UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAR 14 1991

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: ToxChem ID# 497E, Imidacloprid (NTN 33893), Minutes of the 3/12/91 Meeting with Mobay Company

FROM: Myron S. Ottley, Ph.D.
Review Section II
Toxicology Branch I
Health Effects Division (H7509C)

TO: Dennis H. Edwards, PM 12
Insecticide-Rodenticide Branch
Registration Division (H7505C)

THRU: Marion Copley, D.V.M., Section Head
Review Section II
Toxicology Branch I
Health Effects Division (H7509C)

EPA personnel met with representatives of Mobay Company (see attached meeting attendance list) to discuss the registration of Imiacloprid (NTN 33893), a new insecticide. Of particular concern is a nitrosamine by-product called WAK 3839, which is also an expected metabolite of the active ingredient.

Some weeks prior to the meeting, Mobay had submitted summary (abstracted) toxicity data on both the active ingredient and the nitrosoamine contaminant/metabolite. These data were again presented in the meeting.

EPA maintained that while there appeared to be no obvious data gaps in the information presented, EPA would make no evaluatory statements concerning toxicity until it had reviewed in detail the actual data submissions.

EPA further advised Mobay to submit the EUP package without the comprehensive toxicity data package in order to speed up the regulatory process.

Attachment

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Myron Ottley	HED/TBL	557-4383
Ghena Sangha	Mobay	913-897-9243
W. Barnaba	Mobay	913-780-6275
John J. Murphy	Mobay	913-897-9330
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Thomas H. Thyssen	MOBAY	913-897-9272
Dennis Edwards	RD/IRB	

3-14-91

417 E

NTN 33893
INSECTICIDE

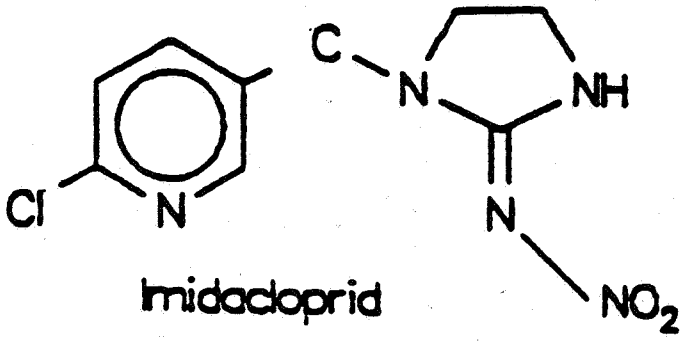
CASWELL FILE

PRODUCT CHEMISTRY:

CHEMICAL NAME	:	1-[6-Chloro-3-pyridinyl)methyl]-4,5-dihydro-N-nitro-1-H-imidazol-2-amine
COMMON NAME	:	imidacloprid (proposed)
STRUCTURAL FORMULA	:	See below
EMPIRICAL FORMULA	:	$C_9H_{10}Cl\ N_5O_2$
MOLECULAR WEIGHT	:	255.66
APPEARANCE	:	light yellow powder
MELTING RANGE	:	120-134°C
VAPOR PRESSURE	:	8.0 X 10^{-9} mbar at 20°C
DENSITY	:	1.542 g/cm³

SOLUBILITY (g/l of solvent at 20°C) :

water	0.58	ppm
acetone	20- 50	ppm
acetonitrile	20- 50	ppm
dichloromethane	50-100	ppm
DMF	>200	ppm
DMSO	>200	ppm
n-hexane	<0.1	ppm
toluene	0.5-1	ppm
2-propanol	1-2	ppm



Imidacloprid

NTN 33893

CONCLUSIONS

1. NTN 33893 USED FOR TOXICITY TESTING CONTAINED TRACE AMOUNTS (30 PPM) OF THE BY-PRODUCT WAK 3839 .
2. THE BY-PRODUCT WAK 3839 ALSO OCCURS AS A BIOTRANSFORMATION PRODUCT (UP TO 7%) IN THE RODENTS.
3. THE TOXICOLOGY STUDIES CONDUCTED WITH NTN 33893 SHOW THE PRODUCT TO BE:
   - MODERATELY ACUTELY TOXIC;
   - NEITHER AN IRRITANT NOR A SENSITIZER;
   - NON-TERATOGENIC
   - A NON-REPRODUCTIVE TOXICANT
   - IN CHRONIC STUDIES, THE LIVER WAS THE MAIN TARGET ORGAN
   - NON-ONCOGENIC AT 900 AND 1000 PPM (RAT AND MICE)
   - NON-GENOTOXIC IN EXTENSIVE MUTAGENICITY DATA BASE
4. ONE OF THE BIOTRANSFORMATION PRODUCTS, WAK 3839 (OF CONCERN) TESTED FOR RELEVANT TOXICOLOGY ENDPOINTS:
   - THE PRODUCT HAS LOW ACUTE TOXICITY
   - SUBCHRONIC STUDY IN RATS (UP TO 1000 PPM) HAD NON SPECIFIC TOXICITY PROFILE.
   - EXTENSIVE MUTAGENICITY DATA BASE SHOWED IT IS NOT GENOTOXIC
   - THE PRODUCT WAS CO-TESTED ALONG WITH THE PARENT COMPOUND IN THE ONCOGENICITY STUDIES AND SHOWED NO ONCOGENIC POTENTIAL.
   - THE CONTRIBUTION OF THE BIOTRANSFORMED PRODUCT IN ONCOGENICITY STUDIES WAS >2000 TIMES THAN AS A BY-PRODUCT.
5. IN VIEW OF THE ABOVE NO FURTHER TESTING IS NECESSARY.
6. BASED ON NOELS IN TOXICOLOGICAL STUDIES, ENOUGH MARGINS OF SAFETY EXIST AND AN ADI OF 0.057 MG/KG/BW/DAY CAN BE SUPPORTED ON THE BASIS OF RAT CHRONIC/ONCO STUDY.

NTN 33893

ACUTE TOXICITY DATA

ACUTE ORAL

Animal	Sex	Formulation Aid	LD50 (mg/kg b.w.)
Rat (Fasted)	M	Cremophor EL/water	424
	F	Cremophor EL/water	450-475
Mouse (Fasted)	M	Cremophor EL/water	131
	F	Cremophor EL/water	168

ACUTE DERMAL

Rat	M & F	Paste with 0.9% NaCl	> 5000

ACUTE INHALATION (LC50)

Rat (1X4H)	M & F	Aerosol (Highest Possible)	> 69 mg/m^3 air
		Dust	> 5323 mg/m^3 air

SKIN IRRITATION

Rabbit	M	Semiocclusive	Not irritant

EYE IRRITATION

Rabbit	M		Not irritant

DERMAL SENSITIZATION (M&K)

Guinea Pigs	M	Freund's adjuvant	Not sensitizer

OH3/91/GKS

SUBACUTE DERMAL STUDY IN RABBITS

(LIMIT-TEST, 15 DAYS ADMINISTRATION)

PARAMETER	DOSE IN MG/KG BW/DAY 1000
SYMPT.:	
MORT.:	
FEED CONS.:	
BW-GAIN:	
HEMATOL.:	
CLIN. CHEM.:	
GROSS PATH.:	
HISTOPATH.:	
NOEL: 1000 MG/KG BW/DAY	

OH3/91/GKS

SUBACUTE INHALATION STUDY WITH NTN 33893 TECHNICAL
REPORT # 100262

EXPOSURE: 4 WEEKS; 6 H/DAY, 5 DAYS/WEEK, DUST

PARAMETER		CONCENTRATION, MG/M³ 5.5	30.5	191.2
DUST	MMAD	2.4	4.8	5.7
	GSD	1.5	2.0	1.9
OBSERVATIONS		-	-	-
BODY WTS		-	-	♂ ↓ WKS 1-4
MORTALITY		-	-	-
OPHTHALMIC		-	-	-
CLIN CHEM				♀ (1)
HEMATOLOGY				♂↓ THROMBOCYTES
URINALYSIS				♀↑ PH
GROSS PATH		-	-	-
HISTOPATH		-	-	-
LIVER P 450		-	-	↑♀♂ ACTIVITY ↑♂ CONTENT
SERUM		-	♀♂↑α1-GLOBIN	♀♂ ↓ 1-GLOBIN
ORGAN WTS:		-	♀↑LI	♀ ↓ THYMUS, HEAR

(1) BILIRUBIN, GLDH, ALAT, APL, CHE, TRIGLYCERIDES
BLOOD COAGULATION

NOEL 5.5 MG/M³ ♀ ♂

OH3/91/GKS

NTN 33893

TERATOLOGY STUDY IN RABBITS

DOSES: 0, 8, 24 AND 72 MG/KG ON POST COITUM DAYS 6-18

	DOSE (MG/KG)			
MATERNAL TOXICITY:	0	8	24	72
CLINICAL SIGNS	-	-	-	-
DEATHS	-	-	-	(2)
FOOD CONSUMPTION	-	-	↓	↓
BODY WEIGHT	-	-	↓	↓
NECROPSY	-	-	-	- (autolysis)
FETAL TOXICITY:				
ABORTIONS	-	-	-	1
POST-IMPLANTATION LOSSES	-	-	-	↑
BODY WEIGHTS	-	-	-	↓
VISCERAL ABNORMALITIES	-	-	-	-
SKELETAL ABNORMALITIES	-	-	-	↑*

NOEL: MATERNAL = 8 MG/KG
FETAL = 24 MG/KG

*SLIGHT INCREASE IN NON-OSSIFIED BONES. CONSIDERED A CONSEQUENCE OF FETAL IMMATURITY, AS INDICATED BY THE REDUCED WEIGHT OF AFFECTED FETUSES.

TERATOLOGY STUDY IN RATS

DOSES: 0, 10, 30 AND 100 MG/KG ON DAYS 6-15 POST COITUM

	DOSE (MG/KG)			
MATERNAL TOXICITY:	0	10	30	90
CLINICAL SIGNS	-	-	-	-
DEATHS	-	-	-	-
BODY WEIGHT	-	-	↓	↓*
NECROPSY	-	-	-	-
FETAL TOXICITY:				
POST-IMPLANTATION LOSSES	-	-	-	-
BODY WEIGHTS	-	-	-	-
VISCERAL ABNORMALITIES	-	-	-	-
SKELETAL ABNORMALITIES	-	-	-	↑**

NOEL: MATERNAL = 10 MG/KG
FETAL = 30 MG/KG

*STATISTICALLY SIGNIFICANTLY DIFFERENT FROM THE CONTROL GROUP.
**SLIGHT INCREASE IN WAVY RIBS.

NTN 33893

TWO-GENERATION STUDY IN RATS

PARAMETER	DOSE IN FEED (PPM)		
	100	250	700
PARENTAL.TOX:			
SYMPT.:			
MORT.:			
FEED CONS.:			↓(P-♂,P+F1♀)
BW:			↓(P-♂,P-♀)
HEMATOL.:			
CLIN. CHEM.:		1)	2)
HISTOPATH.:			
REPROD.TOX.:			
FERTILITY:			
VIABILITY:			
BW:			↓
MALFORMATIONS:			

1) F1♀: O-DEMETHYLASE ↑
2) F1♂: CYTOCHROME P450 + N-DEMETHYLASE ↑
F1♂+♀: O-DEMETHYLASE ↑

NOAEL (PARENTALTOX.): 250 PPM, EQUIVAL. TO 12.5 MG/KG BW/DAY
NOEL (REPROD.TOX.) : 250 PPM, EQUIVAL. TO 12.5 MG/KG BW/DAY

OH3/91/GKS

NTN 33893

SUBCHRONIC ORAL STUDY IN DOGS

(13-WEEK FEEDING)

4 MALES, 4 FEMALES/DOSE LEVEL

PARAMETER	DOSE IN FEED (PPM)		
	200	600	1800/1200*
SYMPT.:		1)**	1)** 1)**
MORT.:			
FEED CONS.:		↓**	↓ ↓**
BW-GAIN:			↓ (↓)
OPHTHALMOSC.:			
HEMATOL.:			
CLIN. CHEM.:			
GROSS PATH.:			
HISTOPATH.:			

* DOSE REDUCED FROM THE 4TH WEEK ONWARDS

1) EMACIATED STATE OF NUTRITION, TEMPORARY TREMBLING

** EFFECTS WERE PROBABLY DUE TO A POOR PALATIBILITY OF THE DIET

NOEL: 200 PPM, EQUIVALENT TO 5 MG/KG BW/DAY

OH3/91/GKS

NTN 33893

CHRONIC STUDY IN DOGS

(12-MONTH FEEDING)

4 MALES, 4 FEMALES/DOSE LEVEL

PARAMETER	DOSE IN FEED (PPM)		
	200	500	1250/2500*
SYMPT.:			
MORT.:			
FEED CONS.:			↓
BW-GAIN:			
HEMATOL.:			
CLIN. CHEM.:			1)
GROSS PATH.:			2)
HISTOPATH.:			

* DOSE INCREASED FROM THE 17TH WEEK ONWARDS

1) CHOLESTEROL ↑ (♀), HEPATIC CYTOCHROME P-450 ↑

2) LIVER WEIGHT ↑

NOEL: 500 PPM, EQUIVALENT TO 15 MG/KG BW/DAY

OH3/91/GKS

NTN 33893

SUBCHRONIC ORAL STUDY IN RATS

(13-WEEK FEEDING, 4-WEEK RECOVERY (2400 PPM))

10 MALES, 10 FEMALES/DOSE

10 MALES, 10 FEMALES FOR RECOVERY AT HIGH DOSE

PARAMETER	DOSE IN FEED (PPM)		
	150	600	2400
SYMPT.:			
MORT.:			
FEED CONS.:			
WATER CONS.:			
BW-GAIN:		+ (♂) 8%	+ * 16% ♂ 14% ♀
HEMATOL.:			1)
CLIN. CHEM.:			2) (♂)
GROSS PATH.:			
HISTOPATH.:			3) (♂)

* PARTIALLY REVERSIBLE DURING RESTITUTION PERIOD

1) SLIGHTLY INCREASED THROMBOPLASTIN TIME AND PLATELET COUNT; PARTIALLY REVERSIBLE DURING RESTITUTION PERIOD

2) AP, ALT (+); PROTEIN, ALBUMIN, CHOLESTEROL, TRYCLYCERIDE +; REVERSIBLE DURING RESTITUTION PERIOD

3) LIVER: CELL NECROSIS, ROUND CELL INFILTRATION, CYTOPLASMIC TRANSFORMATIONS, NUCLEAR SWELLING; REVERSIBLE DURING RESTITUTION PERIOD

OH3/91/GKS

NTN 33893

CHRONIC ORAL STUDY IN RATS

(24-MONTH FEEDING)

AND

ADDITIONAL CHRONIC STUDY IN RATS OVER 24 MONTHS (0 AND 1800 PPM)

(MTD-DETERMINATION)

50 MALES, 50 FEMALES/DOSE LEVEL ONCOGENECITY PORTION

10 MALES, 10 FEMALES/DOSE LEVEL FOR CHRONIC PORTION

PARAMETER	DOSE IN FEED (PPM)			
	100	300	900	1800
SYMPT.:				
MORT.:				
FEED/WATER CONS.:				(+)
BW-GAIN:			(♂:5.0%)	↓(11-12%)
			↓(♀:7.5%)	
OPHTHALMOSC.:				
HEMATOL.:			1)	
CLIN. CHEM.:				1,2,3)
GROSS PATH.:				4(♀))
HISTOPATH.:		5(♂))	5)	5(INT.SECT.))

1) INCREASED PROTEIN EXCRETION IN URINE (♂)
2) CHOLESTEROL +, ASAT (↑) (♂)
3) T3-, T4- AND TSH-VALUES IN BLOOD EQUIVALENT TO CONTROL VALUES
4. INCREASED RELATIVE LIVER WEIGHT
5. INCREASED INCIDENCE OF MINERALIZATION OF COLLOID OF THYROID FOLLICLES

NOEL: 100/300 PPM, EQUAL TO 5.7/24.9 MG/KG BW/DAY (♂/♀)

OH3/91/GKS

NTN 33893

CHRONIC ORAL STUDY IN RATS

AND

ADDITIONAL CHRONIC STUDY IN RATS OVER 24 MONTHS (0 AND 1800 PPM); INCIDENCE OF MINERALIZATION OF COLLOID OF THYROID FOLLICLES

	MALES		FEMALES	
DOSE (PPM)	WEEK 52	WEEK 104	WEEK 52	WEEK 104
0	3/ 9	2/50	0/ 9	11/50
100	3/10	12/50**	0/10	6/50
300	5/ 9	32/50***	0/ 9	11/50
900	10/10	44/50***	3/ 9	27/50**
0	6/10	-	3/10	-
1800	10/10	-	6/10	-

** : $P \leq 0.01$

***: $P \leq 0.001$

- MINERALIZATION OF COLLOID OF THYROID FOLLICLES INDICATES AN (SENILE) INVOLUTION OF THE ORGAN
- THE TOXICOLOGICAL SIGNIFICANCE OF THE INCREASED INCIDENCE OF THIS EFFECT IS NOT CLEAR
- THERE IS OBVIOUSLY NO MEASURABLE INFLUENCE ON THE ORGAN FUNCTION
- CALCULATION OF THE NOEL:
  THE INCIDENCE IN BOTH CONTROL GROUPS (=9/19 (47%)) IS MUCH HIGHER THAN THE INCIDENCE IN THE 100 PPM MALES (12/50 (24%))

OH3/91/GKS

NTN 33893

CARCINOGENICITY STUDY IN MICE

(24-MONTH FEEDING)

AND

ADDITIONAL CHRONIC STUDY IN MICE OVER 24 MONTHS (0 AND 2000 PPM)

(MTD-DETERMINATION)

PARAMETER	DOSE IN FEED (PPM)			
	100	330	1000	2000
SYMPT.:				1)
MORT.:				
FEED/WATER CONS.:			↓(♀)	↓
BW-GAIN:			↓(♂:10%) ♀5%	↓(♂:25%,♀:18%)
HEMATOL.:				
CLIN. CHEM.:				2)
GROSS PATH.:				3)
HISTOPATH.:				4)

1) CHICK-LIKE VOCALIZATION
2) AP ↓, GLUCOSE ↓, CHOLESTEROL ↓, PROTEIN↓
3) END SECTION: NO TREATMENT-RELATED MACROSCOPIC FINDINGS
4) INTERIM SECTION: LOSS OF VACUOLATION IN THE RENAL TUBULES (♂)

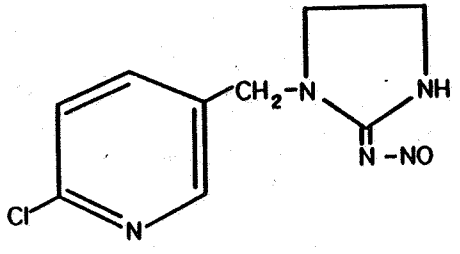
EXP. NOEL: 330 PPM, EQUAL TO 65.6/103.6 MG/KG BW/DAY (♂/♀)

OH3/91/GKS

Results of Mutagenicity Assays

Test System	Test Object	Concentration	Purity	Results	Reference
In vitro Assays:					
Salmonella/microsome test(*)	S. typhimurium TA98, TA100, TA1535, TA1537	10–12500 µg/plate	95.0%	Negative	HERBOLD, 1989
Reverse mutation test(*)	E. coli WP2 her S. typhimurium TA98, TA100, TA1535, TA1537	5–5000 µg/plate	95.3%	Negative	NATANAKA, 1987
HGPRT test(*)	Chinese hamster ovary (CHO) cells	40–125 µg/ml (without S9-Mix), 100–1222 µg/ml (with S9-Mix)	95.2%	Negative	LENN, 1989
Mitotic recombination assay	Saccharomyces cerevisiae D7	625–10000 µg/ml	95.3%	Negative	HERBOLD, 1988a
Rec-assay	Bacillus subtilis N17 Rec+, M45 Rec-	200 µg/disc	95.3%	Negative	NATANAKA, 1987
Rec-assay	Bacillus subtilis N17 Rec+, M45 Rec-	312.5–5000 µg/disc	94.7%	Negative	WATANABE, 1990
Unscheduled DNA synthesis (UDS)	Primary rat hepatocytes	0.5–3000 µg/ml	95.2%	Negative	CIFONE, 1988
Sister chromatid exchange assay(*)	Chinese hamster ovary (CHO) cells	16.7–5000 g/ml	95.2%	(1)	TAALMAN, 1988
Sister chromatid exchange assay(*)	Chinese hamster ovary (CHO) cells	25–1250 µg/ml	95.2%	Negative	PUTMAN und MORRIS, 1989
Cytogenetic (*)	Human lymphocytes	50–5200 µg/ml	95.2%/99.8%	(2)	HERBOLD,1989b,
In vivo Assays:					
Sister chromatid exchange assay	Chinese hamster bone marrow	500, 1000 or 2000 mg/kg bw	95.0%	Negative	HERBOLD, 1989d
Micronucleus test	Male and female NMRI-mice bone marrow cells	80 mg/kg bw	95.3%	Negative	HERBOLD, 1988b
Cytogenetic study	Chinese hamster bone marrow cells	2000 mg/kg bw	94.6%	Negative	HERBOLD, 1989e
Cytogenetic study	NMRI-mice spermatogenia	80 mg/kg bw	94.1%	Negative	VOLKNER, 1990

(*) Test was carried out both with and without metabolic activation (S9-Mix)
(1) Both with and without S9-Mix, a weekly increased SCE-rate was observed at concentrations of 250 - 1000 µg/ml (without S9-Mix) and of 2000 - 3000 µg/ml (with S9-Mix
(2) Only in the cytotoxic range (500 - 5200 µg/ml) a higher aberration rate was observed with S9-Mix; with S9-Mix an equivocal result was found

name of test substance	:	WAK 3839, a metabolite of the insecticide NTN 33893
manufacturer	:	BAYER AG
batch number	:	WAK 3839/C-E
content	:	98.9% (analytical result dated February 28, 1989)
approved	:	until August 26, 1989
appearance	:	yellow to green powder
storage	:	refrigerator
synonyms	:	NTN 37571
chemical name	:	1-(2-Chloropyridin-5-ylmethyl)-2-(nitroso imino)-imidazolidine
structure	:	

WAK 3839

ACUTE TOXICITY

SPECIES	SEX	ROUTE	NOEL	LLD (MG/KG BW)	LD50
RAT	M*	ORAL			> 2500**
	F*	(DMSO/PEG)			> 2500**
*	FASTED ANIMALS				
**	HIGHEST DOSE ADMINISTERED; TOLERATED WITHOUT DEATHS				
SYMPTOMS:	DECREASED BODY TEMPERATURE, EXOPHTHALMOS, SWAYING HEAD AND HIP				
MICE	M*	ORAL			~200
	F*	(DMSO/PEG)			~200
	M**				~240
	F**				~300
*	FASTED ANIMALS				
**	NON FASTED ANIMALS				
MICE	M, F	IP			>30 <60

OH3/91/GKS

WAK 3839

SUBCHRONIC ORAL STUDY IN RATS

(13-WEEK ADMINISTRATION IN DRINKING WATER)

(ORIGINALLY PLANNED AS A 4-WEEK DOSE-FINDING STUDY FOR A LONG-TERM STUDY AND EXTENDED DURING THE COURSE OF THE STUDY)

PARAMETER	DOSE IN WATER (PPM)		
	100	300	1000*
SYMPT.:			
MORT.:			
FEED CONS.:			
WATER CONS.:		(+) (♂)	+
BW-GAIN:			
HEMATOL.:			
CLIN. CHEM.:		1,2)	1,2,3,4)
GROSS PATH.:			
HISTOPATH.:			

* MAXIMUM TECHNICALLY PRODUCIBLE CONCENTRATION

1) Na^+ (4-WEEK DETERMINATION)

2) TRIGLYCERIDES IN LIVER TISSUE (↑) (4-WEEK DETERMINATION)

3) GLDH ↑ (4-WEEK DETERMINATION)

4) GLUCOSE ↑ (♀) (13-WEEK DETERMINATION)

EXP. NOEL: 100 PPM, EQUAL TO 12.6/13.1 MG/KG BW/DAY (♂/♀)

OH3/91/GKS

Results of Mutagenicity Assays

Test System	Test Object	Concentration	Purity	Results	Reference
In vitro Assays:					
Reverse mutation test(*)	S. typhimurium TA98, TA100, TA1535, TA1537 E. coli WP2/uvrA	312.5-5000 µg per plate	98.3%	Negative	WATANABE, 1990
HGPRT-test(*)	Chinese hamster ovary (CHO) cells	62.5-2000 µg/ml (without S9-mix) 500-2000 µg/ml (with S9-mix)	94.3%	Negative	LEHN, 1989a
HGPRT-test(*))	Chinese hamster V79 cells (lung)	0.5-2.0 mg/ml	98.9%	Negative	LEHN, 1989b
Unscheduled DNA synthesis (UDS)	Primary rat hepatocytes	0.04-1333.33 µg/ml	98.9%	Negative	FAUTZ, 1989
Cytogenetic Study(*) (pilot)	Chinese hamster ovary (CHO) cells	0.25-1.0 mg/ml	(§)	Negative	USAMI, 1988a
Cytogenetic Study(*)	Chinese hamster V79 cells	0.1-1.0 mg/ml	98.8%	Negative	HEIDEMANN, 1989
In vivo Assays:					
Micronucleus test (pilot study)	Male BDF1-mice bone marrow cells	40-160 mg/kg bw oral	96.4%	Negative	USAMI, 1988b
Micronucleus test (pilot study)	Male BDF1-mice bone marrow cells	20-80 mg/kg bw i.p.	96.4%	Negative	USAMI, 1988c
Micronucleus test	Male and female NMRI-mice bone marrow cells	100 mg/kg bw oral	98.9%	Negative	HERBOLD, 1989a
Micronucleus test	Male and female NMRI-mice bone marrow cells	50 mg/kg bw i.p.	98.9%	Negative	HERBOLD, 1989b

(*) Test was carried out both with and without metabolic activation (S9-Mix)
(§) Purity not specified

NTN 33893

CONCENTRATION OF THE TEST SUBSTANCES IN THE DIET IN CHRONIC/ONCOGENICITY STUDIES AT THE HIGHEST DOSES

SPECIES	SEX	CONCENTRATION IN MG/KG/B.W./DAY		CONCENTRATION OF THE WAK 3839 AS METABOLITE IN THE ANIMAL MG/KG/B.W./DAY	RATIO OF WAK 3839 IN TEST ARTICLE: AS METABOLITE
		NTN 33893	WAK 3839		
RAT	MALE	51.3 (900 PPM)	0.0015*	3.5	1:2333
RAT	FEMALE	73.0 (900 PPM)	0.0022*	5.0	1:2272
RAT	MALE/FEMALE	- (1800 PPM)	-	6.8	-
MOUSE	MALE	208.2 (1000 PPM)	0.0062	NOT	-
MOUSE	FEMALE	274.4 (1000 PPM)	0.0082	QUANTIFIABLE	-

*MAXIMUM OF 30 PPM IN DIET (10-50 PPM RANGE).

OH3/91/GKS

NTN 33893

NOEL (MG/KG BW/DAY)

SUBACUTE RAT (INHALATION) 5.5 (MG/M3 AIR)

SUBACUTE RABBIT (DERMAL) 1000

SUBCHRONIC RAT	14 (= 150 PPM)
SUBCHRONIC DOG	5 (= 200 PPM)
CHRONIC RAT AND ADD. CHR. RAT	5.7 (= 100 PPM) ADI: 0.057 MG/KG BW/DAY
CARCINOGENICITY MOUSE AND ADD. CHR. MOUSE	65.6 (= 300 PPM) (EXP.)
CHRONIC DOG	15 (= 500 PPM)
TWO - GENERATION RAT	
PARENTALTOX.:	6.7 (= 100 PPM) (NOAEL)
REPROD.TOX.:	12.5 (= 250 PPM)
EMBRYOTOXICITY RAT	
DAMS	10
FETUSES	30
EMBRYOTOXICITY RABBIT	
DAMS	8
FETUSES	24