pigs. This was true in case of the pretest as well as in the main study (induction application and challenge, too). The 40 % (w/w) preparation was found to be the maximum non-irritant concentration.
The results of the challenge applications of the main study are compiled in Table B.6.11-12. The only skin reactions seen during induction applications were slight erythema in animals of the test group 4 (60 % induction concentration).
After the first challenge 1 animal of test group 7 (2 % induction concentration) exhibited a moderate erythema (24 and 48 hours after application) and a slight oedema (24 hours after application) at the area applied with the 60 % test substance concentration.
After the second challenge 2 animals of control group 1 showed skin findings: one had a moderate erythema (48 and 72 hours reading) and a slight oedema (48 hours after application) at the area treated with the 60 % concentration, the other showed a slight oedema at the area treated with the 60 % concentration (48 and 72 hours after application). One animal of test group 4 (60 % induction concentration) showed a slight to moderate erythema (48 and 24 hours reading, respectively) and a slight oedema (24 hours reading), one other animal exhibited a slight erythema at the area treated with the 60 % concentration respectively (72 hours

reading only). In one animal of test group 6 (7 % induction concentration) a slight erythema was seen at the area applied with the 60 % concentration (48 hours reading). In summary all skin effects seen in control and test group animals after the challenge applications were attributed to the area applied with the minimal irritant test substance concentration of 60 %.

Table B.6.11-12: Open Epicutaneous Test with BAS 119 33 H in Guinea pigs (48 hours readings)

Induction		1st challenge				2nd challenge			
% in Vehicle*		60	20	7	2	60	20	7	2
Control group 1	No treatment	0/8**	0/8	0/8	0/8	2/8	0/8	0/8	0/8
Control group 2	No treatment	No treatment	No treatment	No treatment	No treatment	0/8	0/8	0/8	0/8
Test group 4	60 % in vehicle	0/8	0/8	0/8	0/8	1/8	0/8	0/8	0/8
Test group 5	20 % in vehicle	0/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8
Test Group 6	7 % in vehicle	0/8	0/8	0/8	0/8	1/8	0/8	0/8	0/8
Test group 7	2 % in vehicle	1/8	0/8	0/8	0/8	0/8	0/8	0/8	0/8

* Vehicle = distilled water
** Number of animals with positive findings/number of animals in the test group

Discussion:
Based on the evaluation criteria of the Open Epicutaneous Test and the results obtained in this study BAS 119 33 H was not a skin sensitiser under the test conditions chosen. This supplementary study supports the result of the modified Buehler Test.

Conclusion:
BAS 119 33 H showed no skin sensitising effect in the Open Epicutaneous Test.

B.6.11.7 Supplementary studies for combinations of plant protection products

No supplementary studies are necessary and available.

B.6.12 Dermal absorption (Annex IIIA 7.3)

Report: Leibold E., Ravenzwaay B., 2002
^{14}C-BAS 119 H - Study of the dermal absorption in rats
[redacted].
unpublished
BASF RegDoc# 2002/1008654

GLP: Yes (laboratory certified by Landesanstalt fuer Pflanzenbau und Pflanzenschutz Rheinland-Pfalz, Mainz)

Guideline: OECD 427, EPA 870.7600

Deviations: None.

Acceptability: The study is considered to be acceptable.

Material and Methods:
Test material: radiolabelled material:
^{14}C-Chloridazon, Reg. No. 13 033, BAS 119 H, Batch/purity: 43-72, > 95 %;
unlabelled material:
BAS 119 50 H, Batch/purity: 98-1, 435.7 g/L (Reg. No. 13 033).
Test animals: Wistar rats

The absorption, distribution and excretion of radioactivity was studied in male Wistar rats following a single dermal administration of ^{14}C-chloridazon in the formulation (BAS 119 50 H) and 1/6 and 1/33 aqueous dilutions thereof. The low concentration was representative of the spray dilution to be used for field application. These preparations resulted in nominal dose levels of 4.3, 0.7 and 0.1 mg/cm² (corresponding nominally to about 43, 7 and 1.3 mg/animal and about 159, 26 and 4.5 mg/kg body weight). Groups of four animals were exposed according to the following regimen:

Table B.6.12-1: Experimental design

Duration of exposure [h]	**1**	**4**	**10**	**24**	**10***	**10**
Sacrifice after [h]	1	4	10	24	24*	72

* only at low-dose level

Twenty-four hours prior to dosing the back shoulders of the rats were clipped free of hair and the area (about 10 cm^2) was washed with acetone. A silicone ring was glued to the skin; the test substance preparation (about 10 µL/cm^2) was administered with a syringe, which was weighed before and after application. A nylon mesh was then glued to the surface of the silicone ring and a porous bandage used to encircle the trunk of the animal.
The animals were dosed and then placed in metabolism cages in order to collect excreta up to 72 hours. After the respective exposure period, the protective cover was removed and the exposed skin was washed with a mild soap solution. For animals with a post-observation period, new gauze and a new bandage were applied and an additional skin wash was performed before sacrifice. At the end of the various collection periods animals were killed and the following specimens/tissues were checked for remaining radioactivity: excreta, blood cells, plasma, liver, kidneys, carcass, treated skin (application site) and non-treated skin areas (surrounding skin).
For balance estimates the cage wash and skin wash(es) as well as the protective cover (including the silicone ring) were also checked for radioactivity.

Findings:
The stability of the test item in the vehicle, the homogeneity and the correctness of the test substance preparations were analytically verified.
Mean recoveries of radioactivity from all dose groups were in the range of 93.23 - 112.86 % of the total radioactivity administered. The largest proportion of radioactivity was recovered from skin wash. The relative amount of radioactivity absorbed (including excreta, cage wash, tissues/organs and carcass) generally increased with increasing exposure and sacrifice time and was in the same range for all dose levels. For the formulation concentrate (4.3 mg/cm^2), maximum relative absorption was about 0.42 %. For the aqueous dilutions, maximum relative

absorption were 0.41 % and 0.67 % for the intermediate and low dose respectively. These results are summarised in the table below.

Table B.6.12-2: Mean percentage of radioactivity absorbed and in skin (application side)

Exposure time (h)	Sacrifice time (h)	4.3 mg/cm²	0.7 mg/cm²	0.1 mg/cm²
		absorbed / skin	absorbed / skin	absorbed / skin
1	1	0.10 / 1.40	0.02 / 2.77	0.14 / 2.78
4	4	0.15 / 5.16	0.27 / 8.90	0.36 / 7.04
10	10	0.21 / 3.30	0.09 / 8.43	0.58 / 7.27
24	24	0.22 / 4.84	0.08 / 7.78	0.58 / 9.57
10	24	---	---	0.67 / 3.71
10	72	**0.41 / 3.54**	**0.41 / 4.03**	**0.42 / 3.05**

The radioactivity absorbed was excreted mainly via the urine. Highest tissue and organ concentrations of radioactivity were found in the remaining carcass and particularly in the skin (at the application side).

Conclusion:
The in vivo dermal absorption of chloridazon in rats was found to be low under the study conditions chosen. The absorption after 10 hours of exposure and sacrifice after 72 hours was approximately 0.4 % for the undiluted formulation and for the dilutions when the radioactivity detected at the application side after washing was not included, and about 4 % when the radioactivity in the skin was included.

For the estimation of operator, worker and bystander exposure a dermal absorption of 4 % for both the diluted and the undiluted product is proposed.

B.6.13 Toxicological data on non active substances (Annex IIIA 7.4 and point 4 of the introduction)

BAS 119 33 H (trade names: Pyramin WG; Pyramin DF) is formulated as water-dispersible granules containing nominal 650 g/kg of the active ingredient chloridazon.
Besides its active ingredient chloridazon, BAS 119 33 H contains different co-formulants. The respective data are given in Safety Data Sheets. The possibly acute toxic and irritating properties of all co-formulants are covered by the studies with the preparation.

B.6.14 Exposure data (Annex IIIA 7.2)

BAS 119 33 H is formulated as a wettable granulate (WG) containing nominal 650 g/kg of the active substance (as) chloridazon. The intended use is as pre- or post-emergence herbicide for the control of annual weeds in sugar beet, fodder beet, beetroot and onions. The maximum application rate is 4 kg product/ha corresponding to 2.6 kg as/ha in 200 - 400 L water.
Besides this standard application BAS 119 33 H is intended to be used for band spraying application in combination with sowing. As only a limited area is treated with this application technique, e.g. only the band where the crop is sown will be treated, the maximum application rate of 4 kg product/ha is reduced to 2.1 kg product/ha (i. e. 1.365 kg as/ha; band width 22 cm, row distance 42 cm; applied in 100 - 200 L water/ha). A maximum work rate of approximately 15 ha/day by means of band spraying equipment is expected. Furthermore, band

spraying application results in a lower spray drift than tractor-mounted application to field crops as the spraying nozzles during band spraying are closer to the soil when compared to application to field crops (15 cm vs. 40 - 60 cm, respectively).
Thus the standard spraying application of chloridazon as pre- or post-emergence herbicide represents worst case when compared to band spraying application due to reduced application rates, lower daily work rate and spray drift. Therefore, the following, operator, bystander and worker exposure calculations were prepared on the basis of the maximum application rate of 4 kg product/ha in 200 - 400 L water as intended with normal spraying equipment.

B.6.14.1 Operator exposure

The operator exposure estimates are calculated using both the German model and the UK-POEM:

Uniform Principles for Safeguarding the Health of Applicators of Plant Protection Products (Uniform Principles for Operator Protections); Mitteilungen aus der Biologischen Bundesanstalt für Land- und Forstwirschaft, Berlin-Dahlem, H° 277, 1992;

Scientific Subcommittee on Pesticides and British Agrochemicals Joint Medical Panel. Estimation of Exposure and Absorption of Pesticides by Spray Operators (UK MAFF) 1986 and the Predictive Operator Exposure Model (POEM) (UK MAFF) 1992.

The assessed scenarios are summarised in Table B.6.14-1.

Table B.6.14-1: Scenarios/use conditions for the exposure calculation

Technique	Treated surface per working day	Max. use rate		max. in-use concentration (mg as/mL)	Models used
		kg as/ha	product: kg/ha		
Vehicle-mounted or drawn boom sprayer	20 ha	2.6	(4)	–	German model
	50 ha	(2.6)	4	13	UK-POEM

B.6.14.1.1 Estimation of operator exposure; risk assessment

The calculations were carried out for three different conditions, as recommended by the notifier:

Scenario 1: No PPE, disregarding the recommendations on the label, no protective equipment used when handling the undiluted product and during application

Scenario 2: PPE: gloves only during mixing/loading

Scenario 3: PPE: gloves during mixing/loading and during spray application

B.6.14.1.1.1 Operator exposure (German model)

The following assumptions are made for estimation of operator exposure with the German model:

Formulation type:	WG
Application technique:	tractor-mounted equipment
Application rate:	2.6 kg as/ha
Area treated per day:	20 ha
Dermal absorption rate:	4 %
Body weight of an operator:	70 kg
Penetration rate of gloves	1 %

Using the input parameters and the scheme of the calculation model (Appendix 1), the estimated operator exposure can be calculated for mixing/loading (m/L) and application (appl.). The results for the estimated dermal and inhalation exposures are given in Table B.6.14-2.

Table B.6.14-2: Estimated operator exposure using the German model

Exposure route and type of work	Estimated operator exposures (mg/person/day)		
	Scenario 1 **(no PPE)**	Scenario 2 **(gloves: m/L)**	Scenario 3 **(gloves: m/L and appl.)**
Dermal exposure			
– Mixing/loading	104.00	1.04	1.04
– Application	106.08	106.08	86.52
– Total, dermal	210.08	107.12	87.56
Inhalation exposure			
– Mixing/loading	0.416	0.416	0.416
– Application	0.052	0.052	0.052
– Total, inhalation	0.468	0.468	0.468
Total exposure: (dermal + inhalation)	**210.548**	**107.588**	**88.028**
Systemic exposure (absorbed dose)*	8.871	4.753	3.970

* dermal absorption rate: 4 %; inhalation absorption rate: 100 %

Using the German model without PPE, the estimated exposure is calculated to be 210.55 mg/person/day. Taking into account 4 % dermal absorption, the calculated systemic exposure/absorbed dose amounts to 8.87 mg/person/day. Wearing of gloves reduces this value to 4.75 and 3.97 mg/person/day, respectively.

B.6.14.1.1.2 Operator exposure (UK-POEM)

In view of the intended uses operator exposure was estimated for tractor-mounted equipment. The product will be packed in 1 or 5 kg containers. It is anticipated that if 50 ha are treated per day the container size used will be 5 kg, which would result in less hand contamination. The 1 kg container might be considered if a considerable smaller area is treated per day. Therefore, for estimations using the UK POEM model the 5 kg container size is taken into account.

The following assumptions are made for the estimation of operator exposure:

Formulation type:	WG
Application technique:	Vehicle-mounted; hydraulic boom and nozzles
Application rate:	4 L product/ha (2.6 kg as/ha); application volume: 200 L/ha
Area treated per day:	50 ha
Packaging:	5 kg container
Dermal absorption rate:	4 %
Body weight of an operator:	60 kg
Penetration rate of gloves	During mixing/loading: 1 % (solid formulation); during application: 5 % (aqueous solution)

Using the input parameters and the scheme of the calculation model (Appendix 2), the estimated operator exposure can be calculated for mixing/loading (m/L) and application (appl.). The results for the estimated dermal and inhalation exposures are given in Table B.6.14-3.

Table B.6.14-3: Estimated operator exposure using the UK-POEM

Exposure route and type of work	Estimated operator exposure (mg/person/day)		
	Scenario 1 **(no PPE)**	Scenario 2 **(gloves: m/L)**	Scenario 3 **(gloves: m/L and appl.)**
Dermal exposure			
– Mixing/loading	2600.00	26.00	26.00
– Application	540.15	540.15	58.50
– Total, dermal	3140.15	566.15	84.50
Inhalation exposure			
– Mixing/loading	-	-	-
– Application	0.78	0.78	0.78
– Total, inhalation	0.78	0.78	0.78
Total exposure: (dermal + inhalation)	**3140.93**	**566.93**	**85.28**
Total systemic exposure (absorbed dose)*	126.386	23.426	4.160

* dermal absorption rate: 4 %; inhalation absorption rate: 100 %

Using the UK-POEM without PPE, the estimated exposure is calculated to be 3140.93 mg/person/day. Taking into account 4 % dermal absorption, the systemic exposure/absorbed dose amounts to 126.386 mg/person/day. PPE reduces this value to 23.426 and 4.16 mg/person/day, respectively.

Determination of tolerable exposure

To assess the estimated exposure, a comparison with tolerable exposure values has to be performed. In the German model, the different parts of the estimated exposure should be compared with the route-specific AOELs (dermal or inhalation) to see whether the estimated exposure exceeds the tolerable and, if so, to take into consideration specific PPEs in order to reduce the critical part of exposure. In the UK-POEM, the total estimated systemic exposures are to be compared with the systemic AOEL. In cases where no route-specific AOELs can be derived, the estimated exposures of both models have to be assessed via the absorption rates on the basis of the systemic AOEL that was derived for the active substance. To derive the oral AOEL, the NOAEL from the 90-d study in rats (21 mg/kg bw/d) should be used (see B.6.10).
The systemic AOEL can be calculated by using an assessment factor of 100, which takes into account differences attributable to inter- and intraspecies variability. Due to the high level of gastro-intestinal absorption, the application of an additional correction factor is not required.

The systemic AOEL results in 0.2 mg/kg bw/d (rounded).

For direct extrapolation of the inhalation or dermal exposure, there are no appropriate toxicological studies available investigating the critical endpoints via specific routes. In a subacute dermal study on rabbits, no systemic effects were seen even in the highest dose of 1000 mg/kg bw/d. Therefore, the NOAEL of the oral toxicity study should be used to derive both the tolerable dermal and inhalation exposure. The "degree of exposure" in the German model is then comparable to the calculation of the total absorbed dose as percentage of the AOEL, oral/systemic, if the same value for body weight is used.
Assuming 4 % for dermal absorption (see B.6.12) and 100 % for inhalation absorption, a body weight of 70 kg, and an assessment factor of 100, the tolerable dermal (D_{tol} = AOEL, dermal) and inhalation (I_{tol} = AOEL, inhalation) exposures are calculated to be:

$$D^{tol} = \frac{21\,\text{mg/kg bw} \times 70\,\text{kg bw/person}}{100 \times 0.04}$$

D^{tol} = 350 mg/person/d (equiv. to a dermal AOEL of 5 mg/kg bw/d).

$$I^{tol} = \frac{21\,\text{mg/kg bw} \times 70\,\text{kg bw/person}}{100 \times 1}$$

I^{tol} = 14 mg/person/d (equiv. to an inhal. AOEL of 0.2 mg/kg bw/d).

Comparison of estimated and tolerable exposures

The calculated systemic exposures are compared with the proposed systemic AOEL of 0.2 mg/kg bw/d. The values are given in Table B.6.14-4.

Table B.6.14-4: Results of the model calculations and a comparison with the proposed oral/systemic AOEL

Model used	Treated area	Protective clothing (relevant for calculation)	Systemic exposure* (mg/person/d)	(mg/kg bw/d)	Amount of the syst. AOEL (0.2 mg/kg bw/d)
German-model	20 ha/d	none	8.87	0.127	63
		m/L: gloves	4.75	0.068	34
		m/L: gloves; appl.: gloves	3.97	0.057	28
UK-POEM	50 ha/d	none	126.386	2.106	1053
		m/L: gloves	23.426	0.390	195
		m/L: gloves; appl.: gloves	4.160	0.069	35

* See table

see B.6.14-2 and B.6.14-3; in the calculations a body weight of 70 kg (German model) or 60 kg (UK-POEM) and a dermal absorption rate of 4 % is used.

On the basis of the German model without PPE, the estimated systemic exposure to chloridazon accounts for up to 63 % of the proposed systemic AOEL (0.2 mg/kg bw/d). By using gloves during mixing/loading and application, the exposure can be reduced to a value which would result in 28 % of the proposed systemic AOEL. On the basis of UK-POEM calculations without PPE, the exposure estimate exceeds the systemic AOEL (1053 %). However, if gloves are worn during mixing/loading and application, the estimated exposure can be reduced to 35 % of the systemic AOEL.

Conclusion:
In conclusion it can be demonstrated that an operator applying the product BAS 119 33 H containing the active ingredient chloridazon to field crops (sugar beet, fodder beet, beetroot and onions) is safe under the recommended conditions of use.

B.6.14.1.2 Measurement of operator exposure

Since the risk assessment carried out indicates that the health-based limited value (systemic AOEL) will not be exceeded under practical conditions of application, a study to provide a measurement of operator exposure is not submitted and not required.

B.6.14.2 Bystander exposure

BAS 119 33 H with its active substance chloridazon is used as a selective systemic herbicide (max. application rate 4 kg/ha; i. e. 2.6 kg as/ha; application vulume 200 L, i. e. 13 mg as/mL spray solution). It will be used outdoors to control annual broad-leaved weeds in sugar beet, fodder beet, beetroot and onions by application pre-plant incorporated, pre-emergence or post-emergence and will be applied by means of tractor-mounted boom sprayer with hydraulic nozzles. Due to the application technique used the spraying nozzles are directed downward and are positioned not far above the soil surface. Therefore, drift of the spray is limited. In view of the recommended application technique in combination with Good Agricultural Prac-

tice (GAP) bystanders may be exposed briefly and to relatively low quantities of spray compared to an operator. Therefore, the bystander exposure should not be subject of special concern.

B.6.14.2.1 Estimation of bystander exposure

For bystander exposure no formally approved models exist. As an estimate, assumptions from EU Technical Guidance Documents for chemicals (TGD) and draft values proposed for the EUROPOEM II model will be used. These values represent the 90th percentile exposure values for bystanders.
For dermal exposure a maximum of 0.41 % (arable spraying; 7 m distance) of the application rate (kg as/ha) on a body surface of 2 m^2 is assumed. For inhalation exposure the estimation is done on the basis of a ventilation rate of 20 m^3/d (0.83 m^3/h) and a concentration of 0.03 mL spray per m^3 of breathed air. The duration of the possible inhalation exposure is calculated to be 1 minute:

Dermal exp.	= appl.-rate (mg/m^2)	x % (drift value)	x body surface (m^2)
	= 260 mg/m^2(2.6 kg/ha)	x 0.41 %	x 2 m^2
	= 2.132 mg/person/d		
	= 0.0355 mg/kg bw/d		
	i. e. 0.00142 mg/kg bw/d dermal absorbed (derm. abs. rate: 4 %)		
Inhalation exp.	= resp.-rate (m^3/min)	x inhal. spray (mL/m^3)	x spray conc.(mg/mL)
	= 0,01389	x 0.03 mL/m^3	x 13
	= 0.0054 mg/person/d (1 min)		
	= 0.00009 mg/kg bw/d (1 min)		
	i. e. 0.00009 mg/kg bw/d inhal. absorbed (inhal. abs. rate: 100 %)		

Thus the estimated bystander exposure would be 0.03559 mg/kg bw/d. Using the proposed absorption rates of 4 % for dermal exposure and 100 % for inhalation exposure, it results in a possible systemic exposure of 0.0015 mg/kg bw/d, which is 0.76 % of the proposed systemic AOEL of 0.2 mg/kg bw/d.
In conclusion, bystanders are not considered to be at risk if exposed to spray drift of chloridazon under the conditions of use for which BAS 119 33 H will be authorised.

B.6.14.2.2 Measurement of bystander exposure

Estimations of bystander exposure taking into account worst-case scenarios showed that bystander exposure should be without risk. Therefore, no study to measure bystander exposure was conducted.

B.6.14.3 Worker exposure

The application of BAS 119 33 H is recommended once a year in field crops (sugar beet, fodder beet beetroot and onions). Hand operations in these crops do not belong to standard growing procedures and thus contact of relevant duration with treated plants is not the rule. However, worker exposure was estimated for a worst-case scenario, where a worker is walking into the field to elucidate plant growth or health status after the spray solution has dried.

B.6.14.3.1 Estimation of worker exposure

The recommended applications of BAS 119 33 H are as a pre- and post emergence herbicide. Crop height at these stages is low and no hand labor tasks are performed. At the time of application it is not necessary to enter the treated crops shortly after spraying. A relevant re-entry scenario actually does not exist. However, for a restricted period of time scouting may be practiced to control the herbicidal effect or to check the need for additional applications (e.g. with other plant protection products). In order to consider such a situation an estimation will be based on the model as developed by the German BBA (Biologische Bundesanstalt) [Hoernicke E. et al.; 1998; Hinweise in der Gebrauchsanleitung zum Schutz von Personen bei Nachfolgearbeiten in mit Pflanzenschutzmitteln behandelten Kulturen (worker re-entry); Nachrichtenbl. Deut. Pflanzenschutzd. 50, Berlin] and the US EPA [EPA, Science Advisory Council for Exposure; 1998; Agricultural Default Transfer Coefficients, Policy #1998/11675]. The following estimations on potential exposure are based on a maximum application rate of 2.6 kg as/ha in field crops, and a re-entry after the spray solution has dried up was taken into consideration.

The re-entry/dermal exposure (D) is calculated by the formula:

D (dermal exposure) = FDR x TF x A x (P) x R

Assumptions of the re-entry model / by the notifier		
FDR:	Foliar dislodgeable residues	1 µg/cm^2/kg as
TF:	Transfer factor	1000 cm^2/person x h*
A:	Work rate/d	8 h/d
P:	Penetration through clothing (PPE)	5 %
R:	Application rate	2.6 kg as/ha

* The worst-case figure in the model is 30000 cm^2/person x h. This value has been reduced, taking into account the recommended uses and the comparably low or limited leaf surface.

Resulting dermal exposure = 1 µg/cm^2/kg as x 1000 cm^2/pers. x 8 h x (5 %) x 2.6 kg as/ha

= 20800 µg/person/d (without PPE)

= 1040 µg/person/d (wearing PPE)

The systemic burden resulting from dermal exposure is calculated using the following formula:

Systemic exposure = D (µg/person/d) x AF / bw (kg)

Assumptions / derived values		
AF:	Dermal absorption rate / absorption factor	4 %
bw:	Worker body weight	70 kg

Resulting systemic exposure

=	20800	µg/person/d	x	4 %	/ 70 kg bw
=	**0.0119**	**mg/kg bw/d**	**(without PPE)**		
=	1040	µg/person/d	x	4 %	/ 70 kg bw
=	**0.0006**	**mg/kg bw/d**	**(wearing PPE)**		

Based on the assumption that the value for the Transfer Factor in the re-entry model can be reduced from 30000 to 1000 cm^2/person x h, the systemic worker exposure would be 0.0119 mg/kg bw/d for a person not wearing PPE and 0.0006 mg/kg bw/d for a person wearing PPE. This corresponds to 5.9 % and 0.3 % of the proposed systemic AOEL (0.2 mg/kg bw/d), respectively.
Therefore, assuming dried spray deposit, the estimated exposure to chloridazon during re-entry operations does not present an undue risk to workers, even if no PPE is worn.

B.6.14.3.2 Measurement of worker exposure

Estimations of worker exposure taking into account worst case scenarios showed that re-entry of workers and other persons is possible without risk after spray deposits has dried up. Therefore, no study to measure worker exposure was conducted.

Appendix 1: German model: Operator exposure for BAS 119 33 H in field crops, tractor-mounted

Assumptions and input parameters considered for the estimation during operator exposure:

Formulation type:	WG	$D_{M(H)}$	=	2 mg/person x kg as
Application technique:	field: tractor-mounted	$D_{A(H)}$	=	0.38 mg/person x kg as
Application rate:	2.6 kg chloridazon/ha	$D_{A(B)}$	=	1.6 mg/person x kg as
Area treated per day:	20 ha	$D_{A(C)}$	=	0.06 mg/person x kg as
		I_M	=	0.008 mg/person x kg as
		I_A	=	0.001 mg/person x kg as

Route of exposure			Scenario 1 (no PPE)	Scenario 2 (gloves, mix./load)	Scenario 3 (gloves, all operations)
Dermal/mixing					
exposure (hands):	$D_{M(H)}$	=	2 x 2.6 x 20		
		=	104 mg/person/d	1.04 mg/person/d*	1.04 mg/person/d*
Dermal/application					
exposure	$D_{A(H)}$	=	0.38 x 2.6 x 20		
(hands, body, head)		=	19.76 mg/person/d	19.76 mg/person/d	0.1976 mg/person/d*
	$D_{A(B)}$	=	1.6 x 2.6 x 20		
		=	83.2 mg/person/d	83.2 mg/person/d	83.2 mg/person/d
	$D_{A(C)}$	=	0.06 x 2.6 x 20		
		=	3.12 mg/person/d	3.12 mg/person/d	3.12 mg/person/d
Total dermal exposure		**=**	**210.08 mg/person/d**	**107.12 mg/person/d**	**87.56 mg/person/d**
Inhalation/mixing					
	I_M	=	0.008 x 2.6 x 20		
		=	0.416 mg/person/d	0.416 mg/person/d	0.416 mg/person/d
Inhalation/application					
	I_A	=	0.001 x 2.6 x 20		
		=	0.052 mg/person/d	0.052 mg/person/d	0.052 mg/person/d
Total inhalation exposure		**=**	**0.468 mg/person/d**	**0.468 mg/person/d**	**0.468 mg/person/d**

* reduction factor of gloves = 0.01

Appendix 2: Predictive Operator Exposure Model (UK-POEM) - Tractor-mounted boom sprayer with hydraulic nozzles

A. PRODUCT DATA					
1. Product name	BAS 119 33 H				
2a. Active substance	Chloridazon				
2b. Concentration	650	mg/g			
3. Formulation type	WG				
4a. Main solvent					
4b. Concentration of solvent	n.a.				
5. Maximum in-use as concentration	13.000	mg/mL			
B. EXPOSURE DURING MIXING AND LOADING					
1a. Container size	5	kg			
1b. Hand contamination/operation	0.1	g			
2. Application dose	4	kg prod-uct/ha	130	kg as/day	
3. Work rate	50	ha/day			
4. Number of operations	40	/day			
5. Hand contamination	4	g/day			
6. Protective clothing	NONE		GLOVES		
7. Transmission to skin	100		1	%	
8. Dermal exposure to formulation	4		0.04	g/day	
9. Concentration of as	650		650	mg/g	
10. Dermal exposure to as	2600		26	mg/day	
11. Percent absorbed	4		4	%	
12. Absorbed dose	104		1.04	mg/pers./day	
C. EXPOSURE DURING SPRAY APPLICATION					
1. Application technique - Vehicle with cab boom hydraulic nozzles					
2. Application volume	200	spray/ha			
3. Volume of surface contamination	10	mL/h			
4. Distribution	Hands	Hands	Trunk	Legs	
	65	65	10	25	%
5. Clothing	NONE	GLOVES	PERMEABLE	PERMEABLE	
6. Penetration	100	5	5	15	%
7. Dermal exposure	6.5	0.325	0.05	0.375	mL/h
8. Duration of exposure	6	h			
PPE	NONE	GLOVES			
9. Total dermal exposure to spray	41.55	4.5	mL/day		
10. Concentration of as	13.000	13.000	mg/mL		
Dermal exposure to as	540.150	58.5	mg/day		
11. Percent absorbed	4	4	%		
12. Absorbed dose	21.606	2.34	mg/pers./day		
E. INHALED EXPOSURE DURING SPRAY APPLICATION					
1. Inhalation exposure	0.01	mL/h			
2. Duration of exposure	6	h			
3. Concentration of as	13.000	mg/mL			
4. Inhalational exposure to as	0.780	mg/day			
5. Percent absorbed	100	%			
6. Absorbed dose	0.78	mg/pers./day			
F. PREDICTED EXPOSURE					
1. No gloves	126.386 2.106	mg/person/day mg/kg bw/day			
2. Gloves only when mixing/loading	23.426 0.390	mg/person/day mg/kg bw/day			
3. Gloves during mixing/loading and spray application	4.160 0.069	mg/person/day mg/kg bw/day			

B.6.15 References relied on

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner
AIIA-5.1	Bornemann, V.	1991	The metabolism of ^{14}C-chloridazon (BAS 119 H) in the rat - The identification and quantification of metabolites. 1991/10524 GLP, unpublished TOX2003-1476	N	BAS
AIIA-5.1	Hoffmann, H.D. and Hildebrand, B.	1991	Study on the biokinetics of ^{14}C Reg. No. 13 033 in rats. 1991/10585 GLP, unpublished TOX2003-1475	N	BAS
AIIA-5.2.1	Gaines, T.B. and Linder, R.E.	1986	Acute toxicity of pesticides in adult and weanling Rats. Fundamental and Applied Toxicology, 7, 1986, 299-308 86/10369 not GLP, published TOX93-00388	N	-
AIIA-5.2.1	Gamer, A.O. and Kirsch, P.	1988 a	Reg. No. 13 033: Report on the study of the acute oral toxicity on the rat based on OECD and EPA (FIFRA). 1988/0445 GLP, unpublished TOX2003-1527	N	BAS
AIIA-5.2.1	Jaeckh, R. and Gelbke, H.-P.	1981	Report on the study of the acute oral toxicity of chloridazon in the rat. 1985/291 not GLP, unpublished TOX2003-1440	N	BAS
AIIA-5.2.1	Toyoshima, S. et al.	1979	Acute oral, subcutaneous and intraperitoneal toxicity studies of Pyramin in the mouse. 1979/10098 not GLP, unpublished TOX2003-1442	N	BAS
AIIA-5.2.2	Gamer, A.O. and Kirsch, P.	1988	Reg. No. 13 033: Report on the study of acute dermal toxicity on the rat based on OECD and EPA (FIFRA). 1988/0469 GLP, unpublished TOX2003-1426	N	BAS

[1] Only notifier listed

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AIIA-5.2.2	Toyoshima, S. et al.	1979	Acute dermal toxicity studies of Pyramin in the rat. 1979/10099 not GLP, unpublished TOX2003-1439	N	BAS
AIIA-5.2.3	Gamer, A.O.	1989	Study on the acute inhalation toxicity LC_{50} of Reg. No. 13 033; isomer reduced as a dust aerosol in rats - 4-hour exposure. 1989/0405 GLP, unpublished TOX2003-1427	N	BAS
AIIA-5.2.3	Leuschner, F.	1980	The acute toxicity of test compound Reg. No. 13 033 (chloridazon) when administered to rats by inhalation. 1980/042 not GLP, unpublished TOX2003-1443	N	BAS
AIIA-5.2.4	Kirsch, P. and Hildebrand, B.	1989	Reg. No. 13 033: Report on the acute dermal irritation/corrosivity to the intact dorsal skin of the white rabbit based on OECD and EPA (FIFRA). 1989/0101 GLP, unpublished TOX2003-1425	N	BAS
AIIA-5.2.5	Hildebrand, B.	1984	Study of the primary irritation of 'Reg. No. 13 033 (pyrazon)' to the eye of white rabbits. 1984/124 not GLP, unpublished TOX2003-1444	N	BAS
AIIA-5.2.5	Kirsch, P. and Hildebrand, B.	1989	Reg. No. 13 033: Report on the study of the acute irritation to the eye of the white rabbit based on OECD and EPA (FIFRA). 1989/0102 GLP, unpublished TOX2003-1528	N	BAS
AIIA-5.2.6	Gamer, A.O. and Kirsch, P.	1988	Report on the maximisation test for the sensitising potential of Reg. No. 13 033, isomer reduced in guinea pigs. 1988/0464 GLP, unpublished TOX2003-1441	N	BAS

Annex point/ reference number	Author(s)	Year	Title source (where different from company) report no. GLP or GEP status (where relevant), published or not BBA registration number	Data protection claimed Y/N	Owner[1]
AIIA-5.3.1	Hellwig, J. and Hildebrand, B.	1991	Amendment No. 1 to the report of June 5, 1991. Study of the toxicity of Reg. No. 13 033; 95 % in Beagle dogs - Administration via the diet over 4 weeks (range-finding-study). 1991/11248 GLP, unpublished TOX2003-1484	N	BAS
AIIA-5.3.1	Hellwig, J. and Kirsch, P.	1991	Report on the study of the toxicity of Reg. No. 13 033; 95 % in Beagle dogs. Administration via the diet over 4 weeks (range-finding-study). 1991/10437 GLP, unpublished TOX2003-1483	N	BAS
AIIA-5.3.1	Kirsch, P. and Hildebrand, B.	1993	Study of the oral toxicity of Reg. No. 13 033 in Wistar rats. Administration in the diet over 4 weeks (comparative study of test substances Nos. 86/98 and 86/99). 1993/11975 GLP, unpublished TOX2003-1482	Y	BAS
AIIA-5.3.1	Kirsch, P. and Hildebrand, B.	1993	Study of the oral toxicity of Reg. No. 13 033 in Wistar rats. Administration in the diet over 4 weeks (comparative study of test substances Nos. 86/98 and 86/99). 1993/11974 GLP, unpublished TOX2003-1481	Y	BAS
AIIA-5.3.2	Hellwig, J. and Hildebrand, B.	1992	Report on the study of the toxicity of Reg. No. 13 033; 95 % in Beagle dogs - Administration via the diet over 3 months. 1992/11648 GLP, unpublished TOX2003-1487	N	BAS
AIIA-5.3.2	Hunter, B. et al.	1975	Toxicity of pyrazon to rats. Dietary administration for 13 weeks (final report 0 - 19 weeks). 1975/028 not GLP, unpublished ANA2003-301	N	BAS
AIIA-5.3.2	Leuschner, F. et al.	1975	Oral toxicity of pyrazon, Reg.Nr. 13033, techn. (88.7 %) - called for short 'pyrazon' - in Beagle dogs (repeated dosage for 3 months). 1975/029 not GLP, unpublished TOX2003-1486	N	BAS

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AIIA-5.3.2	Mellert, W.	1993	Supplementary study of the toxicity with Reg. No. 13 033; 95 % in Beagle dogs - Administration in the diet for 3 months. 1993/10823 GLP, unpublished TOX2003-1488	Y	BAS
AIIA-5.3.2; AIIA-5.5	Mellert, W. et al.	1993	Chronic toxicity study with Reg. No. 13 033; 95 % in Beagle dogs. Administration in the diet for 12 months. 1993/10815 GLP, unpublished TOX2003-1499	Y	BAS BAS
AIIA-5.3.2	Schilling, K. and Hildebrand, B.	1990	Study on the oral toxicity of Reg. No. 13 033 in B6C3F1 mice. Administration via the diet over 3 months. 1990/0568 GLP, unpublished TOX2003-1485	N	BAS
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AIIA-5.4.1	Cifone, M.A. and Myhr, B.C.	1986	Evaluation of chloridazon technical (ZNT No. 86/99) in the rat primary hepatocyte unscheduled DNA synthesis assay. 1986/257 not GLP, unpublished TOX2003-1497	N	BAS
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AIIA-5.4.1	Engelhardt, G. and Hoffmann, H.D.	1989	Report on the study of Reg. No. 13 033; isomer reduced (ZST test substance No.: 88/174) in the AMES Salmonella/mammalian microsome mutagenicity test and reverse mutation assay - *E. coli* WP2 uvrA (standard plate test and preincubation test). 1989/0173 GLP, unpublished TOX2003-1489	N	BAS
AIIA-5.4.1	Engelhardt, G. and Hoffmann, H.D.	1988	Report on the study of reg. no. 13 033/chloridazon; isomer reduced in the Ames Test. 88/0208 GLP, unpublished TOX2001-1285	N	BAS
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AIIA-5.4.1	Jagannath, D.R.	1989	Mutagenicity test on 88/174, 'Reg. No. 13 033 isomer reduced' in the recombination assays with *Bacillus subtilis* strains H17 (rec+) and M45 (rec-). 1989/0192 GLP, unpublished TOX2003-1495	N	BAS
AIIA-5.4.1	Oesch, F.	1977	AMES test for chloridazon. 1977/037 not GLP, unpublished TOX2003-1492	N	BAS
AIIA-5.4.1	Shirasu, Y. et al.	1976	Mutagenicity testing on Pyramin in microbial systems. 1976/012 not GLP, unpublished TOX2003-1496 TOX2003-1491	N	BAS

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AIIA-5.4.3	Anonymous	1975	Study on the mutagenic effect of 5-amino-4-chloro-2-phenyl-3(2H)-pyridazinone on the male mouse following repeated oral administration. 1975/008 not GLP, unpublished TOX2001-1286	N	BAS
AIIA-5.4.3	Merkle, J.	1981	Statement: Pyramin dominant lethal assay of Feb. 13, 1975. 1981/10088 not GLP, unpublished TOX2003-1445	N	BAS
AIIA-5.5	Cherry, C.P. and Gopinath, C.	1987	Long term dietary administration of pyrazon to mice. Microscopic pathology. 1987/0243 GLP, unpublished TOX2003-1507	N	BAS
AIIA-5.5	Hunter, B. et al.	1977	Long-term feeding of pyrazon to mice. 1977/075 not GLP, unpublished TOX2003-1506	N	BAS
AIIA-5.5	Hunter, B. et al.	1977	Long-term dietary administration of pyrazon to rats. 1977/038 not GLP, unpublished TOX2003-1503	N	BAS
AIIA-5.5	Mellert, W. et al.	1993	Study of the oral toxicity of Reg. No. 13 033; 95 % in Wistar rats. Dietary administration for 25 months. 1993/10819 GLP, unpublished TOX2003-1501	Y	BAS
AIIA-5.5	Mellert, W. et al.	1993	Study of the potential carcinogenicity of Reg. No. 13 033; 95 % in Wistar rats. Dietary administration for 30 months. 1993/10818 GLP, unpublished TOX2003-1502	Y	BAS

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AIIA-5.5	Mellert, W. et al.	1993	Carcinogenicity study with Reg. No. 13 033; 95 % in B6C3F1 mice. Administration in the diet for 24 months. 1993/10820 GLP, unpublished TOX2003-1505	Y	BAS
AIIA-5.5	Mellert, W. et al.	1993	Supplementary chronic toxicity study with Reg. No. 13 033; 95 % in Beagle dogs. Administration in the diet for 12 months. 1993/10824 GLP, unpublished TOX2003-1500	Y	BAS
AIIA-5.5	Offer, M.J. and Gopinath, C.	1987	Addendum: Long-term dietary administration of pyrazon to rats. Microscopic pathology addendum report to HRC report BSF 87/7766. 1987/0241 GLP, unpublished TOX2003-1504	N	BAS
AIIA-5.6.1	Hellwig, J. et al.	1993	Report reproduction toxicity study with Reg. No. 13 033; 95 % in Rats, continuous dietary administration over 2 generations (2 litters in the first and 1 litter in the second generation). 93/10632 /// 71R0174/88032 GLP, unpublished TOX94-01208	Y	BAS
AIIA-5.6.1	Palmer, A.K. and Allen, T.R.	1977	Effect of pyrazon on reproductive function of multiple generations in the rat. 1977/076 not GLP, unpublished TOX2003-1446	N	BAS
AIIA-5.6.1	Peh, J. and Hofmann, H.T.	1975	Trial report on the pre-, peri- and postnatal toxicity of 5-amino-4-chloro-2-phenyl-3(2H)-pyridazinone in the mouse. 1975/009 not GLP, unpublished TOX2003-1447	N	BAS
AIIA-5.6.2	Becker, H.	1987	Embryotoxicity (including teratogenicity) study with chloridazon technical (ZNT-No. 86/99) in the rabbit. 1987/0413 GLP, unpublished TOX2003-1510	N	BAS

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AIIA-5.6.2	Becker, H. et al.	1987	Dose-finding embryotoxicity (including teratogenicity) study with chloridazon technical (ZNT-No. 86/99) in the rabbit. 1987/0412 not GLP, unpublished TOX2003-1509	N	BAS
AIIA-5.6.2	Hellwig, J. and Hildebrand, B.	1990	Report: Study of the prenatal toxicity of Reg No. 13 033 in rats after oral administration (gavage). 1990/0163 GLP, unpublished TOX2003-1508	N	BAS
AIIA-5.6.2	Joosten, H.F.P. and Hoekstra, A. et al.	1981	Cysts in Rabbit foetal brains. Arch. Toxicol. , 47, 1981, 25-37 81/10184 not GLP,published TOX93-00394	N	-
AIIA-5.8.1	Engelhardt, G. and Hoffmann, H.D.	2000	In vitro unscheduled DNA synthesis (UDS) assay with metabolite B-1 in primary rat hepatocytes. 2000/1018814 GLP, unpublished TOX2003-1455	Y	BAS
AIIA-5.8.1	Engelhardt, G. and Hoffmann, H.D.	2000	Bone marrow chromosome analysis in vivo with metabolite B-1 in Wistar rats single oral administration. 2000/1018864 GLP, unpublished TOX2003-1456	Y	BAS
AIIA-5.8.1	Engelhardt, G. and Hoffmann, H.D.	2000	In vitro gene mutation test with metabolite B-1 in CHO cells (HPRT locus assay). 2000/1010207 GLP, unpublished TOX2003-1454	Y	BAS
AIIA-5.8.1	Engelhardt, G. and Hoffmann, H.D.	1999	*Salmonella typhimurium* / *Escherichia coli* reverse mutation assay (Standard plate test and preincubation test) with metabolite B-1. 1999/11415 GLP, unpublished TOX2003-1453	Y	BAS
AIIA-5.8.1	Engelhardt, G. and Hoffmann, H.D.	1993	In vitro cytogenetic investigations of chloridazon-metabolite B; reg. no. 14 456 in human lymphocytes. 30M0435/904407 ! 93/10075 GLP, unpublished TOX2001-1294	Y	BAS

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AIIA-5.8.1	Engelhardt, G. and Hoffmann, H.D.	1992	Report on the study of chloridazon-metabolite B; reg. nr. 14 456 (ZST test substance no.: 90/435) in the Ames Test (standard plate test and preincubation test with *salmonella typhi-murium*). 40M0435/904349 ! 92/10844 GLP, unpublished TOX2001-1293	N	BAS
AIIA-5.8.1	Hellwig, J. and Hildebrand, B.	1997	Reg. No. 14 456 - Prenatal toxicity in rats after oral administration (gavage). 1997/10597 GLP, unpublished TOX2003-1450	Y	BAS
AIIA-5.8.1	Kaspers, U. et al.	2002	Metabolite B-1 - Prenatal developmental toxicity study in Wistar rats, oral administration (gavage). 2002/1000102 GLP, unpublished TOX2003-1457	Y	BAS
AIIA-5.8.1	Kuehlem, C. and Hellwig, J.	1998	Reg. Nr.: 014456 - Acute oral toxicity in rats. 10A0022/981003 ! 98/10413 GLP, unpublished TOX2001-1290	Y	BAS
AIIA-5.8.1	Leuschner, F. et al.	1977	Oral toxicity of metabolite B, assay 98 %, in the Sprague-Dawley rat - repeated dosage over 4 weeks. 1977/0155 not GLP, unpublished TOX2003-1448	N	BAS
AIIA-5.8.1	Manciaux, X.	1999	Metabolite B-1: Acute oral toxicity in rats. 1999/10903 GLP, unpublished TOX2003-1451	Y	BAS
AIIA-5.8.1	Mellert, W. and Hildebrand, B.	1996	Study of the oral toxicity of reg. no. 14 456 (chloridazon-metabolite B) in Wistar rats administration in the diet for 3 months. 31S0435/90081 ! 96/10818 GLP, unpublished TOX2001-1292	Y	BAS
AIIA-5.8.1	Mellert, W. and Hildebrand, B.	1996	Study of the oral toxicity of reg. no. 14 456 (chloridazon-metabolite B) in Wistar rats administration via the diet over 3 months. 31S0435/90031 ! 96/10817 GLP, unpublished TOX2001-1291	Y	BAS

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AIIA-5.8.1	Mellert, W. et al.	2001	Metabolite B-1 - Subchronic oral toxicity study in Wistar rats - Administration in the diet for 3 months. 2001/1014868 GLP, unpublished TOX2003-1452	Y	BAS
AIIA-5.8.1	Wollny, H.E.	1999	First Amendment to report: Gene mutation assay in Chinese hamster V79 cells in vitro (V79/HPRT) with Reg. No. 14 456. 1999/1003077 GLP, unpublished TOX2003-1449	Y	BAS
AIIA-5.8.2	Bloch, I. et al.	1987	Study of effect on vital functions of animals - General pharmacology - of chloridazon. 1987/0431 GLP, unpublished TOX2003-1458	N	BAS
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AIIA-5.8.2	Munro, I.C. et al.	1996	Correlation of structural class with no-observed-effect levels: A proposal for establishing a threshold of concern. Food and chemical toxicology 34 (9), 829-867 1996/1003074 not GLP, published TOX2004-1274	N	-
AIIA-5.8.2	Seiferlein, M.	2004	Deschloro-chloridazon: Information on the toxicological relevance of the metabolite dechlorinated chloridazon. 2004/1016093 not GLP, unpublished TOX2004-1273	Y	BAS
AIIA-5.8.2	Teschendorf, H.J.	1988	Study on the EEG effects in the conscious rat of chloridazon. 1987/0461 GLP, unpublished TOX2003-1459	N	BAS
AIIA-5.10	Anonymous	1992	Summaries of toxicity studies on chloridazon. ADMSCI, 17, 1992, 171-176 1992/11238 not GLP, published TOX2003-1460	N	-

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AIIIA-7.1.1	Kieczka, H.	1987	BAS 119 33 H: Report on the study of acute oral toxicity on the rat based on OECD and EPA (FIFRA). 1987/032 GLP, unpublished TOX2003-1511	N	BAS
AIIIA-7.1.2	Kieczka, H. and Kirsch, P.	1987	BAS 119 33 H: Report on the study of acute dermal toxicity on the rat based on OECD and EPA (FIFRA). 1987/033 GLP, unpublished TOX2003-1512	N	BAS
AIIIA-7.1.3	Klimisch, H.-J. et al.	1987	Test Report: Acute inhalation toxicity LC_{50} 4 hours (rat); liquid aerosol study of BAS 119 33 H (Pyramin DF). 1987/099 GLP, unpublished TOX2003-1516	N	BAS
AIIIA-7.1.4	Kieczka, H. and Kirsch, P.	1987	BAS 119 33 H: Report on the acute dermal irritation/corrosivity to the intact dorsal skin of the white rabbit based on OECD and EPA (FIFRA). 1987/004 GLP, unpublished TOX2003-1513	N	BAS
AIIIA-7.1.5	Kieczka, H. and Kirsch, P.	1987	BAS 119 33 H: Report on the acute irritation to the eye of the white rabbit based on OECD and EPA (FIFRA) of BAS 119 33 H. 1987/005 GLP, unpublished TOX2003-1514	N	BAS
AIIIA-7.1.6	Kieczka, H. and Kirsch, P.	1987	Report on the open epicutaneous test (OET) for the sensitising potential of BAS 119 33 H in the guinea pig. 1987/008 GLP, unpublished TOX2003-1515	N	BAS
AIIIA-7.1.6	Wiemann, C. and Hellwig, J.	2001	BAS 119 33 H - Modified buehler test (9 inductions) in guinea pigs. 2001/1009207! 33H0775/002211 GLP, unpublished TOX2003-1117	Y	BAS
AIIIA-7.3	Leibold, E.	2002	^{14}C-BAS 119 H - Study of the dermal absorption in rats. 2002/1008654! 01B0321/006043 GLP, unpublished TOX2003-1118	Y	BAS

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