Human & Environmental Risk Assessment on ingredients of European household cleaning products

Substance: Fluorescent Brightener FWA-5 (CAS 27344-41-8)

D R A F T

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2. Executive Summary

FWA-5 is a Fluorescent Whitening Agent (FWA) mainly used in household detergents in concentrations ranging from 0,02 to 0,1%, and to a far lesser extent in textiles and paper.

An extensive research program has been conducted by the Swiss Institute of Technology (ETH) and the chemical industry to characterise and assess the final fate and environmental risks of FWA-5.

It has been shown that DSBP-type FWAs undergo in aqueous system a rapid isomerization, followed by a photodegradation of >70% within 28 days. The two defined yielding photodegradation products are readily biodegradable according to OECD 301F.

Due to the comprehensive database it was possible to conduct Environmental Risk Assessments (ERA) with the default values of EUSES 1.0 as well as with a HERA specific detergent scenario and to compare with monitoring values from 18 Swiss and German rivers. All results in the calculated/measured environmental compartments (water, sediment, terrestrial, air) indicate PEC/PNEC ratios of well below 1. These findings were confirmed by the Dutch RIVM (Dutch National Environmental Protection Agency). The comparison of the EUSES defaults and HERA detergent scenario with monitoring data confirmed that the HERA detergent scenario is more conservative than monitoring but far closer to the measured values then EUSES default.

Exposure estimates from consumer product uses indicate the aggregate estimated FWA-5 internal exposure is 1.03 μg/day which is the Systemic Estimated Dose (SED) and accounts for all relevant dermal and oral exposures. Inhalation exposures are considered to be negligible. Considering the lifetime exposure of consumers to products containing FWA-5, the critical endpoint selected was from the lifetime feeding study in rats that indicated the relevant NOAEL is 190 mg/Kg/day.

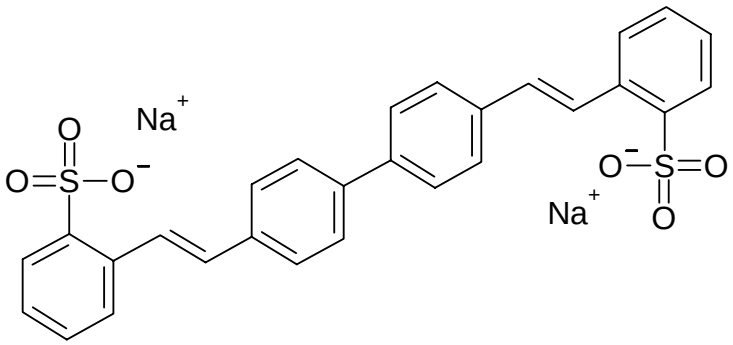
The estimated human exposure to FWA-5 shows a **Margin of Exposure of > 330’000**. Risk characterisation indicates this is an adequate difference to cover all uncertainties in the toxicology database and extrapolations and supports a conclusion that FWA-5 is not of concern for use in consumer products.

From the available data it can be concluded that FWA-5 as applied to detergent uses is not expected to result in adverse effects to humans or the environment.

3. Substance Characterisation

3.1 Chemical Structure and composition

FWA-5 has the CAS chemical name Benzenesulfonic acid, 2,2'-([1,1'-biphenyl]-4,4'-diyldi-2,1-ethenediyl)bis-, disodium salt with the chemical structure



The purity of the active ingredient is >98,5%. The main by-product is Methylene-bis-benzenesulfonic acid, 2,-([1-biphenyl], the minor products identified consist of derivatives of benzenesulfonic acid, 2,-([1-biphenyl]. In literature, FWA-5 is often referred to DSBP (Distyrylbiphenylsulfonate).

Summary of Physico-chemical data

Test	Method	Result	*Literature cited*	*Reliability (Klimisch*)*
General name		FWA-5	*1[HEDSET]*	
Description		Benzenesulfonic acid, 2,2'-([1,1'-biphenyl]-4,4'-diyldi-2,1-ethenediyl)bis-, disodium salt	*1 [HEDSET]*	
CAS-No		27344-41-8	*1[HEDSET]*	
EC-notification no.		-		
EINECS no.		248-421-0	*1[HEDSET]*	
Physical state		yellow powder		
Density	EEC 84/449/A	1490 kg/m^3	*6[CIBA-GEIGY]*	*1b*
Molecular weight		562.58 g/mol	*1[HEDSET]*	
Melting point	OECD 102	>300°C	*2[CIBA-GEIGY]*	*1b*
Boiling point		n/a		
Vapour pressure	OECD 104	<7E-16 Pa at 25°C	*3[CIBA-GEIGY]*	*1b*
Octanol-water partition coefficient [log10]	OECD 107	-2.32 at pH 6.8 and 25°C	*4[CIBA-GEIGY]*	*1b*
Water solubility [mg/l]	OECD 105	17'600 at 20°C	*5[CIBA-GEIGY]*	*1b*
Fat solubility	OECD 116	<0.05 mg/100g fat at 37°C	*7[CIBA-GEIGY]*	*1b*
pH		10.4 at 50 g/L; 20°C		
pKa (free acid)	OECD 112	-2.5>pKa> -3.0	*8[CIBA-GEIGY]*	*1b*
Stability in water	OECD 111	$T_{1/2}$ = > 1 year at	*9[CIBA-GEIGY]*	*1b*

		pH 4 to 9		

3.2 Manufacturing route [Ullmann, 1991]

Accordin to Ullann's *Enzyclopedia of Industrial Chemistry*, the production of Distyryl-biphenylsulfonate FWAs starts with biphenyl, which is produced along with other aromatic compounds during the refining of crude oil. Reacting it with hydrogen chloride and formaldehyde produces the intermediate 4,4'-bis(chloromethyl)biphenyl, which reacts with trimethylphosphite to give 4,4'-bis(dimethoxyphosphonomethyl)biphenyl. This symmetrical biphenylphosphonate is reacted with two molecules of benzaldehyde-2-sulphonic acid, a compound which is produced from 2-chlor-benzaldehyde and sodium sulphite. The content on active ingredient is approx. 90% another <1.2% consist of by-products and the balance is sodium chloride and water.

Ciba Specialty Chemicals Inc. is the only producer of FWA-5 in Europe. The production volume is >1000 t/a therefore, FWA-5 was notified as HPV product. The European usage was approximately 600 tons in 1998; it varies from year to year according to the market trends.

3.3 Use applications summary [Kramer, 1992]

FWA-5 is a Fluorescent Whitening Agent (FWA)based on Distyrylbiphenylsulfonate.
FWA-5 has a higher yield of whiteness then the classical stilbene type brighteners. FWA-5 has also a high affinity to cellulosic fibres and is stable towards chlorine.

More then 90% of this brightener is used in household detergents in concentrations ranging from 0,02 to 0,1%, and the balance in textiles and paper. It is used also in combination with flavon acid type FWAs. To improve the visual aspect of formulations 0.002 to 0.05% are applied but these usages are nor significant.

It is not appropriate to combine DSBP and disulfo flavon acid type FWAs to a family, as their environmental fate is different.

DSBP behaves like colorless direct cotton dyes. A highly conjugated electron system, a significant degree of planarity, and sulfonate-groups should guarantee affinity to cotton. The theories of diffusion and sorption processes referring to dyes are well described [McGregor, 1974], [Rattee et al, 1974]. According to the porous matrix model, the cotton fibre can be regarded as a solidified sponge, a rigid matrix in which a maze of interconnected pores exists [Bikales et al, 1971]. The pores are filled with water and the FWA enters them and penetrates the fibre by diffusing on the surface of the pore walls. FWA molecules move along in the aqueous phase of the pore and will collide with the binding site from time to time, becoming bound and therefore immobilized. However, depending on the strength of the binding, the FWA molecule will desorb after a certain time, re-enter the aqueous phase and resume its movement towards the interior of the fibers. The nature of binding sites is not fully understood.

Washed goods undergo a few to more then 100 washing cycles during their life cycle. During each washing process a dynamic equilibrium takes place, which depends on concentration on the fibre, offered FWAs and many other parameters. From the visual appearance it can be

concluded that there is a build up of whiteness during the life cycle of a textile. Measurements [Ciba, Internal report] have shown that in average 50 to 75% of DSBP is adsorbed on to the fibre and remains there until disposal and/or incineration.

As FWA-5 is widely used in consumer products, it shows a widespread distribution in the environmental compartments water, sediment and soil.

4. Environmental Assessment

4.1 Environmental Exposure Assessment

4.1.1 Substance data used for ERA

Test	Result	*Literature cited*	*Reliability (Klimisch*)*
General name	FWA-5	*1[HEDSET]*	
CAS-No	27344-41-8	*1[HEDSET]*	
Molecular weight [g/mol]	562.58	*1[HEDSET]*	
Melting point [°C]	>300°C	*2[CIBA-Geigy]*	*1b*
Boiling point [°C]	n/a		
Vapour pressure at 25°C [Pa]	<7E-16 at 25°C	*3[CIBA-Geigy]*	*1b*
Octanol-water partition coefficient [log10]	-2.32 at pH 6.8 and 25°C	*14[CIBA-Geigy]*	*1b*
Water solubility [mg/l]	17'600 at 20°C	*5[CIBA-Geigy]*	*1b*
Henry constant	< 1E-15 at 25°C	*na*	*na*
Koc	125 $L_{*}kg^{-1}$	*14[CIBA-GEIGY! 15[Kramer]*	
Total tonnage in continent	600	*10[Ciba-Geigy]*	
Degradability	*not biodegradable but undergoes photodegradation followed by biodegradation of metabolites*	*11[Novartis]*	*1d*
Inherent biodegradability (OECD 302B)	*32% adsorption*	*14[Kramer]*	
Fraction of emission directed to air	0		
Fraction of emission directed to water	approx. 44%	*14[Kramer]*	
Fraction of emission directed to sludge	approx. 56%	*14[Kramer]*	
Fraction of the emission degraded in effluent treatment plant	0	*11[Novartis]*	
Literature cited:			

* Adapted from Klimisch *et al* , "Criteria for reliability Categories", (1997)

4.1.2 EUSES Scenario Description

EUSES (European Union System for Evaluation of Substances) is a software which contains the mathematical models and evaluation processes described in the TGD [TGD, 2003]. The underlying models estimate the distribution of chemical substances in the environmental compartments water, sludge, sediment as well as soil in order to characterise the risk to environment.

In a first step the defaults suggested by EUSES 1.0 and the TGD [TGD, 2003], Part IV, IC-5 Personal/domestic and IC-6 Public domain "Assessment of the environmental release of soaps, fabric washing, dish cleaning and surface cleaning substances", pages 21 - 28 **(default values according to EUSES)** are compared to refined parameters gained through the monitoring studies of household detergents (**Detergent specific scenario)** as described in the HERA Guidance Document-April 2002, 2.6 HERA "Detergent Scenario", pages 29 to 31, and Appendix E [HERA, 2002].

Scenario Default: Default values according to EUSES [TGD, Part II, 2002]

. connection rate to sewage plants 80 %
. 40 % of FWA-5 is disposed of with fibre and 60 % in effluent
. 10 % of Continental Tonnage to Region
. local tonnage increased by factor 4

Scenario HERA: Detergent specific scenario [HERA, Guidance Document Methodology from 22 April 2002, p. 29-31]

. connection rate to sewage plants 80 %
. 40 % of FWA-5 is disposed of with fiber and 60 % in effluent
. 7 % of Continental Tonnage to Region
. local tonnage **not** increased by factor 4 but factor 1.5
. input of measured sludge adsorption of 56 %
. input of photolysis (> 70% in < 28 days)

4.1.3 Monitoring studies

Fluorescent Whitening Agents (FWAs) are in general not considered to be readily biodegradable according to OECD 301. As FWAs are widely used in detergents, paper/board products and textiles they consequently show a wide disperse distribution in the environment. As a consequence, an assessment of the environmental fate has been the focus of in-depth studies of 4,4'-distyrylbiphenyl derivatives (DSBP) a class of FWAs with a unique technical and environmental profile. Field studies in Switzerland prove a quick light-induced reaction in rivers and lakes. This photodegradation finally yields in two products namely benzaldehyde-2-sulphonic acid salt and diphenyl-4,4'-dialdehyde. Both photodegradation

products are shown to be readily biodegradable in OECD test 301F. Thus, the degradation consists of two steps, photolysis followed by biodegradation. The combined rate and DOC reduction justifies the assessment of distyrylbiphenyl derivatives to be biodegradable [Richner et al, 1999].

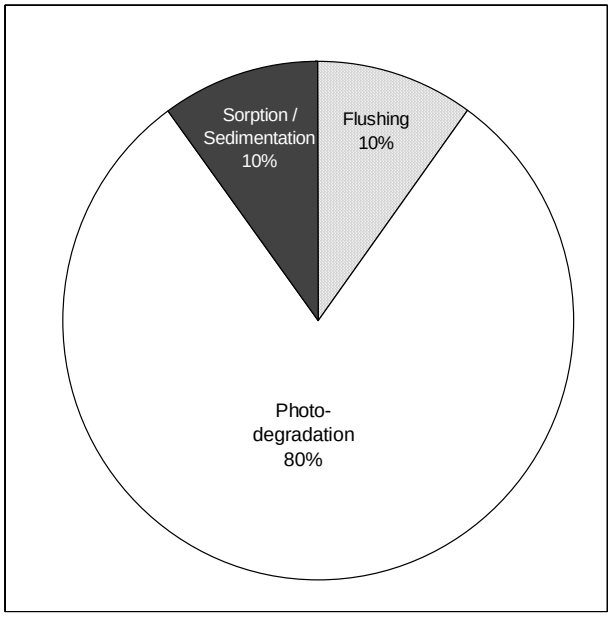
4.1.3.1 Approach and results

The distyrylbiphenyl disulfonic acid disodium salt shows an excellent water solubility and a very low K_{ow} that indicate a negligible potential for bioaccumulation. The extremely low vapor pressure and consequently low Henry Constant confirm that DSBP is not distributed in the atmosphere. Furthermore the substance shows no hydrolysis. Due to these findings, the assessment of the final fate can concentrate on the environmental compartments water, sludge, sediment and soil.

Once FWAs are exposed to sunlight, the first step is the photoisomerization. The data confirm that on exposure to sunlight, DSBP dissolved in water is converted to photoisomers within minutes. 85% remain as the fluorescent E,E isomer while 15% are converted to the E,Z isomer which lacks the fluorescence.

It is known that FWAs undergo a photodegradation what has proved to be significant in the photic zones of lakes and rivers. The kinetic data of the photodegradation are now well known and enable prediction of the photolysis under various conditions of sunlight exposure. Field studies in Switzerland on lake Greifensee and river Glatt substantiate the scale and rate of photolysis under worst case conditions in a heavily populated catchment area. The vertical DSBP concentration profile of lake Greifensee in summer proves a significant photodegradation but also in the river Glatt a photodegradation of >70% within 28 days in winter has occurred. On a cloudless summer day 70% photolysis is achieved after 1.5 days only.

Mass characterisation of DSBP in the lake of Greifensee



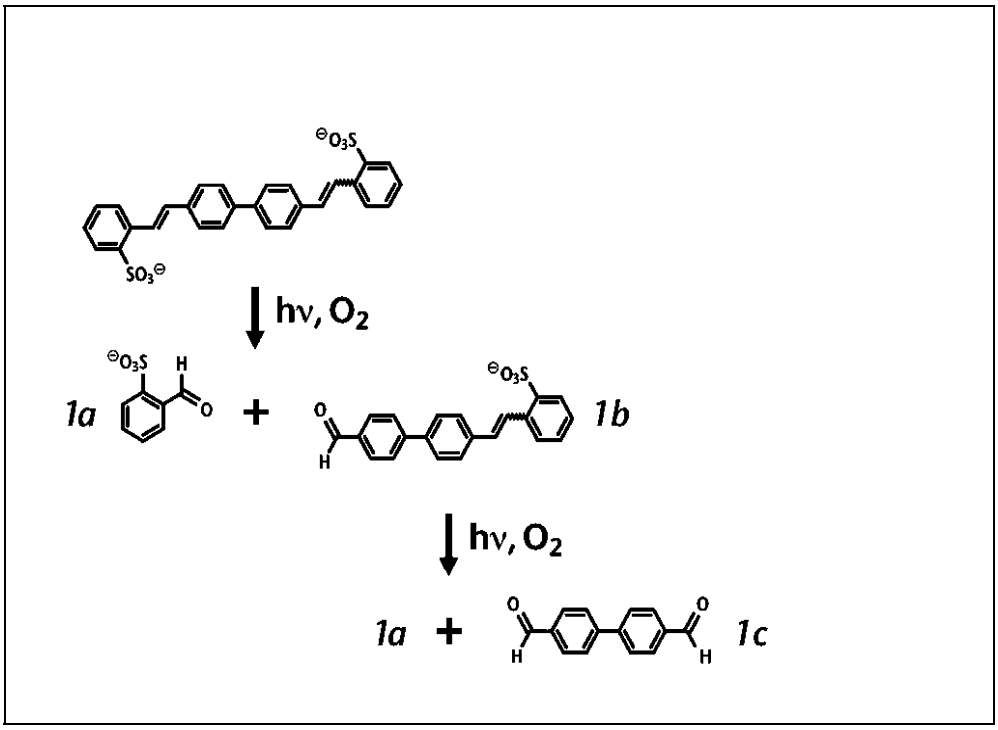
The project at lake Greifensee allowed to measure the mass balance as well as the total elimination of DSBP under “real world” conditions as the necessary hydrological data are available.

The mass balance indicates that 80% of the DSBP was degraded by photolysis. The balance of 20% is evenly allocated to flushing and sorption/sedimentation [Stoll, 1996]. The dominant portion of photodegradation leads to the question of the mode of action of photolysis and the chemistry of the photodegradation products.

Photodegradation initially yields a main product **1a** (benzaldehyde-2-sulphonic acid salt, and a photo-unstable intermediate **1b** which, at a slower rate, breaks down to form a second main

product **1c** (diphenyl-4,4'-dialdehyde). Both photodegradation products are shown to be readily biodegradable in OECD test 301F. Diphenyl-4,4'-dialdehyde is unstable and oxidizes to diphenyl-4,4'-dicarboxylic acid (**1c, oxide.**) within 24 h [Richner et al, 1999]0.

Pathways of photodegradation



4.1.3.2 FWA-5 in natural waters

A German FWA monitoring program was launched 1993 to assess the data in the aquatic compartment [Hochberg et al, 1997]. The sampling took place between August and October 1993 at five representative STPs in Germany. The daily samples were collected by regional authorities in the framework of a tenside-monitoring study which was co-ordinated by TEGEWA. The five rivers - two of them situated in Eastern Germany - should give a representative cross section regarding the geological background and the flow rate. To have reasonable worst case conditions, small rivers with STPs with a highly populated catchment area were chosen. The result from the sampling above and below the STPs are listed.

River	Above STP	Below STP
Isar	51 ng/L (s=23, n=7)	27 ng/L (s=19, n=7)
Wupper	51 ng/L (s=53, n=7)	117 ng/L (s=76, n=7)
Leine	61 ng/L (s=29, n=7)	Point A : 85 ng/L (s=52, n=7) Point B : 134 ng/L (s=112, n=7)
Chemnitz	157 ng/L (s=110, n=7)	Point A : 144 ng/L (s=102, n=7) Point B : 258 ng/L (s=173, n=7)
Teltow-Kanal	23 ng/L (s=9; n=7)	Point A : 98 ng/L (s=66, n=7) Point B : 142 ng/L (s=122, n=7)

s standard deviation

n number of samples measured

Another Swiss monitoring program was conducted in a thesis of the Swiss Federal Institute of Technology Zurich also in 1993 to complement the aquatic data in Switzerland [Stoll 1997]. For the sampling the sites of an existing national program (NADUF) were available. 11 hydrologically controlled river stations were selected which represent three different types of catchment areas in Switzerland

I **Alpine rivers** with small influence of human activity.

II **Large rivers** in the Swiss plateau with lakes and changing human activity.

III **Small rivers** with **highly** populated catchment areas.

From each of the ten sampling sites 13 samples consisting of 2-week-composite-samples were collected (from January 95 to January 96) and analysed.

Group	River	90th percen-tile [ng/L]	Average [ng/L]	Range [ng/L]	s	n
I	Rhine (1A)	36	23.5	11.3 - 40.8	9.9	13
I	Saane (5)	34	28.1	17.9 - 44.9	7.1	13
I	Rhone (6A)	61	41.6	18.9 - 71.2	14.8	13
II	Aare (4A)	35	23.5	11.4 - 42.4	10.1	11
II	Aare (4B)	56	43.3	24.0 - 65.7	11.2	12
II	Aare (4C)	85	70.8	52.9 - 87.0	15.5	6
II	Rhine (1B)	60	43.1	25.7 - 65.8	13.0	13
II	Rhine (1C)	210	151.3	46.2 - 539.5	136.6	12
II	*Rhone (6B)	683*	358.3*	59.0 - 821.1	224.0	13
III	Thur (2)	154	114	47.1 - 190.8	34.4	12
III	Glatt (3)	869	633.9	339.8 - 1090.7	211.0	13

* sampling point below production site of FWA-5
s Standard deviation
n Number of samples analysed

The Swiss river Glatt with an extremely high population density of the catchment area represents probably not “the” but a worst-case scenario in Europe [Stoll 1997]. The dilution factor can be as low as 2,5. The 90th percentile is 869 ng/L with an average of 634 ng/L and a median of 634 ng/L.

The river Rhone below the production site of FWA-5 has a 90th percentile of 683 ng/L, an average of 358.3 ng/L a median of 299 ng/L. Here, the production site of FWA-5 drives the high concentrations. All maximum concentrations origin from the river Glatt and the production site of FWA-5 and therefore represent a real worst-case situation.

All monitored rivers in Germany and Switzerland have very low concentrations of FWA-5 with a median of around 50 ng FWA-5/L. The monitored concentrations are compared in 4.4.1 Sensitivity Analysis I with EUSES 1.0 and the HERA scenario.

4.1.3.3 Monitoring of lake sediment

Monitoring of lake sediment was done in the lake of Greifensee. The analysis of a sediment core had a maximum concentration of 800 ng FWA-5/kg sediment in 1993/94. Analysis of 13 samples of sediment traps had concentrations ranging from 100 to 1632 ng/kg sediment with an average of 666 ng/kg. For the risk assessment, the highest value found, namely **1632 ng FWA-5/kg sediment** [Stoll, 1997 : Tables A10 and A21, p 107 and 115] was used. This approach is reasonable as the lake Greifensee represents a worst case area [Stoll, 1997] in Europe.

4.1.3.4 Conclusions

An extensive research program has been conducted by the Swiss Institute of Technology (ETH) and the chemical industry to characterise and assess the final fate and environmental risks of FWAs.

It is scientifically confirmed that DSBP-type FWAs undergo a rapid isomerization, followed by a photodegradation of >70% within 28 days. The two defined yielding photodegradation products are readily biodegradable according to OECD 301F. The average concentrations measured in more then 20 rivers and lakes in Germany and Switzerland range between 20 and 644 ng/L with a median of approximately 50 ng FWA-5/L.

4.1.4 PEC calculations

The two scenarios give the following PECs for the local and regional compartments.

FWA-5 distribution in *local* compartments	**Scenario Default**	**Scenario HERA**
Concentration in dry sewage sludge [mg/kg]	0.0084	0.0009
PEC surface water [mg/l]	0.018	0.0001
PEC Soil 30d [mg/kg]	3E-08	1E-06
PEC Sediment [mg/kg]	0.001	0.0008
PEC STP [mg/l]	0.164	0.0076

FWA-5 distribution in *regional* compartments	**Scenario Default**	**Scenario HERA**
PEC surface water [mg/l]	0.0018	0.00024
PEC Soil [mg/kg]	3E-08	0.00033
PEC Sediment [mg/kg]	0.001	0.00014

The calculations of **Scenario Default** (Default values according to EUSES) and **Scenario HERA** (Detergent specific scenario) are both shown to be conservative, by comparison with environmental monitoring data. Nevertheless, **Scenario HERA** (Detergent specific scenario)

is far closer to reality then **Scenario Default** (Default values according to EUSES)**.** This is discussed in Section 4.5.

4.2 Environmental Effects Assessments

4.2.1 Ecotoxicological Data used for ERA

Assay	**Test Method**	**Result**	***Literature cited***	***Reliability*** (Klimisch*)
AQUATIC				
LC50 algae [mg/l]	OECD 201	8	*15[RCC]*	*1a*
LC50 daphnia [mg/l]	OECD 201/I	>1000	*16[RCC]*	*1a*
LC50 fish [mg/l]	OECD 203	76	*17[Ciba-Geigy]*	*1a*
LC50 other *fish* [mg/l]		130 - 550	*18[Ciba-Geigy]*	*2-4*
NOEC algae [mg/l]	OECD 201	3.1	*15[RCC]*	*1a*
NOEC daphnia [mg/l]	OECD 202/II	7.5	*19[RCC]*	*1a*
NOEC fish (28 d) [mg/l]	OECD 204	1	*20[RCC]*	*1a*
TERRESTRIAL				
LC50 plants [mg/l]		-		
LC50 earthworms [mg/l]	OECD 207	>1000	*21[CIBA-GEIGY]*	*1a*
LC50 microorganisms [mg/l]		-		
NOEC plants [mg/l]				
NOEC earthworms [mg/l]	OECD 207	1.37	*21[CIBA-GEIGY]*	*1a*
NOEC microorganisms [mg/l]		-		
WWTP MICRO-ORGANISMS				
EC50 [mg/l]	OECD 209	>100	*22[CIBA-GEIGY]*	*1a*
specific bacterial population ?		no		
EC10 [mg/l]				

* Adapted from Klimisch *et al*, “Criteria for reliability Categories”, (1997)

4.2.2 Data evaluation for PNEC-derivation of FWA-5

There exist long-term toxicity data (NOEC values) for Daphnia and algae. The 28-d fish toxicity study had a NOEC of 1 mg/L and was therefore the most sensitive species. According to the TGD (page 101), a prolonged toxicity test can not be considered as suitable because it does not examine a sensitive stage in the fish life-cycle. Therefore, the 28 days assay with fish was not considered to be a chronic result and will therefore not be included into the risk assessment.

4.2.2.1. Algae

There is one assay with 48 and 96h duration available, conducted with *Scenedesmus suspicatus*. Endpoint was the growth rate. The results are for the NOEC (96h) 3,1 mg/L and for EC_{50} (growth) 10 mg/L after 72h and 8 mg/L after 96h. Algae is in the acute assay the most sensitive species and in the chronic assay less sensitive then fish.

4.2.2.2 Invertebrates

For invertebrates an acute and a chronic assay with *Daphnia magna* are available. The acute toxicity was >1000mg/L and therefore far less sensitive then algae and fish. The chronic toxicity with the endpoints survival and reproduction has a NOEC of 7.5 mg/L and is therefore as sensitive as the algae. The average recovery rate at the NOEC concentration (nominal 10 mg/L) was 75%, what leads to a NOEC effective of 7.5 mg/L.

4.2.2.3 Fish

Acute toxicity exists for *Brachydanio rerio* (LC50 : 76 to 130 mg/L), and rainbow trout (LC50 : 120 to 450 mg/L).

A prolonged semistatic assay over 28 days was conducted with the more sensitive species *Brachydanio rerio*. Endpoints were mortality, signs of intoxication, length and weight. There was no clear concentration-effect-relation observable. The mortality was between 0 and 20% at concentrations of 0.32 to 100 mg/L without a clear concentration-effect-correlation. The mean body weight was significantly reduced at 32 mg/L and the mean length at 100 mg/L. These results indicates a low bioavailability.

The lowest concentration with toxic effects (LOEC) was determined to be 3.2 mg/L, since here and in all higher concentrations signs of intoxification were observed. The NOEC was determined to be 1 mg/L. Nevertheless as already explained above, a prolonged fish test does not address the most sensitive life-stage of fish and cannot be used to derive a chronic value.

4.2.2.4 Terrestrial

For the terrestrial toxicity of industrial chemicals only a limited number of protocols are available. Therefore, presently only a test result for earthworm is available. A 14 days study with the endpoint flaccidity and survival has a LC_{50} of >1000 mg/kg and a NOEC of 1.67 mg/kg soil. All values are based on nominal concentrations. No clear concentration-effect relationship could be found with the test substance. Only a slight toxic effect fluctuating between LC 12,5% and LC 30% was observed in the test range of nominal 1.37 to 1000 mg/kg soil.

4.2.2.5 Estrogenic effects

Estrogenic activity is a general concern for all down-the-drain chemicals. We have carefully compared the listed structures of 188 natural and xenochemicals [Blair et al, 1999] with FWA-5 and cannot deduce a similarity. Endocrine and androgenic effect were tested in vitro on rat and revealed no observable effect (see 5.2.1.7 Additional data).

4.2.2.6 Derivation of PNEC

From the two chronic assays (algae and daphnia), daphnia was slightly less sensitive with 7.5 mg/L. Therefore; the algae value will be used for the calculation of the PNEC. The prolonged fish toxicity cannot be considered. Thus, an assessment factor of 50 can be applied according to the TGD of the EC.

	NOEC	Assessment factor	PNEC
Aquatic Organisms	3.1 mg/L	50	0.06 mg/L
Sediment dwellers	Partition method	--	0.038 mg/kg
Terrestrial Organisms	1000 mg/kg	1000	1 mg/kg
Microorganisms	300 mg/L	100	3 mg/L

4.3 Environmental Risk Characterisation

4.3.1 Risk characterisation of EUSES scenario "Default" and "HERA"

The calculation program of EUSES 1.0 gives the following results.

Parameter		Scenario Default	Scenario HERA
RCR Surface water	regional	0.029	0.004
	local	0.292	0.016
RCR Soil	regional	2.8E-08	3.3E-04
	local	1E-05	1E-06
RCR Sediment	regional	0.0284	0.004
	local	0.374	0.020
RCR STP	regional	--	--
	local	0.016	0.0025

The Environmental Risk Assessment (ERA) was conducted for the Scenario Default (Default values according to EUSES) and the Scenario HERA (Detergent specific scenario suggested

by HERA). As **all** risk quotients of FWA-5 even under worst conditions are well below 1 in all environmental compartments it can be concluded that the use of FWA-5 in detergents does not pose an environmental risk.

4.3.2 Risk characterisation of the monitoring results

The availability of a representative database is restricted to the aquatic compartment where data from more then 20 European rivers and lakes are available.

RCR for **aquatic** compartment

local	0.005
regional	0.0008

For the sediment are only few results available from the Swiss lake "Greifensee". Greifensee is in an area with an extremely high population density of the catchment area and therefore represents a worst case scenario in Europe.

The highest measured concentration of FWA-5 in lake sediment (sediment core and sediment traps) was 1632 ng FWA-5/kg and leads to a

RCR for sediment **0.0016**

Finally is the question of the risk in soil if sewage sludge is used as fertiliser. Presently no data are available. Nevertheless there is a study running at the Swiss Federal Institute for Water Resources and Water Pollution Control. The results will be available in first semester 2003. In the meantime values from the partition method are applied.

RCR for soil **results not yet available but expected to be <0.0001**

4.3.3 Conclusions

All available PEC/PNEC ratios from modelling with EUSES 1.0 and monitoring have in all calculated/measured environmental compartment values well below 1. It can therefore be concluded that FWA-5 has no adverse effect to the environment.

4.4 EUSES Sensitivity Analysis to ERAs for FWA-5

4.4.1 EUSES Scenario "Default" versus "HERA" and monitoring

In 3.1 "EUSES Scenario description", the difference between defaults and the HERA specific scenario has been demonstrated. The sensitivity analyses includes now the monitoring values as well.

Scenario Default: Default values according to EUSES [TGD, Part II, 2003)

. 40 % of FWA-5 is disposed of with fibre and 60 % in effluent
. 10 % of Continental Tonnage to Region
. local tonnage increased by factor 4
. calculated sludge/water partition coefficient

Scenario HERA: Detergent specific scenario [HERA, Guidance Document Methodology, 2002, p. 29-31]

. 40 % of FWA-5 is disposed of with fibre and 60 % in effluent
. 7 % of Continental Tonnage to Region
. local tonnage **not** increased by factor 4 **but** factor 1.5
. input of measured sludge adsorption of 56 %
. input of photolysis (> 70% in 28 days)

The comparison of the PEC results from the EUSES default scenario and from the HERA detergent specific scenario with the available monitoring data are shown in the tables below.

The two scenario give the following **PECs** for the local and regional compartments, compared with monitoring data.

FWA-5 distribution in *local* compartments	**Scenario Default**	**Scenario HERA**	**Monitoring[1)]**
Concentration in dry sewage sludge [mg/kg]	0.0084	0.0013	na[2)]
PEC surface water [mg/l]	0.018	0.0029	0.000322
PEC Soil 30d [mg/kg]	9E-12	2E-06	3)
PEC Sediment [mg/kg]	0.014	0.0008	0.0016
PEC STP [mg/l]	0.164	0.026	na

1) 90 Percentille of the monitoring data represents local concentration
2) na = not available
3) study running at the Swiss Federal Institute for Water Resources and Water Pollution Control. Results by end 2003

FWA-5 distribution in *regional* compartments	**Scenario EUSES**	**Scenario HERA**	**Monitoring[1)]**
PEC surface water [mg/l]	0.0018	0.00027	0.000049
PEC Soil [mg/kg]	3E-08	0.00035	2)
PEC Sediment [mg/kg]	0.001	0.00016	0.0016

1) Median of the monitoring data represents the regional concentration
2) study running at the Swiss Federal Institute for Water Resources and Water Pollution Control. Results expected end 2003.

Risk Characterisation:

Parameter		Scenario EUSES	Scenario HERA	Monitoring
RCR Water	regional	0.029	0.004	0.0008
	local	0.294	0.046	0.0054
RCR Soil	regional	2.5E-08	3.5E-04	na
	local	1E-05	1.7E-06	na
RCR Sediment	regional	0.0284	0.004	0.0016
	local	0.374	0.059	0.0016
RCR STP	regional	--	--	--
	local	0.055	0.0086	na

As the risk quotients of FWA-5 even for the default values and under worst conditions are well below 1 in all environmental compartments, it can be concluded that the use of FWA-5 in detergents does not pose an environmental risk. The HERA scenario is based on additional substance-specific data and thus more realistic what is reflected in the improvement of the PEC and Risk Characterisation by a factor of 6. Monitoring data – even representing the river Glatt as an European worst case [Stoll 1997] - have an improvement of a factor of 35 to 470 compared to the default model.
Thus, the modelling with EUSES 1.0 underestimates the real situation by more then one order of magnitude. The resulting RCR from monitoring are below 0.006 and therefore truly in a comfortable range of safety.

4.4.2 Variability of the European consumption figures

The annual consumption of household detergents expressed kg per capita shows little fluctuations from year to year. The same applies for the main ingredients of household detergents. Fluorescent Whitening Agents (FWA) are effect chemicals that depend on fashion trends and market penetration as well as promotion concepts of the detergent formulators. As a consequence, concentrations of FWA-5 have greater variability in the aquatic compartment.
It was agreed upon to use the consumption figures for 1998 for the HERA risk assessment. That leads to the difficulty that the modelling figures do not coincide with the monitoring data. The annual consumption for FWA-5 ranges from 500 to 900 ton per year with a consumption of 600 ton (figure 1998) used in the modelling. During the monitoring in 7 German rivers in 1993 the consumption was approximately 900 ton and during the monitoring in 11 Swiss rivers in 1995 approximately 800 ton.

A normalisation of the EUSES data to the consumption figures leads to the following regional concentrations in surface waters:

Year	Consumption FWA-5 in Europe	EUSES* Scenario Default/ HERA [ng/L]	Monitoring* median [ng/L]	Monitoring* 75th Percentile [ng/L]	Monitoring* 90th Percentile [ng/L]
1993	approx. 900 ton	(2700 to 27'000)	(56)	(145)	(362)
1995	approx. 800 ton	(2400 to 24'000)	50	129	322
1998	approx. 600 ton	1800 to 18'000	(40)	(97)	(240)

* figures in brackets are extrapolated from measured figures

The differences in the annual consumption have a variation of approx. +/- 20 %. This variation will be propagated to the environmental compartments.
The distribution of the monitoring data is very flat as indicated by low mean (50 ng/L) and 75 percentile (129 ng/L) followed by a far higher 90 percentile (322 ng/L). TGD suggests to derive the local and regional PEC's from 90-percentile and median.
The comparison of the normalised river concentrations with the monitoring data which were based on the consumption figures for 1998.

Source	**local**	**regional**
EUSES 1.0, Scenario Default	18'000 ng/L	1800 ng/L
EUSES 1.0, Scenario HERA	2900 ng/L	270 ng/L
Monitoring data	240 ng/L*	40 ng/L**

* local PEC was derived from the monitoring data by using the 90th percentile [TGD, 2003].
** regional PEC was derived from median [TGD, 2003]

The normalisation increases the difference between EUSES calculations and monitoring data, indicating that EUSES defaults overestimates the environmental concentrations for FWA-5 by a factor of 75 for the local and 45 for the regional PEC. Therefore, the variations of the annual consumption figures (+/- 20%) can be neglected.

These findings confirm that the "Scenario Default" as well as the "Scenario HERA" of EUSES 1.0 are conservative as the PECs from default values are overestimated by a factor of 45 to 75 compared to monitoring results. This is a more significant contribution to the risk assessment result than the variation of the annual consumption figures.

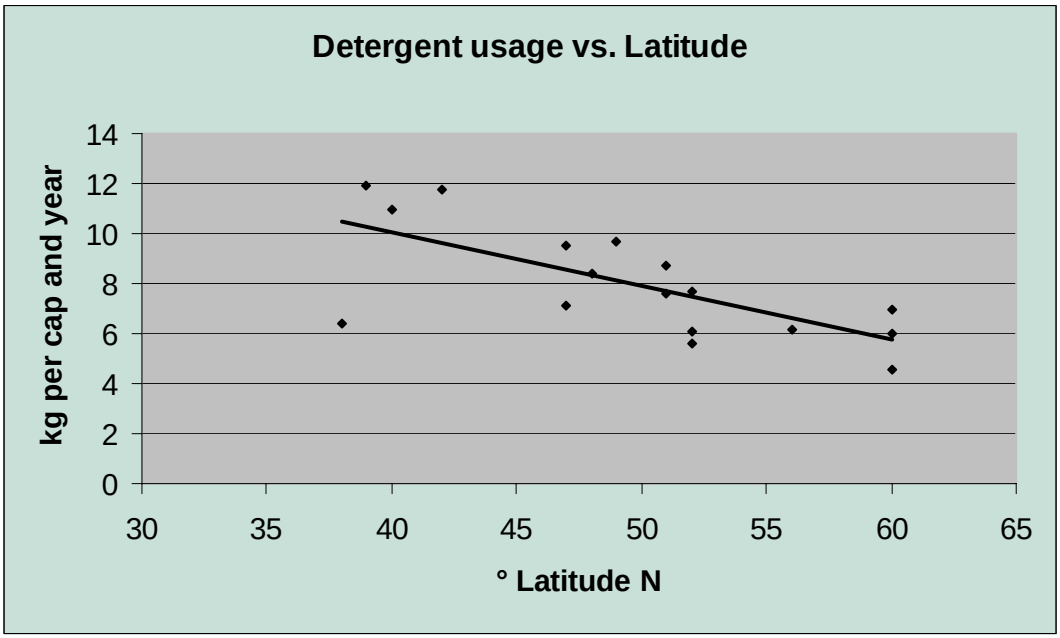
4.4.3 Variability of FWA-5 usage in laundry detergents of selected European countries

Washing habits is country specific depending on culture and climate. To check dependence from latitude, the usage figures of laundry detergents of selected European countries are listed and ranked below according to the latitude.

National laundry detergents usage versus Latitude[Cahn, 1999]

City	Country	Latitude	Laundry detergents [$kg_* cap^{-1}{}_* y^{-1}$]
Athens	Greece	38° N	6.4
Lisbon	Portugal	39° N	11.9
Madrid	Spain	40° N	11.0
Rome	Italy	42° N	11.8
Zurich	Switzerland	47° N	7.1
Budapest	Hungary	47° N	9.5
Vienna	Austria	48° N	8.4
Paris	France	49° N	9.7
London	Great Britain	51° N	7.6
Brussels	Belgium	51° N	8.7
Amsterdam	Netherlands	52° N	6.1
Berlin	Germany	52° N	7.7
Warsaw	Poland	52° N	5.6
Copenhagen	Denmark	56° N	6.2
Oslo	Norway	60° N	7.0
Stockholm	Sweden	60° N	6.0
Helsinki	Finland	60° N	4.6

Plot of national laundry detergents usage versus latitude



With few exceptions, the per capita consumption of the national laundry detergent usage increases from North to South from approx. 5 to 12 kg per capita and year.

FWA-5 concentrations in laundry detergents of European countries

FWA-5 has a high market share in Switzerland and Spain. In Germany and Italy the market is dominated by **D**isulfo **A**mino **S**tilbene (DAS)-type FWAs. In the Nordic countries (S, N, FIN) the majority of the detergent brands do not contain FWAs.

FWA-5 concentrations in laundry detergents of selected European countries

	Country	Popula-tion [Mio]	Detergent usage [kg/cap*y](1997)[1]	Estimated average concentrations of FWA-5 [%]	Calculated relative concentrations of FWA-5 in natural waters
Latitude 50 N					
Glatt (CH)	Switzerland	**7.3**	**7.1**	**0.045**	**100%**
Chemnitz (D)	Germany	82	7.7	0.015	36%
Latitude 40 N					
Naples (I)	Italy	58	11.9	0.01	37%
Madrid (E)	Spain	40	11	0.035	121%
Latitude 60 N					
Stockholm (S)	Sweden	9	6	**(0.045)***	**84%**
Helsinki (FIN)	Finnland	5	4.6	**(0.045)***	**65%**
Oslo (N)	Norway	4.5	7	**(0.045)***	**99%**

* The incorporation rate of FWA-5 in Switzerland was taken for the sensitivity analysis of the Northern European countries.

Estimated average concentrations of FWA-5 are based on a Ciba internal market study. Nordic countries have usually no FWA in its laundry detergents. To get a meaningful estimation for the Nordic countries, the Swiss concentration of 0.045% was input in red digits.

Calculated relative concentrations of FWA-5 in natural waters are based on the Swiss figures of 0.045% FWA-5 and 7.1 kg laundry detergents per capita and year. The result is taken as 100% and the other sites/countries adjusted according to their concentration of FWA-5 and the country-specific laundry detergent usage.

Use and mix of FWAs (FWA-5 versus DAS types) differs from country to country depending on the preferences of the detergent producers. In Switzerland, the proportion of FWA-5, calculated on the contribution to achieved whiteness is very high. In Germany, FWAs based on DAS are more important. That is the reason the monitoring concentration in the river Chemnitz is far lower then the calculated ones. The relative concentrations are therefore

adjusted to the annual per capita consumption of 7.1 kg/y in Switzerland. Southern European countries with a higher usage have an increased relative concentration and Northern European countries have lower relative concentrations. These figures of the relative concentrations are taken for further modelling.

4.4.4 Variability of photolysis within Europe depending on latitude

Photolysis depends on intensity and duration of UV exposure. Halftime of photolysis is expected to decrease if going south. An independent consulting company has modelled photolysis as a function of latitude.

Modeling of photolysis with GCSOLAR 1.2

GCSOLAR is a set of routines that computes direct photolysis rates and half-lives of chemical substances in the aquatic environment. The half-lives are calculated as a function of season, latitude, time-of-day, depth in water bodies, and ozone layer thickness.

This program operates in an interactive screen mode to facilitate data and program command entry by the user. Input values, with few restrictions, are format free. This release (1.10 February 1988 and 1.20 July 1999) of the GCSOLAR program permits the user also to compute photolysis rate constants as a function of elevation above sea level.

An overview is available on website [http://www.epa.gov/ceampubl/swater/gcsolar/index.htm]. For a complete discussion of the chemistry associated with this program, refer to the publication [Zepp et al, 1977].

GCSolar has been used for the modeling of photolysis rates for the latitudes 50° N and 60° N for rivers, lakes and marine [Madsen et al, 2001]. The calculation for lakes at 40° N have been added [Rasmussen, 2002] but not for rivers and marine waters as the lowest rate of photolysis is 98% at Latitude 50° N in winter. We have input 99% for rivers with Latitude 40° N in winter.

Estimated photodegradation within 28 days for FWA-5 in running waters, lakes and marine waters

Water body	Latitude	Spring	Summer	Autumn	Winter	Whole year
Flowing waters	40° N*	100%	95%	100%	99%	99%
	50° N	100%	93%	100%	98%	99%
	60° N	100%	91%	99%	74%	94%
Lakes	40° N	94%	97%	80%	60%	82%
	50° N	91%	96%	64%	36%	63%
	60° N	85%	94%	42%	15%	36%
Marine waters	40° N*	100%	100%	≅98%	≅90%	≅98%
	50° N	100%	100%	95%	74%	95%
	60° N	100%	100%	81%	38%	74%

* estimated from Latitude 50° N

The monitoring was done in rivers only. Therefore, further calculations were conducted with the photolysis of rivers in winter.

Derivation of risk characterizations (PEC/PNEC ratio) of the modeled river concentrations.

The column "Relative concentrations of FWA-5 [%] in natural waters" and photolysis rates in rivers at winter time from above tables were taken to estimate the concentrations in rivers from North to South of Europe. Modeled concentrations and PEC/PNEC ratios are typed in blue, while the estimated values for Northern European countries are typed in red.

Modeled concentrations of FWA-5 considering photolysis and resulting risk quotient expressed as PEC/PNEC ratios

Country	Monitored worst case river [ng/L]	Modeling of expected relative concentrations of FWA-5 [%]	Calculation of expected concentrations of FWA-5 [ng/L]	Modeled photolysis in winter after 28 days [%] [Rasmussen, 2002]	Modeled concentrations adjusted to photolysis [ng/L]	**Adjusted PEC/ PNEC* ratios**
Latitude 50°				98%		
Glatt (CH)	634	100	634		634	**0.011**
Chemnitz (D)	144	36	228		228	**0.004**
Latitude 40°				99%		
Naples (I)	na	37	235		233	**0.004**
Madrid (E)	na	121	767		759	**0.013**
Latitude 60°4				74%		
Stockholm (S)	na	84	533		706	**0.012**
Helsinki (FIN)	na	65	412		546	**0.009**
Oslo (N)	na	99	628		848	**0.014**

* PNEC (Predicted no effect concentration) is 60'000 µg/L.
PEC = Predicted Environmental Concentration

Basis of the calculation is the relative concentration set as 100% for the Swiss situation. Therefore, monitored and modeled values for the river Glatt are identical. The other modeled values are adjusted to the country-specific detergent usage and FWA-5 concentration as well as Latitude specific photolysis.

River Chemnitz has a modeled concentration of 228 ng/L based on the relative concentration and adjusted to the specific laundry detergent usage per capita. The monitoring value was only 144 ng FWA-5/L. This is due to a lower detergent usage and/or different mix of FWAs.

The monitoring program leads to risk characterization ratios (PEC/PNEC) of 0.011 for Glatt and 0.004 for Chemnitz and is far below 1. This suggests no adverse effect to the environment.

The concentrations in Italy and Spain are slightly adjusted from 98 to 99% photolysis. The respective PEC/PNEC ratios are 0.004 and 0.013 and therefore in the same range then Germany and Switzerland.

The river concentrations in the Nordic countries increase due to the lower photolysis rates in winter. Estimated photolysis in running waters drops in winter from 98 to 74%. The actual concentration of FWA-5 in the Nordic countries is expected to be very low as the majority of the detergent brands do not contain FWAs. To estimate the influence of FWA-5 if it were used, the Swiss figure of 0.045% incorporation rate of FWA-5 has been input and adjusted to the country-specific detergent usage and latitude. The highest PEC/PNEC ratio was 0.014, calculated for the Oslo region. This value is very close to the one in the river Glatt as a reasonable worst-case scenario. Thus, it can be shown that if the Nordic countries were to use FWA-5 to the same extent as the Swiss, FWA-5 would also not have an adverse effect on the environment.

4.5 Conclusions

An extensive research program has been conducted by the Swiss Institute of Technology (ETH) and the chemical industry to characterise and assess the final fate and environmental risks of FWA-5.

It has been shown that DSBP-type FWAs undergo a rapid isomerization, followed by a photodegradation of >70% within 28 days. The two defined yielding photodegradation products are readily biodegradable according to OECD 301F.

Environmental risk assessments were conducted with the default values of EUSES 1.0 as well as with a specific detergent scenario. The assessment was complemented with a monitoring study in 18 Swiss and German rivers. All results in the calculated/measured environmental compartments (water, sediment, terrestrial, air) indicate a PEC/PNEC ratio of well below 1. The Dutch Competent Authority [van de Plassche, 1999] confirmed these findings.

During discussions of the results with competent authorities, scientists and consumer organizations, the question was raised whether these results can also be applied to the Northern and Southern countries of Europe or whether extensive monitoring studies for each and every European country are necessary. To answer this question we conducted a modelling of photolysis depending on latitude by a program called CGSOLAR 1.2. The photolysis rate is almost independent of the temperature but is a direct function of the available light. Consequently, photolysis rates decrease with the rising geographic latitude of European surface waters. On the other hand, the discharge of laundry detergents and therefore FWAs to effluent treatment plants and surface water decreases from South to North as a consequence of regional differences in detergent usage.

These contrary effects result in risk characterization ratios that are similar for the geographic regions from North to South in Europe. Thus, the conclusion of the draft HERA risk

assessment that the use of FWA-5 has no adverse effect on the aquatic environment has been confirmed.

It can therefore be concluded that FWA-5 has no adverse effect to the environment.

5. Human Health Assessment

5.1 Consumer Exposures to FWA-5

5.1.1 Product Types

The use of FWA-5 is mainly in washing powders and liquid detergents; a smaller market is in laundry soap bars. The FWA-5 concentration in these products is about 0.05% in soap bars, washing powders and liquids range in concentration from 0.05 to 0.1%, and the maximum concentration is likely to be 0.14% (Ciba Specialty Chemicals, Inc., internal communication).

The use of FWA-5 in laundry products is designed to produce an optical brightening of the fabric by deposition of the substance to the fiber. In some instances or in certain geographical areas, clothes are hand-washed with detergents and laundry soap bars may be the principal product used. It is also predictable that food-contact household items such as eating utensils or dishes may be washed in detergents containing FWA-5.

5.1.2 Consumer Contact Scenarios

Based on the product types we anticipate the consumer exposure routes for FWA-5 to include the following:

1. Direct skin contact with the finished consumer product
2. Release from clothes fibers to skin
3. Inhalation of detergent dust
4. Immersion during hand-washing of garments or dishes
5. Oral ingestion of residue on eating utensils and dishes
6. Oral ingestion from mouthing or sucking on treated fabric
7. Oral ingestion from food and drinking water
8. Eye contact with products
9. Accidental or intentional over exposure

5.1.3 Consumer Exposure Estimations

The consumer exposure models given in the HERA guidance document are used along with the data presented in the Table of Habits and Practices for Consumer Products in Western Europe, which was issued by the European Soap and Detergent Industry Association, AISE [AISE/HERA, 2002]. This table presents use data for cleaning products in grams/task, use frequency, duration of task and other intended uses. While minimum, maximum and typical use frequencies and amounts are given in the table, we have taken the average or median figures are used for the exposure estimations with the understanding that further refinement will be possible if necessary…… In some cases, it is necessary to make additional assumptions, where so, these are described.

5.1.3.1 Direct Skin Contact: Hand-washed Laundry

It is not uncommon that laundry is washed by hand and results in direct contact of detergent

solutions with skin of the hands and forearms (1980 cm^2; TGD Part I, Annex IV). Laundry detergent, containing 0.1% FWA-5, is generally added at 1% in water for hand washing (10 mg detergent per mL wash water). The transfer rate from water to skin is not known but an estimated highest likely systemic exposure can be made by using 20 mL as the volume of liquid on the exposed skin surface as the source of FWA-5 for absorption, for which 1% is assumed to be the maximum amount absorbed percutaneously (Schaefer and Redelmeier 1996). This skin-contact volume is based on assuming a film thickness of 0.01 cm (EU TGD, 1996) uniformly over the 1980 cm^2 skin area. The detergent in bar form is assumed to give the same exposure to FWA-5 as would powder or liquid detergents, although it is clear that the exposure could be somewhat different in the time course to reach the same concentration of FWA-5 in the water or from direct hand contact with the soap bar. Hand washing of laundry may average 4 times per week (4/7 =0.57 per day) based on information compiled in the HERA Table of Habits and Practices (AISE/HERA, 2002)

Using the above information, the systemic exposure (Exp_{sys}) to FWA-5 is estimated according to the following approach:

[Volume on skin x detergent conc. x FWA-5 conc. x absorption rate x frequency] / BW

$Exp_{sys\ (direct\ skin\ contact)}$ = [20 x 0.01 x 0.001 x 0.01 x 0.57] / 60 **= 0.00002 mg/kg BW/day**

5.1.3.2 Direct skin contact: Hand washing of dishes and utensils

To our knowledge FWA-5 is not added to dishwashing powders or liquids, but it is conceivable that a laundry detergent containing FWA-5 could be put to this use. Accordingly, the human exposure to FWA-5 is estimated for hand washing dishes, utensils, and food preparation items. As presented in the previous scenario we use the following parameters:

F_1	percentage weight fraction of substance in product	0.1% (0.001)
C	product concentration in mg/ml:	10 mg/ml
A	dermal penetration rate, estimated	1% of applied
t	duration of exposure or contact	45 min (0.75h)
S_{der}	surface area of exposed skin	1980 cm^2
Sv	liquid volume on skin surface (S_{der} x 0.01 cm)	20 mL
n	product use frequency (tasks per day)	3
BW	body weight	60 kg

Exp_{sys} = (F_1 x C x S_v x A x n)/ BW

= [0.001 x (10 mg/ml) x 20 mL x 0.01 x 3] / 60 kg=

Exp_{sys} = 0.0001 mg/kg BW/day

5.1.3.3 Direct Skin contact: Pre-treatment of Clothing

Commonly, clothing stains are spot-treated by hand with detergent. If a powdered detergent is used a paste of about 60% (AISE, 2002) will be made or a liquid will be applied directly.

The skin surface area exposed will be only the hands (840 cm^2; HERA document) and the treatment duration will be 10 minutes or less. Because this exposure will be about an order of magnitude less (i.e., 2 x 10^{-6}) than that from hand washing of laundry as calculated above, we will not separately present it as contributing significantly to the total exposure to FWA-5.

5.1.3.4 Indirect Skin Contact: Transfer of FWA-5 from Clothing

FWA-5 is designed to remain on the clothing fibers after washing. Consequently, wearing the clothes will give skin contact with fabric containing FWA-5. The exposure to FWA-5 is estimated according to the following algorithm from HERA Guidance Document:

$$\mathbf{Exp_{sys} = F_1 \times C` \times S_{der} \times n \times F_2 \times F_3 \times F_4 / BW} \qquad \text{[mg/kg BW/day]}$$

For this exposure estimate the terms are defined with the following values for the calculation:

F_1 percentage (%) weight fraction of substance in product: Not used, = 1
C` product load in [mg/cm²] : Not used, = 1
S_{der} surface area of exposed skin in [cm²] = 17,600 cm^2 (excludes head and hands)
n product use frequency in number [events/day] : = 4/7 = 0.57, not used
F_2 percentage (%) weight fraction transferred from medium to skin: = 0.17 µg/cm^2
F_3 percentage (%) weight fraction remaining on skin: Not used, = 1
F_4 percentage (%) weight fraction absorbed via skin: = 1%
BW body weight in [kg]: = 60

The value of F_2 = 0.17 µg/cm^2 is based on experimental data with fabric and FWAs (Anliker and Müller 1975). These results indicate FWAs retained on fabric during washing may release from the fabric and transfer to skin, particularly in sweat-moistened areas, at this concentration. Daily Systemic Exposure Calculation:

$$\mathbf{Exp_{sys\ (indirect\ skin\ contact)}} = [(17{,}600\ cm^2)(0.17\ \mu g/cm^2)(1/100)(1mg/1000\mu g)] / 60\ Kg$$
$$= \mathbf{0.0005\ mg/Kg/day}$$

5.1.3.4 Oral Exposures to FWA-5

Oral exposures can be assumed to originate from drinking water, eating of fish or other aquatic organisms, plant products, and residues on eating utensils and dishes washed in detergents. For the oral intake from food and drinking water, the Environmental Risk Assessment for FWA-5, presented in Section 4, has estimated the human total daily intake as 1.49 x 10^{-5} mg/kg body weight/day. This is an amount that can be considered too low to be relevantly included in the total estimated systemic exposure calculation.

The daily exposure to FWA-5 from eating with utensils and dishware that have been washed in laundry detergents, which is a foreseeable unintended use of such a product, can be estimated according to the following algorithm from the HERA guidance document:

Exp_{sys} = F1 x C` x Ta' x Sa / BW

For this exposure estimate, the HERA Table of Standard Exposure factors (HERA Guidance Document) has been used to provide values for several of the terms in this algorithm:

F_1	percentage weight fraction of FWA-5 in product	0.1% (0.001)
C`	concentration of product in dish wash solution:	10 mg/cm^3
$T_{a'}$	amount of water left on dishes after rinsing	5.5 x 10^{-4} ml/cm^2
S_a	area of dishes in daily contact with food	5400cm^2
BW	body weight	60 kg

$Exp_{sys\ (oral\ dish\ deposition)}$ = [0.001 x (10 mg/cm^3) x (5.5 x 10^{-4} ml/cm^2) x (5400 cm^2)]/60 kg = **0.0005 mg/kg BW/day**

Assuming that 1% of the ingested FWA-5 is absorbed from the gut (Rose 1972), the estimated systemic dose is **SED_{oral}** = (5 x 10^{-4} mg/kg/day) x 1% = **5 x 10^{-6} mg/kg/day.**
This is an exceedingly small amount and can be considered as not contributing significantly to the total systemic estimated dose of FWA-5.

5.1.3.5 Inhalation Exposure: Detergent Powder Dust

The pouring and use of powdered laundry detergent has been estimated to release 0.27 µg dust per cup of detergent (van de Plassche et al., 1999). At 0.1% FWA-5 in the product the expected FWA-5 exposure could be **0.0004 µg/use**, or about 4 x 10^{-9} mg/Kg/day. This amount may also be considered insignificant and to not contribute to the total exposure of FWA-5.

5.1.3.6 Other Sources of Exposure

Eye Exposures. Accidental exposure of the eye to FWA-5 will occur in consumers only via a formulated product. Systemic absorption of FWA-5 is not likely to occur from such exposures. Data for 1% FWA-5 solutions in rabbit eye did not cause irritation. Because FWA-5 is used at concentrations less than 1%, we conclude that the eye irritation potential for FWA-5 will not contribute to the overall eye irritation hazard of a formulated product.

Accidental Over-exposures. Accidental or intentional over-exposure to FWA-5 directly is not considered a likely occurrence in the household, but it may occur secondarily via one of the finished consumer products. The low concentrations (0.14%) of FWA-5 in finished products compared to acute lethality values greater than 2000 mg/Kg body weight, makes it reasonable to assume a very low degree of risk for adverse effects from acute exposures to FWA-5. Accordingly, this assessment will not address this route of exposure.

5.2 Hazard Assessment

5.2.1. Summary of Available Toxicological Data

A large number of toxicity tests have been conducted with FWA-5 since its commercial inception in mid-1970. In this targeted risk assessment, those toxicology studies with the highest data reliability factors have been selected and are summarized below.

5.2.1.1 Acute toxicity

Five of the 7 studies listed in Table 1 pre-date GLP regulations but the study designs included at least 5 animals per sex per dose group and would meet the critical aspects of current testing standards as defined in OECD methodologies. The acute lethality test with a 21.3% formulation is relevant because this is the FWA-5 active ingredient concentration in the product as sold.

Table 1. Acute Oral (Gavage) Toxicity of FWA-5

Species	**Sex**	**LD50** (mg test material / kg body weight)	**Test Material**	**Reference** (all are unpublished studies)
Mouse	m, f	11,390	pure	Pericin & Thomann 1973
	m, f	4,420	pure	Pericin & Thomann 1974a
	m, f	4,130	pure	Pericin & Thomann 1976
Rat	m, f	6,725	pure	Sachsse & Bathe, 1975
	m f	>5000 >2000 < 5000	21.3% FWA-5	Thevenaz,P. 1984
	m, f	> 2000	pure	Ullmann et al. 1990a
Chinese hamster	m, f	6,030	pure	Pericin & Thomann 1974b

5.2.1.1.a Acute Inhalation toxicity

The acute inhalation toxicity of FWA-5 was evaluated in Wistar rats (Duchosal 1990). Three groups of 5 males and 5 females were exposed, nose only, to 3 concentrations of FWA-5 during a single four-hour period. Observations for clinical signs of toxicity and mortality were conducted during and following the exposure up to 28-day (group 3). Body weights were recorded prior to exposure and weekly thereafter. All animals were necropsied and subjected to gross examination.

The test substance was a powder of 90% purity (7% NaCl; 3% water) prepared for inhalation by an aerosol generator connected to a Brush-feed Micronising Jet Mill and then discharged to the exposure tube through a charge neutralizer. Test substance concentrations were determined gravimetrically and the aerosol relative concentration determined by a light scattering monitor. Particle size distribution of the atmosphere was determined with a Mercer 7-stage cascade impactor once during each exposure period. The oxygen concentration (20.9 02 vol %) was stable during the exposure periods. The exposure concentrations and chamber parameter are summarized in the following table.

FWA-5 Inhalation Acute test: Dose Group	Exposure (mg/L air) mean ± SD	Chamber Conditions		
		% particles below 3 μm	Temperature ° C	Relative humidity (%)
1	1.44 ± 0.20	75.0	20.3	20.2
2	2.83 ± 0.42	71.1	20.7	32.0
3	3.94 ± 0.51	70.8	22.5	16.7

Mortality: Deaths did not occur in the low exposure concentration (group 1). At the middle concentration (Group 2) one male died on test day 8 (20% mortality) and one female on test day 9 (20%). In Group 3, one male died on test day 2, two others on test day 10 (60%), and two females on test day 9 (40%).
Body Weights: No treatment-related effects were noted in animals of group 1. The mean body weight increase was less in group 2 than in group 1 during the first week of observation. In group 3, one surviving male lost weight during the first three weeks of observation whereas the other male gained weight at a normal rate. The average body weight of the three surviving females of this group decreased until the end of the second week of observation and then increased again.
Clinical Signs: No clinical signs were noted during exposure in any dose group.
After exposure, hunched posture, labored respiration and rales were noted in one female of group 1 on test day 3.
Sedation, hunched posture, stiff gait, labored respiration, rales and ruffled fur were noted in most animals of group 2. Sedation (one male and one female) and stiff gait were seen only on test day 1 whereas most other signs were observed for more than two weeks.
The same signs as well as tachypnea and alopecia (1 female only) were seen in animals of group 3. Rales were noted until the end of the third week of observation. Hunched posture, stiff gait, labored respiration and ruffled fur were observed until the end of the 4-week observation period.

Macroscopic Observations: At necropsy dark red foci were observed in lung of 2 males in Group 1, in 2 males and 2 females of Group 2, and 3 males and 2 females of Group 3.
As derived from the overall study results the acute LC50 values are shown in the following table:

LC_{50} Estimation	Males	Females	Combined
LC_{50} (mg/L air)	3.66	4.32	3.92
95 % Confidence Limit	3.44 - 3.90	3.82 - 4.89	3.61 - 4.27

5.2.1.1.b Acute Dermal toxicity
A group of five male and five female HanIbm: WIST (SPF) rats was treated with FWA-5 at 2000 mg/kg by dermal application (Ullmann et al., 1990b). Purity of the powdered test substance was 90% FWA-5, 7% NaCl, 3% water. A dosing solution prepared just before use was made by dissolving the test article in distilled water at a concentration of 0.5 g/ml and

then administering at a volume of 4 ml/kg body weight. To the back of each animal, clipped free of hair, the dosing solution was applied and then covered with a semi-occlusive dressing for 24-hours. The animals were examined for clinical signs four times during day 1 and once daily during days 2-15. Mortality/viability were recorded together with clinical signs at the same time intervals. Body weights were recorded on day 1 prior to administration and on days 8 and 15. All animals were necropsied and examined macroscopically.

No deaths occurred during the study. Recorded observations included slight scaling of the treated skin and yellow discoloration was observed in all animals. Clinical signs of toxicity did not occur. All of the local signs were reversible after 7 days. The body weight of the animals was within the range commonly recorded for animals of this strain and age. No macroscopic findings were observed at necropsy.

The median lethal dose of FWA-5 after single dermal administration to rats of both sexes, observed over a period of 14 days, could not be estimated as no death occurred. Therefore, the LD50 is estimated to be greater than 2000 mg/kg body weight. This study is judged to provide reliable information on the dermal toxicity of FWA-5.

5.2.1.2 Corrosiveness/Irritation

5.2.1.2.a Skin Corrosion/ Irritation

One skin corrosion/irritation test with FWA-5 (Maurer 1984a) was considered to provide reliable data and information. Although the study was not conducted under GLPs, the study design and final report are in accordance with OECD guideline number 404 (1981).

The test was performed on 3 young adult male New Zealand White rabbits weighing 2.2 to 2.3 kg. They were housed individually in metal cages, were kept at a constant room temperature of 20±3 °C, at a relative humidity of 30-70%, and on a 12 hours light cycle day. The animals received ad libitum standard pelleted rabbit food (Nafag No. 814; Gossau, Switzerland) and water. Prior to treatment they were acclimatized for a minimum of 5 days. The test article was applied as a liquid formulation containing 21.3% FWA-5 in water.

About 24-hours before treatment an area of about 6 sq. cm was shaved on both flanks of each rabbit. Gauze patch of 2.5 x 2.5 cm covered with 0.5 mL of the test material was applied to one flank and a control patch to the contralateral flank. The patches were covered with an impermeable material and were fastened to the body of the rabbit with adhesive tape. The duration of treatment was four hours. The scoring of skin reaction was performed 1, 24, 48 and 72 hours after removal of the dressing. These scores were used in calculating the respective mean values for each type of lesion.

At one hour, erythema was observed in each animal (one with grade 2; two with grade 1) as was grade 1 edema. At 24-hours, no signs of erythema or edema were observed and the calculated primary irritation index was 0.00 (max.8.0). The substance did not cause any staining of the treated skin. No corrosive effects were noted on the treated skin of any animal at any observation time. Body weights were not affected.

Under the conditions of the present experiment FWA-5 was found to cause no irritation when applied to intact rabbit skin.

5.2.1.2.b Eye Corrosion/ Irritation

The studies judged to provide reliable hazard informatin for eye corrosion/irritation are summarized in Table 2. Three of the 7 studies listed in Table 2 pre-date GLP regulations, however, the study designs did include the number of animals and observations specified in the current testing standards laid down in OECD methodologies. The various test concentrations of FWA-5 were used to assess the hazard of the concentrations commonly used in consumer products.

Table 2. Eye Corrosion /Irritation of FWA-5

Species	Test Substance	Result	Reference
Rabbit	10% in distlled-water pure (powder)	irritating irritating	Küger 1974
Rabbit	pure (powder)	irritating	Ullmann 1975
Rabbit	21.3% solution	Irritating	Maurer 1984b
Rabbit	Tech. Grade (87% ai)	irritating (R 41)	Ullmann et al. 1991
Rabbit	30% solution	Irritating	Rijcken 1993
Rabbit	15% solution	not irritating	Braun 1995
Rabbit	1% solution	not irritating	Wnorowski 1999

In each of the studies in Table 2, FWA-5 was determined to be not corrosive. The body weights of animals were not adversely affected in the several tests.

5.2.1.2.c Sensitization

In order to assess the cutaneous sensitising potential of FWA-5, the Maximization-Test was performed in 30 (20 test and 10 control) female albino Guinea pigs (Ullmann et al., 1990). The test substance was composed of 90% pure FWA-5, 7% NaCl, and 3% water.

The intradermal induction of sensitisation was performed with a 5% dilution of the test article in physiological saline and in an emulsion of Freund's Complete Adjuvant (FCA) / physiological saline. The epidermal induction of sensitisation was conducted under occlusion with the highest non-irritating concentration of test article, 25 % in Vaseline. Two weeks after the epidermal induction application the challenge was completed by epidermal application of the test article at 25 % in Vaseline under occlusive dressing. The animals of the control group were induced with Vaseline and FCA/physiological saline and challenged similarly to those animals of the test group.

Cutaneous reactions, i.e. erythema and eschar, as well as edema formation were evaluated at 24 and 48 hours after removal of the dressing. In each of the control and treated animals, at both 24- and 48-hours, all skin reaction readings were zero, no sign of erythema. Signs of toxicity were not evident in the Guinea pigs of the control or test group. No deaths occurred.

In this study none (0%) of the animals of the test group were observed with erythematous reactions after treatment with a non-irritant test article concentration of 25 % in Vaseline. No skin reactions were observed in the control group. Therefore, FWA-5 is considered to be a

non-sensitiser when used under the described test conditions.

5.2.1.3 Repeated Dose Toxicity

Chronic-Oncogenicity Feeding Study. A GLP-compliant life-time study (Basler 1990) was completed with rats (Tif:RAIf, SPF) exposed to FWA-5 in their feed at 0, 500, 5000, or 50,000 ppm. The equivalent dosages, based on chemical analysis of the feed and consumption, were 19, 190, and 2300 mg/kg/day in males and 21, 226, and 2620 mg/kg/day in females. The test article purity as determined during the study was about 86% FWA-5, 7% NaCl, and 7% water.

The test substance did not affect mortality and appearance and behavior were similar in all groups on test. Increased food consumption and a 10% decrease in body weight were observed in both sexes of the high dose group. Water consumption showed a dose-related increase in the two highest dose groups with a corresponding increase in urine output observed in these groups. Hematology and clinical blood chemistry parameters did not show treatment-related effects. In the high dose group, significantly increased organ-to-body weight ratios for liver ($p \leq 0.01$) were seen in males, and in males and females for kidney ($p \leq 0.05$). The test substance did not adversely affect other parameters.

Macroscopic examinations at necropsy revealed an increased incidence of pancreateic nodules and masses in the high dose group males and females. Histopathology revealed statistically significant test article-related neoplastic effects to the pancreas of high dose males and females. Nodular hyperplasia of the exocrine pancreas was observed in 51 of 78 ($p \leq 0.001$) high dose males versus 6 of 78 control group males, and in 10 of 79 ($p \leq 0.05$) high dose females versus 1 of 78 control group females. Other non-neoplastic lesions seen in the dosed animals were not related to treatment with FWA-5.

Exocrine pancreas adenoma, a benign tumor, was observed in males of the 5,000 and 50,000 ppm dose groups at an incidence of 2/79 and 18/78 ($p \leq 0.05$), respectively, compared with 0/78 in control. Pancreatic carcinoma, a malignant tumor, was also observed in 2/78 high-dose males and although not statistically significantly increased, the rarity of this tumor and the treatment-related finding of adenomas in this group suggest the carcinomas could be related to the treatment. In females, adenomas in exocrine pancreas occurred only in the high dose group (2/79) and were within the historical control range; carcinomas were not observed in any of the females.

For this study, the No Observable Adverse Effect Level (NOAEL) is 5000 ppm or 190 mg/kg/day for males and 226 mg/kg/day for females.

The mechanism of pancreas responses to FWA-5 was further investigated and the findings are summarized below in Additional Data section, 5.2.1.8.

5.2.1.4 Genetic Toxicity

The outcomes of the genotoxicity tests with FWA-5 are summarized in the following table and full details for each test are given below.

Table 3. Genotoxicity Results for FWA-5 tested as pure material. Study details are given below.		
Test System/ Assay	**Result**	**Reference**
S. typhimurium; E. coli; Ames	Negative with and without S9	Poth 1989
Chinese Hamster V79: Chromosome aberration	Negative without S9 Positive with S9	Heidemann 1990
Mouse bone marrow; micronucleus	Negative	Völkner 1990
Rat hepatocytes- UDS	Negative	Fautz 1991

Bacterial Reverse Mutation. The test article FWA-5 was assessed for its potential to induce gene mutations according to the plate incorporation test using *Salmonella typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 (Poth 1989).

The assay was performed in two independent experiments, using identical procedures, both with and without liver microsomal activation. Each concentration, including the controls, was tested in triplicate. The test article was tested at concentrations of 10 to 5000 µg/plate.

Toxic effects, evidenced by a reduction in the number of spontaneous revertants, occurred in strain TA1538 at 1000 and 5000 µg/plate with metabolic activation and in strain TA 98 at 5000 µg/plate with and without metabolic activation. These effects occurred in both experiment I and II.

In all strains used the test article showed normal background growth up to 5000 µg/plate with and without S9 mix. An increase in the reversion rate occurred concurrent to cytotoxicity in strain TA 1535 (exp. I) at 5000 µg/plate with S9 mix, in strain TA 1537 (exp. II) at 1000 µg/plate without S9 mix, and in strain TA 98 (exp. II) at 33.3 and 100 µg/plate in the presence of S9 mix. Up to the highest investigated dose, no dose-dependent and reproducible increase in revertant colony numbers was obtained in the *Salmonella typhimurium* strains used. The presence of liver microsomal activation did not influence these findings. Appropriate reference mutagens were used as positive controls and showed a distinct increase in induced revertant colonies.

In conclusion, it can be stated that in the described mutagenicity test and under the experimental conditions reported, the test article did not induce point mutations by base pair substitutions or frameshifts in the genome of the strains used.

In vitro Chromosome Aberration. FWA-5 was assessed for its potential to induce structural chromosome aberrations in V79 cells of the Chinese hamster in vitro in the absence and presence of metabolic activation by S9 mix (Heidemann 1990).

Preparation of chromosomes was done 7 h (high dose), 18 h (low, medium and high dose) and 28 h (high dose) after start of the treatment with the test article. The treatment interval was 4 h. In each experimental group two parallel cultures were used. Per culture 100 metaphases were scored for structural chromosome aberrations. The following dose levels were evaluated:

	without S9 mix:	with S9 mix:
7 h:	100.0 µg/ml	50.0 µg/ml
18 h:	5.0; 50.0; 100.0 µg/ml	5.0; 50.0; 100.0 µg/ml
28 h:	100.0 µg/ml	50.0 µg/ml

In the pre-experiment on toxicity, the colony forming ability was clearly reduced, in the absence and presence of S9 mix, after treatment with test substance concentrations higher than 30.0 µg/ml. In the cytogenetic experiment the mitotic index was reduced after treatment with the highest dose levels in the absence (28 h) and presence (7 h, 18 h) of S9 mix, indicating that FWA-5 had cytotoxic properties.

In the absence of S9 mix the test article did not increase the frequency of cells with aberrations at any fixation interval. The aberration rates of the cells after treatment with the test article (0.50 % - 2.00 %) were in the range of the control values (1.00 % - 2.50 %).

However, in the presence of S9 mix, at fixation intervals 7 h and 28 h, the aberration rates in the samples treated with 50.0 µg/ml were statistically significantly increased as compared to the corresponding solvent controls. At fixation interval 18 h, after treatment with 50.0 µg/ml only a slight increase in cells carrying exchanges (1.50 %) was observed as compared to the corresponding solvent controls (0.00 %). This effect gives additional indication of the mutagenic potential of the test article.

The occurrence of polyploid metaphases after treatment with the test article did not show relevant deviations from the control data. EMS (0.72 mg/ml) and CPA (1.40 µg/ml) were used as positive controls and showed distinct increases in cells with structural chromosome aberrations.

In conclusion, it can be stated that in the described study and under the experimental conditions reported, FWA-5 induced structural chromosome aberrations in the V79 Chinese hamster cell line.

Mouse Bone Marrow Micronucleus Test. This study was performed to investigate the potential of FWA-5 to induce micronuclei in polychromatic erythrocytes (PCE) in the bone marrow of the mouse (Völkner 1990). The test article was dissolved in NaCl-solution (0,9%). This solvent was used as the negative control. Six male and six female NMRI mice were assigned to the solvent control, test substance, or positive control group. The test substance was administered as a single dose by gavage once at 5000 mg/kg body weight at a volume of 10 ml/kg body weight. Cyclosphosphamide was used as the positive control and was administered at 40 mg/kg body weight as a single oral dose.

In a pre-experiment this dose level was estimated to be the maximum attainable dose because the animals expressed slight toxic reactions indicated as reduction of spontaneous activity followed by apathy. Additionally, after treatment with the test article the number of NCEs per 1000 PCEs was enhanced as compared to the corresponding negative controls, thus indicating that FWA-5 induced cytotoxic effects at this dose.

In the main experiment, at 24 h, 48 h and 72 h after a single application of the test article the bone marrow cells were collected for micronuclei analysis. Ten animals (5 males, 5 females) per test group were evaluated for the occurrence of micronuclei as observed in 1000

polychromatic erythrocytes (PCE) scored per animal.

To describe a cytotoxic effect due to the treatment with the test article the ratio between polychromatic and normochromatic erythrocytes (NCE) was determined in the same sample and reported as the number of NCE per 1000 PCE.

In comparison to the corresponding negative controls there was no enhancement in the frequency of the detected micronuclei at preparation intervals 24 hours and 72 hours after application of the test article. Biometric analysis (Mann-Whitney test) demonstrated a statistically significant difference ($p<0.05$) between control and test article data at preparation interval 48 hours. However, this biometric result is considered to be of no relevance, because the negative control value at this preparation interval was very low as compared to the actual negative control rates and in comparison to the historical laboratory control value.

Results for cyclophosphamide, the reference mutagen used as positive control, showed a distinct increase of induced micronucleus frequency.

In conclusion, it can be stated that during the study described and under the experimental conditions reported, the test article did not induce micronuclei as determined by the micronucleus test with bone marrow cells of the mouse. Therefore, FWA-5 is considered to be non-mutagenic in this in vivo micronucleus assay.

Unscheduled DNA Synthesis in Rat Hepatocytes. The test article FWA-5 was assessed in the in vivo/ in vitro UDS assay for its potential to induce DNA repair (UDS) in the hepatocytes of Wistar rats (Fautz 1991). The positive control substance, 2-acetylaminofluorene (2-AAF) prepared in DMSO/polyethylene glycol 400 (1+9), was administered once by gavage at 100 mg/kg body weight.

The test article was formulated in bi-distilled water. This vehicle was used as the negative control. Five male rats were assigned to each of the negative control, test substance and positive control group. The volume administered orally was 10 ml/kg body weight (b.w.). The test article was administered at dose levels of 1000 mg/kg b.w. for a 4-hour treatment period and at 100 or 1000 mg/kg b.w. for the 16-hour treatment period.

For each dose level, including the controls, hepatocytes from three treated animals were assessed for the occurrence of UDS. After a treatment period of 4 and 16 hours, respectively, the animals were narcotized and sacrificed by liver perfusion. Primary hepatocyte cultures were established and exposed for 4 hours to ^{3}HTdR, which is incorporated if UDS occurs.

No toxic reactions of the animals occurred at any of the treatment periods or in any of the dose groups. In addition, neither the viability nor the in vitro attachment of the hepatocytes was dramatically affected due to the in vivo pre-treatment with the test article. The inter-individual variations obtained for the numbers of isolated hepatocytes as well as for the attachment-efficiency (NR assay) are in the range of the historical laboratory control. In case of hepatotoxicity the NR-values expected would be approximately zero.

No dose level of the test article revealed UDS induction in the hepatocytes of the treated animals as compared to the current negative controls. Neither the nuclear grains nor the resulting net grains were enhanced due to the in vivo treatment of the animals with the test

article for 4 hours or 16 hours, respectively. In the positive control group the in vivo treatment with 2-AAF caused distinct increases in the number of nuclear and net grain counts.

In conclusion, it can be stated that during the described study and under the experimental conditions reported, the test article did not induce DNA-damage leading to repair synthesis in the hepatocytes of the treated rats.

Overall conclusion for Genetic Toxicity: FWA-5, by the weight of the evidence from in vitro and in vivo assays, is considered to be not mutagenic.

5.2.1.5 Carcinogenicity

Photocarcinogenicity. Test article-related tumors did not occur in hairless mice exposed to FWA-5 as a 0.1% aqueous suspension and 20-minutes of simulated full sunlight 5 days per week for 40 weeks (Forbes and Urbach 1975).

Hairless mutant mice (Skh:hairless-1) were housed in custom-built stainless steel irradiation cage units. The animals were put into the cages at 6-8 weeks of age and had free access to laboratory chow and tap water throughout the period of study. The light source was a 6 kw-long arc xenon burner (Osram XBF 6000) with a filter to eliminate UV shorter than 290 nm and to attenuate the IR (ATLAS Electric; Chicago). The output curve is a good match for a mid-latitude sea level solar spectrum. The long axis of the lamp was hung vertically and animal housing units were arranged around the lamp. The UV flux at the side (exposed surface) of the cage was monitored with a zirconium WL 767 phototube. The average flux was .042 W/m2 erythema effective energy (EEE) during a daily (Mon. -Fri.) 2 hour exposure period for a maximum surface dose of 300 J/m2 per day (EEE).

The actual skin dose was influenced by the position of mice during exposure. The cages on each rack were rotated daily to minimize cage position-related differences. Mice were moved to clean cages once weekly. Dosing for all animals was by bathing each for 2 minutes in a test solution 30 to 60 minutes before light treatment. The solution was at treatment room temperature (27 C), contained in a glass tray. Cage units with 6 mice in individual cubicles were set into the glass trays, bringing the fluid level to within one cm of the top of the unit. The mice could swim or cling to the unit, with all but the head bathed. The animals adapted quickly to this mode of treatment; growth and longevity compared favorably with those of untreated conventionally-housed mice. Mice were treated daily with solutions for 2 weeks prior to the first light treatment.

All treatment solutions were made fresh daily and contained 1 g of XTA-154 brightener-free detergent (Proctor and Gamble Co, Cincinnati, Ohio) per liter of distilled water. One solution contained only detergent and was used as the vehicle control. A second solution contained the detergent and 0.1 g 8-methoxy psoralen (8-MOP) per liter, suspended by heating. FWA-5 was tested at 0.1 g/1 in a detergent solution.

For the study of phototoxicity, a group of 10 mice was pretreated once as described above with each of the test solutions, followed 30 minutes later by exposure for 2 hours to the long-arc xenon lamp. To study photocarcinogenesis, 24 of the 48 mice treated with each solution were exposed to the xenon lamp daily, 5 days per week for 40 weeks. The other 24 mice were kept as un-irradiated controls.

Results

Phototoxicity Experiment. A single two-hour exposure to the xenon lamp produced a moderately severe phototoxic response in mice pretreated with 8-MOP and only a barely perceptible erythema in all others.

Carcinogenesis Experiment. The fluorescence of the skin of FWA-5 -treated mice increased during the first 2 weeks. No direct determination was made of the amount of FWA on the skin, but the bathed mice were compared under black light with mice that had received once to controlled areas of skin various concentrations of FWA-5 dissolved in methanol. The FWA-5 residue on bathed mice was estimated to be approximately 1-µg/cm^2 skin. Xenon lamp exposure did not appreciably alter the skin fluorescence.

All irradiated mice had transitory erythema during the 2nd to 3rd weeks of UV treatment. By 10 weeks, the mice exposed to 8-MOP were distinguishable from all others: They showed areas of more severe erythema, hyperplasia and dry desquamation. Except for skin fluorescence, the groups of unirradiated mice were indistinguishable. The 8-MOP treated mice had higher tumor yield and prevalence than the irradiated, detergent only treated controls. The FWA-5 -treated group had lower tumor yield and prevalence than the controls. Most of the tumors developed on the animals' sides, with very few on the midline of the back, or on the head, ears, snout, or abdomen.

This study is of limited reliability because the dosage of FWA-5 is not known, the number of animals is too low, and insufficient information is contained in the report to evaluate animal responses. The study does support the concept that under a worst case exposure to a detergent solution containing FWA-5 and UV irradiation, phototoxicity and carcinogenicity is an unlikely outcome.

5.2.1.6 Reproduction and Developmental Toxicity

a. Reproductive effects

The following study does not provide reliable data or results because it was conducted at Industrial Bio-Test Laboratories, Inc. (Northbrook, Illinois, USA).

A 3-generation reproduction study employing albino rats fed diets containing either 40, 200, or 1,000 ppm FWA-5 (Haley 1973). The following results were obtained during the investigation.

Test and control group body weight data were similar throughout the investigation. There were no untoward behavioral reactions noted during the investigation. Gross autopsy performed on the animals found dead failed to reveal any relationship between the death of the animals and the exposure to FWA-5. Gross and histopathologic examinations of sacrificed parental animals from each generation, as well as organ weights and organ to body and organ to brain weight ratios, revealed no differences between treated and control animals which could be correlated with the ingestion of FWA-5. No alterations in the reproductive performance of animals fed FWA-5 were observed which could be attributed to the test material ingestion.

Test and control dams delivered essentially the same numbers of pups throughout the investigation.

The numbers of pups retained through weaning and pup survival indices revealed various reductions among treated groups in comparison to the control group. These reductions failed

to reveal any consistent relationship with the level of the compound exposure and could not be correlated with the ingestion of FWA-5.

All pups obtained during the investigation were judged to be free of gross external anomalies. Test and control pup body weights were similar throughout the investigation. Gross and histopathologic examinations conducted upon test and control progeny chosen randomly from the F1b litters revealed no findings that could be correlated with the exposure to FWA-5.

The OECD Provisional Guidance for the Initial Assessment of Health Effects (Draft, http://www.oecd.org/ehs/guide/sd96-4-6.html) recommends, when a Developmental toxicity study is available, that data for reproductive toxicity endpoint may be taken from repeat dose study that has documented examinations of reproductive organs. Such data are available for FWA-5: In the chronic (lifetime) feeding study in rats summarized below (Basler 1990), the primary sex organs of the males and females did not show treatment-related adverse effects as indicated by organ weight differences, gross examination, and microscopic histology examination.

From this indirect evidence it can be inferred that FWA-5 is not expected to have adverse effects on reproduction.

b. Developmental toxicity (Teratogenicity).
In this study, FWA-5 was tested for maternal toxicity and its embryotoxic, fetotoxic, and teratogenic potential in albino rats (FitzGerald 1991). Results from a range-finding study were the basis for testing FWA-5 at 1000 mg/kg body weight. The test substance purity was 86.4% and for dosing was administered by gavage in an aqueous solution of carboxymethylcellulose (0.5% w/w). The control group received the vehicle solution.

Female Tif:RAI f (SPF) hybrid rats, about 2-months of age and nulliparous, were randomly assigned, 24 each, to the two study groups. Within each group, a proven fertile male rat of the same strain was placed in a mating cage with 3 females each. The female was removed and indicated as pregnant if vaginal lavage showed spermatozoa or a vaginal plug was observed; this was designated as gestation day zero.

Single daily doses of 0 or 1000 mg/kg body weight were administered from day 6 through day 15 of gestation, inclusive. The dose volume in both groups was 20 ml/kg body weight, based on the daily body weight.

Females were caged individually in Macrolon cages containing standardized soft wood bedding material. Room temperature was 20±3 °C, relative humidity 30-70%, and a daily cycle of 12 hours light. The animals received ad libitum standard pelleted rat food (Nafag No. 890; Gossau, Switzerland) and water. Prior to mating the females were acclimatized for a minimum of 7 days. Dams were killed on gestation day 21 and fetuses removed by cesarean section for examination. About one-half of each litter was taken for visceral evaluation by the Wilson slicing technique after fixation. The remaining fetuses from each litter were fixed, cleared with KOH solution and then treated with alizarin red S for examination of skeletal features.

Results
Maternal Data. There were no remarkable cage-side observations during the study. Maternal

body weights and food consumption were not affected by treatment. All animals survived to necropsy on gestation day 21, except for one dam from the treated group, found dead on gestation day 15. Necropsy revealed no pathological findings. Necropsy of all other animals did not reveal adverse effects or abnormal findings.

Reproduction and Cesarean Section Data. Three animals in the control group were not pregnant, and one in the treated group died on gestation day15. Thus, the number of pregnant animals with viable fetuses at necropsy was 21 and 23 for the control and treated group, respectively.

The number of implantation sites and preimplantation losses were comparable in the two groups. Early resorption rate was not affected by treatment, and there were no late resorptions, abortions or dead fetuses. Thus, the number of viable fetuses was comparable in the two groups. Statistical analysis of these endpoints did not show significant differences from the control group.

Fetal Examination. Fetal sex ratios and body weights were not affected by treatment. The findings observed during fetal examinations were of equal frequency in the control and treated groups; thus, treatment-related effects on fetal external, visceral, or skeletal development did not occur in this study.

In the present study, the test article was not toxic to dams or fetuses at the limit dose of 1000 mg/kg. There was no evidence for embryotoxic or teratogenic potential. The no observed effect level of FWA-5 for rat dams and fetuses in this study was 1000 mg/kg body weight/day.

5.2.1.7 Additional Data

A. Metabolism. One study is available. Rats dosed once orally with ^{14}C-FWA-5 at 5 mg/kg body weight (2.09 µCi/mg) were sacrificed after 96 hours and tissues assayed for the labeled test material (Rose 1972). Daily collections were made for expired carbon dioxide, urine, and feces individually from each of the 4 males and 4 females dosed. The results indicate that for both males and females FWA-5 did not accumulate in liver, kidney, brain, muscle, body fat, or blood, and only traces (0.03% of dose) were observed in urine. Expired air did not contain labeled carbon dioxide.

Feces was the main route of removal: after 48-hours 90% of the administered dose was found unchanged in the feces. This was confirmed by TLC on Silica gel plates of feces extract vs. FWA-5 standard. The excretion half-life time was 8.2 hours for males and 13.6 hours for females.

The study showed 94% to 96% recovery of the total radioactivity and use of methods suitable for the determination of reliable endpoints.

B. Percutaneous Absorption.
In vitro skin penetration of ^{14}C-FWA-5 was assessed in porcine (Wollny 1995).

Porcine ears were obtained from a local slaughter-house on the day of slaughter and before

the pigs were steam-cleaned. The outer ear region was washed and cleaned with cold water. After carefully shaving, the skin was removed by dissection. The skin sample was then stored in a freezer until use (within a week). The thickness of the skin varied between 2 and 3 mm. The surface area of the skin which was in contact with the test substance during the penetration-assay was 1.13 cm2.

For the determination of the absorption of the test article the skin was mounted in glass diffusion chambers with a diameter of 1.13 cm2 (area of skin) and a volume of 7 ml. These chambers are subdivided in an upper part (donor chamber) and in a lower part (receptor chamber). A recorded volume of physiological saline (0.9% NaCl-solution) was placed in the receptor chamber of each diffusion cell, followed by the application to the donor chambers of 200 µl of the test article dissolved in bi-distilled water.

Three concentrations of the test article (100-, 10-, and 1 µg/ml chamber volume) where tested using 4 chambers at each concentration. The top of the donor chamber was covered with Parafilm. The diffusion chambers were placed in an incubator at 37 °C. Samples (0.5 ml) were taken from the receptor chambers after 0, 0.5, 1, 4, 8, and 24 hours and analysed by liquid scintillation counting. The volume of the fluid in the receptor chamber was kept constant by the addition of 0.5 ml of fresh receptor fluid to the receptor chamber immediately after removal of each sample. By plotting the time dependent increase in concentration of the test article in the receptor chamber, the permeation rate was determined.

The positive control was 14C-mannitol since it is known to permeate porcine skin. The control chambers showed a time dependent permeation of 14C-mannitol with a permeation constant of 1.3x10-4 cm/h. Due to a leaking chamber only 3 chambers could be evaluated of the four in the test group with 100 µg/ml FWA-5.
For FWA-5 exposed porcine skin, penetration to receptor fluid was not detected at any concentration tested in the time range up to 24 hours.

Results from this study are considered reliable as indication of skin penetration by the test substance. The study design is acceptable. Porcine skin is considered a suitable representative of human skin as indicated by the Opinion (23 June 1999) of the EU Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP).

From the study results it appears FWA-5 will not penetrate full thickness skin. However, current interpretation of in vitro percutaneous penetration study results (SCCNFP 1999, above) indicate a substance is considered to be absorbed not only if detected in the receptor chamber (penetration), but also if found in skin layers below the stratum corneum where it may be taken up by the cutaneous circulation. Accordingly, it is conservative to assume some portion of dermally occurring FWA-5 will be available for absorption by the circulation.

The FWA-5 molecule was designed to have substantivity to fabric and it is not unreasonable to assume percutaneous penetration to be restricted by substantivity to skin. A **1% absorption factor** of the total FWA-5 on exposed skin, not a time-rate of transfer, will be used throughout this assessment to estimate the systemic contribution from dermal exposures.

C. Mechanistic Studies of Pancreatic Tumorigenicity.
This study (Bouis 1998) was intended to identify possible acute stimulatory effects of FWA-5

on the rat exocrine pancreas by means of two experimental designs:
(1) Animals were fed overnight with FWA-5 admixed to the diet at 50000 ppm. Additional animals were fed overnight with cholestyramine, a bile salt binding resin known to exert a trophic effect on the rat pancreas, admixed to the diet at 60000 ppm. Following treatment, the animals were sacrificed and a possible stimulation of the exocrine pancreas was investigated by analysis of alpha amylase and lipase activities in pancreas homogenates.
(2) Animals were treated by single oral administration of FWA-5 at 1000 mg/kg body weight and sacrificed after 90 min or 6 h. Additional animals were treated with camostat, a known trypsin inhibitor and stimulator of exocrine pancreatic growth (Goke et al. 1986), at 200 mg/kg body weight and also sacrificed after 90 min or 6 h. A possible stimulation of the exocrine pancreas was investigated by analysis of pancreatic alpha amylase and lipase activities in pancreas homogenates of animals sacrificed 90 min after treatment as well as by the determination of pancreatic ornithine decarboxylase (ODC) activity and polyamine content in animals sacrificed 6 h after treatment.

Overnight feeding or single oral administration of FWA-5 resulted in a statistically significant ($p \leq 0.05$) decrease of pancreatic alpha amylase activity to 56 and 69% of control, respectively, as well as in a statistically significant ($p \leq 0.05$) decrease of pancreatic lipase activity to 78 and 62% of control, respectively. Similarly, overnight feeding with cholestyramine or a single oral administration of camostat statistically significantly ($p \leq 0.05$) decreased pancreatic hydrolytic enzyme activities to 57 and 37% of control for alpha amylase, and to 80 and 45% of control for lipase, respectively.

Upon single oral administration of FWA-5, pancreatic ODC activity and pancreatic putrescine, spermidine and spermine contents were similar to control. In contrast, a single oral administration of camostat caused a strong, 150-fold statistically significant increase in pancreatic ODC activity, as well as a 7-fold increase in pancreatic putrescine content.

In conclusion, the results show that FWA-5, like cholestyramine and camostat, stimulated pancreatic enzyme release but was without an effect on pancreatic ODC activity and polyamine content.

A second study (Weber 1998) was designed to investigate an stimulating effect of FWA-5 on the exocrine pancreas. For that purpose, male rats were treated with FWA-5 admixed to the diet at 10000 or 50000 ppm for different time periods up to 28 days. Additional animals were treated by oral intubation with camostat at 200 mg/kg/day for the same time periods. The rats used were Tif:RAIf (SPF), from the same strain and supplier as in the lifetime feeding study (Basler 1990).

Treatment with FWA-5 at 10000 or 50000 ppm resulted in an overall mean daily test article intake of 810 or 4306 mg/kg body weight, respectively. Treatment with FWA-5 or the reference compound camostat was well tolerated and no treatment-related deaths or clinical signs were observed except for grayish/softened/sticky feces of animals treated with 50000 ppm FWA-5.

Treatment with FWA-5 resulted in a statistically significant ($p \leq 0.05$) dose-related decrease in body weight. Since the food consumption, except for the first two days with a clear reduction at 50000 ppm, was similar in control and both FWA-5 groups, the food consumption ratio was increased in a dose-related manner after treatment with 10000 or 50000 ppm FWA-5. This may indicate a reduced ability of food utilization or may at least partially be due to the

lower caloric content of food, admixed with 1% or 5% FWA-5. Treatment with camostat had no significant effect on body weight, food consumption or food consumption ratio.

In the absence of a significant effect on the absolute pancreas weight, treatment with FWA-5 at 50000 ppm resulted in significantly ($p \leq 0.05$) increased relative pancreas weights at days 7 and 28. This weight effect is attributed to the observed hypertrophy and increased proliferation of pancreatic acinar cells. The acinar cell hypertrophy, observed from day 7 on, was determined by histopathology and by morphometry of acinar cell number per unit area. The observed hypertrophy was also reflected by moderately increased pancreatic protein content after 14 days of treatment with 50000 ppm FWA-5. An increased proliferation of acinar cells, likewise contributing to the increased organ weight, was found at day 7. Treatment with 10000 ppm FWA-5 had no significant effects on pancreatic weight, protein content, histopathology and cell proliferation. Treatment with the reference compound camostat at 200 mg/kg/day induced strong hypertrophy and hyperplasia and consequently a strong increase in pancreatic weight and some increase in pancreatic protein content.

In addition to measurements on pancreatic acinar cell size and number, the contents of the pancreatic polyamines putrescine, spermidine and spermine were determined. These naturally occurring polyamines are known to play an important role in cell proliferation and differentiation. Increased pancreatic contents of polyamines putrescine and spermidine have also been reported in camostat stimulated pancreatic tissue (Loser et al. 1989). Statistically significant ($p \leq 0.05$) increased levels of putrescine (day 3) and spermidine (day 28) were found after treatment with FWA-5 or camostat (days 14 and 28). Although the absence of a clear time - and dose-relationship with FWA-5 and camostat was not apparent in this relatively short study, the biological significance of these findings may suggest some adaptive response to the treatments or insufficient duration of the test. However, it can be concluded that this study indicates a statistically significant increase in pancreatic polyamines and stimulation in growth of the exocrine pancreas of male rats treated with 50000 ppm of FWA-5 for up to 28 days.

Other investigations indicate enhanced pancreatic growth can promote non-genotoxic pancreatic tumor formation (Woutersen et al. 1990). The initial indications of this pancreatic stimulation were observed with FWA-5 after 28-days of dosing at 50000 ppm, which over a life-time of exposure could provide sufficient time to follow the classic course to malignancy: hyperplasia and adenoma leading to pancreatic carcinoma, as was seen in the 2-year study in rats (Basler 1990).

As reported above, FWA-5 is not mutagenic and not genotoxic in standard assays. According to the concept of non-genotoxic carcinogenesis, thresholds exist below which no subchronic changes are observed and consequently no tumor development occurs (Purchase 1994). From the data presented, 5000 ppm and 10000 ppm FWA-5 are considered below the threshold for subchronic effects and, accordingly, no tumorigenicity was observed in the life-time carcinogenicity study at these doses (Basler 1990). For FWA-5 it is concluded that the pancreatic tumorigenicity is not a genetic effect and may be viewed as a threshold event in light of the genotoxicity data, the low incidence of carcinomas, and the additional dose-response mechanism studies summarized here.

D. Receptor binding assay: Androgen and Estrogen receptors in vitro

The potential for FWA-5 to bind in vitro with fresh cytosolic preparations of rat prostate gland to derive androgen receptors was conducted with FWA-5 at concentrations from $5x10^{-4}$ to $5x10^{-10}$ and compared to the positive control substance tritiated methyl trienolone (Twomey 2003a). The results indicate FWA-5 does not bind to the androgen receptor and it does not successfully displace or compete with androgen for the receptor.

In a second test, the potential for FWA-5 to bind in vitro with fresh cytosolic preparations of rat uterine tissue to derive estrogen receptors was conducted with FWA-5 at concentrations from $5x10^{-4}$ to $5x10^{-10}$ and compared to the positive control substance tritiated estradiol (Twomey 2003b). The results indicate FWA-5 does not bind to the estrogen receptor and it does not successfully displace or compete with naturally occurring estrogens for the receptor.

5.2.2 Identification of Critical Endpoints

Summary of Toxicological Endpoints:

1. Oral lethality >2500 mg/Kg body weight
2. Inhalation LC_{50} = 3.92 mg/L
3. Not eye irritant in a 1% solution; concentrated substance is eye irritant
4. Not skin irritant
5. Not a skin sensitizing substance in Guinea pig
6. Not genotoxic and not mutagenic
7. Developmental toxicity not observed in rat dams, embryos, or fetuses at 1000 mg/Kg/day
8. Reproductive toxicity endpoint, by indirect data, considered negative; Negative for in vitro binding to estrogen and androgen receptors.
9. Repeat dose lifetime feeding study in Wistar rats supports NOAEL of 5000 ppm feed, or 190 mg/Kg/day for males and 226 mg/Kg/day for females.
10. Mechanistic studies in rats support the absence of a genotoxic mechanism as the origin of the benign adenomas and carcinomas of the male exocrine pancreas observed at 50,000 ppm and are early indications that the pancreas effects are likely associated with the excessive dose level acting as a growth stimulator in the exocrine pancreas.
11. Hairless mice did not show a photocarcinogenic response to exposures of 0.1% FWA-5 solutions and simulated sunlight.

From these endpoints, we have selected the life-time feeding study in rats as the most relevant to FWA-5 use in consumer products. The key factor substantiating this selection is the use of FWA-5 mainly in laundry products that may be used repeatedly by consumers for a long period of time.

5.2.3 Determination of NOAEL

Because the lifetime feeding study of rats has been selected as representative of the critical endpoint for consumer exposure, for the risk assessment the overall **NOAEL is 190 mg/Kg/day**.

5.3 RISK ASSESSMENT

5.3.1 Margin of Exposure (MOE) Calculation

The MOE is the ratio of the No Observed Adverse Effect Level and the systemic estimated dose (SED) as calculated above in section 5.1.2. From the available animal studies, the 2-year life-time feeding study in rats provides a **NOAEL = 190 mg/Kg/day** from the males.

5.3.1.1 Direct Skin Contact: Hand-washed Laundry

$\mathbf{MOE_{direct\ skin}}$ = systemic oral NOAEL /estimated systemic dose =
190,000/0.02 [µg/kg BW/day] = $\mathbf{9.5 \times 10^6}$

As shown in section 5.1.2, the other possible direct skin contact scenarios for direct contact with laundry powder and pre-treatment of clothing will result in even lower estimated systemic doses and will give a larger MOE. These are not given additional consideration in this risk assessment.

5.3.1.2 Direct Skin Contact: Hand-washing dishes

Using laundry detergent for washing eating utensils and dishware is not a usual occurrence but can be a foreseeable mis-use of detergents. The anticipated human systemic exposure from this activity would give a large margin of exposure and is as follows:

$\mathbf{MOE_{direct\ skin}}$ = systemic oral NOAEL /estimated systemic dose =
190,000/0.01 [µg/kg BW/day] = **1900**

5.3.1.3 Exposure scenario: indirect skin contact wearing clothes

$\mathbf{MOE_{indirect\ skin}}$ = systemic oral NOAEL /estimated systemic dose =
190,000/ 0.5 [µg/kg BW/day] = **380,000**

5.3.1.4 Exposure scenario: inhalation of detergent dust- laundry processes with powder detergents

The pouring and use of powdered laundry detergent has been estimated to release 0.27 µg dust per cup of detergent (van de Plassche et al., 1999). At 0.14% FWA-5 in the product the

expected FWA-5 exposure could be **0.0004 µg/use**, or about 4 x 10^{-9} mg/Kg/day. This amount may also be considered insignificant, will not contribute to the total exposure of FWA-5, and is not addressed further for the risk assessment.

5.3.1.5 Exposure scenario: oral route via eating utensils and dishware

$MOE_{oral\ route}$ = systemic oral NOAEL /estimated systemic dose =
190,000/0.5 [µg/kg BW/day] = **3.8×10^5**

5.3.1.6 Exposure scenario: accidental overexposure -oral ingestion and accidental contact with the eyes

These exposure scenarios are not expected to be sources of adverse risk to humans from FWA-5.

5.3.1.6 Total Consumer Exposure

The consumer exposure via direct and indirect skin contact as well as via oral route results in an estimated total body burden of 0.02 + 0.01 + 0.5 +0.5 = 1.03 µg/kg BW/day. Comparison with the systemic NOAEL of 190,000 µg/kg BW/day yields an MOE of 184,466. As shown above, it is assumed that inhalation does not contribute to the systemic total consumer exposure.

MOE_{total} = systemic oral NOAEL /estimated total systemic dose =
190,000/ 1.03 [µg/kg BW/day] = **184,466**

5.3.2 Risk Characterization

The estimated human exposure to FWA-5 shows a very large Margin of Exposure. This large MOE will be more than adequate to cover any uncertainties in the toxicology (hazard) database and those associated with extrapolations from animal tests to human safety.

Therefore, FWA-5 is considered safe for use in consumer products resulting in human exposure.

5.4 DISCUSSION AND CONCLUSIONS

Exposure estimates from consumer product uses indicate the aggregate estimated FWA-5 internal exposure is SED = 1.03 µg/kg/day, which accounts for the relevant dermal and oral

exposures. Inhalation exposures are considered to be negligible. Considering detergent products containing FWA-5 are used throughout most of the life of consumers, the critical endpoint selected was from the lifetime feeding study in rats. This study indicated the relevant NOAEL is 190 mg/Kg/day.

The estimated human exposure to FWA-5 shows a **Margin of Exposure of 337,478**. Risk characterization indicates this is an adequate difference to cover all uncertainties in the toxicology database and extrapolations and supports a conclusion that FWA-5 should be considered safe for use in consumer products.

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