www.oecd.org/document/63/0,3343,en_2649_34379_1897983_1_1_1_1,00.html

SIDS Initial Assessment Report

for

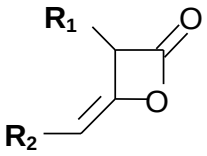
SIAM 20

Paris, France, 19-22 April 2005

1.	**Chemical Name:**	Alkyl ketene dimer
2.	**CAS Number:**	84989-41-3
3.	**Sponsor Country:**	United Kingdom Contact Point: Dr. Steve Robertson Environment Agency – Science Group Chemicals Assessment Unit Isis House, Howbery Park Wallingford OX10 8BD, UK Fax: +44 1491 828 556
4.	**Shared Partnership with:**	Sponsor Country and Consortia Members
5.	**Roles/Responsibilities of the Partners:**	The industry consortium [BASF, Eka Chemicals, Hercules, Kemira, Mare, NOF and Raisio] collected the data, prepared the documentation and discussed it fully with the sponsor country.
•	Name of industry sponsor/consortium	Global Producers of Alkyl Ketene Dimers (GPA)
•	Process used	Discussion and meetings.
6.	**Sponsorship History**	
•	How was the chemical or category brought into the OECD HPV Chemicals Programme?	This substance is sponsored by the UK under the ICCA Initiative and is submitted for first discussion at SIAM 20.
7.	**Review Process Prior to the SIAM:**	The industry consortium collected new data and prepared the updated SIDS dossier, and draft versions of the SIAR and SIAP. UK government peer-reviewed the documents and audited key studies.
8.	**Quality check process:**	Robust summaries prepared by the industry consortium.
9.	**Date of Submission:**	August 2004
10.	**Date of last Update:**	January 2005
11.	**Comments:**	The industry contact point is Dr P. Ungeheuer, TEGEWA,

Germany acting on behalf of the GPA [BASF, Ciba, Eka Chemicals, Hercules, Kemira, Mare and NOF]

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	84989-41-3* *CAS No 68390-56-7 is used in the USA
Chemical Name	2-Oxetanone, 3-C_{12-16}-alkyl-4-C_{13-17}-alkylidene (Alkyl Ketene Dimer, AKD)
Structural Formula	 $R_1 = C_{12-16}$, $R_2 = C_{12-16}$

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

There are no specific toxicokinetic data for alkyl ketene dimer (AKD). Due to the high lipophilicity and the effects in rat feeding studies, intestinal absorption and distribution in the body is anticipated. Cross reading from a newly developed alkyl ketene dimer demonstrated that dermal absorption is very low. AKD is of low toxicity after a single exposure (LD_{50} oral, rat >40 000 mg/kg bw). It is neither irritating to skin and eyes nor a skin sensitiser, as concluded from experimental animal and human studies. AKD was not genotoxic *in vitro* (three Ames tests and a mammalian cell chromosomal aberration test). There are no other data regarding the carcinogenic potential of AKD. In an OECD TG 422 screening test, repeated oral gavage of 100, 350 and 1000 mg/kg bw/day to rats resulted in inflammation of several organs, including female reproductive organs. As a result of ovary inflammations, an increase in pre-implantation losses (the number of implantation sites compared to corpora lutea was reduced) was observed at all doses; this effect is secondary to the general organ inflammation and therefore not a specific reproductive effect. No effects on male reproductive organs and pup development were observed. In a 90-day feeding study in rats inflammation of several organs (typically lymph nodes, liver, heart, kidney, pancreas and lung) were observed at concentrations of 650 ppm and 6500 ppm (which was the highest dose tested) in the feed; at a concentration of 65 ppm in the feed no adverse effects were observed. The LOAEL was 63.4 and 69.6 mg/kg bw/day and the NOAEL was 6.3 and 6.8 mg/kg bw/day for males and females, respectively (estimated from dietary concentrations of 650 and 65 ppm, respectively). The observed inflammation is considered a generic response in the rats to higher molecular weight hydrocarbons, and is not considered to be a response specific to AKD.

Environment

Alkyl ketene dimer (AKD) is a waxy solid material with a low melting point. i.e., between 43.6 °C and 56.4 °C, and decomposes above 200° Celsius without boiling. It has a very low solubility in water, predicted to be 5.6×10^{-7} to 4.8×10^{-11} mg/l. Its predicted Log Kow of 11 – 15 suggests a high bioaccumulation potential. Its vapour pressure is predicted to be very low, 5.85×10^{-13} – 6.12×10^{-10} hPa. Distribution modelling using Mackay Level I indicates that AKD will partition to sediment and soil (49.54% to soil and 50.10% to sediment) and the estimated Koc of 1.51×10^{7} - 2×10^{9} indicates that AKD will adsorb strongly to soil and sediments. Its Henry's law constant is predicted to be 46 – 648 indicating that AKD could partition from water into the atmosphere but in practice this is unlikely to be an important route of transport in the environment due to its low water solubility.

AKD is predicted to photodegrade rapidly in air with a half life for indirect photolysis of 3.7 hours. Studies on the hydrolysis of commercial AKD preparations show that AKD hydrolyses readily under neutral and alkaline conditions but only slowly under acid conditions. Half lives of between 23 – 140 hours have been calculated for AKD emulsion at 30˚C, pH 8, under the conditions of a paper mill. There is no information available on the hydrolysis half lives in the aquatic environment. Based on the available data, AKD is expected to hydrolyse readily under neutral and alkaline conditions in the environment and is assumed to be stable to hydrolysis at acidic

pHs in the environment, pH 5-7. AKD has been shown to be readily biodegradable when tested in the presence of small amounts of emulsifier, used to increase bioavailability of the substance to micro-organisms, with >94% biodegradation in 28 days.

Alkyl ketene dimer showed no toxicity in acute toxicity tests on the fish *Danio rerio*, the aquatic invertebrate Daphnia magna and the algae *Selenastrum capricornutum*. The E/LC50s were all above the water solubility limit. In a 21 day reproduction test with *Daphnia magna*, conducted on a dispersion of AKD, no effects on either reproduction or growth were observed at the highest concentration tested (mean measured concentration of 0.8 mg/l). This indicates that the NOEC is greater than the water solubility limit. There is no data available on toxicity to sediment dwelling organisms. AKD is not inhibitory to activated sludge microorganisms, in an activated sludge respiration inhibition test the 30 minute EC20 was > 1000 mg/l.

AKD is of low acute toxicity to plants and earthworms. The 14d EC50 (emergence) and 28d EC50 (vegetative growth) for oat (*Avena sativa*), sunflower (*Helianthus annuus*) and mung bean (*Phaseolus aureus*) were all > 1000 mg/kg soil. The 14 day LC50 for the earthworm *Eisenia foetida* is >1000 mg/kg.

Exposure

Alkyl ketene dimers are produced in a Best Available Technology [BAT] closed process in Belgium, China, France, Finland, Germany, Italy, Japan, Sweden, United Kingdom and United States of America. The total production volume amount is between 10 000 and 50 000 tonnes per annum. AKD is normally transported and used as a dispersion containing between 5 and 25% AKD.

Alkyl Ketene Dimer [AKD] is used exclusively as a process chemical by the paper industry to add some hydrophobic character to the surface of the cellulose fibres. This is traditionally known within the industry as “sizing”. Typical examples of paper products manufactured with AKD are office paper, liquid packaging board and folding-box board. The amount used is between 0.05 and 0.3% by weight of the end product.

Releases into the environment may occur during the production and processing of AKD. AKD itself is unlikely to be detected in paper as it either reacts with the cellulose to form a covalent bond or with the water present in the paper making system to form the dialkyl ketone. Releases of AKD itself are therefore not anticipated from paper recycling. Release of AKD to wastewater treatment plants could potentially occur from production, formulation and paper making sites.

A survey completed by the GPA consortium demonstrated that, for the five production sites covered by the survey, 29 people (2 of whom were female) worked continuously with the product and another 20 people (no females) worked intermittently, i.e., up to 50% of their time. The recommended personal protection equipment [PPE] included gloves, goggles and overalls in the manufacturing, maintenance and disposal/waste management areas.

Consumer exposure to AKD is negligible because it is only used in the manufacture of paper and board. Paper made with AKD can be used in the manufacture of packaging materials intended to come into contact with food. However, the AKD itself will not be detected in the paper as it will have either reacted with the cellulose fibre to form a covalent bond or with the water present in the paper making system to form the dialkyl ketone. AKD has many national approvals for use in food contact packaging materials, e.g., in America, France, Germany, Italy and The Netherlands.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses properties indicating a hazard for human health (inflammation of several organs following repeated oral exposure, and secondary to this, pre-implantation loss). Based on data presented by the Sponsor country, exposure to humans is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: The high Log Kow of AKD suggests it has a high bioaccumulation potential. However, the concern that AKD could cause long term effects in the environment is reduced by the data which indicate that AKD is readily biodegradable by micro-organisms when tested in the presence of a 1.5% concentration of emulsifier and hydrolyses under neutral and alkaline conditions. AKD shows low acute toxicity to aquatic organisms, plants and earthworm and low chronic toxicity to Daphnia and algae. It is therefore of low priority for further work due to its low hazard potential.

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1 IDENTITY

1.1 Identification of the Substance

CAS Number:	84989-41-3
IUPAC Name:	2-Oxetanone, 3-C12-16-alkyl-4-C13-17-alkylidene derivs.
Molecular Formula:	$C_{28}H_{52}O_2$ to $C_{36}H_{68}O_2$
Structural Formula:	Refer to Figure 1a
Molecular Weight:	420 to 532
Synonyms:	AKD Alkylketendimers Alchildichetene a catena grassa Alkyl ketene dimer wax

The substance 2-Oxetanone, 3-C12-16-alkyl-4-C13-17-alkylidene has the CAS Number 84989-41-3. It is more commonly referred to in the industry as alkyl ketene dimer (AKD). It is manufactured from the linear, saturated natural fatty acids obtained from the rendering of animal fats and plant oils. The first stage in the manufacturing process is to make a fatty acid chloride, which is then dimerised in the presence of an aliphatic amine to form the alkyl ketene dimer. For historical reasons, the CAS Number used in the USA is different, i.e., 68390-56-7 and is listed on TSCA.

The only products currently available commercially are manufactured from mixtures of technical grade palmitic- (C16) and stearic acid (C18). Aquapel® 364, which is also manufactured from a mixture of technical grade palmitic- and stearic acid, was chosen as the test sample as it is not only the dominant product on the market but also, as confirmed by a survey of producers, is representative of what is available commercially.

2-Oxetanone, 3-C12-16-alkyl-4-C13-17-alkylidene and all the other products listed below are manufactured from technical grade palmitic and stearic fatty acids. All of the substances are low melting point, solid materials and, although many different CAS Numbers are listed on EINECS, all describe the same product and they could even be covered by the use of the one CAS Number, i.e., 84989-41-3.

This assessment refers to the single substance, 2-Oxetanone, 3-C12-16-alkyl-4-C13-17-alkylidene, as represented by CAS Number 84989-41-3. The CAS number 68390-56-7 is used in the USA for historic reasons, as explained above. GPA Members, who represent all the current AKD manufacturers, have already agreed to use only the 84989-41-3 CAS Number in Europe for this substance. The other CAS numbers listed in table 3 are no longer commercially supplied Historically the CAS numbers 10126-68-8, 42272-70-8, 67845-94-7 and 67845-95-8 have been used and can still be located when searching on the Scandinavian SPIN Database [http://195.215.251.229/spin.html]although they will not be used in the future**.**

1.2 Purity/Impurities/Additives

The typical purity ranges from 80 to 95% alkyl ketene dimer. Typical impurities are small amounts of unreacted fatty acid (~2 to 5%), hydrolysed alkyl ketene dimer (~1 to 5%) and alkyl ketene trimers and tetramers (~2 to 10%).

1.3 Physico-Chemical properties

Table 1 Summary of Physico-Chemical Properties*

Property	Value	Notes	Reference
Physical state	Solid	None	None
Melting point	43.6 to 56.4°C	Determined	Hercules Analytical Lab Report Nos. TSWR BLD 00-448 [29] and AD-99-232 [30]
Boiling point	-	Decomposes above 200° Celsius without boiling	Syngenta Process [47] Hazards Section, 2001
Density	0.84 g/cc	Determined	Mare, 2004 [37]
Vapour pressure	5.85×10^{-11}–6.12×10^{-8} Pa	Calculated	BASF, 2004 [8]
Water solubility	4.805×10^{-11}–5.64×10^{-7} mg/L at 25°C	Calculated	BASF, 2004 [8]
Partition coefficient n-octanol/water (log value)	>6 (11.25 – 15.18)	Calculated	BASF, 2004 [8]
Henry's law constant	0.643 – 6.2 atm*m^3/mole	Calculated	HENRY v 3.10 [48] [**Note:** Bond method used for the C12:C12 and C18:C18 AKD] Values of 46 – 648 Pa * m^3/mol are obtained using the following equation: Henry's Law Constant = vapour pressure (Pa) x molecular weight (g/mol) /water solubility (mg/l)]
Flash Point	171°C	Determined	Hercules Analytical Laboratory, 2001 [31]

* Measured water solubility and Log Kow data are available for a structurally related new chemical notified in the EU. The Log Kow is 5.5 and water solubility is 0.3 mg/l. Water solubility was measured using the turbidimetric method and may not therefore be particularly accurate. However, these values support the conclusion that AKD is of low water solubility and has a high Kow.

Figure 1a - Structural representation of the alkyl ketene dimer
see Table 2 for details of chain lengths

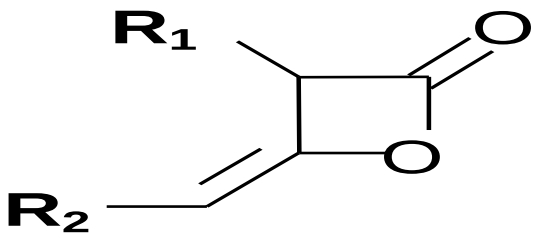


Table 2 Chain Lengths of Currently Available Alkyl Ketene Dimers

CAS No.	R1	R2	Chemical Name	Fatty Acids Used
84989-41-3	C_{12-16}	C_{12-16}	2-Oxetanone, 3-C12-16-alkyl-4-C13-17-alkylidene derivs.	Stearic acid and palmitic acid
68390-56-7	C_{12-16}	C_{12-16}	Fatty acids, tallow, hydrogenated, dimers, diketene derivatives	Stearic acid and palmitic acid

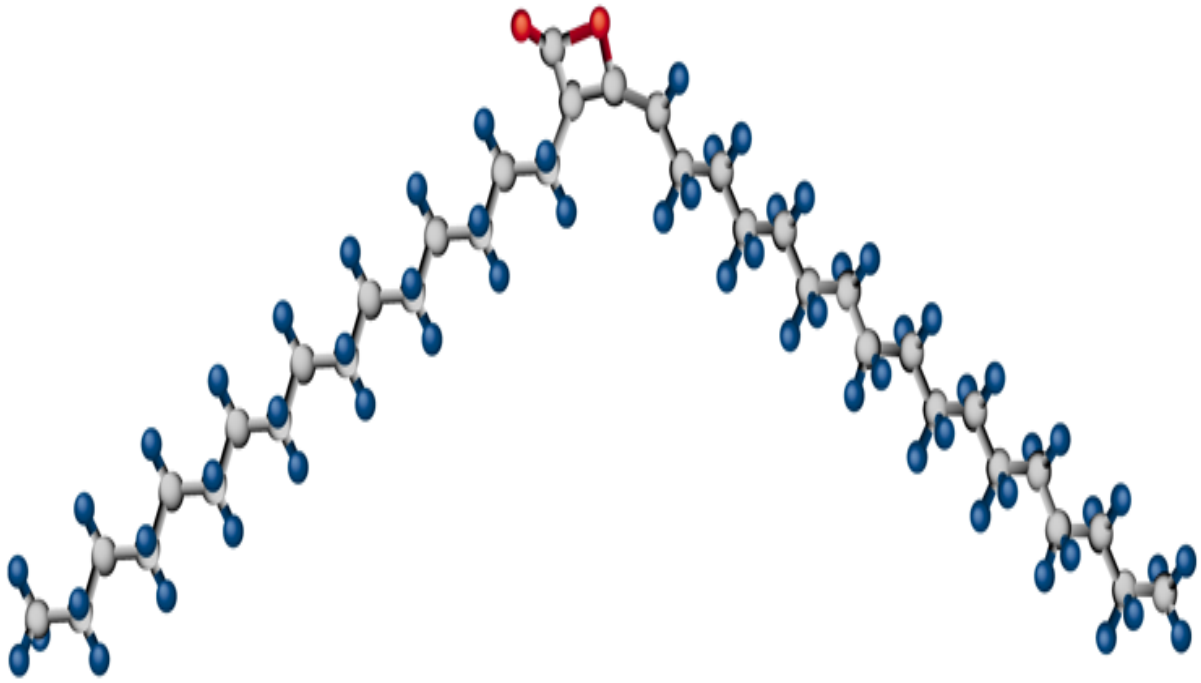
The following alkyl ketene dimers are listed on EINECS and have been included in Table 3 for completeness. Note that all fall within the scope of the CAS Numbers 84989-41-3 [Europe] and 68390-56-7 [USA], and none are currently being sold commercially.

Table 3 Chain Lengths of the Historically Registered Alkyl Ketene Dimers

CAS No.	R1	R2	Chemical Name	Fatty Acids Used
10126-68-8	C_{16}	C_{16}	2-Oxetanone, 4-heptadecylidene-3-hexadecyl-	Stearic acid
98246-87-8	C_{14-16}	C_{14-16}	2-Oxetanone, 3-C14-16-alkyl 4-C15-17-alkylidene derivs.	Stearic acid and palmitic acid
42272-70-8	C_{14}	C_{14}	2-Oxetanone, 4-pentadecylidene-3-tetradecyl-	Palmitic acid
67845-94-7	C_{14}	C_{16}	2-Oxetanone, 4-heptadecylidene-3-tetradecyl-	Stearic acid and palmitic acid
67845-95-8	C_{16}	C_{14}	2-Oxetanone, 3-hexadecyl-4-pentadecylidene-	Stearic acid and palmitic acid

Alkyl ketene dimer, as can be seen from Figures 1a and 1b, consists of a four membered lactone ring with an exocyclic double bond and two long chain aliphatic side chains. The chain lengths of R_1 and R_2 can vary within the limits given in Table 1.2, i.e., between C_{12} and C_{16} in each case.

Figure 1b – Visual representation of AKD



In addition to the "existing" products listed above a number of "new" alkyl ketene dimers have been notified to the European Regulatory Authorities. Details of the products and the toxicological reports on the substances were made available to the Sponsor Country during the lifetime of this programme. However, this hazard assessment does not cover these new substances.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Alkyl ketene dimers are produced in a Best Available Technology [BAT] closed process in Belgium, China, France, Finland, Germany, Italy, Japan, Sweden, United Kingdom and United States of America. The total production volume amount is between 10 000 and 50 000 tonnes per annum.

Alkyl ketene dimers are transported in drums (100 to 200 kg), big bags (500 to 1000 kg), IBC containers (~880 kg) or road tankers (15000 kg).

Alkyl ketene dimers are only used in one industrial process, i.e., the pulp and paper industry is the only recipient. Alkyl ketene dimers are used as paper-sizing agents, to improve resistance against aqueous based liquids by making the cellulose fibers slightly hydrophobic. Alkyl ketene dimer is used as a sizing agent in the manufacture of office paper, liquid packaging board and folding-box board. The amount used is between 0.05 and 0.3% by weight of the end product. However, it is important to recognise that the alkyl ketene dimer will not be detected in the paper as it has either reacted with the cellulose to form a covalent bond or with the water present in the paper making system to form the dialkyl ketone. There are several national food contact approvals for alkyl ketene dimers. A typical food contact application is internal sizing for liquid packaging board but, because paper cannot be used to store aqueous liquids for long periods of time, a barrier layer of polyethylene or aluminium is required for the packaging to perform effectively.

The most referred to food contact approvals are as follows:

- FDA (Food and Drug Administration, revised as of April 1, 2002) 21 CFR 176.120 "alkyl ketene dimers" allowing to use the alkyl ketene dimers and their hydrolysis products dialkyl ketones not to exceed 0.4 % by weight of the paper and paperboard. The petition dossier of this approval covers comprehensive studies of possible exposure via the packaging chain of Alkyl Ketene Dimers and the hydrolysis product including also complete toxicity studies for the hydrolysis product. **[Reference: 22]**

- BfR (Bundesinstitut für Risikobewertung [formerly known as the BgVV], Teil A, 52. Lieferung, Stand Januar 2002), Empfehlung XXXVI „Papiere, Kartons und Pappen für den Lebensmittelkontakt", Part B, additives, paragraph I.11. Di-alkyl(C10-C18)diketene, die bis zu 65 % iso-Alkylgruppen enthalten können, höchstens 1.0%. Empfehlung XXXVI/2 „Papiere, Kartons und Pappen für Backzwecke", II.A.5: Dialkyl (C10-C18)diketene, höchstens 0.5 %. **[Reference: 13]**

- Warenwet, Verpakkingen en Gebruiksartikelenbesluit, Hoofdstuk II – Papier en Karton (VGB/Aanv. 14, 12-2002) par 1.2.2.h. lijmen en vezelbindmiddelen: alkylketeendimeren, bereid uit gehalogeneerde vetzuren afkomstig an dierlijke of plantaardige oliën en vetten, ten hoogste 0.4 %. Hoofdstuk X-Deklagen, par. 6 Oplossinger in water, l. Watervastmakende middelen: alkylketeendimeren. **[Reference: 49]**

Schultz (Schultz, 1997) described the fate of Alkyl Ketene Dimers [AKD] (and other sizing agents), over the entire process of paper production. The main conclusion is that all products remain nearly quantitatively on the fiber. **[Reference: 45]**

To clarify the fate of the AKD during the recycling of paper, the content of both the AKD reacted with the fibre and the hydrolysed AKD (when added together they constitute the "total AKD" in the original paper) was determined in a screening study. The methods used were standard industry laboratory methods. **[Reference: 43]**

The Paper Industry is unusual as much of it is based on recycled fibre. Recycling falls into two general categories, i.e. 1.- where the paper is repulped and reused directly, and 2.- where it is also deinked prior to being reused. The term deinking, as its name suggests, involves separating the ink, used to either decorate the package or convey the message, from the paper fibre before it is reused.

Two types of paper were evaluated in the study: fine paper and liquid packaging board [LPB], i.e., specifically the plastic coated paperboard used in milk packaging. Samples were selected from grades typically found on the market. The LPB samples were pulped, the plastic film removed and no pulping chemicals were added. The fine paper samples were pulped, diluted and deinked using some standard deinking chemicals [no surface active chemicals, e.g., soap, were used in order to avoid problems with the analysis of the various samples]. The rejected material, consisting primarily of fillers and inks, along with the reclaimed, deinked and washed pulp from the flotation process were collected.

The samples were then analysed and the level of both fibre-reacted and hydrolysed AKD was determined and the "total AKD" in each of the various samples calculated. The analyses were performed by extraction followed by gas chromatography and the details can be found in a confidential report made available to the Sponsor Country. The liquid packaging board samples contained AKD 0.131% from which 0.069% was unreacted and 0.062% reacted AKD. After pulping the amount of AKD was 0.173%. The slight increase of AKD content can be explained by the removal of the plastic layer that did not contain AKD. After washing the amount of AKD was 0.12%. During extraction the "fibre-reacted AKD" does not separate from the fibres unless the paper is first treated with strong alkali to break the covalent bonds formed between AKD and fibre.

Most of the "fibre-reacted" and "hydrolysed" AKD in the liquid packaging board remained in the washed pulp and shall thus be further recycled. No further recycling to food contact paper and board is likely to occur as the deinked liquid packaging board is generally used for core board in paper reels.

The distribution of the "fibre-reacted" and "hydrolysed" AKD in fine paper samples seemed to be somewhat different compared to the liquid packaging board samples. The fine paper samples contained AKD 0.091 % from which 0.042 % was unreacted and 0.049 % reacted AKD. Before flotation the amount of total AKD was 0.040 % and after flotation 0.042%. The reject contained 0.30 % AKD and after washing the amount of AKD was 0.01 % in the pulp. The result from the reject was rechecked. The high amount clearly shows that there has been a substantial enrichment in the flotation foam. The unchanged level in the accept can be explained by dilution effect and due to the fact that the amount of reject in the flotation was low, only 3.7 %. A probable reason for this is that no surfactants were used. The washing removed the rest of the AKD. Only traces of the "fibre-reacted" and "hydrolysed" AKD were found in the washed fibres. The bulk of the "fibre-reacted" and "hydrolysed" AKD remains attached to the fines and fillers which are efficiently removed in the flotation deinking process so nearly all the AKD present in the paper ends up in the rejected material. The rejected material is then normally disposed of by either incineration followed by land filling the remaining ash or direct land filling in a waste deposit. In some countries, the sludge is spread onto agricultural land as a soil improver.

Alkyl ketene dimers are not used directly in consumer products.

Production of Alkyl Ketene Dimer

Exposure data are available for five production sites, all manufacturing products with the CAS No. 84989-41-3 [Reference 25]. All are waxy solids containing greater than 80% alkyl ketene dimer and typically the values are greater than 85%. Three producers reported using closed, automated or semi-automated, batch processes, one producer reported a closed continuous automated process and another, a campaign process. All the processes are in closed buildings except for one, which is outdoors. The number of operating days varies from 300 to 365 days per annum.

The total volume of alkyl ketene dimer produced globally in 2001 was less than 50,000 tonnes. Two producers reporting annual volumes of less than 5000 tonnes per annum and three others volumes of greater than 5000 tonnes per annum. Alkyl ketene dimer is transported in drums (100 to 200 kg), big bags (500 to 1000 kg), IBC containers (~880 kg) or road tankers (15000 kg). The survey revealed that all of the alkyl ketene dimer produced is used in the paper and board industry. The total number of people potentially exposed to alkyl ketene dimer during production is low. For the five sites surveyed, 29 people (two females), are working continuously with alkyl ketene dimer and another 20 (no females), are working intermittently, i.e., up to 50% of their time. Potential worker exposure to alkyl ketene dimers occurs during the packing, flaking, storing and sampling of the product. All producers reported, as Personal Protection Equipment [PPE], gloves and goggles in the process and laboratory, filling, emptying and transferring operations and all, except one, in maintenance and during disposal/waste management. For the process and maintenance areas all sites either have overall protection or a protective suit. The processes either have local- (two sites) or general ventilation (two sites) and one is segregated. No monitoring data for Alkyl Ketene Dimer was reported, although the sites have some monitoring data for other chemicals used in the manufacturing process. There are no reported contact allergy cases at any of the five production sites.

Two of the alkyl ketene dimer production sites have biological Waste Water Treatment Plants [WWTP], one uses the municipal biological WWTP, another one reported using an industrial WWTP based on flotation and activated carbon and another used a WWTP with iron phosphate

particles. There are no measured concentrations of Alkyl Ketene Dimers available for the WWTP influent or effluent. Flow through rate (size) of the WWTP for three sites was given as between 40 and 823 cubic metres per day. The sludge of the WWTP was either incinerated (two sites) or landfilled (two sites). The receiving water system is river for three sites, unknown for two sites. The low water flow rate of the receiving river (10 percentile) was given for two sites as between 350 and 734 cubic metres per second. Two sites reported the amount of Alkyl Ketene Dimers released with the waste, i.e., one at 47.5 tonnes/year and the other at 100 tonnes/year.

Use of Alkyl Ketene Dimers in the Formulating Plants

Alkyl ketene dimer wax is formulated into an aqueous emulsion before it is transported to paper mills where it is used as a production aid in the manufacture of paper and board. The formulated products are transported to customers in drums (sizes 100, 120 and 200 kg), IBC containers (1000 kg) and road tankers, sizes 16000, 20000, 23000 and 40000 kg. The formulated products are stored in tanks and dosed after dilution with water into a closed part of the paper machine.

Exposure data are available for nine formulation sites. The total volume of formulated alkyl ketene dimer manufactured at these sites was 7500 tonnes in 2001. All the alkyl ketene dimer emulsions are used as a sizing agent in the in the manufacture of paper and board. The concentration range of the alkyl ketene dimer in the emulsions is between 5% and 30%. Three of the formulations report end product usage at the same site, while the others supply to down-stream users.

One process is continuous, seven are batch processes and one is a campaign process. Three processes are open and seven are closed. Seven of the processes are semi-automated and two are manual. All are housed in closed buildings except for one, which is outside under a roof. The number of days they operate varies from 100 to 350 days per annum with seven of the sites operating for more than 250 days per annum.

The potential for human exposure during the manufacture of the formulated products, occurs via the dermal route, i.e., when opening the alkyl ketene dimers containers and during the dosing, sampling, maintenance and cleaning operations. PPE used at the sites are gloves, goggles, protective suits at four sites and one having overall protection. A respirator is used by one site in all operations and another reports its use during the filling/emptying/transferring operations. Six sites have general ventilation for the dosing, process, maintenance and laboratory areas. Three sites reported local ventilation for the process itself and one for the maintenance area. One site has segregated the filling, emptying, transferring and pouring operations and two others the weighing and mixing operations. The total number of people potentially exposed is 41 working continuously (no females) and 57 working (six females) intermittently. No monitoring data for alkyl ketene dimers at any of the sites was reported, although some measurements are reported for some of the other chemicals used in the manufacturing process. There are no reported contact allergy cases at any of the production sites.

Five of the Alkyl Ketene Dimer formulation sites have biological industrial WWTP; three use the biological municipal WWTP. One site reports using ultra-filtration and another flocculation before the biological WWTP. One plant has an electrolysis process with pressurised flotation followed by a physical/chemical separation process. One site has outsourced the wastewater handling. No measured data on the concentration of Alkyl Ketene Dimers in either the influent or the effluent of the WWTP were reported. The flow rates for the various WWTPs are 60, 150 and 984 (only less than 5% of the total for Alkyl Ketene Dimers wastewater) cubic metres per day. The sludge from the WWTP is incinerated at two sites, landfilled at four and one reported composting as sludge treatment. The receiving water system is reported to be river for five sites and other (canal) for one site. The reported low water flow rates of the receiving rivers (10 percentile) are 0.0219 and 734 cubic metres per second. The emissions to the environment are reported to be between 47 and 153

tonnes per annum as total sludge but the concentration of alkyl ketene dimers in the waste was not reported.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Schultz described the fate of alkyl ketene dimers (and other sizing agents), over the entire process of paper production. The main conclusion is, that all products remain nearly quantitatively on the fibre and, as with the earlier study, the only potential source of environmental exposure is during the recycling of the paper. **[Reference 45]**

Releases into the environment may occur during the production and processing of AKD. AKD itself is unlikely to be detected in paper as it either reacts with the cellulose to form a covalent bond or with the water present in the paper making system to form the dialkyl ketone. Releases during formulation and use of AKD are likely to be of AKD in the emulsified form since it is supplied as an emulsion. **[Reference 38]**

Releases of AKD itself are therefore not anticipated from paper recycling. Roughly half of the fibre used in global paper production is recycled fibre, packaging grades being the biggest user of recovered paper. There are paper grades not containing AKD, e.g. tissue and grades that seldom contain AKD, e.g. newsprint. Part of the paper not ending up into recycling process will be incinerated and the paper to be landfilled contains either covalently to cellulose bound AKD or hydrolysed AKD. If any AKD reached the environment it would however, be likely to hydrolyse in neutral or alkaline conditions.

Release of AKD to wastewater treatment plants could potentially occur from production, formulation and paper making sites. In a wastewater treatment plant, the SIMPLETREAT model predicts partitioning to the following compartments:

Air 0.1 – 1%
Water 7.7– 7.9%
Sludge 90 –91%
Degraded 1%

Two runs were conducted, for C12:C12 AKD and C18:C18 AKD to determine the range of possible values. The input parameters were as follows:

Log Kow: 8 (the maximum value advised by EUSES 2.0)

Vapour pressure: 5.85×10^{-11}, 6.12×10^{-8} Pa

Water solubility: 4.8×10^{-11}, 5.64×10^{-7} mg/L

MW: 420.73, 532.94

There is therefore the potential for exposure to soil from spreading of sewage sludge onto agricultural land. A small amount of AKD, which has not been hydrolysed through the reaction with water under alkaline conditions, is predicted to partition to water. **[Reference: 32]**

2.2.2 Photodegradation

Given the use and physico-chemical properties of alkyl ketene dimer, photodegradation is not seen as a relevant degradation pathway. However, model calculations (AOP v1.51) for indirect photolysis in the air predicted 50 % degradation after 3.7 hours, suggesting rapid photodegradation in the air. **[Reference 3]**

2.2.3 Stability in Water

Alkyl ketene dimer hydrolyses readily under neutral and alkaline conditions to form the dialkyl ketone but only slowly under acid conditions (Further details are available in the document 'GPA_SizingReactionScheme'[see Annex]). Studies are available on the hydrolysis of commercial AKD preparations but there are no valid hydrolysis studies available for AKD described by CAS Numbers 84989-41-3 [Europe] and 68390-56-7 [USA].However, a hydrolysis test is available for a structurally related alkyl ketene dimer notified as a new chemical in the EU under Directive 92/32/EEC. Hydrolysis was >10% after 5 days at pH 7 and 9, indicating that at these pHs alkyl ketene dimer could be considered to hydrolyse under environmental conditions. The test [OECD Guideline 111, GLP] indicated that the test substance hydrolysed under alkaline conditions (pH 7 (>95% after 5 days at 50°C, half life 10.4 hours at 30°C) and pH 9 (>95% after 5 days at 50°C, half life 4.4 hours at 30°C)]. No conclusion could be reached regarding hydrolysis at pH 4 due to inconsistencies in the data. The test report can be made available in confidence to regulatory authorities if required.

However, in practice it is well known that in alkaline conditions and at room temperature, hydrolysis will occur, leading to formation of the dialkyl ketone. Commercial experience at low pH is not available because wastewater treatment plants are normally run at neutral-to-mild alkaline conditions. AKD sizes are stored at relatively low pH, typically around 3, in cooled containers in order to avoid formation of the ketone hydrolysis product which reduces the technical sizing effect. **[Reference: 38 and Reference: 32]**

A stability study on AKD dispersion conducted at pH 3 over 4 weeks at temperatures 25˚C and 32˚C showed AKD losses of 4.5 % and 16.6 % respectively. **[Reference: 32]**

The hydrolysis of AKD in sizing emulsions has been studied by Marton who reviewed published data discussing sizing effects, hydrolysis of AKD and describes the hydrolysis of two types of AKD sizes:

- Weakly cationic sizing agent, pre-emulsified with cationic starch (mainly), containing 9% AKD and stabilized at pH 3,5 (known as AP emulsion)
- Strongly cationic size, containing 6% AKD and 9% emulsifier-stabilizer-promoter polymer solids, mainly polyamine amide-epichlorohydrin (PAE) resin (known as HC emulsion).

It was shown that the rate of hydrolysis was six times faster in the presence of PAE resin at room temperature than in the weekly cationic AKD emulsion. Raising the temperature to 50 degrees Celsius accelerated the hydrolysis still further to 18 times the reference value. Marton also calculated the approximate half lives of AKD in the emulsions, assuming a pseudo first order reaction, as:

T 1/2 at 30˚C, pH 8 = 140 h (AP emulsion) and 23 h (HC emulsion)

T 1/2 at 50˚C, pH 8 = 27 h (AP emulsion) and 1,5 h (HC emulsion)

In conclusion, based on the available data, AKD is expected to hydrolyse readily under neutral and alkaline conditions in the environment and is assumed to be stable to hydrolysis at acidic pHs in the environment, pH 5-7.

The toxicity of the dialkyl ketone has been extensively studied and the reports were made available to sponsor country as part of this programme. **[Reference: 22]**

Transport between Environmental Compartments

Releases into the environment may occur during production and processing of AKD. Distribution modelling using Mackay Level I V2.11 indicates that soil and sediment will be the target compartments with 50.10% predicted to partition to sediment and 49.54% predicted to partition to soil. The amount of AKD predicted to partition to the other compartments is negligible. **[Reference: 8]**

The estimated Koc using the PCKOCWIN model (v 1.66) is $1.51 \times 10^7 - 2.0 \times 10^9$. This indicates that AKD will adsorb strongly to soil and sediments.

The calculated Henry's Law Constant using the HENRYWIN v 3.10 model (bond method) is 0.643 - 6.2 atm/m^3/mole. This indicates that AKD could partition from water into the atmosphere but this is unlikely to be an important route of transport in the environment due to its low water solubility. Values for Henry's Law Constant of 46 – 648 Pa*m^3/mol are obtained using the following equation: Henry's Law Constant = vapour pressure (Pa) x molecular weight (g/mol) /water solubility (mg/l). This also indicates that AKD could partition from water into the atmosphere but this is unlikely to be an important route of transport in the environment due to the low water solubility.

2.2.4 Biodegradation

Alkyl ketene dimer is poorly soluble in water. Only dispersions of alkyl ketene dimer are used in the paper mill and this is the only form in which it is actually marketed and used. Dispersions of alkyl ketene dimer were demonstrated to be readily biodegradable in an OECD 301 B (Sturm) test and a MITI test for biodegradation. Degradation of 96% and >94% respectively was observed in these tests over 28 days. The emulsifier used in these tests was naphthalene sulfonic acid, polymer with formaldehyde, sodium salt (CAS 9084-06-4). **[Reference: 9 and Reference: 41]**

A combination test for both biodegradation and elimination, demonstrated that alkyl ketene dimer can also be eliminated. The observed biodegradation of more than 90% (CO_2 evolution) in these tests was clearly attributed to the alkyl ketene dimer, since the contribution of the emulsifier cannot exceed its concentration in the test material (about 1.5% of TOC). **[Reference: 10]**

If AKD is tested without an emulsifier, the test material separates from the aqueous phase thus preventing intimate contact between the bacteria and the test material. As a result, very little of the alkyl ketene dimer is biodegraded by the bacteria and this was clearly demonstrated in a manometric respirometry test conducted without the emulsifier admixture being present. <10% biodegradation was observed over 28 days. **[Reference: 11]**

In conclusion, AKD has been shown to be readily biodegradable when tested in the presence of small amounts of emulsifier which increases the availability of the substance to micro-organisms.

2.2.5 Bioaccumulation

The predicted Log Kow for AKD ranges from 11 to 15 which suggests a high bioaccumulation potential. BCF Program v 2.15 predicts a BCF of 3, whereas the polynomial QSAR[1] in the EU Technical Guidance Document for substances with Log Kow >6 predicts a BCF between 14 and 6 x 10^{15}. For substances with Log Kow > 6, it is known that QSAR determinations of BCF may not accurately represent true bioaccumulation potential so the there is uncertainty as to the true level of the BCF.

A bioaccumulation test is available for a structurally related AKD notified as a new chemical in the EU under Directive 92/32/EEC. This test indicates that the test substance has a fish BCF < 100. However, the result should be treated with caution since the test was conducted above the water solubility limit in the presence of dispersant and may not be the most appropriate method to determine the bioaccumulation of such a poorly soluble substance. The test report can be made available in confidence to regulatory authorities if required.

Using a measured Log Kow of 5.5, from the structurally related new chemical notification, the BCFs are predicted to range from 3.2 to 343 respectively for C12:C12 AKD and C16:C16 AKD using BCF Program v 2.15. Using the equation in the EU Technical Guidance Document for substances with Log Kow <6, log BCF = 0.85 logKow - 0.70, the BCF is predicted to be 9440. This also suggests that AKD has the potential to bioaccumulate.

2.2.6 Other Information on Environmental Fate

No additional data are available.

2.3 Human Exposure

2.3.1 Occupational Exposure

The survey completed by the industry showed that the total number of people potentially exposed to alkyl ketene dimers during production is low. For the five sites surveyed, 29 people (two females), are working continuously with Alkyl Ketene Dimers and another 20 (no females), are working intermittently, i.e., up to 50% of their time. Potential worker exposure to Alkyl Ketene Dimers occurs during the packing, flaking, storing and sampling of the product. All producers reported, as Personal Protection Equipment [PPE], gloves and goggles in the process and laboratory, filling, emptying and transferring operations and all, except one, in maintenance and during disposal/waste management. For the process and maintenance areas all sites either have overall protection or a protective suit. The processes either have local- (two sites) or general ventilation (two sites) and one is segregated. No monitoring data for alkyl ketene dimer was reported, although the sites have some monitoring data for other chemicals used in the manufacturing process. There were no contact allergy cases reported at any of the production sites. **[Reference: 25]**

2.3.2 Consumer Exposure

Consumer exposure to alkyl ketene dimer is negligible as it is only used industrially. Paper made with alkyl ketene dimer is used in the manufacture of packaging materials and articles intended to

[1] $\log BCF = 6.9.10^{-3} (\log Kow)^4 - 1.85.10^{-1} (\log Kow)^3 + 1.55 (\log Kow)^2 - 4.18 \log Kow + 4.79$

come into contact with food, e.g., folding box board and liquid packaging board. However, it is important to recognise that the alkyl ketene dimer will not be detected in the paper because it will have either reacted with the cellulose fibres to form a covalent bond or with the water present in the paper making system to form the dialkyl ketone. There are several national approvals for the use of alkyl ketene dimers in packaging materials intended to come into contact with food, i.e., in America, Belgium, France, Finland, Germany, Italy and The Netherlands.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

There are no specific studies available on the kinetics, metabolism and distribution of AKD in mammals, including humans. However, AKD is expected to be rapidly absorbed from the intestine due to its high lipophilicity (log Kow > 6). In an OECD 422 screening and a 90 day feeding study AKD caused effects in various organs (see Section 3.2.1), indicating a wide distribution in the body. A recent Toxicokinetics study completed on structurally related AKD notified as a new chemical in the EU under Directive 92/32/EEC demonstrated that dermal absorption is very low. The full report can be supplied in confidence if required.

3.1.2 Acute Toxicity

Studies in Animals

Inhalation

No mortality were observed when 12 Wistar rats were exposed for 8 hours to an atmosphere that had been saturated at 20 degrees Celsius with the volatile part of the substance Stearyldiketen TV 194/37. **[Reference: 2]**

This is an inhalation hazard test (IRT), which tests for the mortality within 8 hours exposure to an atmosphere saturated with AKD vapour. The actual AKD vapour concentration has not been determined. However, very little AKD vapour is expected to be present in an atmosphere saturated, since the vapour pressure of AKD is extremely low with an estimated 3x10-6 hPa at 40 degrees Celsius.

Dermal

A LD_{50} of 6730 mg/kg b.w. was given in the ECB-published IUCLID [February 19, 2000]. The study report is, however, no longer available. The reliability of this data cannot be confirmed.

Oral

There are three oral tests available (with Stearyldiketen TV 194/37, Alkyl Ketene Dimers batch 339, and Aquapel 380). The first study was performed prior to the implementation of the OECD TG and GLP, but followed an acceptable protocol and is scientifically valid. This study gave an LD_{50} of >40,000 mg/kg b.w. in Wistar rats. **[Reference: 36]**

Two further study reports provide insufficient details to judge the validity of the studies, but are included here as supporting data; these studies reported LD_{50} values of >10,000 and >2000 mg/kg b.w.

The second available study, a limit test with Alkyl Ketene Dimers batch 339, performed according to OECD TG 401, resulted in an oral LD_{50} >2000 mg/kg bw Alkyl Ketene Dimers batch 339 is chemically identical to the standard batch of Aquapel 364 referred to elsewhere in this report . Unfortunately, the report could not be found so the validity of this study could not be verified. **[Reference:** 18**]**

The third study gave an oral LD_{50} of >10 000 mg/kg bw, but unfortunately there was insufficient detail available to judge the validity of this study. **[Reference:** 2**]**

Studies in Humans

No reliable data are available.

Conclusion

AKD is of low acute oral toxicity with an oral LD_{50} of >40 000 mg/kg bw. From the available data it is not possible to conclude whether AKD is toxic via the dermal or inhalation routes.

3.1.3 Irritation

Skin Irritation

Studies in Animals

A 50% aqueous dispersion of Stearyldiketen TV 194/37 did not cause skin reactions in rabbits within 24 hours after a 15-minute exposure. A 20 hour exposure caused very slight erythema 24 hours after exposure. 8 Days after the short and prolonged exposure slight flaking of the skin was observed (BASF Aktiengesellschaft, 1976). The 20 hour exposure exceeds the 4 hour exposure, as required by the OECD TG 404. The very slight erythema (< 1 grading on the Draize scheme) may be the result of mechanical irritation by the solid material and water under occlusive conditions. Since there was only very slight erythema after excessive exposure and no significant effects following shorter exposure, it is concluded that AKD is not a skin irritant. **[Reference:** 2**]**

Studies in Humans

In a human patch test, which does not meet today's standards of performance and documentation, a 40% w/v slurry of Aquapel® 380 (5 parts of Aquapel 364 and 1 part emulsifier), itself caused no skin irritation in 200 test subjects. The AKD present in Aquapel® 380 is chemically identical to the standard batch of Aquapel 364 referred to elsewhere in this report. Preparations with an emulsifier, however, caused a skin reaction in one test subject. In a follow-up study, the effect was attributed to the emulsifier rather than alkyl ketene dimer. **[Reference:** 33**]**

Eye Irritation

Studies in Animals

50 mg of AKD (of Stearyldiketen TV 194/37) caused the same reaction in the eyes of rabbits as the negative control substance, talcum powder, did. The effects seen with talcum powder and AKD were slight erythema and edema after an hour and slight erythema after 24 hours. The effects were

fully reversible within 8 days. In this study the eye was not rinsed (as required by the current OECD TG 405). Since talcum powder caused the same slight irritations as the solid AKD and the effects can be attributed to mechanical irritation by the solid substances. Due to the extensive exposure, the slight effects, which are fully reversible, and no differences when compared to the negative control substance, it is concluded that AKD is not an eye irritant (BASF Aktiengesellschaft, 1976). **[Reference:** 2 **]**

Studies in Humans

No reliable data are available.

Respiratory Tract Irritation

There is no information available on the irritation of the respiratory tract. An exposure of the respiratory tract is however, almost impossible since the vapour pressure of AKDs is extremely low, they decompose before boiling, and virtually no dust is formed during production and processing due to the procedures employed and the fact that the compounds are waxes.

Conclusion

The data demonstrates that AKD is neither a skin nor an eye irritant.

3.1.4 Sensitisation

Studies in Animals

Skin

There are several studies available regarding the sensitisation properties of AKDs: Initially one batch (Basoplast 20 konz., batch 216) was found to be positive in a Guinea Pig Maximisation Test when administered as a 5% aqueous emulsion [Reference - GPMT; according to OECD test guideline 406]. However, the formulated product, a 20% emulsion of Basoplast 20 konz., batch P224, was tested in a Bühler test and found to be negative.

As a follow-up to the positive GPMT of one batch, batches of four other major products on the market were tested in GPMTs at challenge concentrations of up to 75% in oil (Aquapel 291, Aquapel 364 (batch 12MW1313), Keywax SF100 and Raisares (batch No E133), – All the products are chemically identical to Aquapel 364 and fall within the scope of CAS Number 84989-41-3): All turned out to be negative.

Since the chemical composition of all tested products was virtually the same (see chapter 1.4) the positive result with the one batch must have been an artifact of the test conditions or caused by a potent major impurity. In fact, this was the only test, in which applied hot (60°C) melted product to the skin whereas the other studies used 75% solutions of AKD in oil. Recently, the production process for this product was changed and the new product (Basoplast 20 konz. K batch PE251001 at 75% in oil) was tested in a GPMT using the same test conditions as the studies on the other four products: The GPMT was negative.

Eventually, five AKD products, which are currently produced, were tested negative in the GPMT. **[Reference: 6, Reference: 7, Reference: 34, Reference: 35, Reference: 21 and Reference: 42]**

Respiratory Tract

There is no information available on the sensitisation of the respiratory tract. An exposure of the respiratory tract is, however, unlikely (see respiratory tract section of chapter 3.2).

Studies in Humans

In a human patch test, which does not meet today's standards, a 5% aqueous emulsion of AKD caused no skin sensitisation in 200 test subjects. Preparations with an emulsifier, however, caused delayed skin reactions after the second dermal application (challenge) in eight test subjects. In an incomplete follow-up study on six of the eight cases, the effect was not seen. **[Reference:** 33**]**

A recent survey among the producers of AKDs revealed no reported contact allergy cases at any of the production sites.

Conclusion

The weight of evidence from six GPMT and a human patch test on the AKDs does not indicate a skin sensitising potential. There were no case reports on contact allergy at production sites.

3.1.5 Repeated Dose Toxicity

Studies in Animals

The repeated-dose toxicity of Aquapel 364 was investigated in a combined repeated dose toxicity study with the reproduction/developmental toxicity-screening test in Wistar-derived rats (10/sex/dose) according to OECD Guideline for testing chemicals 422. Doses of 100, 350 and 1000 mg/kg bw/day were administered by oral gavage. Histopathological examinations were conducted on day 5 *post partum* (Central Toxicology Laboratories, 2002).

A dose of 1000, 350 and 100 mg/kg bw/day for at least 28 days in males (2 weeks prior to mating to day 29 or 30) and two weeks prior to mating throughout pregnancy to day 4 of lactation in females produced inflammatory changes in a number of tissues (most consistently in the liver and mesenteric lymph nodes; furthermore in cervix, kidney, Peyer's patch, spleen, uterus hepatic lymph node, cervical lymph node and jejunum. The severity was typically moderate in the mesenteric lymph nodes and minimal or slight in other organs[a]). Statistically significant increases in specific relative organ weights were noted in treated animals compared with controls, which, in many cases demonstrated a dose-relationship. These comprised the kidney (110, 109 and 111% of control at low, mid and high dose, respectively, for females and no significant changes for males), liver (112, 128 and 132% of control at low, mid and high dose, respectively , in females and no significant changes for males), ovaries (121 and 119% of control at mid and high dose, respectively and no significant change at the low dose) and spleen (113, 123 and 124% of control for males and 110, 109 and 111% of control for females at low, mid and high dose respectively)]. Statistically significant increases were also noted for white blood cell counts [119, 126 and 136% of control for males and 154, 184 and 211% of control for females at low, mid and high dose, respectively] and splenic extramedullary haemopoiesis in all treated females and in most animals at the mid- and high dose. In addition there was a mild, but statistically significant, perturbation of some clinical chemistry parameters in both genders. The majority of the changes occurred at decreased severity and/or incidence in animals given 350 or 100 mg /kg bw/day, compared with the high dose. However, in males and females the liver and mesenteric lymph nodes were affected at all doses. A

[a] according to the grading for histopathological findings: N.A.D., minimal, slight, moderate, marked

NOAEL for general toxicity to the adults was not achieved in this study due to inflammation of various organs, including female reproductive organs. The LOAEL was 100 mg/kg bw/day (Central Toxicology Laboratories, 2002).

To further investigate the effects after repeated oral application of AKD, a 90-day feeding study conducted according to OECD TG 408 was performed in rats (Central Toxicology Laboratories, 2004). Groups of twelve male and twelve female rats were fed diets containing 0 (control), 65, 650 or 6500 ppm AKD (Aquapel® 364; equivalent to 6.3, 63.4 or 645 mg/kg bw/day in males and 6.8, 69.6 or 690.6 mg/kg bw/day in females) for 90 consecutive days.

Administration of AKD in the diet resulted in a dose-related reduction in bodyweights from weeks 8 and 6 in males [6, 8 an 11% compared to control group for the low, mid and high dose, respectively]; in females a significant reduction was only seen at the high dose [7% compared to control group]. Food consumption and utilisation were reduced in both genders. Red blood cell parameters were reduced, the white blood cell count was increased [182% compared to controls at the high dose in males and 225% compared to controls at the high dose in females. At the mid dose, there were increases in females in monocyte, basophil and large unstained cell counts (240, 247 and 264% of control, respectively). Animals of the low and mid dose in males and the low dose in females showed no significant changes], and there were liver enzyme changes in both genders when compared to controls. Spleen weights were increased in both genders [152% compared to controls at the high dose, in males and 128% and 173% at the mid and high dose, in females; males of the low and mid dose and females of the low dose in showed no significant changes]. In females, liver [127% compared to controls at the high dose, females of the low and mid dose showed no significant changes] and kidney weights [110 and 106% compared to controls at the mid and high dose, respectively; females of the low dose showed no significant changes] were increased.

Treatment related inflammatory changes, were observed in a variety of tissues: histiocytosis was seen in the lymph nodes, liver, spleen, jejunum, ileum and Peyer's patch, and inflammation was observed in the liver, lung, kidney, heart, pancreas, muscle, adrenal gland, sciatic nerve and stomach. At the high dose, the severity was typically moderate to marked in the mesenteric lymph nodes and slight in other organs[a]. At the mid dose, inflammation and histiocytosis were reduced in incidence and severity when compared to the high dose group).

When AKD was administered in the diet at the low dose there were no changes of biological or toxicological significance when compared to the controls. The no observed adverse effect level (NOAEL) for this study was considered to be the low dose, 65 ppm AKD, which was equivalent to 6.3 and 6.8 mg/kg bw for males and females, respectively. (Central Toxicology Laboratories, 2004)

It would appear that the generalised inflammations are a specific response to administration of AKDs, but a review of pertinent toxicology literature (Baldwin *et al*., 1992 **[Reference 1]**, Firrioli *et al*., 1995 **[Reference 22]**, Smith *et al*., 1996 **[Reference 46]**, Nash *et al*., 1996 **[Reference 40]**, Halladay **[Reference 28]**, *et al*., 2002, Scotter *et al*., 2003 **[Reference 44]**) suggests that these represent a generic response of rats to administration of higher molecular weight hydrocarbons, i.e. mineral hydrocarbon oils and waxes. Depending on the viscosity and chain length of the paraffins the observed effects included organ weight changes of the mesenteric lymph nodes, spleen, liver and kidney as well as lesions of the mesenteric lymph nodes, liver and spleen (these findings being more marked in females). Inflammatory changes were seen in these organs, together with increased splenic extramedullary haematopoesis. Hydrocarbons distribute primarily to the liver, spleen, mesenteric lymph nodes and fat pads, the former three being key sites at which histological changes were seen with both hydrocarbons and AKDs. The close similarity of effects of feeding hydrocarbon oils to those seen in the AKD studies is strong evidence for the effects of the AKDs being attributable to their hydrocarbon chain structures rather than any unique characteristic.

The variable response of different rat strains to exposure to mineral waxes in the context of potential human exposure has been addressed by Miller *et al*. (1996) **[Reference:** 39**]** and Fleming *et al*. (1998) **[Reference:** 24**]**. While recognising distinct species and strain differences in responses to hydrocarbon oils, it is also apparent that both the F-344 rat and human respond to the presence of saturated hydrocarbons at similar tissue concentrations. However, the type and severity of the response is different, i.e. it is an inflammatory lesion in the rat compared with oil droplet formation in humans. The human response has not been associated with any adverse clinical effects and is generally regarded as inconsequential (Miller *et al*., 1996 **[Reference:** 39**]** and Carlton *et al*., 2001 **[Reference:** 14**]**).

There is quite a lot of data available on the relationship between size of the mineral hydrocarbon waxes/oils and accumulation in rat tissues and toxic responses. Preferential accumulation is in the alkane range C20-C35. Both size and structure play a role. Thus it is important to have full details of the compounds covered. These factors are included in the current specifications for food grade mineral hydrocarbons that set minimum viscosity and average molecular weight limits and restricts the amount of low MW species (no more than 5% below carbon number 25). The recent paper by Scotter (2003) **[Reference 44]** suggests that the current specifications are not prescriptively adequate in controlling the amount of MHC material between C-25 and C-35 that can accumulate.

The inflammatory response is determined by the viscosity, average molecular weight and average carbon number distribution of the hydrocarbon (Smith et al., 1996) **[Reference 46]**. One key factor is probably the absorption and distribution, which is dependent on these physicochemical parameters. AKD has a molecular weight of 420 to 532 Daltons and the chain length of the two hydrocarbon are 12 to 16 and 14 to 18 C-atoms plus the oxetanone ring (with the longest chains of 28 to 36 C-atoms). It is unclear how this relates to the chain length of simple hydrocarbons and how it would affect absorption and distribution and ultimately the response of the body.

For hydrocarbons, a distinct strain difference in the response to oral administration of hydrocarbons is known. The respective studies were performed with F344 and Sprague-Dawley derived (SD) rats (Firrioli et al.,1995). There is little information on the response of Wistar rats to hydrocarbon oil administration. Differences in absorption, accumulation and metabolism probably account also for the species and strain differences observed in hydrocarbon oil responses. We used a the Alpk:APfSD (Wistar Derived) rat in the OECD 422 and 90-day study. It is difficult to estimate how this strain would compare to Fisher or SD rats. However, according to Miller et al. (1996) **[Reference 39]** the F-344 rat strain is most susceptible to the inflammatory response. The nature of the results for AKD imply that the Alpk:APfSD rat is somewhere between the Sprague-Dawley and the F-344 rat in sensitivity, i.e. assuming a similarity of potency between AKD and the mineral oil, the liver response in the AP rat was greater than the SD rat but was not extensive as the granulomatous changes seen in the F344 rat .

Since these rat data are used to define what is acceptable in terms of food grade mineral hydrocarbon waxes and oils, it is considered appropriate to assume that the toxicity seen is of some potential relevance to humans.

Studies in Humans

No experience with long-term exposure of humans is available.

Conclusion

Based on an animal study with oral exposure for 28 and 90 days, the predominant effect of AKD is the induction of generalised tissue inflammation. This included female reproductive organs upon oral gavage for 28 days. The inflammations are most likely not a specific response to AKD, but a

generic response of rats to administration of higher molecular weight hydrocarbons. The relevance of this effect for humans is questionable, although it would be prudent to assume that the toxicity is relevant to humans. There is a clear threshold for this effect: the NOAEL for repeated oral uptake of AKD was established at 6.8 mg/kg bw/day in the 90-day rat feeding study.

3.1.6 Mutagenicity

The chemical structure of AKD does not alert for a mutagenic potential as determined by MULTICASE software. However, this prediction is currently of limited value. Multi-case has a database of chemical "fragments" (2-10 atoms long), which have been associated with toxicity. It splits the query molecule into fragments and sees whether any of them are in the database. Therefore, it is possible that Multicase's database doesn't contain all the fragments in AKD. With (Q)SAR systems like this a negative could be a true negative or a "non-hit" just because the structure / fragment hasn't been seen before.

In vitro Studies

Three reliable Ames Tests conducted in accordance with OECD test guideline 471 are available for AKDs (Basoplast 20 konz. batch 838 **[Reference 4]**, and Alkyl Ketene Dimers Batch 339 **[Reference 20]** and 354 **[Reference 19]**, which represent batches from different manufacturers of the AKD CAS No. 84989-41-3). In the key test, *Salmonella typhimurium* TA1535, TA100, TA1537, TA98 were tested with and without metabolic activation, up to a concentration of 5000 micrograms Basoplast 20 konz. batch 838/plate (BASF Aktiengesellschaft, 1992). In the second study, *Salmonella typhimurium*, TA 1535, TA 100, TA 1538, TA 98, TA 1537 were tested up to 1000 µg/plate, with and without metabolic activation. There was no indication of a mutagenic effect in the test bacteria in either of these studies. Likewise, a reliable *in vitro* chromosomal aberration test conducted according to OECD test guideline 473, which used human lymphocytes and Aquapel 364 concentrations up to 1000 µg/mL (with and without metabolic activation) did not indicate a clastogenic or aneugenic effect. These tests were performed according to OECD Guideline for Testing of Chemicals no. 471 and no. 473, respectively.
The maximum concentration in the chromosomal aberration test was 1000 microgram Aquapel 364/mL, which was limited by precipitation that made reading of the slides difficult. None of the tests indicated a mutagenic effect of AKDs. **[Reference: 4, Reference: 19, Reference: 20 and Reference: 26]**

In vivo Studies

No *in vivo* studies on mutagenicity were performed, since there was no evidence of gene mutation or chromosomal aberration in the *in vitro* studies (see above).

Studies in Humans

No experience on mutagenicity by exposure of humans is available. There is, however, an *in vitro* study with human lymphocytes (see above), which was negative.

Conclusion

Based on *in vitro* studies on gene mutations and chromosomal aberrations there is no indication of mutagenic effects of AKDs.

3.1.7 Carcinogenicity

The mutagenicity testing gave no reason to suspect any carcinogenic potential (see section 3.1.6). No animal studies on carcinogenicity and no experience with carcinogenicity by exposure of humans is available.

Conclusion

Based on the results of the mutagenicity testing, there is no reason to suspect a carcinogenic potential of AKDs. No further information is available.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

Effects on reproductive performance were evaluated in a combined repeated dose toxicity study with reproductive and developmental toxicity screening in Wistar-derived rats (10/sex/dose) according to OECD Test Guideline 422. The test was performed with Aquapel 364 at doses of 100, 350 or 1000 mg/kg bw/day, which was administered by oral gavage two weeks prior to mating until day four of lactation (see Section 3.5.1)(Central Toxicology Laboratories, 2002). There was no effect on male and female reproductive performance and no effect on male reproductive organs. Based on data from five females from each dose group, AKD caused inflammation of the ovaries, uterus and cervix, which was associated with a statistically significant, but not dose related, increase in pre-implantation losses (the ratio of corpora lutea to implantation sites was reduced in all treated groups compared to control group). Few animals, however, showed pre-implantation losses without inflammation. This was most often observed in the control group.

A NOAEL for reproductive performance could not be achieved in this study due to pre-implantation losses at the lowest dose tested.

Developmental Toxicity

Developmental effects were evaluated in a combined repeated dose toxicity study with reproductive and developmental toxicity screening according to OECD Test Guideline 422 (see chapter 3.5). There were no signs of developmental toxicity in this study. The NOAEL for developmental toxicity was 1000 mg/kg bw/day.

Studies in Humans

No experience of reproductive effects following exposure of humans is available.

Conclusion

Based on the results of the screening in the combined study (OECD Guideline for Testing of Chemicals Number 422) there is no indication on developmental toxicity or impairment of male reproductive performance. Inflammation was however observed in several organs of both genders, including the female reproductive organs, and may result in pre-implantation losses. The observed inflammation of several organs, including the female reproductive organs, was further investigated in a 90-day feeding study.

3.2 Initial Assessment for Human Health

AKD is of low toxicity after a single exposure (LD_{50} oral, rat >40 000 mg/kg bw). It is neither irritating to skin and eyes nor a skin sensitiser, as concluded from experimental animal and human studies. AKD was not genotoxic in vitro (three Ames tests and a mammalian cell chromosomal aberration test). There are no other data regarding the carcinogenic potential of AKD. In an OECD TG 422 screening test, repeated oral gavage of 100, 350 and 1000 mg/kg bw/day to rats resulted in inflammation of several organs, including female reproductive organs. As a result of ovary inflammations, an increase in pre-implantation losses (the number of implantation sites compared to corpora lutea was reduced) was observed at all doses; this effect is secondary to the general organ inflammation and therefore not a specific reproductive effect. No effects on male reproductive organs and pup development were observed. In a 90-day feeding study in rats inflammation of several organs (typically lymph nodes, liver, heart, kidney, pancreas and lung) were observed at concentrations of 650 ppm and 6500 ppm (which was the highest dose tested) in the feed; at a concentration of 65 ppm in the feed no adverse effects were observed. The LOAEL was 63.4 and 69.6 mg/kg bw/day and the NOAEL was 6.3 and 6.8 mg/kg bw/day for males and females, respectively (estimated from dietary concentrations of 650 and 65 ppm, respectively). The observed inflammation is considered a generic response in the rats to higher molecular weight hydrocarbons, and is not considered to be a response specific to AKD.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Test data are available on the acute and chronic toxicity of alkyl ketene dimer to aquatic organisms, as reported in Table 4.

Acute Toxicity Test Results

Table 4

Species	Method	Effect Concentration [mg/L]	Remark / Reference
Acute toxicity to fish			
Danio rerio (freshwater species)	OECD 203, static	LC_{50} (96h) >10,000 (nominal)	GLP, no effects seen(*) (reliability 2). **[Reference 5]**
Acute toxicity to aquatic invertebrates			
Daphnia magna (freshwater species)	Directive 79/831 EEC, C2, static	EC_{50} (48h) >500 (nominal)	Non GLP, no effects seen(*) (reliability 2); **[Reference 12]**
Acute toxicity to algae			
Selenastrum capricornutum (fresh water)	OECD 201	$Er(b)C_{50}$ (72h) > 0.17 (mean measured)	GLP, no effects seen(*) (reliability 2); **[Reference 27]**

(*) AKD concentration studied above the limit of solubility

Conclusion:

Alkyl ketene dimer showed no toxicity up to its solubility limit in the above tests. It is of low acute toxicity to fish, aquatic invertebrates and algae.

No analysis of test concentrations was conducted for the acute fish and Daphnia tests but undissolved test material was present throughout the tests which would suggest that a saturated solution had been prepared. The acute fish test was conducted at pH 7.7. – 8.0.and the Daphnia test was conducted at pH 7.98 –8.08 so it is possible that hydrolysis of the test substance could have occurred, although this could not have been prevented. Whilst the actual concentration of AKD is not known, they do indicate that AKD is of low acute toxicity. The conclusion for Daphnia is supported by the Daphnia reproduction test which was conducted with analysis and showed no effects on Daphnia reproduction.

Concentrations at the end of the algal growth inhibition test were below the detection limit, <0.073 mg/l. Since the pH rose to 9.7 at the end of the test, hydrolysis may have occurred. However, such hydrolysis is unavoidable. Because of these problems, the study is assigned reliability (2). A test on a structurally-related new chemical notification showed no effects up to the water solubility limit with a 72h Eb/rC50 > 0.46 mg/l and 72h NOEC (growth rate and biomass) of 0.46 mg/l. This supports the conclusion that AKD is of low acute toxicity to algae.

Chronic Toxicity Test Results

Aquatic invertebrates

A 21-day Daphnia reproduction study has been conducted on the dispersion of AKD (AKD content 90.1% w/w). The test was conducted according to OECD 211, with reproduction, growth and mortality monitored. No effects on either reproduction or growth were observed at the highest concentration tested (mean measured concentration of 0.8 mg/l). Concentrations were measured during the test and showed a generally stable exposure. Stock solutions of AKD were prepared in acetone, and aliquots added to the test media to prepare the final solutions. The media were changed at two day intervals. The test solutions were recorded as clear and colourless. The true water solubility is not definitively known, so the true exposure level is uncertain. Nevertheless, the absence of effects in the test indicate that the long-term NOEC is above the water solubility limit.

EC_{50} (21 day) Daphnia magna (mortality): >0.8 mg/L .

21-day NOEC(body length) =0.8 mg/l, 21-day NOEC (reproduction) =0.8 mg/L.

Algae

A NOEC was obtained in the 72h test with *Selenastrum capricornutum*:

72h NOEC (biomass and growth rate) >0.17 mg/l. No effects were observed in this test.

Conclusion:

Alkyl ketene dimer is of low chronic toxicity to algae and aquatic invertebrates.

Toxicity to Microorganisms

The following toxicity tests with microorganisms are available:

Species	Method	Effect Concentration [mg/L]	Remark / Reference
Activated sludge	OECD 209 – respiration inhibition test	EC20 (30 min) > 1000	Non GLP, reliability 2 [Reference 12]

Conclusion:

AKD is not inhibitory to activated sludge microorganisms.

4.2 Terrestrial Effects

Plants

An OECD 208 test was conducted to determine the effect of AKD on the seed germination and early plant growth of oat (*Avena sativa*), sunflower (*Helianthus annuus*) and mung bean (*Phaseolus aureus*). Emergence was significantly reduced in the 1000 mg/kg test concentration for sunflower and mung bean compared with the mean of the control and solvent control. However, this reduction is considered to be due to watering difficulties and not toxicity since the soil between the surface and approximately 0.5 cm depth was dry at the highest test concentration. This is likely to be due to the water-repelling properties of the test material which was sufficient to hinder the percolation of water through the soil. This effect was to be expected as the test material is naturally hydrophobic and its use in industry is to make paper hydrophobic. On day 28, all plants appeared healthy and showed no symptoms of toxicity. There was no dose- related effect on vegetative growth of any of the species tested, in any of the test concentrations.

28d NOEC (vegetative growth) 1000 mg/kg.

28d EC50 (vegetative growth) > 1000 mg/kg.

28d LOEC (vegetative growth) > 1000 mg/kg.

14d NOEC (emergence) 100 mg/kg.

14d EC50 (emergence) > 1000 mg/kg.

14d LOEC (emergence) 1000 mg/kg.

Soil dwelling organisms: Earthworm

An acute toxicity test with the earthworm *Eisenia foetida* is available. No mortality was observed at the highest dose tested:

14day LC_{50} Earthworm >1000 mg/kg soil and NOEC = 1000 mg/kg soil.

Conclusion

Alkyl ketene dimer is of low acute toxicity to plants and earthworms

4.3 Other Environmental Effects

None reported in the literature.

4.4 Initial Assessment for the Environment

AKD is a hydrophobic solid with very low solubility in water, predicted to be 5.6×10^{-7} to 4.8×10^{-11} mg/l. Its predicted Log Kow of 11 – 15 suggests a high bioaccumulation potential. Its vapour pressure is predicted to be very low, 5.85×10^{-13} – 6.12×10^{-10} hPa.

Distribution modelling using Mackay Level I indicates that AKD will partition to sediment and soil and the estimated Koc of 1.51×10^{7} - 2×10^{9} indicates that AKD will adsorb strongly to soil and sediments.

AKD is predicted to photodegrade rapidly in air with a half life for indirect photolysis of 3.7 hours. Studies on the hydrolysis of commercial AKD preparations show that AKD hydrolyses readily under neutral and alkaline conditions but only slowly under acid conditions. Half lives of between 23 – 140 hours have been calculated for AKD emulsion at 30˚C, pH 8, under the conditions of a paper mill. There is no information available on the hydrolysis half lives in the aquatic environment. Based on the available data, AKD is expected to hydrolyse readily under neutral and alkaline conditions in the environment and is assumed to be stable to hydrolysis at acidic pHs in the environment, pH 5-7. AKD has been shown to be readily biodegradable when tested in the presence of small amounts of emulsifier, used to increase bioavailability of the substance to micro-organisms, with >94% biodegradation in 28 days.

Alkyl ketene dimer showed no toxicity in acute toxicity tests on the fish *Danio rerio*, the aquatic invertebrate *Daphnia magna* and the algae *Selenastrum capricornutum*. The E/LC50s were all above the water solubility limit. In a 21 day reproduction test with Daphnia magna, conducted on a dispersion of AKD, no effects on either reproduction or growth were observed at the highest concentration tested (mean measured concentration of 0.8 mg/l). This indicates that the NOEC is greater than the water solubility limit. There is no data available on toxicity to sediment dwelling organisms. AKD is not inhibitory to activated sludge microorganisms, in an activated sludge respiration inhibition test the 30 minute EC20 was > 1000 mg/l.

AKD is of low acute toxicity to plants and earthworms. The 14d EC50 (emergence) and 28d EC50 (vegetative growth) for oat (*Avena sativa*), sunflower (*Helianthus annuus*) and mung bean (*Phaseolus aureus*) were all >/= 1000 mg/kg soil. The 14 day LC50 for the earthworm *Eisenia foetida* is >1000 mg/kg.

AKD is potentially released to the environment during its production and formulation and during the paper coating process. The high Log Kow of AKD suggest it has a high bioaccumulation potential and it is predicted to partition to the soil and sediment. However, the concern that AKD could cause long term effects in the environment is reduced by the data which indicate that AKD is readily biodegradable by micro-organisms when tested in the presence of a 1.5% concentration of emulsifier and hydrolyses under alkaline pH. AKD shows low acute toxicity to aquatic organisms, plants and earthworm and low chronic toxicity to Daphnia and algae. It is therefore of low priority for further work due to its low hazard potential.

5 RECOMMENDATIONS

Human Health

The chemical possesses properties indicating a hazard for human health (inflammation of several organs following repeated oral exposure, and secondary to this, pre-implantation loss). Based on data presented by the Sponsor country, exposure to humans is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment

The high Log Kow of AKD suggests it has a high bioaccumulation potential. However, the concern that AKD could cause long term effects in the environment is reduced by the data which indicate that AKD is readily biodegradable by micro-organisms when tested in the presence of a 1.5% concentration of emulsifier and hydrolyses under neutral and alkaline conditions. AKD shows low acute toxicity to aquatic organisms, plants and earthworm and low chronic toxicity to Daphnia and algae. It is therefore of low priority for further work due to its low hazard potential.

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7 ANNEX 1 – LITERATURE SEARCH DETAILS

Literature for the CAS no. 84989-41-3 was searched in the following databases:

AGRICOLA
AQUASCI
CABA
CANCERLIT
CSNB
EMBAL
EMBASE
ESBIOBASE
ESBIOBASE
HEALSAFE
JICST-EPLUS
LIFESCI
NTIS
OCEAN
POLLUAB
SCISEARCH
TOXCENTER
TOXLIT
ULIDAT

STN-Recherche Ecology und Toxicology (Cas. no.:84989-41-3), 13.03.2002

.toxallg

FILE 'AGRICOLA' ENTERED AT 09:51:25 ON 14 MAR 2002

FILE 'CANCERLIT' ENTERED AT 09:51:25 ON 14 MAR 2002

FILE 'CABA' ENTERED AT 09:51:25 ON 14 MAR 2002
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FILE 'TOXCENTER' ENTERED AT 09:52:00 ON 14 MAR 2002

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FILE 'NTIS' ENTERED AT 09:53:00 ON 14 MAR 2002

FILE 'LIFESCI' ENTERED AT 09:53:00 ON 14 MAR 2002

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FILE 'OCEAN' ENTERED AT 09:53:00 ON 14 MAR 2002

FILE 'POLLUAB' ENTERED AT 09:53:00 ON 14 MAR 2002

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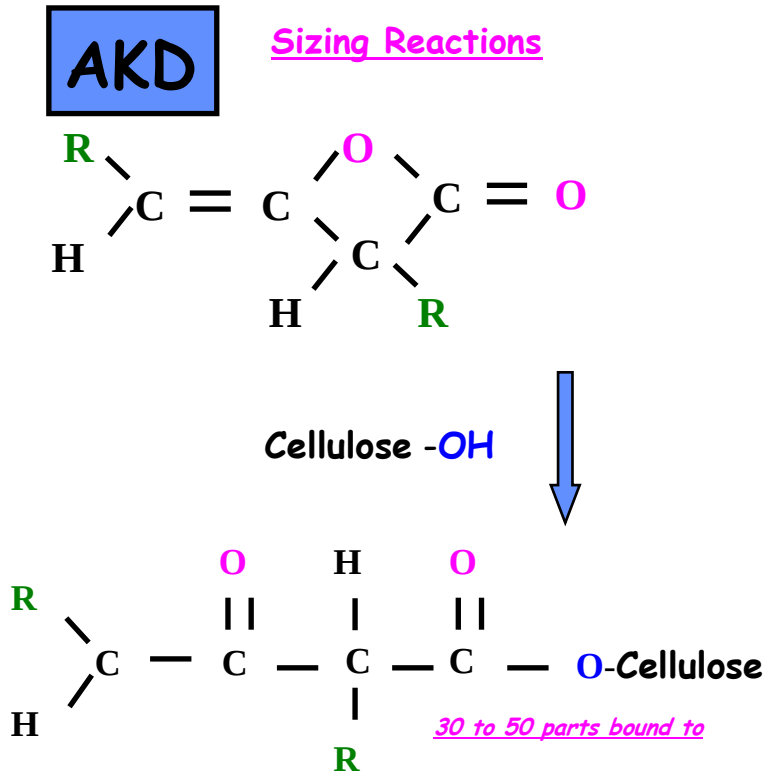
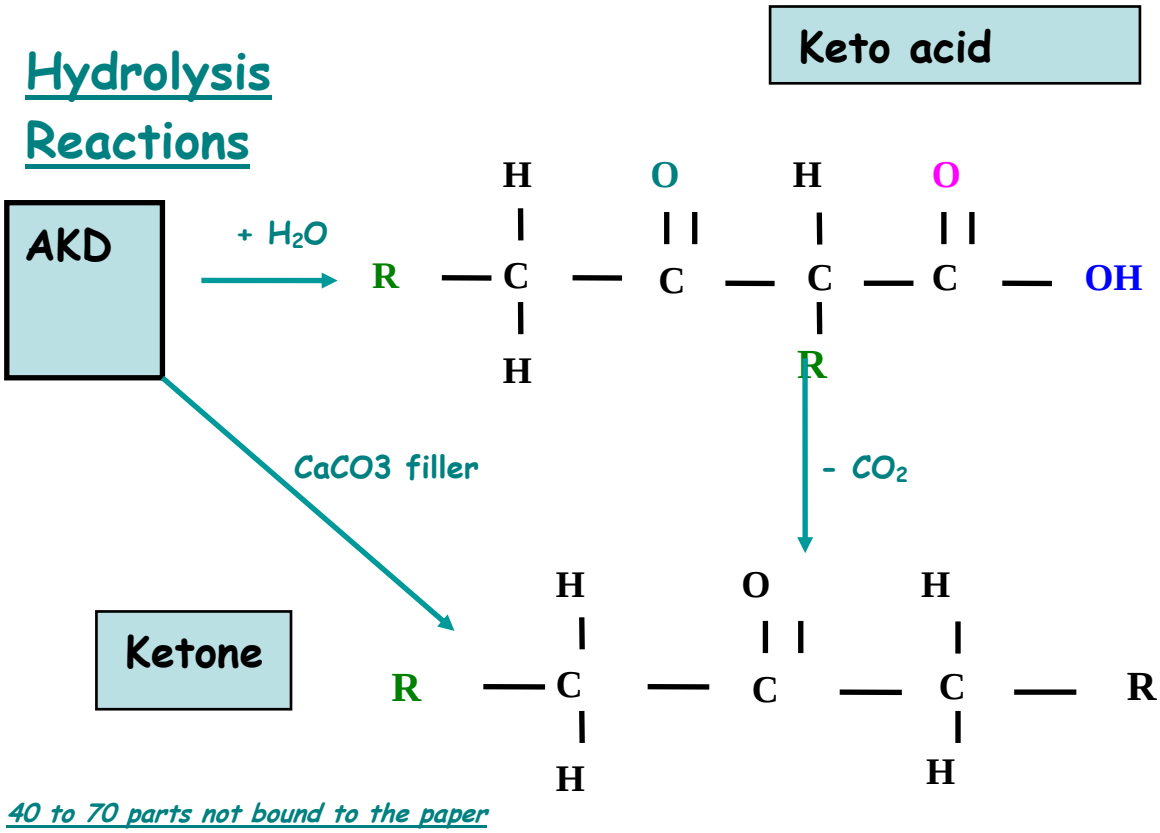
ANNEX 2 – GPA REACTION SCHEME





SIDS DOSSIER
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ALKYL KETENE DIMER

CAS No.: 84989–41–3

Sponsor Country:
United Kingdom of Great Britain and Northern Ireland

Date of submission to OECD: 21st January 2005

1. General Information

1.01 Applicant and Company Information

A. CAS Number
84989-41-3

B. Name (OECD Name)
Alkyl ketene dimer

C. Name (IUPAC)
2-Oxetanone, 3-C_{12-16}-alkyl-4-C_{13-17}-alkylidene derivs.

D. CAS Descriptor
Not required.

E. EINECS Number
284-932-5

F. Molecular Formula and Weight
$C_{28}H_{52}O_2$ to $C_{36}H_{68}O_2$
Molecular weight 420 to 532

G. Structural Formula
See Figure 1-1 and 1-2

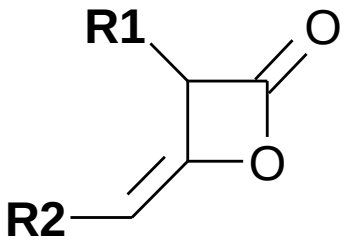


Figure 1-1 Structural formula of Alkyl Ketene Dimers, for an explanation of the side chains see Tables 1-1 and 1-2.

Table 1-1 Chain Lengths of Currently Available Alkyl Ketene Dimers

CAS No.	R1	R2	Chemical Name	Fatty Acids Used
84989-41-3	C_{12-16}	C_{12-16}	2-Oxetanone, 3-C12-16-alkyl-4-C13-17-alkylidene derivs.	Stearic acid and palmitic acid
68390-56-7	C_{12-16}	C_{12-16}	Fatty acids, tallow, hydrogenated, dimers, diketene derivates	Stearic acid and palmitic acid

The following alkyl ketene dimers are listed on EINECS and have been included in Table 1.3 for completeness. Note that all fall within the scope of the CAS Numbers 84989-41-3 [Europe] and 68390-56-7 [USA], and none are currently being sold commercially. Historically, the 10126-68-8 CAS Number has been used to register products in Sweden and Denmark and the 42272-70-8, 67845-94-7 and the 67845-95-8 CAS Numbers have been used to register products in Denmark. They can still be located when searching on the Scandinavian SPIN Database [http://195.215.251.229/spin.html] although they will not be used in the future. It is not always possible for Industry to view the data as it is often given in confidence to the Regulatory Authorities.

Table 1-2 Chain Lengths of the Historically Registered Alkyl Ketene Dimers

CAS No.	R1	R2	Chemical Name	Fatty Acids Used
10126-68-8	C16	C16	2-Oxetanone, 4-heptadecylidene-3-hexadecyl-	Stearic acid
98246-87-8	C14-16	C14-16	2-Oxetanone, 3-C14-16-alkyl 4-C15-17-alkylidene derivs.	Stearic acid and palmitic acid
42272-70-8	C14	C14	2-Oxetanone, 4-pentadecylidene-3-tetradecyl-	Palmitic acid
67845-94-7	C14	C16	2-Oxetanone, 4-heptadecylidene-3-tetradecyl-	Stearic acid and palmitic acid
67845-95-8	C16	C14	2-Oxetanone, 3-hexadecyl-4-pentadecylidene-	Stearic acid and palmitic acid

For historical reasons, the 84989-41-3 CAS Number is listed on EINECS and used in Europe to describe the alkyl ketene dimers used commercially. The CAS Number used in America is different, i.e., 68390-56-7 and is listed on TSCA. Both products are manufactured from stearic and palmitic fatty acids and are chemically and physically identical.

The only products currently available commercially are manufactured from a mixture of technical grade palmitic- and stearic acid. Both fatty acids contain minor amounts of other chain lengths varying from C12 through to C20. Aquapel® 364, which is manufactured from a mixture of technical grade palmitic- and stearic acid, was chosen as the test sample as it is not only the dominant product on the market but also, as confirmed by a survey of producers, is representative of what is available commercially.

2-Oxetanone, 3-C12-16-alkyl-4-C13-17-alkylidene and all the other CAS Numbers listed below are manufactured from technical grade palmitic and stearic fatty acids. All of the substances are low melting point, solid materials and, although many different CAS Numbers are listed on EINECS, all describe the same product and they could even be covered by the use of the one CAS Number, i.e., 84989-41-3 [See Tables 1-1 an 1-2].

It has not been possible to confirm either the logic involved in listing so many different CAS Numbers for AKD on EINECS or why the CAS Number used in America for the TSCA listing was different.

The AKD products placed on the market and listed in the report contain a variety of trade names:

Alkyl Ketene Dimer Batch 339 – AKD manufactured from a mixture of technical grade stearic and palmitic acids [CAS Nos.- 84989-41-3/68390-56-7 (see explanation)].
Alkyl Ketene Dimer Batch P224 – AKD manufactured from a mixture of technical grade stearic and palmitic acids [CAS Nos.- 84989-41-3/68390-56-7 (see explanation)].
Aquapel® 291 – AKD manufactured from technical grade stearic acid [CAS No.- 84989-41-3/68390-56-7 (see explanation)].
Aquapel® 364 – AKD manufactured from a mixture of technical grade stearic and palmitic acids [CAS Nos.- 84989-41-3/68390-56-7 (see explanation)].
Aquapel® 380 – AKD manufactured from a mixture of technical grade stearic and palmitic acids contains 5 parts AKD plus 1 part emulsifier [CAS Nos.- 84989-41-3/68390-56-7 (see explanation)].
Basoplast® 20 conc – AKD manufactured from a mixture of technical grade stearic and palmitic acids [CAS Nos.- 84989-41-3/68390-56-7 (see explanation)].
Basoplast® 20 konz – AKD manufactured from a mixture of technical grade stearic and palmitic acids [CAS Nos.- 84989-41-3/68390-56-7 (see explanation)].
Basoplast® 88 conc – AKD manufactured from a mixture of technical grade stearic and palmitic acids [CAS Nos.- 84989-41-3/68390-56-7 (see explanation)].
Keywax® SF100 – AKD manufactured from a mixture of technical grade stearic and palmitic acids [CAS Nos.- 84989-41-3/68390-56-7 (see explanation)].
Raisares® Batch E133 – AKD manufactured from a mixture of technical grade stearic and palmitic acids [CAS Nos.- 84989-41-3/68390-56-7 (see explanation)].
Stearyldiketen TV194/37 – AKD manufactured from technical grade stearic acid [CAS No.- 84989-41-3/68390-56-7 (see explanation)].

The products are chemically and physically similar. They are all manufactured from mixtures of technical grade stearic- and palmitic acid. The melting point varies with the stearic acid content, i.e., from 40℃ to 45℃ for those containing significant quantities of palmitic acid to 55℃ to 60℃ for those containing mostly stearic acid.

Alkyl ketene dimer, as can be seen from the structural formula below, consists of a four membered lactone ring with an exocyclic double bond and two long chain aliphatic side chains.

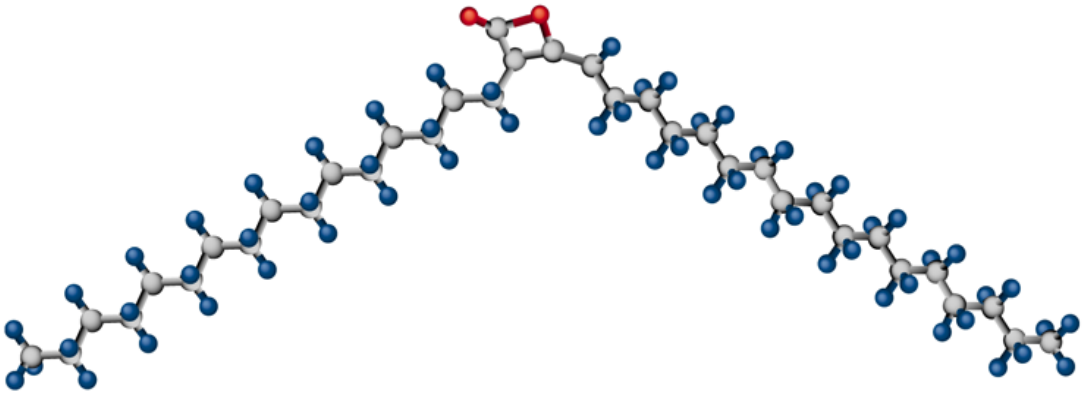


Figure 1-2 Visual representation of the alkyl ketene dimer

The other CAS Numbers listed have been included for completeness but please note that commercially the global market is dominated by the 84989-41-3/68390-56-7 CAS Numbers.

In addition to the “existing” products listed above a number of “new” alkyl ketene dimers have been notified to the European Regulatory Authorities. Details of the products and the toxicological

reports on the substances were made available to the Sponsor Country during the lifetime of this programme. However, this hazard assessment does not cover these new substances.

1.02 OECD Information

A. Sponsor Country

United Kingdom of Great Britain and Northern Ireland

B. Lead Organisation

Global Producers of Alkyl Ketene Dimers (GPA)
Karlstraβe 21
60329 Frankfurt am Main
Germany
Telefone: +49 69 2556 1340
Telefax: +49 69 2556 1342

C. Names of Responders (Companies)

Name: BASF Aktiengesellschaft
Street: Karl Bosch-Straβe
Town: 67056 Ludwigshafen am Rhein
Country: Germany
Phone: +49 621 60 40277
Telefax: +49 620 60 44048
Name: Eka Chemicals AB
Town: 445 80 Bohus
Country: Sweden
Phone: +46 31 58 70 00
Telefax: +46 31 58 7745

Name: Hercules International Ltd
Street: Veraartlaan 8
Town: 2288 GM Rijswijk
Country: Netherlands
Phone: +31 70 4134 368
Telefax: +31 70 3902 715

Name: Kemira Oyj
Street: P.O. Box 330
Town: 00101 Helsinki
Country: Finland
Phone: +358 10 8611
Telefax: +358 10 862 1119

Name: MARE S.p.A.
Street: Via Verdi, 3

Town: 20010 Ossona/Fraz. Asmonte (MI)
Country: Italy
Phone: +39 02 903 261
Telefax: +39 02 903 80 474

Name: NOF
Street: Industriezone Klein-Gent Bouwelven 1
Town: B-2280 Grobbeldonk
Country: Belgium
Phone: +32 14 25 98 29
Telefax: +32 14 22 45 63

Name: Ciba Specialty Chemicals Oy (former Raisio Chemicals Oy)
Street: Raisionkaari 55 (P.O. Box 250)
Town: 21201 Raisio
Country: Finland
Phone: +358 2 442 5111
Telefax: +358 2 442 5442

1.03 Details on Chemical Category

Not applicable

1.1 General Substance Information

Aquapel® 364 Batch No 3LP1456 is the standard material studied in this programme and reported in this dossier. The product has been fully characterised according to standard industry practice and the full analytical report is available.

1.1.1 Type of Substance

Organic

1.1.2 Physical State

Solid
Alkyl ketene dimers are waxes.

1.1.3 Purity

The typical purity ranges between 80 and 95% alkyl ketene dimer. The sample of Aquapel® 364 used was fully analysed and the distribution of chain lengths (recalculated to be based on the fatty acids used in the manufacture of the product), are set out below. Unsurprisingly, the results show that Aquapel 364 consists primarily of the three isomers based on palmitic and stearic acid.

Sample:	**Aquapel® 364**
C12:0/C16:0 & C14:0/C14:0	0.12%
C12:0/C17:0 & C13:0/C16:0	0.10%
C14:0/C16:0	1.89%
C13:0/C18:0 & C14:0/C17:0 & C15:0/C16:0	0.48%
C16:0/C16:0	**22.59%**
C14:0/C19:0 & C15:0/C18:0 & C16:0/C17:0	1.78%
C16:0/C18:0	**45.01%**

Sample:	Aquapel® 364
C15:0/C20:0 & C16:0/C19:0 & C17:0/C18:0	1.49%
C18:0/C18:0	**25.37%**
C18:0/C19:0	0.21%
C18:0/C20:0	0.69%
C19:0/C20:0	0.14%
C20:0/C20:0	0.13%
Total	**100.00%**

The fatty acid used to make the above AKD was also analysed and the composition is:

Sample:		Fatty acids
Saturated linear unbranched total	**[%]**	*100*
	C12:0	0.1
	C13:0	0.1
	C14:0	1.3
	C15:0	0.6
	C16:0	45.6
	C17:0	0.7
	C18:0	50.0
	C19:0	0.8
	C20:0	0.9

The chemical name for Aquapel 364 is 2-Oxetanone, 3-C12-16-alkyl-4-C13-17-alkylidene [CAS Number 84989-41-3 (Europe) and 68390-56-7 (America)]. It is manufactured from the linear, saturated natural fatty acids obtained from the rendering of animal fats and plant oils. The first stage in the manufacturing process is to make a fatty acid chloride, which is then dimerised in the presence of an aliphatic amine to form the alkyl ketene dimer.

1.2. Impurities

Small amounts of unreacted fatty acid (~2 to 5%), hydrolysed alkyl ketene dimer (~1 to 5%) and alkyl ketene trimers and tetramers (~2 to 10%)

1.3. Additives

None

1.4. Synonyms

2-Oxetanone, 4-heptadecylidene-3-hexadecyl- (8CI, 9CI)
Alkyl Ketene Dimers
Alchildichetene a catena grassa
AKD
Alkylketenedimers
Alkyl ketene dimer wax
Aquapel® 291
Aquapel® 364
Basoplast 20 konz.
Basoplast 20 conc.
Basoplast 88 conc.

Basoplast 88 FL.
Basoplast 20 konz. P
Basoplast Dimer conc.
Basoplast Dimer 50 conc.
Hexadecyl ketene dimer
Keywax SF100
Newpel 1000
Octadecylketene dimer
Palmitylketene dimer
Raisares
Stearyldiketene

All of the commercial products listed above fall within the scope of CAS Nos. - 84989-41-3 and/or 68390-56-7 depending on the geographical region where they are sold.

1.5. Quantity

10 000 to 50 000 tonnes per annum.
The total volume of Alkyl Ketene Dimers produced globally in 2001 was less than 50000 tonnes. Two producers reported annual volumes of less than 5000 tonnes per annum and the other five, volumes of greater than 5000 tonnes per annum. See also chapter 7.1 아래.

1.6. Use Pattern

1.6.1. General Use Pattern

Alkyl ketene dimers are produced in a Best Available Technology [BAT] closed process in Belgium, China, France, Finland, Germany, Italy, Japan, Sweden, United Kingdom and United States of America. See also chapter 7.1 아래.

Alkyl ketene dimers are transported in drums (100 to 200 kg), big bags (500 to 1000 kg), IBC containers (~880 kg) or road tankers (15000 kg). See also chapter 7.1 아래.

Alkyl ketene dimers are only used in one industrial process, i.e., the pulp and paper industry is the only recipient. Alkyl ketene dimers are used as paper-sizing agents, to improve resistance against aqueous based liquids by making the cellulose fibers slightly hydrophobic. See also chapter 7.1 아래.

1.6.2. Uses in Consumer Products

Alkyl ketene dimers are not used directly in consumer products.

Alkyl Ketene Dimer [AKD] is used exclusively as a process chemical by the paper industry to add some hydrophobic character to the surface of the cellulose fibres. This is traditionally known within the industry as “sizing”. Typical examples of paper products manufactured with AKD are office paper, liquid packaging board and folding-box board. The amount used is between 0.05 and 0.3% by weight of the end product. However, it is important to recognise that the alkyl ketene dimer itself will not be detected in the paper as it has either reacted with the cellulose to form a covalent bond or with the water present in the paper making system to form the hydrolysed alkyl ketene dimer.

There are several national approvals for the use of alkyl ketene dimer in food contact packaging materials. A typical food contact application is internal sizing for liquid packaging board but, because paper cannot be used to store aqueous liquids for long periods of time, a barrier layer of polyethylene or aluminium is required for the packaging to perform effectively.

The most referred to food contact approvals are as follows:

- FDA (Food and Drug Administration, revised as of April 1, 2002) 21 CFR 176.120 "alkyl ketene dimers" allowing to use the alkyl ketene dimers and their hydrolysis products dialkyl ketones not to exceed 0.4 % by weight of the paper and paperboard. The petition dossier of this approval covers comprehensive studies of possible exposure via the packaging chain of Alkyl Ketene Dimers and the hydrolysis product including also complete toxicity studies for the hydrolysis product.

[Reference: 1]

- BfR (Bundesinstitut für Risikobewertung [formerly known as the BgVV], Teil A, 52. Lieferung, Stand Januar 2002), Empfehlung XXXVI „Papiere, Kartons und Pappen für den Lebensmittelkontakt", Part B, additives, paragraph I.11. Di-alkyl(C10-C18)diketene, die bis zu 65 % iso-Alkylgruppen enthalten können, höchstens 1.0%. Empfehlung XXXVI/2 „Papiere, Kartons und Pappen für Backzwecke", II.A.5: Dialkyl (C10-C18)diketene, höchstens 0.5 %.

[Reference: 2]

- Warenwet, Verpakkingen en Gebruiksartikelenbesluit, Hoofdstuk II – Papier en Karton (VGB/Aanv. 14, 12-2002) par 1.2.2.h. lijmen en vezelbindmiddelen: alkylketeendimeren, bereid uit gehalogeneerde vetzuren afkomstig an dierlijke of plantaardige oliën en vetten, ten hoogste 0.4 %. Hoofdstuk X-Deklagen, par. 6 Oplossinger in water, l. Watervastmakende middelen: alkylketeendimeren.

[Reference: 3]

7.1 Source of Exposure

Production of Alkyl Ketene Dimer

Exposure data are available for five production sites, all manufacturing products with the CAS No. 84989-41-3. All are waxy solids containing greater than 80% alkyl ketene dimer and typically the values are greater than 85%. Three producers reported using closed, automated or semi-automated, batch processes; one producer reported a closed continuous automated process and another, a campaign process. All the processes are in closed buildings except for one, which is outdoors. The number of operating days varies from 300 to 365 days per annum.

The total volume of alkyl ketene dimer produced globally in 2001 was less than 50000 tonnes. Two producers reporting annual volumes of less than 5000 tonnes per annum and the three volumes of greater than 5000 tonnes per annum. Alkyl ketene dimer is transported in drums (100 to 200 kg), big bags (500 to 1000 kg), IBC containers (~880 kg) or road tankers (15000 kg). The survey revealed that all of the alkyl ketene dimer produced is used in the paper and board industry.

The total number of people potentially exposed to alkyl ketene dimer during production is low. For the five sites surveyed, 29 people (two females), are working continuously with alkyl ketene dimer and another 20 (no females), are working intermittently, i.e., up to 50% of their time. Potential worker exposure to alkyl ketene dimers occurs during the packing, flaking, storing and sampling of the product. All producers reported, as Personal Protection Equipment [PPE], gloves and goggles in the process and laboratory, filling, emptying and transferring operations and all, except one, in maintenance and during disposal/waste management. For the process and maintenance areas all

sites either have overall protection or a protective suit. The processes either have local- (two sites) or general ventilation (two sites) and one is segregated. No monitoring data for Alkyl Ketene Dimer was reported, although the sites have some monitoring data for other chemicals used in the manufacturing process. There are no reported contact allergy cases at any of the five production sites.

Use of Alkyl Ketene Dimers in the Formulating Plants

Alkyl ketene dimer wax is formulated into an aqueous emulsion before it is transported to paper mills where it is used as a production aid in the manufacture of paper and board. The formulated products are transported to customers in drums (sizes 100, 120 and 200 kg), IBC containers (1000 kg) and road tankers, sizes 16000, 20000, 23000 and 40000 kg. The formulated products are stored in tanks and dosed after dilution with water into a closed part of the paper machine.

Exposure data are available for nine formulation sites. The total volume of formulated alkyl ketene dimer manufactured at these sites was 7500 tonnes in 2001. Eight sites reported using alkyl ketene dimers with the CAS No. 84989-41-3 and one with CAS No. 10126-68-8. All the alkyl ketene dimer emulsions are used as a sizing agent in the in the manufacture of paper and board. The concentration range of the alkyl ketene dimer in the emulsions is between 5% and 30%. Three of the formulations report end product usage at the same site, while the others supply to down-stream users.

One process is a continuous, seven are batch processes and one is a campaign process. Three processes are open and seven are closed. Seven of the processes are semi-automated and two are manual. All are housed in closed buildings except for one, which is outside under a roof. The number of days they operate varies from 100 to 350 days per annum with seven of the sites operating for more than 250 days per annum.

The potential for human exposure during the manufacture of the formulated products, occurs via the dermal route, i.e., when opening the alkyl ketene dimers containers and during the dosing, sampling, maintenance and cleaning operations. PPE used at the sites are gloves, goggles, protective suits at four sites and one having overall protection. A respirator is used by one site in all operations and another reports it's use during the filling/emptying/transferring operations. Six sites have general ventilation for the dosing, process, maintenance and laboratory areas. Three sites reported local ventilation for the process itself and one for the maintenance area. One site has segregated the filling, emptying, transferring and pouring operations and two others the weighing and mixing operations. The total number of people potentially exposed is 41 working continuously (no females) and 57 working (six females) intermittently.

No monitoring data for alkyl ketene dimers at any of the sites was reported, although some measurements are reported for some of the other chemicals used in the manufacturing process. There are no reported contact allergy cases at any of the production sites.
[Reference: [4]]

1.8. Additional Information

1.8.1. Classification and Labelling

AKD is not classified as hazardous within the European Union.

Water Hazard Classification (WGK) in Germany: nwg [Kenn Nr 2307]
[Reference: [5]]

1.8.2. Occupational Exposure Limits

No exposure limit values have been set for AKD within the European Union.

1.8.3. Options for Disposal

Small amounts can be placed in a wastewater treatment plant and large amounts should be swept up and either reused or placed in a container for disposal.

1.8.4. Last Literature Search

See Annex to SIAR

1.8.5. Other Remarks

None

2. Physical-Chemical Data

2.1. Melting Point

Test substance: Aquapel® 364 Batch No 3LP1456 P224 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Value: = 43.6 °C
Method: Differential Scanning Calorimetry [DSC] - OECD Guidelines for Testing of Chemicals No 102.
GLP: No
Year: 2003
Reliability: 2, The study followed the OECD test guideline and is scientifically valid. It was, however, not performed under GLP.
KEY STUDY for OECD SIDS
[Reference: [6]]

Test substance: Aquapel® 291 Batch No 17LY1200
[CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids but with more stearic acid present]
Value: = 56.4 °C
Method: Differential Scanning Calorimetry [DSC] - OECD Guidelines for Testing of Chemicals No 102.
GLP: No
Year: 2004
Reliability: 2 - The study followed the OECD test guideline and is scientifically valid. It was, however, not performed under GLP.
KEY STUDY for OECD SIDS
[Reference: [7]]

Test substance: Basoplast 20 konz.
Value: 43 °C to 65 °C
Method: Unknown
GLP: No
Year: Unknown
Reliability: 4 – The data was included in the IUCLID File but the report is not available.
[Reference: [8]]

2.2. Boiling Point

Test substance: Aquapel® 364 Batch No 3LP1456 P224 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Value: Decomposes without boiling with decomposition occurring above 200 °C.
Method: Differential Scanning Calorimetry [DSC] - OECD Guidelines for Testing of Chemicals No 103
GLP: Yes
Year: 2001
Reliability: 1
KEY STUDY for OECD SIDS
[Reference: [9]]

2.3. Density

Test substance: Aquapel® 364 Batch No 3LP1456 P224 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Value: ca. 0.84 g/cm^3 at 70 °C
Method: Standard Industry Laboratory procedure - Mare
GLP: No
Year: 2004
Reliability: 2 - The study followed the principles outlined in Annex V of EC92/69/EEC [A3] test guideline and is scientifically valid. It was, however, not performed under GLP.
KEY STUDY for OECD SIDS
[Reference: [10]]

Test substance: Not specified
Value: ca. 0.85 g/cm^3 at 70 °C
Method: Not specified
GLP: No
Year: Not specified
Reliability: 4 - The data was included in the IUCLID File but the report is not available.
[Reference: [11]]

2.4. Vapour Pressure

Test substance: Not applicable - Calculation
Value: = 1.0 x 10^{-11} hPa at 20 °C
Method: Estimated by graphic extrapolation of vapour pressures of a C38-alkane [Value cannot be validated. The value at 40 °C is therefore the key value. The molecular weight of the C38 alkane was assumed to be close enough to the molecular weight and therefore the vapour pressure of the alkyl ketene dimer].
GLP: No
Year: 1989
Reliability: 3
[Reference: [12]]

Test substance: Basoplast 20 konz., [non-volatile components: 99.1%] [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Value: ca. 3 x 10^{-6} hPa @ 40 °C
Method: Extrapolated from effusion measurement.
Year: 1985
GLP: No
Remark: Analytical precision about +100 to -50%
Other values calculated are:
1 x 10^{-5} hPa @ 60 °C
2.2 x 10^{-5} hPa @ 80 °C
5 x 10^{-5} hPa @ 100 °C
1 x 10^{-4} hPa @ 120 °C
Reliability: 4
[Reference: [13]]

Test substance: Alkyl ketene dimers, chain lengths C12/C12 to C16/C16 [CAS No. 84989-41-3/68390-56-8]
Value: 6.12 x 10^{-8}–5.85 x 10^{-11} Pa for the CAS No. 84989-41-3/68390-56-8 AKD
Method: EPIWIN Version 3.1
GLP: No
Year: 2004
Results:

QSAR Calculation - Alkyl Ketene Dimer [CAS No 84989-41-3]

R1	R2	Fatty Acid Feedstock	Vapour Pressure
C_{12}	C_{12}		6.12 x 10^{-8} Pa
C_{14}	**C_{14}**	**palmitic acid**	2.17 x 10^{-9} Pa
C_{14}	**C_{16}**	**stearic acid and palmitic acid**	3.60 x 10^{-10} Pa
C_{16}	**C_{14}**	**stearic acid and palmitic acid**	3.60 x 10^{-10} Pa
C_{16}	**C_{16}**	**stearic acid**	5.85 x 10^{-11} Pa

KEY STUDY for OECD SIDS
Reliability: 2
[Reference: [14]]

2.5. Partition Coefficient

Test substance: Not applicable - Calculation for AKD [CAS No. 84989-41-3/68390-56-8]
Results: log Pow: >6 (calculated value: 15.4)
Method: **Calculated according to the Rekker method. Method details are given in the reference together with detailed background information.**

GLP: No
Year: 1989
Reliability: 2 - Estimated using reliable calculation method..
[Reference: [15]]

Test substance: Alkyl ketene dimers, chain lengths C12/C12 to C16/C16 [CAS No. 84989-41-3/68390-56-8]
Results: log Pow: >6 (calculated values: 11.25–15.18)
Method: EPIWIN Version 3.1
GLP: No
Year: 2004

Results:

QSAR Calculation - Alkyl Ketene Dimer [CAS No 84989-41-3]

R1	R2	Fatty Acid Feedstock	Log Pow
C_{12}	C_{12}		11.25
C_{14}	**C_{14}**	**palmitic acid**	13.21
C_{14}	**C_{16}**	**stearic acid and palmitic acid**	14.19
C_{16}	**C_{14}**	**stearic acid and palmitic acid**	14.19
C_{16}	**C_{16}**	**stearic acid**	15.18

KEY STUDY for OECD SIDS
Reliability: 2 – Estimated using reliable calculation method
[**Reference: [16]**]

Test substance: CONFIDENTIAL – structurally related new chemical
Results: log Pow 5.5 at 25 ℃
Method: HPLC method, Annex V to EU Directive 92/32/EEC, Test A8
GLP: Yes
Year: Not available
Reliability: 1 – Data for structurally related new chemical provided to EU Regulatory Authorities

2.6. Solubility and Dissociation in Water and Surface Tension

2.6.1. Water Solubility

Test Substance: Basoplast 20 konz. [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Method: Determination of organic carbon in a saturated aqueous solution
Result: 10 +/- 5 mg/kg @ 25 °C [Insoluble - pH: ca. 4.7 at 20 g/l and 20 °C]
GLP: No
Year: 1989
Reliability: 4
[Reference: [17]]

Test substance: Alkyl ketene dimers, chain lengths C12/C12 to C16/C16 [CAS No. 84989-41-3/68390-56-8]
Value: $5.64 \times 10^{-7} – 4.81 \times 10^{-11}$ mg/l @ 25 ℃
Method: EPIWIN Version 3.1
GLP: No
Year: 2004
Results: The data show the limited water solubility of alkyl ketene dimers and demonstrated that, at 25℃, the solubility of alkyl ketene dimer decreases as the chain length of the fatty alkyl side chains increases.

QSAR Calculation - Alkyl Ketene Dimer [CAS No 84989-41-3]

R1	R2	Fatty Acid Feedstock	Water Solubility (25 °C)
C_{12}	C_{12}		5.638×10^{-7} mg/l (9.282×10^{-7} mg/l)*
C_{14}	**C_{14}**	**palmitic acid**	5.241×10^{-9} mg/l
C_{14}	**C_{16}**	**stearic acid and palmitic acid**	5.026×10^{-10} mg/l
C_{16}	**C_{14}**	**stearic acid and palmitic acid**	5.026×10^{-10} mg/l
C_{16}	**C_{16}**	**stearic acid**	4.805×10^{-11} mg/l (8.837×10^{-11} mg/l)*

KEY STUDY for OECD SIDS
Reliability: 2 * Results in brackets are for predictions using a generic melting point of 50 °C. The melting point makes little difference to the predicted results.
[Reference: [18]]

Test substance: CONFIDENTIAL – structurally related new chemical
Results: 0.3 mg/l at 23 °C
Method: turbidimetric method, Annex V to EU Directive 92/32/EEC, Test A6
GLP: Yes
Year: Not available
Reliability: 1 – Data for structurally related new chemical provided to EU Regulatory Authorities

2.6.2. Surface Tension

No data are available.

2.7. Flash Point

Value: 171 °C
Test Substance: Aquapel® 364, Batch No 27AR0125 [The chemical composition is technically identical to the standard Aquapel® 364, Batch No 3LP1456 P224 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids].
Method: Hercules Method 010-17e, Closed Tester Flash Point Apparatus
Year: 2001
GLP: No
Reliability: 2. The study is scientifically valid but it wasn't performed under GLP.
KEY STUDY for OECD SIDS
[Reference: [19]]

Value: 171 °C
Test Substance: Aquapel® 291, Batch No 10BR0181 [An AKD manufactured using a stearic acid rich blend of palmitic and stearic fatty acids].
Method: Hercules Method 010-17e, Closed Tester Flash Point Apparatus
Year: 2001
GLP: No

Reliability: 2, The study is scientifically valid but it wasn't performed under GLP.
[Reference: [20]]

Value: > 100 °C
Test Substance: Unspecified
Method: The method used is described in DIN 51 758.
Year: Unspecified
GLP: No
Reliability: 4 - The data was included in the IUCLID File but the report is not available.
[Reference: [21]]

2.8. Auto Flammability

No data available.

2.9 Flammability

Result: Non-flammable.
Test Substance: Unspecified
Method: Unspecified
Year: Unspecified
GLP: No
Note: The [February 19, 2000] contained a note that the ignition temperature is circa 350 C but the reference data could not be located.
Extensive commercial experience with AKD confirms that it is not flammable and the flash point is not less than or equal to 55 C. This statement is supported by an Annex V study completed recently on a new AKD. It demonstrated that it did not propagate combustion, did not evolve highly flammable gases on contact with water and did not spontaneously ignite.
[Reference: [22]]

2.10. Explosive Properties

No data are available.

2.11. Oxidising Properties

No data are available.

2.12. Oxidation/Reduction Potential

No data are available.

2.13. Additional Remarks

No additional remarks.

3. Environmental Fate and Pathways

3.1. Stability

3.1.1 Photodegradation

Type: Indirect Photolysis in the air
Sensitizer: Hydroxyl radicals or Ozone
Rate constant:
Hydroxyl radicals - circa 129.0404 E^{-12} cm^3/(molecule-sec) [Half Lives - 0.995 hours and 0.083 Days (12 hour day; 1.5 E^6 OH molecules/cm^3] .
Ozone - circa 7.393750 E^{-17} cm^3/(molecule-sec) [Half Lives - 3.720 hours and 0.155 Days (12 hour day; 7 E^{11} O_3 molecules/cm^3].
Degradation: circa. 50 % after 1.09 hours with hydroxyl radicals and circa 50 % after 3.72 hours with ozone.
Method: Calculated: AOP, Version 1.90
Year: 2004
GLP: No
Reliability: 2

KEY STUDY for OECD SIDS

Test substance: SMILES : O=C(OC1=CCCCCCCCCCCCCCCCC)C1CCCCCCCCCCCCCCCCC
CHEM : 2-Oxetanone, 4-heptadecylidene-3-hexadecyl-
MOL FOR: C36 H68 O2 , MOL WT : 532.94
[Reference: 23]

3.1.2. Stability in Water

Alkyl ketene dimer hydrolyses readily under neutral and alkaline conditions to form the dialkyl ketone but only slowly under acid conditions (Further details are available in the document 'GPA_SizingReactionScheme' which is an annex to the SIAR). Studies are available on the hydrolysis of commercial alkyl ketene dimer preparations but there are no valid hydrolysis studies available for alkyl ketene dimer described by CAS Numbers 84989-41-3 [Europe] and 68390-56-7 [USA].

However, a hydrolysis test is available for a structurally related alkyl ketene dimer notified as a new chemical in the EU under Directive 92/32/EEC. Hydrolysis was >10% after 5 days at pH 7 and 9, indicating that at these pHs alkyl ketene dimer could be considered to hydrolyse under environmental conditions. The test [OECD Guideline 111, GLP] indicated that the test substance hydrolysed under alkaline conditions [pH 7 (>95% after 5 days at 50°C, half life 10.4 hours at 30°C) and pH 9 (>95% after 5 days at 50°C, half life 4.4 hours at 30°C)]. No conclusion could be reached regarding hydrolysis at pH 4 due to inconsistencies in the data. The test report can be made available in confidence to regulatory authorities if required:

Test substance: CONFIDENTIAL – structurally related new chemical

Results:

pH	Temperature °C	Rate constant/s	Half life /h
7.0	30	0.0000186	10.4
7.0	40	0.0000378	5.1
9.0	30	0.0000439	4.4
9.0	40	0.0000439	4.4

Method: OECD 111
GLP: Yes
Year: Not available
Reliability: 1 – Data for structurally related new chemical provided to EU Regulatory Authorities. Hydrolysis was >10% after 5 days at pH 7 and 9 and indicated that at these pHs the test substance could be considered hydrolytically unstable under environmental conditions. Further testing was conducted to determine the rate of hydrolysis at pH 7 and 9. The preliminary test for pH 4 showed 85% degradation but further testing was inconclusive and a hydrolysis rate constant was not determined. [This data fits with commercial practice where alkyl ketene dimers are stable at acid pH but hydrolyse under neutral or weakly alkaline conditions].

However, in practice it is well known that in alkaline conditions and at room temperature, hydrolysis will occur, leading to formation of the dialkyl ketone. Alkyl ketene dimer sizes are stored at relatively low pH, typically around 3, in cooled containers in order to avoid formation of the ketone hydrolysis product which reduces the technical sizing effect.
[Reference: 24]

The hydrolysis of AKD in sizing emulsions has been studied e.g. by Marton who reviewed published data discussing sizing effects, hydrolysis of AKD and describes the hydrolysis of two types of AKD sizes:

- Weakly cationic sizing agent, pre-emulsified with cationic starch (mainly), containing 9% AKD and stabilized at pH 3.5 (AP emulsion)
- Strongly cationic size, containing 6 % AKD and 9% emulsifier-stabilizer-promoter polymer solids, mainly polyamine amide-epichlorohydrin (PAE) resin (HC emulsion).

It was shown that the rate of hydrolysis was six times faster in the presence of PAE resin at room temperature than in the weekly cationic AKD emulsion. Raising the temperature to 50°C accelerated the hydrolysis still further to 18 times the reference value. Morton also calculated the approximate half lives of AKD in the emulsions, assuming a pseudo first order reaction, as:

- T 1/2 at 30˚C pH 8 = 140 h (AP emulsion) and 23 h (HC emulsion)
- T 1/2 at 50˚C pH 8 = 27 h (AP emulsion) and 1,5 h (HC emulsion)

[Reference: 25]

A stability study is available for AKD dispersion:

Test substance: Aquapel® 364
Method: Internal Hercules Study
Test conditions: The emulsion was stored for 4 weeks at pH 3 and a temperature of 25 °C and 32 °C. During this period the emulsion was regularly analysed for AKD content.

Result: Over a period of 4 weeks the AKD assay is reduced. This effect is more severe at elevated temperatures. At 25℃ the assay dropped by 4.5%, at 32℃ the assay dropped by 16.6%. This is most likely due to hydrolysis of the AKD where the AKD is converted to the dialkyl ketone.
GLP: No
Reliability: 2 – only summary report available, not conducted to GLP
[Reference: 26]

3.1.3. Stability in Soil

No data are available.

3.2.1. Monitoring Data (Environment)

Schultz described the fate of Alkyl Ketene Dimers [AKD] (and other sizing agents), over the entire process of paper production. The main conclusion is that all products remain nearly quantitatively on the fiber.
[Reference: [27]]

As mentioned under 1.6.2, i.e., Uses in Consumer Products, there is no unreacted AKD left in the final paper reaching the consumer and it is impossible in practice to reform the unreacted AKD from the reaction products present in the final paper.

A significant amount of paper is recycled into manufacturing of new paper. During this process, final paper products are broken down into free cellulose fibers in water. The fibre slurry can also be treated by some further process steps. It must be restated here that the statement "there are no conditions under which the unreacted AKD can be reformed from its reaction products" is valid also during all recycling process steps.

To clarify the fate of the AKD during the recycling of paper, the content of both the AKD reacted with the fibre and the hydrolysed AKD (when added together they constitute the "total AKD" in the original paper) was determined in a screening study. The methods used were standard industry laboratory methods.

The Paper Industry is unusual as much of it is based on recycled fibre. Recycling falls into two general categories, i.e. 1.) - where the paper is repulped and reused directly and 2.) - where it is also deinked prior to being reused. The term deinking, as its name suggests, involves separating the ink, used to either decorate the package or convey the message, from the paper fibre before it is reused.

Two types of paper were evaluated in the study: fine paper and liquid packaging board [LPB], i.e., specifically the plastic coated paperboard used in milk packaging. Samples were selected from grades typically found on the market. The LPB samples were pulped, the plastic film removed and no pulping chemicals were added. The fine paper samples were pulped, diluted and deinked using some standard deinking chemicals [no surface active chemicals, e.g., soap, were used in order to avoid problems with the analysis of the various samples]. The rejected material, consisting primarily of fillers and inks, along with the reclaimed, deinked and washed pulp from the flotation process were collected.

The samples were then analysed and the level of both fibre-reacted and hydrolysed AKD was determined and the "total AKD" in each of the various samples calculated. The analyses were performed by extraction followed by gas chromatography and the details can be found in a confidential report made available to the Sponsor Country. The liquid packaging board samples contained AKD 0.131% from which 0.069% was unreacted and 0.062% reacted AKD. After pulping the amount of AKD was 0.173%. The slight increase of AKD content can be explained by

the removal of the plastic layer that didn't contain AKD. After washing the amount of AKD was 0.12%. During extraction the "fibre-reacted AKD" does not separate from the fibres unless the paper is first treated with strong alkali to break the covalent bonds formed between AKD and fibre.

Most of the "fibre-reacted" and "hydrolysed" AKD in the liquid packaging board remained in the washed pulp and shall thus be further recycled. No further recycling to food contact paper and board is likely to occur as the deinked liquid packaging board is generally used for core board in paper reels. The distribution of the "fibre-reacted" and "hydrolysed" AKD in fine paper samples seemed to be somewhat different compared to the liquid packaging board samples. The fine paper samples contained AKD 0.091 % from which 0.042 % was unreacted and 0.049 % reacted AKD. Before flotation the amount of total AKD was 0.040 % and after flotation 0.042%. The reject contained 0.30 % AKD and after washing the amount of AKD was 0.01 % in the pulp. The result from the reject was rechecked. The high amount clearly shows that there has been a substantial enrichment in the flotation foam. The unchanged level in the accept can be explained by dilution effect and due to the fact that the amount of reject in the flotation was low, only 3.7 %. A probable reason for this is that no surfactants were used. The washing removed the rest of the AKD. Only traces of the "fibre-reacted" and "hydrolysed" AKD were found in the washed fibres. The bulk of the "fibre-reacted" and "hydrolysed" AKD remains attached to the fines and fillers which are efficiently removed in the flotation deinking process so nearly all the AKD present in the paper ends up in the rejected material. The rejected material is then normally disposed of by either incineration followed by land filling the remaining ash or direct land filling in a waste deposit.
[Reference: [28]]

3.3. Transport and Distribution

3.3.1. Transport between Environmental Compartments

Type: Adsorption in soil
Method: Calculated (PCKOCWIN v1.66)
Test substance: Alkyl ketene dimers, chain lengths C12/C12 to C16/C16
Result: Koc is predicted to be $1.51 \times 10^7 – 2.0 \times 10^9$
GLP: No
Reliability: 2, standard calculation method
[Reference: [29]]

Type: Henry's Law Constant, partitioning between water and air
Method: Calculated (HENRYWIN v 3.10 model (bond method))
Test substance: Alkyl ketene dimers, chain lengths C12/C12 to C16/C16
Result: Henry's Law constant is predicted to be 0.643 - 6.2 atm/m^3/mole.
GLP: No
Reliability: 2, standard calculation method. However, there are uncertainties with this result since HENRYWIN v 3.10 should be used for highly miscible or highly soluble compounds.
[Reference: [30]]

Type: Henry's Law Constant, partitioning between water and air
Method: Calculated using the following equation: Henry's Law Constant = vapour pressure (Pa) x molecular weight (g/mol) /water solubility (mg/l)
Test substance: Alkyl ketene dimers, chain lengths C12/C12 to C16/C16
Result:

C12:C12 AKD: HLC = 6.12 x 10-8 x 420/5.64 x 10-7 = 46 Pa.m^3/mol
C16:C16 AKD: HLC =5.85 x 10-11 x 532/4.8 x 10-11 = 648 Pa.m^3/mol
GLP: No
Reliability: 2, standard calculation method.

3.3.2. Distribution

Media: air-biota-sediment(s)-soil-water
Method: Calculation according Mackay, Level I
Reliability: 2 (valid with restrictions)
Test substance: 2-Oxetanone, 4-heptadecylidene-3-hexadecyl-

Result:

Air:	8.83E-08 %,
Water:	3.95E-10 %,
Soil:	49.54 %
Sediment:	50.10 %
Susp. Sediment:	0.32 %
Fish:	0.031 %
Aerosol:	0.002 %

Remark:
CHEMICAL PROPERTIES,
Chemical Type, 1,
Molecular Mass (g/mol), 532.94,
Data Temperature (°C), 25,
LogKow, 15.2,
Water Solubility (g/m3), 4.8E-11,
Water Solubility (mol/m3), 9.006642E-14,
Henry's Law Constant (Pa.m3/mol), 646.1898,
Vapour Pressure (Pa), 5.82E-11,
Melting Point (°C), 245.6, calculated
Fugacity Ratio, 6.578856E-03,
Sub-cooled Liquid Vapour Pressure, 8.846523E-09,

Amount of Chemical (kg), 100000,
Amount of Chemical (mol), 187638.4,
Fugacity Pa , 6.848307E-11 ,
Total of VZ Products, 2.739923E+15,

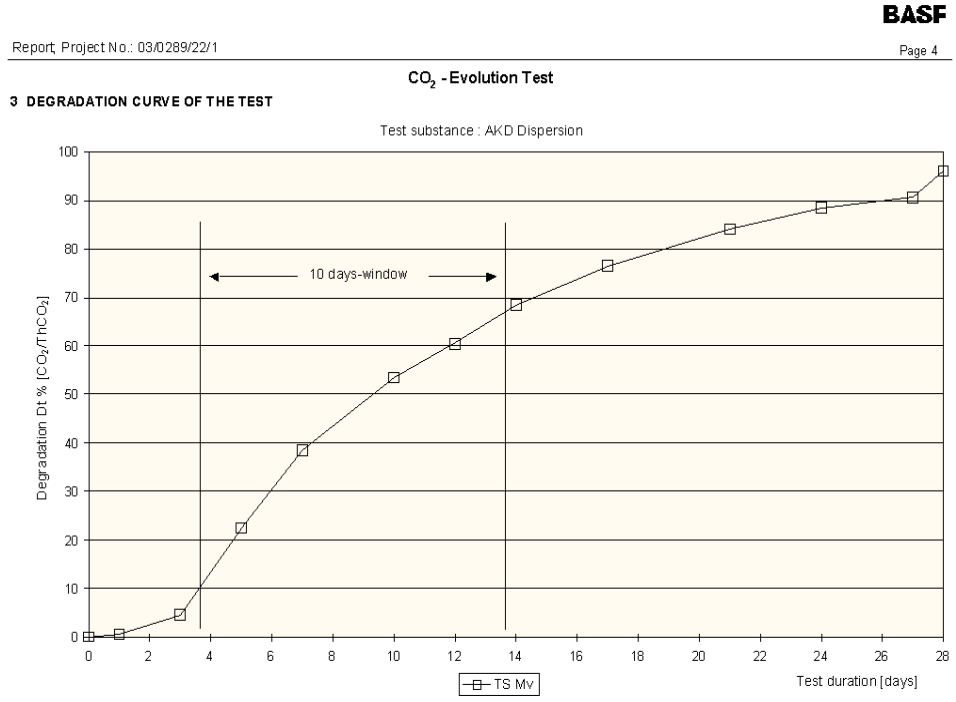
PARTITION COEFFICIENTS,
Log Octanol-Water Partition Coefficient , 15.2 ,
Octanol-Water Partition Coefficient , 1.584892E+15 ,
Organic Carbon-Water Partition Coefficient (L/kg) , 6.498059E+14 ,
Air-Water Partition Coefficient , 0.2606845 ,
Soil-Water Partition Coefficient , 1.949418E+13 ,
Soil-Water Partition Coefficient (L/kg) , 1.299612E+13 ,
Sediment-Water Partition Coefficient , 4.223739E+13 ,
Sediment-Water Partition Coefficient (L/kg) , 3.24903E+13 ,

Suspended Sediment-Water Partition Coefficient , 1.627764E+14 ,
Suspended Sediment-Water Partition Coefficient (L/kg) , 1.085176E+14 ,
Fish-Water Partition Coefficient , 7.924462E+13 ,
Fish-Water Partition Coefficient (L/kg) , 7.924462E+13 ,
Aerosol-Air Partition Coefficient , 6.782326E+14 ,

Reference: Model Level I V 2.11, 2004
Remarks: Using a generic melting point value of 50°C as an input to the model predicts a very similar distribution: 49.1% to soil and 49.64% to sediment.

3.4. Aerobic Biodegradation

Type: Aerobic
Inoculum: Activated sludge from laboratory wastewater plant treating municipal sewage.
Concentration: 30 mg/L (dry substance)
Degradation: 96 % after 28 days, >60% within a 10 day window
Method: OECD Guideline for Testing of Chemicals no. 301 B (CO2 evolution test)
Test conditions: Concentration of the test substance was 250 mg/L (equivalent to 20 mg/L TOC). Since AKD is poorly soluble, a small amount of emulsifier was used (about 1.5% of TOC) to produce a dispersion for testing. The emulsifier was naphthalene sulfonic acid, polymer with formaldehyde, sodium salt (CAS 9084-06-4). Any contribution from the emulsifier to the carbon dioxide evolved will be negligible relative to that from AKD since the emulsifier concentration was so low and it is not readily biodegradable. The CO_2 measurement was performed by collecting it in 0.05 mol sodium hydroxide and detecting sodium carbonate in a TOC-analyzer (Shimadzu, TOC 5000A).
Analine was used as the reference substance and its degradation profile met the validity criteria.



Year: 2003
GLP: No
Result: Readily biodegradable

Test substance: Basoplast 88 conc., Tamol NN 2901 (emulsifier), water (10 + 0.15 + 98.95) [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Reliability: 2, The study followed the OECD test guideline and is scientifically valid. It was, however, not performed under GLP.
KEY STUDY for OECD SIDS
[Reference: 31]

Type: Aerobic
Inoculum: Activated sludge from laboratory wastewater plant treating municipal sewage
Concentration: 150 mg/L (dry substance)
Degradation: 80 - 90% after 28 days, Elimination: 90 - 100%
Method: International Standard ISO 9439 (1999) Annex D
Test conditions: Concentration of the test substance was 488 mg/L (equivalent to 40 mg/L TOC). A small amount of emulsifier was used (about 1.5% of TOC) to produce a dispersion for testing. The emulsifier was naphthalene sulfonic acid, polymer with formaldehyde, sodium salt (CAS 9084-06-4). Any contribution from the emulsifier to the carbon dioxide evolved will be negligible relative to that from AKD since the emulsifier concentration was so low.
Year: 2003
GLP: No
Result: biodegradable and well eliminable
Test substance: **Basoplast 88 conc., Tamol NN 2901 (emulsifier), water (10 + 0.15 + 98.95) [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]**

Reliability: 2, The study followed the ISO test guideline and is scientifically valid. It was, however, not performed under GLP.
[Reference: 32]

Type: Aerobic
Inoculum: Activated sludge
Concentration: 30 mg/l related to test substance
Degradation: >94% after 28 days
Method: MITI Test [Test No 11664]
Test conditions: Test concentration was 30 mg/l. 10.3mg of the test substance was added to 300 ml refined water and the purity corrected to yield 30mg/l). The solution was then warmed to ~30℃ and irradiated with ultrasonic waves for one hour using a desk top ultrasonic cleaner [Branson Sonic 52, 40KHz.]. The temperature was adjusted to 25 ±1 ℃ and the CO_2 measurement was performed by collecting it on soda lime and detecting the sodium carbonate using an Ookura Electricity Coulometer. Analine was used as the reference substance. The test substance showed 62-76% degradation within the 10 day window.

Test results:

	% degradation			
Contents	**7 Days**	**14 Days**	**28 Days**	**Average**
Sludge/AKD -T1	37%	79%	98%	94%
Sludge/AKD -T2	43%	82%	106%	
Sludge/AKD -T3	30%	66%	78%	
Sludge/Aniline	73%	80%	80%	80%

Year: 1989
GLP: Yes
Result: Readily biodegradable
Test substance: NOF alkyl ketene dimer [AKD] [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Reliability: 2 The study followed the OECD test guideline and is scientifically valid.
[Reference: 33]

Type: Aerobic
Inoculum: Activated sludge from a laboratory waste water treatment plant using municipal sewage, not pre-adapted
Concentration: 30 mg/L (dry substance)
Degradation: < 10 % after 28 day
Method: OECD Guideline for Testing of Chemicals no. 301 F "Ready Biodegradability: Manometric Respirometry Test"
Test conditions: The test concentration was 100 mg/L; no emulsifier was used.
Year: 1989
GLP: No
Result: Not readily biodegradable
Test substance: Basoplast 20 konz. [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Reliability: 2, The study followed the OECD test guideline and is scientifically valid. It was, however, not performed under GLP.
[Reference: 34]

3.5. BOD5, COD or BOD5/COD Ratio

No data are available. Since the solid alkyl ketene dimer waxes are insoluble in water, standard testing is not applicable.

3.6. Bioaccumulation

There are no valid bioaccumulation studies available for alkyl ketene dimer described by CAS Numbers 84989-41-3 [Europe] and 68390-56-7 [USA]. The predicted Log Kow for AKD ranges from 11 to 15 which suggests a high bioaccumulation potential. BCF Program v 2.15 predicts a BCF of 3, whereas the polynomial QSAR[2] in the EU Technical Guidance Document for substances with Log Kow >6 predicts a BCF between 14 and 6 x 10^{15}. For substances with Log Kow > 6, it is known that QSAR determinations of BCF may not accurately represent true bioaccumulation potential so the there is uncertainty as to the true level of the BCF.

However, a bioaccumulation test is available for a structurally related alkyl ketene dimer notified as a new chemical in the EU under Directive 92/32/EEC. The new substance showed no significant bioconcentration with overall BCF values of less than 71. However, the result should be treated with caution since the test was conducted above the water solubility limit in the presence of dispersant and may not be the most appropriate method to determine the bioaccumulation of such a poorly soluble substance.

[2] $\log BCF = 6.9.10^{-3} (\log Kow)^4 - 1.85.10^{-1} (\log Kow)^3 + 1.55 (\log Kow)^2 - 4.18 \log Kow + 4.79$

Test substance: CONFIDENTIAL – structurally related new chemical prepared as a dispersion
Species: Lepomis macrochirus
Duration: 28 days, depuration 21 days
Test conditions: Flow through, temperature 21-23 ℃
Method: OECD 305
Year:1997
GLP: Yes
Results:
Exposure phase

2.0 microgram/L nominal	20.0 microgram/L (nominal)
BCF flesh <38	BCF flesh <2.8
BCFcarcass <62	BCFcarcass = 88
BCFwhole body <56	BCFwhole body <71

Depuration phase
Mean levels of the substance are below the limit of detection.

Reliability: 2 – Data for structurally related new chemical provided to EU Regulatory Authorities. Result should be treated with caution since the substance was tested as a dispersion above its water solubility.

Using a measured Log Kow of 5.5, from the structurally related new chemical notification, the BCFs are predicted to range from 3.2 to 343 respectively for C12:C12 AKD and C16:C16 AKD using BCF Program v 2.15. Using the equation in the EU Technical Guidance Document for substances with Log Kow <6, log BCF = 0.85 logKow - 0.70, the BCF is predicted to be 9440. This also suggests that AKD has the potential to bioaccumulate.

3. 7 Additional Remarks

3.7.1. Sewage Treatment

Two of the alkyl ketene dimer production sites have biological Waste Water Treatment Plants [WWTP], one uses the municipal biological WWTP, another one reported using an industrial WWTP based on flotation and activated carbon and another used a WWTP with iron phosphate particles. There are no measured concentrations of Alkyl Ketene Dimers available for the WWTP influent or effluent. Flow through rate (size) of the WWTP for three sites was given as between 40 and 823 cubic metres per day. The sludge of the WWTP was either incinerated (two sites) or landfilled (two sites). The receiving water system is river for three sites, unknown for two sites. The low water flow rate of the receiving river (10 percentile) was given for two sites as between 350 and 734 cubic metres per second. Two sites reported the amount of Alkyl Ketene Dimers released with the waste, i.e., one at 47.5 tonnes/year and the other at 100 tonnes/year.

Five of the Alkyl Ketene Dimer formulation sites have biological industrial WWTP; three use the biological municipal WWTP. One site reports using ultra-filtration and another flocculation before the biological WWTP. One plant has an electrolysis process with pressurised flotation followed by a physical/chemical separation process. One site has outsourced the wastewater handling. No measured data on the concentration of Alkyl Ketene Dimers in either the influent or the effluent of the WWTP were reported. The flow rates for the various WWTPs are 60, 150 and 984 (only less than 5% of the total for Alkyl Ketene Dimers wastewater) cubic metres per day. The sludge from

the WWTP is incinerated at two sites, landfilled at four and one reported composting as sludge treatment.

The receiving water system is reported to be river for five sites and other (canal) for one site. The reported low water flow rates of the receiving rivers (10 percentile) are 0.0219 and 734 cubic metres per second. The emissions to the environment are reported to be between 47 and 153 tonnes per annum as total sludge but the concentration of alkyl ketene dimers in the waste was not reported. **[Reference: 35]**

Test: Fate in wastewater treatment plant
Test method: The SIMPLETREAT model in EUSES 2.0
Test substance: Two runs were conducted, for C12:C12 AKD and C16:C16 AKD to determine the range of possible values. The input parameters were as follows:

Log Kow: 8 (the maximum value advised by EUSES 2.0)
Vapour pressure: 5.85×10^{-11}, 6.12×10^{-8} Pa
Water solubility: 4.8×10^{-11}, 5.64×10^{-7} mg/L
MW: 420.73, 532.94
Readily biodegradable

Result:

Air 0.1 – 1%
Water 7.7-7.9%
Sludge 90-91%
Degraded 1%

Reliability: 2
[Reference: 36]

3.7.2. Other Information

No other relevant information is available.

4. ECOTOXICITY

4.1. Acute Toxicity to Fish

Type: Static
Species: Danio rerio (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/L
Analytical monitoring: No
NOEC: 5000 mg/L [The only substance related effect was the symptom apathy noted at the highest test concentration after 4 h].
LC50: > 10000 mg/L
Method: OECD Guideline for Testing of Chemicals no. 203 "Fish, Acute Toxicity Test"
Test Conditions: Ten fish, five months of age, were placed in 10 liter vessels which contained concentrations of Basoplast 20 konz of either 0, 50, 100, 5000, or 10000 mg/L (static exposure). No further information on the preparation of the test solutions was included in the report. The fish were added within five minutes after the test dispersions were prepared. Food was withdrawn from the fish one day before exposures began and was not offered during the exposures. The pH of the test solution was pH 7.7. – 8.0. Dissolved oxygen was above 6.8 mg/l in all test solutions. The fish were observed for signs of toxicity and mortality at 1, 4, 24, 48, 72, and 96 hours post exposure.
Results: No fish died during the 96-hour exposure period.
Conclusion: The acute toxicity to fish (96-hour LC50 is greater than 10,000 mg/L.
Year: 1984
GLP: Yes
Test substance: Basoplast 20 konz. Batch 216 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Reliability: 2, The study followed the OECD test guideline and is scientifically valid. No analysis of test concentrations was conducted but undissolved test material was present throughout the tests which would suggest that a saturated solution had been prepared. Since the test was conducted at pH 7.7. – 8.0 it is possible that hydrolysis of the test substance could have occurred, although this could not have been prevented.
KEY STUDY for OECD SIDS
[Reference: 37]

4.2. Acute Toxicity to Aquatic Invertebrates

Type: Static
Species: *Daphnia magna* (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/L
Analytical monitoring: None
EC0: = 500
EC50: > 500
EC100: > 500
Test Conditions: Full details of the test conditions are given in the reference report. A 500 mg/L solution of the Bazoplast 20 Konz was made up in water by stirring for 17 hours at 25°C. This solution was used, unfiltered, to prepare the test solution by adding a 10 ml aliquot to test medium and stirring thoroughly. The test began on July 4, 1989 and ended 48 hours later on July 6, 1989. The EC0, EC50 and EC100 values were determined after 3, 6, 24 and 48 hours based on the nominal concentration. 20 Daphnia magna, i.e., 5 per concentration, were used for the

determination. The pH of the test solutions was circa 8.1 at 0 and 48h (pH 7.98 – 8.08). Hydrolysis of the test substance under the test conditions employed may have been possible, but this was not discussed in the test report. Observations for toxicity were made and mortality was determined by lack of movement.
Results: None of the Daphnia magna were affected during the test and the EC0 was reported as 500 mg/L and both the EC50 and EC100 reported as >500mg/L.
Conclusion: The acute toxicity to Daphnia magna [48hr EC50] is >500 mg/L.
Method: EWG 79/831/C.2
Year: 1989
GLP: No
Test substance: Basoplast 20 Konz. [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Reliability: 2, The study followed the EWG test guideline and is scientifically valid. It was, however, not performed under GLP. No analysis of test concentrations was conducted but undissolved test material was present throughout the tests which would suggest that a saturated solution had been prepared. Since the test was conducted at pH 7.98 – 8.08 it is possible that hydrolysis of the test substance could have occurred, although this could not have been prevented.
KEY STUDY for OECD SIDS
[Reference: 38]

4.3. Toxicity to Aquatic Plants e.g. Algae

Species: *Selenastrum capricornutum*
Endpoint: Growth inhibition
Exposure period: 72 hours
Unit: Mean actual (measured) concentration in mg/L
Analytical monitoring: Test concentrations were measured by HPLC at 0 and 72 hours.
Method: OECD Guidelines for Testing of Chemicals 201. Alga, Growth Inhibition Test. Adopted 7 June 1984.
Test conditions: A 0.1 gram sample of Aquapel 364, a waxy solid, dissolved in 10 mL of acetone, resulted in a slightly milky stock solution after 3 minutes of ultrasonification. This solution was used, non-filtered, to prepare the test solution by adding an aliquot to 1 litre of culture medium and stirring thoroughly for 15 minutes and 5 minutes ultrasonification.
The nominal concentration was 1.0 mg/L. For unknown reasons, the test substance disappeared from the test medium within 72 hours. The mean measured concentration ranged from <0.073 to 0.41 mg/L. On the basis of the analytical data the mean measured concentration was 0.17 mg/L and the 72 h concentration was 0.073 mg/L.
The pH at the start of the exposure was 7.4 to 7.5 and was 9.1 to 9.7 at the end. The temperature was approximately 24 °C throughout the study. Hydrolysis could occur under the above experimental conditions – Reference 3.1.2 – Water Stability and may be the reason for the observed concentration loss, although this could not have been prevented.
Year: 2002
GLP: Yes
Result: There was no sign of differences in mean growth rates, as measured by cell density, among the test article and the two controls (solvent and culture medium).
EC50 (biomass): > 0.17 mg/L (highest concentration tested)
NOEC (biomass) = 0.17 mg/L (highest concentration tested)
LOEC (biomass) > 0.17 mg/L (highest concentration tested)
EC50 (growth rate) > 0.17 mg/L (highest concentration tested)
NOEC (growth rate) = 0.17 mg/L (highest concentration tested)

LOEC (growth rate) > 0.17 mg/L (highest concentration tested)
Test substance: Aquapel 364 batch 3LP1456 P224 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Reliability: 2 Concentrations at the end of the test were below the detection limit, <0.073 mg/l. Since the pH rose to 9.7 at the end of the test, hydrolysis may have occurred. However, such hydrolysis is unavoidable. Because of these problems, the study is assigned reliability (2).
KEY STUDY for OECD SIDS
[Reference: 39]

Species: *Selenastrum capricornutum*
Endpoint: Growth inhibition
Exposure period: 72 hours
Test substance: CONFIDENTIAL – structurally related new chemical
Unit: Measured concentration in mg/L
Method: OECD 201
Test conditions: Test substance was dissolved in acetone.
Year: 2002
GLP: Yes
Result: There was no significant growth inhibition
EC50 (biomass): > 0.46 mg/L (highest concentration tested)
NOEC (biomass) = 0.46 mg/L (highest concentration tested)
EC50 (growth rate) > 0.46 mg/L (highest concentration tested)
NOEC (growth rate) = 0.46 mg/L (highest concentration tested)
Reliability: 1 - Data for structurally related new chemical provided to EU Regulatory Authorities

4.4. Toxicity to Microorganisms e.g. Bacteria

Type: Respiration inhibition
Species: Activated sludge
Exposure period: 30 minute(s)
Unit: Nominal concentration in mg/L
Analytical monitoring: No
EC20: > 1000
Method: OECD Guideline for Testing of Chemicals 209 - Activated sludge, respiration inhibition test and ISO 8192. Water quality – Test for inhibition of oxygen consumption by activated sludge.
Test conditions: Activated sludge was used from a laboratory waste water treatment plant using municipal sewage, not pre-adapted. The level of inoculation used was 1 g dry matter /L.
Year: 1989
GLP: No
Test substance: Basoplast 20 konz. [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Reliability: 2, The study followed the OECD test guideline and is scientifically valid. It was, however, not performed under GLP.
[Reference: 40]

Type: Oxygen consumption
Species: *Pseudomonas putida* (Bacteria)
Exposure period: 30 minute(s)
Unit: mg/L
Analytical monitoring: No

Method: ROBRA Test
Year: 1989
GLP: No
Test substance: Basoplast 20 konz. [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]

Remark: At a concentration of 10 mg/L, the substance was accepted by the bacteria. Due to of the low solubility and dispersibility the measurement of a response curve was not possible. A toxic effect is not expected on the basis of the structure. 100 mg *Tween 80/1* was used as dispersing agent.
Reliability: 4 - The study followed the DIN test guideline. The test report could not be retrieved to determine the reliability of the study.
[Reference: 41]

4.5. Chronic Toxicity to Aquatic Organisms

4.5.1. Chronic Toxicity to Fish

No data are available.

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Species: *Daphnia magna* (Crustacea)
Endpoint: Mortality, body length (apex of helmet to base of spine) and reproduction (F1)
Exposure period: 21 days
Unit: actual (measured) concentration in mg/L
Analytical monitoring: Yes
Method: OECD Guidelines for Testing of Chemicals no. 211 "*Daphnia magna* Reproduction Test." (1998)
Test conditions: Ten adult daphnids were added to each of ten individual vessels for each concentration of Aquapel 364. Nominal test concentrations were 0.056, 0.10, 0.32, 0.56 and 1.0 mg/L. A primary stock was prepared by dispersing the test substance in acetone to obtain a cloudy white homogenous suspension after vigorous shaking for 5 minutes. The test solutions were prepared by the addition of aliquots of the primary stock (non-filtered) to dilution water and vigorous stirring by magnetic follower. The dilution water control, solvent control and test solutions were not filtered and were observed to be clear and colourless. A semi-static regime was used and the solutions were replaced 3 times per week. The pH of the new test solutions were between 8.0 and 8.3 and the old test solutions were between 7.6 and 8.2. The overall mean measured concentrations ranged from 80 to <132% of nominal values. Observations for toxicity and reproduction were made from day 4. Mortality was determined by lack of movement for 15 seconds and reproduction was measured by the presence of offspring, live and dead.
Year: 2001
GLP: Yes
EC50: > 0.8 mg/L (highest dose tested, measured concentration)
NOEC (body length): 0.8 mg/L (highest dose tested, measured concentration)
LOEC (body length): > 0.8 mg/L (highest dose tested, measured concentration)
NOEC (reproduction): 0.8 mg/L (highest dose tested, measured concentration)
LOEC (reproduction): > 0.8 mg/L (highest dose tested, measured concentration)
EC50 (reproduction): > 0.8 mg/L (highest dose tested, measured concentration)

Test substance: Aquapel 364 batch 3LP1456 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Conclusions: The overall observed effect concentration was 0.8 mg/L and the overall lowest observed effect concentration was >0.8 mg/L based on mean measured concentrations.
Reliability: 1
KEY STUDY for OECD SIDS
[Reference: 42]
Note: A 21-day Daphnia reproduction study has been conducted on the dispersion of AKD (AKD content 90.1% w/w). The test was conducted according to OECD 211, with reproduction, growth and mortality monitored. No effects on either reproduction or growth were observed at the highest concentration tested (mean measured concentration of 0.8 mg/l). Concentrations were measured during the test and showed a generally stable exposure. Stock solutions of AKD were prepared in acetone, and aliquots added to the test media to prepare the final solutions. The media were changed at two day intervals. The test solutions were recorded as clear and colourless. The true water solubility is not definitively known, so the true exposure level is uncertain. Nevertheless, the absence of effects in the test indicates that the long-term NOEC is above the water solubility limit.

4.6. Toxicity to Terrestrial Organisms

4.6.1. Toxicity to Terrestrial Plants

Species: Oat (*Avena sativa)*, Sunflower (*Helianthus annuus)*,
Mung bean (*Phaseolus aureus*)
Endpoint: Condition of the plant and terminal fresh weight
Exposure period: 28 days
Unit: nominal concentrations**,** mg test substance / kg soil (dry mass)
Method: Proposed update of OECD (1984) Guideline 208 for testing of chemicals, "Terrestrial Plants Growth Test". OECD, Paris Part A (July 2000) Seedling Emergence and Seedling Growth Test
Test conditions: The test substance was mixed with the sand using chloroform; the chloroform was removed after mixing. On day 0 of the study, the soil was mixed with the sand (10% of final dry weight). The test concentrations of Aquapel® 364 in the soil were 0, 1, 10, 100 and 1000 mg/kg of dry weight soil. For each test treatment for each species, four replicate pots were prepared. Each pot contained 9 seeds at the start of the test, which were later thinned to 5 seedlings.
On day 7 of the study a preliminary assessment of germination (emergence of the plumule above soil level) was made.
On day 14 of the study a definitive assessment of germination was carried out and the seedlings thinned to five per pot.
On day 28 of the study, the plants were cropped at soil level and the total fresh from each pot determined.
Year: 2001
GLP: Yes
Result: Emergence was significantly reduced (P=0.05, one-sided) in the 1000 mg/kg test concentration for sunflower and mung bean compared with the mean of the control and solvent control. This reduction is considered to be due to watering difficulties and not toxicity. The soil between the surface and approximately 0.5 cm was dry at the highest test concentration. This was not evident at the other test concentrations. At the highest concentration, the water-repelling properties of the test material, was sufficient to hinder the percolation of water through the soil.

This effect was to be expected as the test material is naturally hydrophobic and its use in industry is to make paper hydrophobic.
The 14 day emergence of seeds in the controls during this test was 100% for oat and mung bean and 94% for sunflower (satisfactory value is 65%).
On day 28, all plants appeared healthy and showed no symptoms of toxicity. There was no dose-related effect on vegetative growth of any of the species tested, in any of the test concentrations.
NOEC (vegetative growth) 1000 mg/kg.
EC50 (vegetative growth) >1000 mg/kg.
LOEC (vegetative growth) >1000 mg/kg.
NOEC (emergence) 100 mg/kg.
EC50 (emergence) >1000 mg/kg.
LOEC (emergence) 1000 mg/kg.
Test substance: Aquapel 364 batch 3LP1456 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Conclusion: There was no dose-related effect on vegetative growth of any of the species tested, in any of the test concentrations.
Reliability: 1
KEY STUDY for OECD SIDS
[Reference: 43]

4.6.2. Toxicity to Soil Dwelling Organisms

Type: Acute Toxicity Test
Species: Earthworm *(Eisenia foetid*a)
Endpoint: Mortality
Exposure period: 14 days
Unit: Nominal concentration in mg/kg soil
Method: OECD Guidelines for Testing of Chemicals No 207 "Earthworm, Acute Toxicity Tests" (1984)
Test conditions: A preliminary range-finding study was performed prior to the main study. A positive control study with chloroacetamide is available. In the range-finding study, ten worms each were exposed to one of three nominal test concentrations, 10, 100, 1000 mg/kg soil. No death occurred. The definitive study was conducted with six replicates of ten worms per replicate administered a nominal 1000 mg/kg concentration of Aquapel® 364.
For the definitive study the test material was prepared by direct addition to the basic soil substrate using deionised water and mixed using a mechanical mixer. The nominal moisture content of the soil was 30% of dry weight. Analysis of the concentration, homogeneity and stability of the test material in the test preparations were not appropriate to the Test Guideline.
Year: 2002
GLP: Yes
Results:
LC50: > 1000 mg/kg (highest dose tested)
NOEC: = 1000 mg/kg (highest dose tested)
Test substance: Aquapel 364 batch 3LP1456 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Reliability: 1
KEY STUDY for OECD SIDS
[Reference: 44]

4.6.3. Toxicity to other Non–Mammalian Terrestrial Species

No data are available.

4.7. Biological Effects Monitoring

No data are available.

4.8. Biotransformation and Kinetics

No data are available.

4.9. Additional Information

No additional remarks.

5. MAMMALIAN TOXICITY

5.1. Toxicokinetics, Metabolism and Distribution

No data are available.

5.2. Acute Toxicity

5.2.1. Acute Oral Toxicity

Type: LD_{50}
Species: rat
Gender: Not specified
Number of Animals: Not specified
Vehicle: Olive oil
Value: > 10 000 mg/kg b.m.
Method: BASF Test
Year: 1976
GLP: No
Test substance: Stearyldiketen TV 194/37 [An AKD manufactured using a stearic acid rich blend of palmitic and stearic fatty acids].
Reliability: 4, The study followed an acceptable protocol and is scientifically valid. It was performed before OECD test guidelines and GLP were established. The documentation is according to the best practice at the time the study was performed. However, some critical details of the test protocol and the results are not available.
[Reference: 45**]**

Type: LD50
Species: rat
Gender: Not specified
Number of Animals: 10 per dose group
Vehicle: Water (a 40% aqueous solution was administered**)**
Value: > 40 000 mg/kg b.m.
Result: No animals died at 5000 and 10000 mg/kg b.m., one animal died at 15000 mg/kg b.m., three animals died at 20000 mg/kg b.m. and four animals died at 40000 mg/kg b.m.
Method: Rats were starved 24 hours prior to substance application. The substance was administered as a 40% aqueous solution by oral gavage; volumes were 12.5, 25, 37.5, 50 and 100 mL/kg b.m. resulting in doses of 5000, 10 000, 15 000, 20 000, 40 000 mg/kg b.m. The observation period was two weeks.
Year: 1954
GLP: No
Test substance: Aquapel® 380 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Reliability: 2, The study followed an acceptable protocol and is scientifically valid. It was performed before OECD test guidelines and GLP were established. The documentation is according to the best practice at the time the study was performed.
KEY STUDY for OECD SIDS
[Reference: 46**]**

Type: Limit test
Species: rat
Method: OECD 401
Test substance: Alkyl Ketene Dimers batch 339 standard production [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Value: > 2000 mg/kg b.m.
GLP: Yes
Year: 1988
Reliability: 4, **The study followed an OECD protocol and is scientifically valid but the report could not be found.**
[Reference: [47]]

5.2.2. Acute Inhalation Toxicity

Type: Inhalation Hazard Test (IRT)
Species: Rat
Gender: Not specified
Number of Animals: 12
Vehicle: none (atmosphere saturated with substance vapour was tested)
Exposure time: 8 hour(s)
Value: Not applicable
Method: BASF Inhalation Hazard Test
This test was performed according to principle described in OECD TG 403. It demonstrates the toxicity of an atmosphere saturated with vapours of the volatile components of the test substance. Groups of three young adult rats were sequentially exposed to the vapours, generated by bubbling 200L/h air through a 5 cm column of the test substance. No analytical determination of the atmosphere concentration was performed. However, very little AKD vapour is expected to be present in an atmosphere saturated with AKD vapour, since the vapour pressure of AKD is extremely low with an estimated $3x10^{-6}$ hPa at 40^{o} Celsius. The study allows for an estimate of the length of time required to cause severe toxicity by exposure to a saturated atmosphere. The study does not allow any estimation of the inhalation toxicity of AKD dusts.
Year: GLP: No
Test substance: Stearyldiketen TV 194/37 [An AKD manufactured using a stearic acid rich blend of palmitic and stearic fatty acids].
Result: No mortality was observed when 12 rats were exposed for 8 hours to an atmosphere that has been saturated at 20 °C with the volatile part of the compound.
Reliability: 4, This study is not comparable with an acute inhalation toxicity study according to OECD test guideline no. 403. The study determined the effects of inhaling a saturated atmosphere at room temperature. Since the vapour pressure of the test substance is extremely low, there was virtually no exposure.
[Reference: 48 **]**

5.2.3. Acute Dermal Toxicity

Type: LD_{50}
Species: Rabbit
Gender: No data available
Number of Animals: No data available
Vehicle: No data available
Value: = 6730 mg/kg b.m.
Method: No data available

Year: No data available
GLP: No
Test substance: Not specified
Reliability: **4, Data taken from the IUCLID File. The study report is no longer available and the reliability cannot be confirmed.**

[Reference: [49]]

5.3. Corrosiveness and Irritation

5.3.1. Skin Irritation

Species: Rabbit
Concentration: 50% aqueous dispersion
Exposure: Epicutaneous
Exposure Time: 1, 5 and 15 minutes and 20 hours
Number of Animals: Not specified
PDII: Not specified
Result: 1, 5 and 15 minutes exposure did not cause skin reactions 24 hours after the exposure. 8 days after the exposure, however, some slight flaking was observed. A 20 hour exposure caused very slight erythema 24 hours after the exposure and slight flaking after 8 days.
Classification: Not irritating
Method: BASF Test
Two White Vienna rabbits were treated for 1, 5 and 15 minutes and two additional animals were treated for 20 hours using occlusive conditions. An application site of 2.5 x 2.5 cm on the dorsal/lateral flank or back of the rabbit was covered with a 50%aqueous suspension of tests substance. After the application time, the skin was washed with water or water containing a mild detergent. The animals were observed for a week and skin changes were recorded on each working day. However, only the observations after 24 hours and 8 days were reported. Additionally, the ear was exposed to the test substance for 20 hours. These results, however, were not evaluated as they do not represent testing of flank or back skin.
Test conditions: 0.5 ml of the test substance per animal was given as a 50% aqueous dispersion.
Year: 1976
GLP: No
Test substance: Stearyldiketen TV 194/37 [An AKD manufactured using a stearic acid rich blend of palmitic and stearic fatty acids].
Reliability: 2, The study followed an acceptable protocol and is scientifically valid. It was performed before OECD test guidelines and GLP were established. The documentation is according to the best practice at the time the study was performed.
KEY STUDY for OECD SIDS
[Reference: 50**]**

5.3.2. Eye Irritation

Species: Rabbit
Concentration: Undiluted test substance
Dose: about 50 mg
Exposure Time: 1 and 24 hours and 8 days

Comment: Not rinsed

Number of Animals: Not specified
Result: 1 hour after the start of the application slight erythema and edema were observed along with white residues of the test substance. After 24 hours only slight erythema were seen. After 8 days no signs of irritation were observed. The negative control substance, talcum powder, caused the same reaction of the eye.
Classification: Not irritating
Method: BASF Test
50 mg of the test substance were administered to the conjunctival sac of one eye of two White Vienna rabbits. The other eye was treated with talcum powder as a negative control for solid substances. The eyes were not rinsed after 24 hours (as the OECD TG 405 requests). The animals were observed for eight days and eye irritation was recorded 1 hour, 24 hours and 8 days after the start of the application.
Test conditions: 0.1 ml bulk volume of the test substance was given undiluted.
Year: 1976
GLP: No
Test substance: Stearyldiketen TV 194/37 [An AKD manufactured using a stearic acid rich blend of palmitic and stearic fatty acids].
Reliability: 2, The study followed an acceptable protocol and is scientifically valid. It was performed before OECD test guidelines and GLP were established. The documentation is according to the best practice at the time the study was performed.
KEY STUDY for OECD SIDS
[Reference: 51**]**

5.4. Sensitization

Type: Buehler Test
Species: Guinea pig
Number of Animals: 20 Animals in the test group and 10 animals in the control group
Vehicle: None (unchanged test substance was used)
Result: 1 out of 20 animals in the test group showed slight erythema 48 hours after the challenge.
Classification: Not sensitizing
Method: OECD Guideline for testing chemicals no. 406 "Skin Sensitization" Buehler Test
Year: 1995
GLP: Yes
Test substance: 20 % aqueous emulsion of alkyl ketene dimer, batch P224 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Test conditions:
Inductions: Unchanged test substance
Challenge: Unchanged test substance
The suitable concentration of the test substance for the induction and challenge was determined in a pretest: Undiluted and different dilutions of the test substance were applied to the skin twice for 6 hours under occlusive conditions. No significant signs of irritation were observed.
Reliability: 1
[Reference: 52**]**

Type: Guinea pig maximization test
Species: Guinea pig
Number of Animals: 20 in the test group and 10 in each control group
Vehicle: Olive oil for intradermal injection (for percutaneous application, however, undiluted, melted substance was used)

Result: 9 and 10 out of 20 animals in the test group showed a skin reaction 24 hours after the first and second challenge, respectively.
Method: OECD guideline for testing chemicals no. 406 "Skin Sensitization" (17 July 1992), Magnussen Kligman GPMT
Year: 1994
GLP: yes
Test substance: Basoplast 20 konz., batch 216 P224 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Test conditions:
Intradermal induction: 5% Test substance in olive oil or adjuvans solution
Epicutaneous induction: Unchanged test substance melted at 60°C
Challenge: Unchanged test substance melted at 60°C
The suitable concentration of the test substance for the challenge was determined in a pretest: Undiluted, melted test substance and solutions of different concentration were applied to the skin for 24 hours under occlusive conditions. No significant signs of irritation were observed. The intradermal injection of a 5% solution caused marked erythema and oedema.
Reliability: 1
[Reference: 53**]**

Type: Guinea pig maximization test
Species: Guinea pig
Number of Animals: 10 in the test group, 5 in each control group
Vehicle: Olive oil
Result: 2 out of 10 animals in the test group showed a skin reaction 24 and 48 hours after challenge with the test substance.
Classification: not sensitizing
Method: OECD Guideline for Testing of Chemicals no. 406 "Skin Sensitization" (17 July 1992), Magnussen–Kligman–GPMT
Year: 2002
GLP: Yes
Test substance: Basoplast 20 konz. K, batch PE251001 P224 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Test conditions:
Intradermal induction: 1% Test substance in olive oil or adjuvans solution
Epicutaneous induction: 75% Test substance in olive oil
Challenge: 75% Test substance in olive oil
The suitable concentration of the test substance for the challenge was determined in a pretest: Different concentrations of the test substance were applied to the skin for 24 hours under occlusive conditions. A 50% solution caused irritation 24 and 48 hours after the end of the exposure. A 75% solution, however, did not cause irritations under the same conditions. The olive oil vehicle probably contributed to the irritation reaction.
Reliability: 1
[Reference: 54**]**

Type: Guinea pig maximization test
Species: guinea pig
Number of Animals:
Vehicle:
Result: not sensitizing
Classification: not sensitizing

Method: OECD Guide–line 406 "Skin Sensitization"
Year: 1995
GLP: yes
Test substance: Raisares, Batch No E133
Reliability: 2 – Draft report only available
[Reference: 55**]**

Type: Guinea pig maximization test
Species: Guinea pig
Number of Animals:
Vehicle:
Result: not sensitizing
Classification: not sensitizing
Method: OECD Guide–line 406 "Skin Sensitization"
Year: 1997
GLP: yes
Test substance: Keywax SF100 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Reliability: 2 – Draft report only available
[Reference: 56**]**

Type: Guinea pig maximization test
Species: Guinea pig
Number of Animals: 20 in the test group and 10 in each control group
Vehicle: Corn oil
Result: 1 out of 19 animals (one bandage slipped) in the test group showed a skin reaction 24 hours after challenge with the 75% test substance solution. No skin reaction was observed upon challenge with the 50% test substance solution.
Classification: Not sensitizing
Method: OECD Guide–line 406 "Skin Sensitization" (17 July 1992), Magnussen–Kligman–GPMT
Year: 1996
GLP: yes
Test substance: Aquapel 364 batch 12MW1313 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Intradermal induction: 1% solution of the test substance in corn oil
Epicutaneous induction: 75% solution of the test substance in corn oil
Challenge: 50 and 75% solution of the TS in corn oil
The suitable concentration of the test substance was determined in a pretest: The intradermal injection of a 3% solution caused necrosis of the skin. Topical application of a 75% solution was well tolerated.
Reliability: 1
KEY STUDY for OECD SIDS
[Reference: 57]

Type: Guinea pig maximization test
Species: Guinea pig
Number of Animals: 20 animals in the test group and 10 in each control group
Vehicle: Corn oil
Result: 2 out of 19 animals (one bandage slipped) in the test group showed a skin reaction 24 hours after challenge with the test substance.

Classification: Not sensitizing
Method: OECD Guideline for testing chemicals no. 406 "Skin Sensitization" (17 July 1992), Magnussen–Kligman–GPMT
Year: 1996
GLP: Yes
Test substance: Aquapel 291 [An AKD manufactured using a stearic acid rich blend of palmitic and stearic fatty acids].
Test conditions:
Intradermal induction: 0.3% Test substance in vehicle or adjuvans solution
Epicutaneous induction: 75% Solution of the test substance in the vehicle
Challenge: 75% Solution of the test substance in the vehicle
The suitable concentration of the test substance for the challenge was determined in a pretest: Solutions of different concentration were applied to the skin for 24 hours under occlusive conditions. No significant signs of irritation were observed. The intradermal injection of a 0.3% solution caused slight to moderate skin reactions, 1% and higher concentrated solutions caused stronger reactions with possible necrosis.
Reliability: 1
[Reference: 58]

5.5. Repeated Dose Toxicity

Species: Rat
Gender: 10 male and 10 female (parents)
Strain: Alpk:APfSD (Wistar-derived)
Route of admin.: oral gavage in corn oil
Exposure period: At least 28 days. Males were dosed two weeks prior to mating continuing throughout day 29 or 30. Females were dosed two weeks prior to mating, during mating, throughout pregnancy and until 4 days *post partum* (day 4 of lactation)
Frequency of treatment: Once per day
Post observation period: none
Doses: 0 (control), 100, 350 or 1000 mg/kg b.m./day
Control Group: Yes, concurrent control received vehicle (corn oil) only
Method: Combined repeated dose toxicity study with reproductive and developmental toxicity screening according to OECD Guideline for Testing of Chemicals no. 422 (22 March 1996)
Year: 14. November 2002
GLP: Yes
Test substance: Aquapel 364 batch 3LP1456 P224 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Test Conditions: Litters were weighed and examined on days 1 and 5 *post partum*. In addition the following were carried out on all animals. Clinical observations, body mass and food consumption were measured throughout the study. Urine samples were collected during week 4 for the assessment of urine clinical pathology. Detailed clinical observations, including quantitative assessments of sensory perception and muscle weakness, and assessment of motor activity were performed on day 28 on 5 animals /gender/group. At the end of the scheduled period, the animals were killed and subjected to an examination *post mortem*. Cardiac blood samples were taken for clinical pathology, selected organs were weighed, corpora lutea were counted in pregnant females and specified tissues were taken for subsequent histopathology examination.

Most parameters were considered by analysis of variance and covariance, separately for males and females. The proportion of implants affected by pre-implantation loss and post-implantation loss,

the proportion of pups born live, the proportion of litters affected by pre-implantation loss and post-implantation loss were considered by Fisher's Exact Test. All statistical tests were two sided.

Result:
At a dose level of 1000 mg/kg b.m./day in adults there were no mortalities, no clinical changes and no adverse effects on body mass or food consumption and no neurotoxic effects. There were no effects on breeding parameters with the exception of a reduced proportion of implantation sites compared to the numbers of *corpora lutea.* In both genders there was an increase in total white blood cell count due to increases in large unstained cells, lymphocytes and monocytes and in females there was an increase in basophils (see Table below). In both genders there was an increase in spleen weight and in liver, kidney and ovary weights in females (see Table below). Macroscopic enlargement of the spleen and lymph nodes was seen in females. Microscopically, inflammatory changes (mostly mononuclear cell infiltration with focal accumulation of macrophages) were seen in a variety of tissues (In females: liver, mesenteric lymph node, cervix, kidney, Peyer's patch, spleen, uterus, hepatic lymph node, cervical lymph node and jejunum, In Males: mesenteric lymph node, liver, kidney and spleen), in both genders but the overall incidence, severity and distribution was greater in females. Extramedullary haemopoiesis was observed in both genders. There was a mild, but statistically significant perturbation of some clinical chemistry parameters in both genders, such as increases in total bilirubin and cholesterol in both genders and albumin, total protein and plasma calcium in females. No treatment related changes were observed in the male reproductive organs. There were no effects on pups.

At a dose level of 350 mg/kg b.m./day in adults there was a reduced proportion of implantation sites compared to the numbers of *corpora lutea.* In both genders there was an increase in total white blood cell count due to increases in large unstained cells, lymphocytes and monocytes and in females there was an increase in basophils. There was an increase in cholesterol, albumin, total protein and plasma calcium in females. In both genders there was an increase in spleen weight and in liver, kidney and ovary weights in females. Macroscopic enlargement of the spleen and lymph nodes was seen in females. Microscopically, inflammatory changes (mostly mononuclear cell infiltration with focal accumulation of macrophages) were seen in a variety of tissues (In Females: liver, mesenteric lymph node, cervix, kidney, Peyer's patch, spleen, uterus, hepatic lymph node, cervical lymph node and jejunum, In Males: mesenteric lymph node, liver and kidney) in both genders but the overall incidence, severity and distribution was greater in females. Extramedullary haemopoiesis was observed in both genders. No treatment related changes were observed in the male reproductive organs. There were no effects on pups.

At a dose level of 100 mg/kg b.m./day in adults there was a reduced proportion of implantation sites compared to the numbers *of corpora lutea*. In both genders there was an increase in total white blood cell count due to increases in large unstained cells, lymphocytes and monocytes and in females there was an increase in basophils. There was an increase in spleen weight and in liver and kidney weights in females. Macroscopic enlargement of the spleen and lymph nodes was seen in females. Microscopically, inflammatory changes (mostly mononuclear cell infiltration with focal accumulation of macrophages) were seen in a variety of tissues (In Females: liver, mesenteric lymph node, cervix, kidney, Peyer's patch, spleen, uterus, hepatic lymph node, cervical lymph node and jejunum, In Males: mesenteric lymph node and liver) in both genders but the overall incidence, severity and distribution was greater in females. Extramedullary haemopoiesis was observed in females. No treatment related changes were observed in the male reproductive organs. There were no effects on pups.

Table 5-1: Body weights and Organ weights (only organs with significant changes are listed)

	Dose [mg/kg b.w./day]			
	0	100	350	1000
TERMINAL B.W.				
MALES				
Mean	467.9	463.5	459.2	446.3
S.D.	30.7	31.4	33.1	33.1
FEMALES				
Mean	331.2	338.9	330.0	319.8
S.D.	11.3	13.1	25.1	26.2
LIVER				
MALES				
MEAN	18.4	18.2	18.5	18.5
S.D.	1.5	1.6	1.8	1.5
Organ Weight Adjusted For Bodyweight	18.1	18.0	18.5	19.0*
FEMALES				
MEAN	13.4 15.7*	17.0**	16.8**	
S.D.	1.0	1.1	2.8	2.4
Organ Weight Adjusted For Bodyweight	13.3	14.9**	17.0**	17.6**
KIDNEYS				
MALES				
Mean	3.21	3.08	3.20	3.20
S.D.	0.23	0.27	0.23	0.38
Organ Weight Adjusted For Bodyweight	3.16	3.05	3.20	3.28
FEMALES				
Mean	1.94	2.18**	2.10*	2.09*
S.D.	0.11	0.17	0.20	0.13
Organ Weight Adjusted for Bodyweight	1.93	2.13**	2.10**	2.15**
SPLEEN				
MALES				
Mean	0.966	1.096*	1.184**	1.200**
S.D.	0.100	0.132	0.156	0.116
Organ Weight Adjusted for Bodyweight	0.943	1.084**	1.184**	1.235**
FEMALES				
Mean	0.708	1.110**	1.403**	1.405**
S.D.	0.085	0.203	0.227	0.253
Organ Weight Adjusted for Bodyweight	1.93	2.13**	2.10**	2.15**
OVARIES				
Mean	0.107	0.118	0.130**	0.127**
S.D.	0.015	0.014	0.015	0.012
Organ Weight Adjusted for Bodyweight	0.107	0.116	0.130**	0.129**

**** Statistically significant difference from the control group mean at the 1% level (Student's t-test, two sided)**

Table 5-2: Haematology (in cell counts $x10^{-9}$/L) (only parameter with significant changes are listed)

Gender	Parameter	control	Dose in mg/kg b.m./day 100	350	1000
♂ **day 30**	**White blood cells**	**7.56**	**9.02***	**9.50****	**10.29****
	Neutrophil	**1.46**	**2.34****	**2.36****	**2.10****
	Lymphocyte	**5.71**	**6.02**	**6.49**	**7.41****
	Monocyt	**0.123**	**0.174**	**0.192**	**0.290****
	Large unstained cells	**0.092**	**0.238****	**0.246****	**0.275****
♀ **day 5 post partum**	**White blood cells**	**5.41**	**8.32****	**9.96****	**11.40****
	Lymphocyte	**53.23**	**5.29****	**6.73****	**7.55****
	Monocyt	**0.066**	**0.332****	**0.395****	**0.536****
	Basophil	**0.012**	**0.133****	**0.152****	**0.160****
	Large unstained cells	**0.063**	**0.609****	**0.697****	**0.922****

**** Statistically significant difference from the control group mean at the 1% level (Student's t-test, two sided)**

NOAEL (general toxicity, parental): No NOAEL was achieved
LOAEL (general toxicity, parental): 100 mg/kg b.m./day based on inflammatory changes in a variety of tissues in both genders
Reliability: 1
KEY STUDY for OECD SIDS
[Reference: 59**]**

Species: Rat
Gender: 12 male and 12 female rats per dose
Strain: Alpk:APfSD (Wistar-derived)
Route of admin.: test substance was admixed to the feed
Exposure period: 90 consecutive days
Frequency of treatment: continuously in the feed
Post observation period: none
Doses: 0 (control), 65, 650 or 6500 ppm (mg/kg b.m./day)
Control Group: Yes, concurrent control received feed only
Method: OECD guideline reference 408 (1998) Repeated Dose 90 Day Oral Toxicity Study in Rodents.
Year: 25. Aug. 2004
GLP: Yes
Test substance: Aquapel 364 batch 3LP1456
Test Conditions:
The test substance was administered by feeding a diet with different concentrations of the TS added for 90 consecutive days. The mean achieved concentrations of the TS in each feed preparation were within 8% of the nominal concentration with the exception of the 65ppm sample prepared on the 21st August 2003 which was within 26% of the nominal, resulting in an actual concentration of 48.3 ppm for weeks 3-6. Dose rates (based on nominal dietary levels) were calculated in terms of mg TS/kg b. m. Mean values for males were: 6.3, 63.4 and 645.0; mean values for females were 6.8, 69.6 and 690.6 mg /kg b.m./day.
Clinical observations, bodyweights and food consumption were measured throughout the study. An ophthalmoscopic examination was performed on all animals pre-study and on the control and top-

dose group in week 12. A functional observation battery, including clinical assessments, measurements of grip strength, time to tail flick, landing foot splay and motor activity were conducted during the last week of the study. Urine samples collected during week 13 were analysed. At the end of the study, the rats were killed and examined post mortem. Cardiac blood samples were taken for clinical pathology, selected organs were weighed and specified tissues were taken for histopathological examination.
Most parameters were considered by analysis of variance and covariance, separately for males and females. All statistical tests were two sided.

Results:
6500 ppm: There was a test substance related reduction in bodyweights from weeks 8 and 6 in males and females respectively (11 an 7%), associated with a reduction in food consumption in both genders and a reduction in food utilisation in males. In both genders, haemoglobin (94 and 92% of control for males and females, respectively), haematocrit (94 and 96% of control for males and females, respectively) and mean cell haemoglobin (97 and 95% of control for males and females, respectively) were reduced and white blood cell counts (182 and 225% of control for males and females, respectively), Liver (110 and 135% of control for males and females, respectively) and spleen relative weights (168 and 184% of control for males and females, respectively) were increased. In males there was a reduction in mean cell volume (94% of control) and platelet count (89% of control). In females, reductions in red blood cell count (97% of control), mean cell haemoglobin concentration (92% of control) and increases in relative kidney weight (110% of control) were observed. Increase in levels of alkaline phosphatase, gamma-glutamyl transferase, alanine aminotransferase and aspartate aminotransferase levels in both genders and a rise in cholesterol in females reflect the underlying liver changes. Pathological findings were evident in a number of tissues. Histiocytosis was seen in the lymph nodes (mesenteric, hepatic and pancreatic, spread throughout the cortex and medulla), liver, spleen, jejunum, ileum and Peyer's patch. Inflammation was observed in the liver (hepatitis), lung, kidney (nephritis), heart (degenerative cardiomyopathy), pancreas (pancreatitis), muscle (myositis and mononuclear cell infiltration), adrenal gland, sciatic nerve and stomach).

Changes in urine volume and urine specific gravity in both genders, total bilirubin, sodium and chloride levels in males and fore limb grip strength and total protein in females were within the historical control range and changes in prothrombin time, plasma triglycerides, creatine kinase and calcium are considered to be of no toxicological significance.

650 ppm: In males there was a reduction in bodyweights (8%) along with reduced food consumption and food utilisation during some weeks and levels of alanine aminotransferase, aspartate aminotransferase and cholesterol levels were increased in both genders. In females there were reductions in haemoglobin levels (96% of control) and increases in monocyte, basophil and large unstained cell counts (240, 247 and 264% of control, respectively), spleen (128% of control), liver (113% of control) and kidney relative weights (108% of control).
Pathological findings included histiocytosis in the lymph nodes and Peyer's patch and inflammation in the stomach of both genders. Effects were more predominant in females with histiocytosis in the liver, jejunum and spleen and inflammation in the liver, kidney, pancreas and lung. In males inflammation was limited to the sciatic nerve and adrenal gland.

65 ppm: There was no evidence of toxicity. Bodyweights were lower in males compared with concurrent controls, however, the mean bodyweight of the control group was greater than historical control data. There were no consistent effects on food consumption or utilisation when compared to the controls. The potassium levels were within the historical control range and not considered to be

related to the administration of the test substance in the diet. There were no differences in organ weights and the pathological findings were similar in incidence and severity as those seen in the control group.

NOAEL 65 ppm (6.3 and 6.8 mg/kg b.m. for males and females respectively)
LOAEL 650 ppm (63.4 and 69.6 mg/kg b.m. for males and females respectively) based on inflammatory changes in a variety of tissues in both genders
Reliability: 1
KEY STUDY for OECD SIDS
[Reference: 60]

ADDITIONAL INFORMATION
It would appear initially that the generalised inflammations are a specific response to administration of alkyl ketene dimers, but a review of pertinent toxicology literature (Baldwin *et al.*, 1992 [Reference: 61], Firriolo *et al.*, 1995 [Reference: 62], Smith *et al*., 1996 [Reference: 63], Nash *et al.*, 1996 [Reference: 64], Halladay *et al.*, 2002 [Reference: 65], Scotter *et al.*, 2003 [Reference: 66]) suggests that these represent a generic response of rats to administration of higher molecular weight hydrocarbons, *i.e.* mineral hydrocarbon oils and waxes, and many studies have been conducted to investigate these in detail. It is now clear that that the effect of these hydrocarbons in rats is dependent upon both the strain of rat used and the characteristics of the particular oil or wax. A study by Baldwin *et al.* (1992) [Reference: 67] compared the effects of two white oils derived from naphthenic crude oil when administered to Fischer (F-344) rats for 90 days at doses ranging from 10 to 20,000 ppm in diet. Minor haematological changes, slight leukocytosis and granulocytosis, were reported at high doses together with clinical chemistry changes indicative of hepatic damage or functional disturbance, with females being more affected than males. At necropsy, organ weight changes were seen in the mesenteric lymph nodes, spleen, liver and kidney. Histopathologically, lesions were seen in the mesenteric lymph nodes, liver and spleen, findings being more marked in females. Inflammatory changes were seen in these organs, together with increased splenic extramedullary haemopoiesis and small granulomata in the liver and mesenteric lymph nodes. While the presence or absence of all effects mentioned above were both concentration and oil-type dependent, it is the similarity of some of the effects to those of AKDs that is pertinent. The major difference between the AKD responses and the results of Baldwin *et al.* (1992) was the development of granulomata in the latter. The author's also recognised that this response differed from results of earlier feeding studies with similar oils in other species or rat strains. To determine if rat strain differences were responsible for the differing patterns and severities of effects resulting from administration of hydrocarbon oils, Firriolo *et al.*(1995) [Reference: 68] fed F-344 and Sprague-Dawley derived (SD) rats a paraffinic white oil (P15H; hydrogenation refined oil; average molecular weight 350; average carbon number distribution 18-30) in diet for 90 days. Findings in the Fischer-344 rat were similar to those reported above by Baldwin *et al.* (1992), whereas the only findings in the SD rats were a slightly increased incidence of minimal multifocal chronic inflammation in the liver at a dose of 20,000 ppm. Firriolo *et al.*(1995), using data to which they had access, concluded that not only were there species differences in the response to administration of hydrocarbon oils, but that there were very distinct rat strain differences. While the studies addressed above used a limited number of hydrocarbon oils, Smith *et al*., (1996) [Reference: 69] conducted a comparison of the effects of administration to F-344 rats for 90-days of a range of oils, covering differences in type (naphthenic or paraffinic), refining method, viscosity, average molecular weight and average carbon number distribution. Marked differences in response were seen between many of the test materials, but overall, where effects were seen, these were consistent with those reported in F-344 rats in the studies by Baldwin *et al.* (1992) and Firriolo *et al.* (1995), However, the induction of any effects appeared to be related to molecular weight, viscosity and

melting point. The high viscosity oils (P70H, P100H) were essentially without effect. Effects with paraffin waxes (LMPW, MP, IMPW) were greater than those with the low-viscosity oils (N10A, N15H, P15H), which in turn were greater than those of the intermediate viscosity oils ((N70A, N70H). Effects seen with the paraffin waxes which were not seen with the other test oils or in previous studies, but are pertinent to the effects seen with AKDs, included inflammation in the heart, and histiocytosis/mononuclear cell accumulation in the cervical lymph nodes and Peyer's patches. From these results the authors considered that the spectrum of biological effects produced by the various test materials was related to the molecular size of the hydrocarbon. This correlated also with the fact that those producing the highest responses were shown in the study to result in the greatest content of saturated hydrocarbons measured in the liver and mesenteric lymph nodes. Additionally, similarities of magnitude of responses between certain oils and waxes were more closely related to molecular weight rather than other characteristics such as viscosity. Nash *et al.* (1996) [Reference: [70]], in reviewing all studies on white mineral oils, provides further information on the above correlations. Absorption of mineral hydrocarbons is partly dependent on the physicochemical nature of the constituents, in that the amount absorbed is inversely related to the length of the carbon backbone. Once absorbed, they distribute primarily to the liver, spleen, mesenteric lymph nodes and fat pads, the former three being key sites at which histological changes were seen with both hydrocarbons and AKDs. Differences in absorption, accumulation and metabolism probably account also for the species and strain differences observed in hydrocarbon oil responses, a hypothesis strengthened by the work of Halladay *et al.* (2002) [Reference: [71]] who administered a radiolabelled surrogate mineral hydrocarbon to F-344 and SD rats and showed distinct differences in the pharmacokinetic profiles between these strains, providing some correlation with the results of the feeding studies. Scotter et al. (2003) [Reference: [72]] fed a range of five different hydrocarbon waxes and oils to F-344 rats for 90 days and showed that the size and structure of individual components of the hydrocarbon mixtures played a role both in determining their propensity to accumulate in different tissues and the severity of any response that they elicited once accumulated.

The close similarity of effects of feeding hydrocarbon oils to those seen in the Alkyl Ketene Dimer studies is strong evidence for the effects of the Alkyl Ketene Dimers being attributable to their hydrocarbon chain structures rather than any unique characteristic.

The variable response of different rat strains to exposure to mineral waxes in the context of potential human exposure has been addressed by Miller *et al.* (1996) [Reference: [73]] and Fleming *et al.* (1998) [Reference: [74]]. While recognising distinct species and strain differences in responses to hydrocarbon oils, it is also apparent that both the F-344 rat and human respond to the presence of saturated hydrocarbons at similar tissue concentrations. However, the type and severity of the response is different, i.e. it is an inflammatory lesion in the rat compared with oil droplet formation in humans. Further consideration of the relevance of the rat liver lesion to potential human effects was addressed by a panel of medical and veterinary pathologists at a workshop sponsored by industry held at the Fraunhofer Institute of Toxicology and Aerosol Research in 2001and the findings were published by Carlton et al. (2001) [Reference: [75]]. The panel reviewed reports and histologic slides from studies on mineral hydrocarbons in rats and also mineral-oil induced alterations in tissues of human patients. They agreed that the lesions seen in the liver and mesenteric lymph nodes and of F-344 rats exposed to mineral hydrocarbons were different morphologically from changes observed in lymph node, liver and spleen of humans that were mineral oil users. They conclude in the publication that " *the lesions in the rats are unlike those tissue changes found in humans associated with ingestion and accumulation over time of MHCs and the data of the histopathologic alterations obtained from the feeding of certain MHCs to F344 rats for 90 days seem irrelevant to the human condition (Fleming et al., 1998). Ample evidence has been obtained over the years and provided in several publications that the accumulation of MHCs in the liver,*

spleen and lymph nodes of humans do not result in the formation of granulomas and do not produce an inflammatory reaction or other adverse effects. The lesions are considered incidental findings at biopsy or autopsy (Kelsall and Blackwell, 1969 [Reference: *[76]]; Klatskin 1977* [Reference: *[77]]). The metabolic handling of the MHCs by rats and humans seem to be greatly different as is the metabolic handling between strain of rats [Sprague-Dawley rat has not developed hepatic granulomas in the reported studies (Firriolo et al., 1995)]. The available data suggest that the granulomatous lesions experimentally induced by MHC-feeding, particularly in the liver of F344 rats, are exaggerated toxicological responses peculiar to the rat*". These conclusions took into account data available to the workshop from a chronic feeding study in F-344 rats of two mineral hydrocarbons. The results of this study have now been published (CONCAWE, 2004 [Reference: [78]]) and show no progression of liver lesions despite continued accumulation of hydrocarbon in the tissues and no evidence of any carcinogenic effects. Similar results were reported by Shoda et al. (1997) [Reference: [79]].

Additionally, recognising the concerns for certain types of mineral hydrocarbons as direct food additives, the AKDs are never used in this context. The only potential for their introduction into foods is from certain types of food packaging materials in which their use is permitted. Since incorporation of AKDs into such packaging is only permitted up to certain limits under US and European Regulations, the migration into food will be very limited and this route of exposure poses no concern for health.

CONCLUSION

Comparison of the results of oral toxicity studies in the rat with three alkyl ketene dimers show similarities of effect that suggest that there may a generic response to administration of such materials. Furthermore, a review of relevant toxicological literature has demonstrated similar findings in studies where mineral hydrocarbons have been administered to rats; differences in the extent and magnitude of the responses were found to be related to hydrocarbon type, molecular weight and rat strain. It is, therefore, concluded on the basis of the similarities in physicochemical properties and toxicological responses seen, that the effects of the alkyl ketene dimers are attributable to their hydrocarbon makeup, and do not constitute a response pattern specific only to this class of chemicals.

5.6. Genetic Toxicity *'in Vitro'*

5.6.1. Gene Mutations

Type: Ames test
System of testing: *Salmonella typhimurium* TA1535, TA100, TA1537, TA98
Concentration: 0 (control) 20, 200, 500, 5000 microgram/plate
Metabolic activation: with and without
Result: negative
Method: Standard plate – and pre-incubation test according to OECD Guideline for Testing of Chemicals no. 471
Year: 1988
GLP: Yes

Test substance: Basoplast 20 konz. Batch 838 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]

Remark: The test substance was dissolved in acetone. A slight precipitation was observed at concentrations of 500 and 1000 microgram per plate. There was a slight decrease in his+ revertants at a concentration of 5000 micrograms per plate.
2-Aminoanthracene, N-methyl-N-nitro-N-nitroso-guanidine, 4-nitro-o-phenylenediamin, 9-aminoacridine served as positive control substances.
Reliability: 1
KEY STUDY for OECD SIDS
[Reference: 80**]**

Type: Ames test
System of testing: *Salmonella typhimurium*, TA 1535, TA 100, TA 1538, TA 98, TA 1537
Concentration: 3, 10, 33, 100, 333, 1000 µg/plate
Metabolic activation: with and without
Result: negative
Method: B.N. Ames J. McCann, E. Yamazaki (1975) Mutation Research, 31, 347-364
Year: 1988
GLP: Yes
Remark: A slight precipitation was observed at the highest concentration. There was no toxicity to the bacteria observed.
Test substance: Alkyl Ketene Dimer Batch 339, standard production [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Reliability: 1
[Reference: 81]

Type: Ames test
System of testing: *Salmonella typhimurium*
Concentration: 3 to 1000 µg/plate
Metabolic activation: no data
Result: negative
Method: B.N. Ames J. McCann, E. Yamazaki (1975) Mutation Research, 31, 347-364
Year: 1988
GLP: Yes
Remark: Acetone was used as a solvent, at concentrations ranging from 3 to 1000 µg/plate, with or without S9 mix. A slight precipitation was observed at the highest concentration. There was no toxicity to bacteria observed.
Test substance: Alkyl Ketene Dimers Batch 354, standard production [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Reliability: 1
[Reference: 82]

5.6.2. Chromosomal Aberrations

Type: Cytogenetic Assay, Chromosome aberration
System of testing: Human lymphocytes
Concentration: 0 (control), 100, 500, 1000 µg/mL
Metabolic activation: with and without
Result: Negative
Method: OECD Guideline for Testing of Chemicals no. 473 **"***In vitro* Mammalian Chromosome Aberration Test"
Year: 2003

GLP: Yes
Test substance: Aquapel 364, batch 3LP1456 P224 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids]
Remark: The test substance was dissolved in dried dimethylsulphoxide (DMSO). The concentration was limited by the solubility of the test substance in the culture medium. Concentrations above 1000 microgram/mL caused precipitation of the test substance on the slides. Virtually no reduction in mitotic activity (compared to solvent control) was observed at concentrations of 1000 microgram/mL. Mitomycin C and cyclophosphamide served as positive control substances.
Reliability: 1
KEY STUDY for OECD SIDS
[Reference: 83**]**

5.7. Genetic Toxicity *'in Vivo'*

No on data on the genetic toxicity *in vivo* are available.

5.8. Carcinogenicity

No data on the carcinogenicity are available.

5.9. Reproductive Toxicity

5.9.1. Fertility

Effects on reproductive performance were evaluated in a combined repeated dose toxicity study with reproductive and developmental toxicity screening according to OECD Guideline for Testing of Chemicals no. 422 (see chapter Repeated Dose Toxicity). Doses of 100, 350 or 1000 mg/kg b.m./day were administered to Wistar-derived rats by oral gavage.

There was no effect on male and female reproductive performance and no effect on male reproductive organs. In females, however, there was an inflammation of the ovaries, uterus and cervix. Along with the inflammations, the ratio of corpora lutea to implantation sites was reduced. This pre-implantation loss, was observed in all treated groups, but the effect was not dose-related. . The number of corpora lutea was slightly higher in females given 1000 mg/kg b.w./day than in the control, 100 and 350 mg/kg b.w./day dose groups. However, the ratio of implantation sites to corpora lutea was similarly reduced in all treated groups when compared to controls. There were no effects on post-implantation loss. The litter size was smaller in all treated groups with the effect being most marked at the low- and mid-dose where the number of corpora lutea and hence the number of implantation sites, was lower than at the high-dose (see Table 2 below).

Table 2: Corpora lutea and implantation sites and incidences of pre-impantation losses

	Dose level of Aquapel 364 [mg/kg b.w./day]			
	0 (control)	**100**	**350**	**1000**
No. of corpora lutea				
MEAN	13.9	14.1	12.2	16.0
S.D.	2.4	2.9	4.5	3.1
N	9	10	9	8
No. of implantations				
MEAN	11.2	9.3	9.1	11.3
S.D.	3.6	4.6	3.1	3.4

	Dose level of Aquapel 364 [mg/kg b.w./day]			
	0 (control)	100	350	1000
N	9	9	8	8
Pre-implantation loss				
Prop. of implants affected	24/125	54/141**	36/110*	47/128**
Percentage				
MEAN	19.8	39.4	28.1	35.6
S.D.	19.8	27.8	27.1	29.9
N	9	10	9	8
No. of live + dead pups				
MEAN	11.2	7.0*	7.1	9.1
S.D.	3.7	4.5	4.7	4.9
N	10	10	9	8

Statistically significant by two-sided Fisher's Exact Test, (* at 5%, ** at 1% level)

Individual animal data (see Table below) seems to confirm a correlation between inflammation of the uterus and cervix and the observed pre-implantation losses. Five animals per group were subjected to micropathology. To analyse the data, a threshold for significant pre-implantation losses was set to five pre-implantation losses, since it is the mean + S.D. for pre-implantation losses in the control group.

Table 3: Pre-implantation losses and inflammations of uterus and/or cervix in animals with micropathological examination (five animals per group were examined)

Dose	Animal no	Cervix	Uterus	Corpora lutea		Implantations		Pre-implantation. losses [a]
				Left	Right	Left	Right	
0	42	0	0	4	10	4	8	2
	44	0	0	9	7	3	6	**7**
	46	0	0	3	8	3	5	3
	48	other		6	10	6	9	1
	50	0	0	6	6	5	0	**7**
100	52	0	0	6	5	0	5	**6**
	54	1	1	6	7	2	3	***8***
	56	2	1	10	8	2	2	***14***
	58	0	0	3	9	3	9	0
	60	other	other	5	4	0	3	***6***
350	62	1	1	4	9	2	4	***7***
	64	2	1	6	8	2	4	***8***
	66	2	2	7	5	3	4	5
	68	1	1	small	small	1	0	0
	70	0	0	small	small	0	0	0
1000	72	1	1	8	8	8	5	3
	74	1	1	5	8	1	1	***11***
	76	1	1	7	7	4	7	3
	78	1	1	small	small	0	0	0
	80	1	0	5	10	5	10	0

[a] bold letters indicate losses above threshold of 5 (mean+S.D. of control), Italic, red fonts indicate significant losses with inflammation of uterus and/or cervix

NOAEL (general toxicity, parental): No NOAEL was achieved
LOAEL (general toxicity, parental): 100 mg/kg b.m./day based on inflammatory changes in a variety of tissues in both genders
NOAEL (reproductive performance): No NOAEL was achieved
LOAEL (reproductive performance): 100 mg/kg b.m./day based on reduced proportion of implantation sites compared to the numbers *of corpora lutea*
Reliability: 1
KEY STUDY for OECD SIDS

5.9.5. Developmental Toxicity

Developmental effects were evaluated in a combined repeated dose toxicity study with reproductive and developmental toxicity screening according to OECD Guideline for Testing of Chemicals no. 422 (see chapter Repeated Dose Toxicity). Doses of 100, 350 or 1000 mg/kg b.m./day were administered to Wistar-derived rats by oral gavage.

NOAEL (general toxicity, parental): No NOAEL was achieved
LOAEL (general toxicity, parental): 100 mg/kg b.m./day based on inflammatory changes in a variety of tissues in both genders
NOAEL (developmental toxicity): 1000 mg/kg b.m./day (highest dose tested)
Reliability: 1
KEY STUDY for OECD SIDS

5.10. Other Relevant Information

5.10.1. Specific Toxicity

There is no specific study on the neurotoxic or immunotoxic effect available. In the combined repeated dose toxicity study for reproductive and developmental toxicity, screening test according to OECD Guideline for Testing of Chemicals no. 422 .
No evidence of neurotoxicity was detected in the functional observation battery, the motor activity measurements or the brain weight of the adult animals.

5.11. Experience with Human Exposure

Aquapel 380 was used for patch tests with humans. Aquapel 380 contains 5 parts of Aquapel 364 P224 [CAS Nos. - 84989-41-3/68390-56-7 manufactured from a mixture of technical grade stearic and palmitic acids] and 1 part emulsifier.
There are two studies available:
In the first study, a 40% w/v slurry of Aquapel 380 was applied as a patch to the backs of the test persons and covered. The first, induction application lasted 48 hours. The patch was removed skin reactions were graded and recorded. Three weeks later the test substance was applied a second time, again for 24 hours. 1 day after removing the patches, the skin was examined for delayed reactions.
There were seven *1+* and one *2+* reactions to the primary application. And there were four *1+* reactions to the challenge application.
It was concluded by Dr Louis Schwartz MD in a letter to Dr J.P. Frawley, that Aquapel 380 is neither a primary irritant nor a sensitiser.
Reliability: 4, Does not meet today's standards of performance and documentation
[Reference: 84**]**

In a second study Aquapel 380 was tested as a 5% aqueous emulsion and a cotton cloth soaked with this emulsion on 50 humans each. Patches were applied to the thighs of the women and the upper, inner arms of the men, and sealed on with adhesive plaster. The patches remained on the skin for 72 hours. The skin reaction was scored after removing the patch. 8 days after the first patch was removed, a second series of patches were placed on the same skin sites of the same 50 subjects, where they remained for 72 hours. The skin reaction was scored after removing the patch.
There was no skin reaction observed after the first and the second application.
This study was extended with 150 new subjects. They were patched with the 5% Aquapel 380 emulsion. The patches were applied in the manner described above and they remained on the skin sites inspected.
After the first application one subject showed a *3-plus* reaction. This subject showed a *2-plus* reaction to the second application. In addition, 7 other subjects showed reactions in degrees of *1* to *3-plus* after the second application.
It was concluded, that a 5% aqueous emulsion of Aquapel 380 was skin irritating to 1 out of 200 subjects and sensitized the skin of 7 more subjects.
As a follow-up of the positive responses, 7 of the 8 subjects who showed reactions to 5% aqueous emulsion of Aquapel 380 were tested with the pure Aquapel 364 and different emulsifiers. The patches were applied for 90 hours and the skin reaction was scored after removing the patches.
There were no reactions to Aquapel 364, but there was a *2-plus* reaction to one of the emulsifier. This reaction occurred in the person who showed a *3-plus* reaction the 5% Aquapel 380 emulsion after the first application and a similar reaction after the second application. In a second follow-up 6 of the 8 subjects were tested and no skin reaction was observed. This was explained by hyposensitisation of the subjects.

It was concluded, that Aquapel 364 by itself causes no skin reaction. And that handling the Aquapel 380 emulsion poses only a low and temporarily risk in few sensitive persons.
Reliability: 4, Does not meet today's standards of performance and documentation.
[Reference: [85]]

A recent survey among producers and formulators revealed no reported contact allergy cases at any of the production sites.**[Reference:** 86**]**

6. REFERENCES

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[7] Hercules Analytical Laboratory Report No. AD-99-232, 2004

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